the correct box. Similar experiments suggest that rats and monkeys also have some metacognitive abilities.

Verification of Subjective Reports Is Challenging

Reports of subjective experience, such as confidence, serve like a meter. Just as an electrical meter converts electrical resistance into the position of a pointer on a dial (reading 100 ohms), so a subject converts a light stimulus into the report of a color ("I see red"). But there is a critical way in which the meter is not like a person. The meter does not experience red and cannot communicate meaning. And, although the meter might be faulty, it can never pretend to see red when it is really seeing blue. Most of the time, we presume that subjective reports are true, that is, the subject is trying as far as possible to give an accurate description of his experience. But how can we be sure that we can rely on these subjective reports?

The problem of verifying subjective reports can partially be addressed with the use of brain imaging. Brain imaging studies have shown that neural activity occurs in localized areas of the brain during mental activity that is not associated with any overt behavior. The content of such mental activity, such as imagining or daydreaming, can be known only from the subject's reports.

If we scan a subject while he says he is imagining moving his hand, activity will be detected in many parts of the motor system. In most motor regions, this activity is less intense than the activity associated with an actual movement, but it is well above resting levels. Similarly, if a subject reports that she is imagining a face she has recently seen, activity can be detected in the fusiform gyrus, the "face recognition area" (Figure 59–10). In these examples, the location of the observed neural activity detected by the scanner

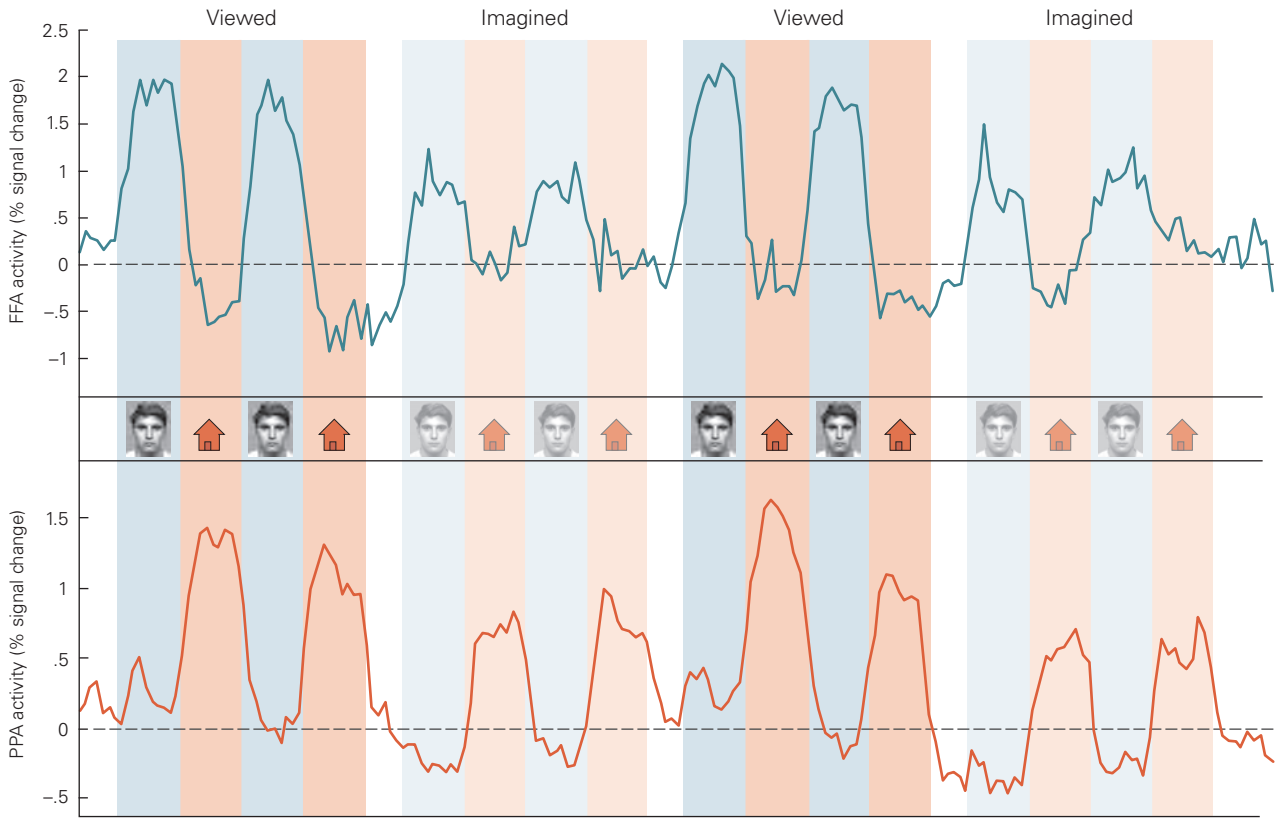

Figure 59–10 Imagining a face or a place correlates with activity in specific areas of the brain. Subjects were scanned while they viewed or imagined faces and houses. In the first block of trials, subjects alternately viewed a face or a house. When viewing a face, brain activity increases in the fusiform face area of the inferior temporal lobe (**FFA**). When viewing a house, brain activity increases in the parahippocampal place area of the inferior temporal cortex (**PPA**). In the next block of trials, subjects alternately *imagined* a face and a house. The same brain regions are active during both the imagining and direct viewing of faces and houses, although the activity is less pronounced during the imagined viewing. (Reproduced, with permission, from O'Craven and Kanwisher 2000. Copyright © 2000 MIT.)

provides independent confirmation of the content of the experience reported by the subject. The content of consciousness can, in certain limited cases, be inferred from patterns of neural activity.

Malingering and Hysteria Can Lead to Unreliable Subjective Reports

What if a subject reports seeing "blue" even though what they experienced was red? How could this arise, and what is the status of the subjective report in such cases?

Consider a patient who has become amnesic as a result of extensive damage to the medial temporal cortex. Shown a photograph of someone whom he sees every day on the ward, the patient denies ever having seen this person, even while physiological measurements (electroencephalogram or skin conductance) show a response to this photo (but not to photos of people he has not seen before). We conclude that conscious memory processes have been damaged while unconscious processes remain intact. This patient's subjective report is an accurate account of what he knows *consciously*, but it excludes those things he "knows" that have not entered consciousness.

Another patient, found wandering on the street, shows no evidence of brain damage but reports he cannot remember anything about himself or his history. When shown photographs of people from his past, he denies any knowledge of them, but at the same time, he shows physiological responses to the photos. In this case, because of the lack of detectable brain damage (and other features of the memory loss), we begin to wonder about the truthfulness of his statements. Perhaps the physiological responses indicate that he does consciously recognize people. Subsequently, the patient is identified by the police, and we discover that he is wanted for a serious crime committed in the neighboring county. Our doubts about the reliability of his reports increase. Finally, our suspicions are confirmed when he foolishly tells a fellow patient, "It's so easy to fool those clinical psychologists."

In this case, we have direct evidence that the patient was deliberately misleading others about himself. To deceive others, we must be conscious not only of our own mental state but also that of others. Is there some way we can test for deceit? One approach is to use a memory test of the kind discussed earlier. The patient studies a list of words. He is then shown a new list consisting of the words he has just studied and new words, and he must decide whether each word is old or new. A genuine amnesic would not recognize any of the words; he would have to guess, but through unconscious priming effects, he would perform better than chance. The malingering patient can recognize the old words but will have a strong tendency to deny that he has seen them before. Unless he is very sophisticated, he may perform worse than chance. It seems we should be able to distinguish between the genuine amnesic and the malingerer.

A third kind of patient also simulates amnesia (or some other disorder) but does so unconsciously and thus is not a malingerer. Such a case would be called hysterical or psychogenic amnesia. Like the malingerer, his performance on the recognition test is worse than chance. Nonetheless, he is not aware of his simulation. The same mechanism occurs in normal people who have been hypnotized and then told that they will have no memory for what has just happened. This phenomenon is sometimes referred to as a dissociated state: That part of the mind that records experiences and makes verbal reports has become dissociated from the part that is creating the simulation. Hysterical simulations can also create sensory loss, such as hysterical blindness, and motor disorders, such as hysterical paralysis or hysterical dystonia.

We are still a long way from understanding the cognitive processes or underlying physiology of these disorders. A key problem is how to distinguish hysteria from malingering. From the standpoint of conscious experience, the two disorders are quite different: The malingerer is aware that he is simulating, whereas the hysterical patient is not. Yet the patients' subjective reports and overt behavior in the two cases are very similar. Is there no measure that can distinguish between these different disorders? Perhaps the only way to demonstrate the critical distinction between these different states of consciousness is through neuroimaging studies.

Highlights

1. The study of mental disorders forces us to confront the conceptual gap between the mental and the physical. It is no longer possible to maintain that mental disorders have mental causes, whereas physical disorders have physical causes.
2. Cognitive neuroscience has had a major impact on our attempts to bridge this gap because its descriptive language, the language of information processing, can be applied simultaneously to psychological and neural processes. Information theory and the development of the computer hint at how science can address the question of how subjective experience can emerge from activity in a physical brain.

3. It is now clear that perception, action, and memory are the result of many parallel processes and that, although some of these processes support conscious experience, the majority occur below the level of awareness.
4. Striking abnormalities occur when some of these processes are damaged while others remain intact. One patient, D.F., with damage to the inferior temporal cortex, is no longer consciously aware of the shape of an object and hence cannot describe it or recognize what it is. She can nevertheless form her hand into the appropriate shape to pick up the object.
5. We have very little awareness of the details of our actions, but we are vividly aware of being in control (the sense of agency). In extreme cases, this sense of agency can become detached from the control of action. After limb amputation, many people experience having a phantom limb that they can move, and after a limb has been paralyzed due to a stroke, some patients believe that they can still move the limb.
6. Recollection of the past is not like replaying a video. Memory is a creative process based on imperfect recall filled out with general knowledge. Through loss of this creativity, patients with amnesia have difficulty with imagining the future as well as remembering the past.
7. Subjective experience is an important part of human life. When we make a decision, our choice is indicated by our behavior, but our confidence in that choice is a subjective experience. We can study such experiences through verbal report. Confidence in our choices is an example of *metacognition* (ie, the ability to reflect on our cognitive processes). Damage to the frontal cortex can impair metacognition, while leaving decision-making intact.
8. Verbal reports are not always reliable. People can fake memory loss in order to escape justice. Malingering of this kind is very difficult to detect, since it closely resembles disorders such as hysterical amnesia, in which the patient is not aware that he is simulating the disorder. The challenge for cognitive neuroscience is to distinguish these cases.

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60

Disorders of Thought and Volition in Schizophrenia

In this chapter and the next, we examine disorders that affect perception, thought, mood, emotion, and motivation: schizophrenia, depression, bipolar disorder, and anxiety disorders. These have been challenging to understand, but recent progress in genetic analysis has begun to yield significant clues to their pathogenesis.

Mental illness has damaging effects on individuals, families, and society. The World Health Organization reports that mental illnesses, in the aggregate, constitute the leading cause of disability worldwide and are the leading risk factors for the 800,000 annual suicides reported by the World Health Organization. In addition, depression and anxiety disorders frequently co-occur with and worsen the outcomes of diabetes mellitus, coronary artery disease, stroke, and several other illnesses.

Medications such as antipsychotic drugs, lithium, and antidepressant drugs discovered during the mid-20th century made it possible to close large and often substandard mental hospitals; however, halfway houses and other less restrictive treatment settings did not materialize in sufficient numbers. As a result, many people with schizophrenia and severe bipolar disorder become homeless at some time in their lives, and in many countries, individuals with severe mental disorders compose a large fraction of prison populations.

In addition, although antipsychotic drugs, lithium, and antidepressant drugs have played important roles in controlling symptoms of mental disorders, significant limitations in treatment efficacy remain. For example, there are no effective treatments for the highly disabling cognitive impairments and deficit symptoms of schizophrenia. Even for symptoms that benefit from existing medications, such as hallucinations and delusions, residual symptoms remain and relapses are the rule. Because of significant scientific challenges posed by the human brain and limitations in animal models of mental disorders, there has been little advance in the efficacy of psychiatric drugs for more than 50 years. However, recent progress in human genetics and neural science has created significant opportunities to improve upon this unfortunate state of affairs.

Schizophrenia Is Characterized by Cognitive Impairments, Deficit Symptoms, and Psychotic Symptoms

In medicine, the understanding of a disease, and therefore its diagnosis, is ultimately based on identification of two features: (1) etiological factors (eg, microbes, toxins, or genetic risks) and (2) mechanism of pathogenesis (the processes by which etiologic agents produce disease). While human genetics and neural science are beginning to provide insights into the etiology and pathogenesis of disorders such as schizophrenia, bipolar disorder, and autism spectrum disorders, this research has not yet yielded objective diagnostic tests or biomarkers. As a result, psychiatric diagnoses still rely on a description of the patient's symptoms, the examiner's observations, and the course of the illness over time.

Schizophrenia is a very severe illness. Its symptoms can be divided into three clusters: (1) cognitive symptoms; (2) deficit, or negative, symptoms; and (3) psychotic symptoms. These symptom clusters exhibit different temporal patterns of onset—with cognitive impairments and deficit symptoms typically the earliest. The different timing of onset and the precise symptoms of each cluster are thought to result from the effects of developmental pathogenic mechanisms on different neural circuits and brain regions. As a result, existing treatments such as antipsychotic drugs, which act on one "downstream" aspect of the disease process, exert no beneficial effects on cognitive impairments or deficit symptoms.

At the beginning of the 20th century, Emil Kraepelin in Germany recognized that cognitive decline was a distinguishing feature of schizophrenia, because psychotic symptoms occur in a variety of psychiatric conditions. Indeed, Kraepelin's term for what later came to be called schizophrenia was *dementia praecox*, a term that highlighted the early onset of cognitive loss. Cognitive impairments in schizophrenia target working memory and executive function, declarative memory, verbal fluency, the ability to identify the emotions conveyed by facial expressions, and other aspects of social cognition. These impairments do not significantly improve with existing medications, but ongoing research shows promising, albeit still modest, benefits from psychological therapies aimed at cognitive remediation.

Deficit symptoms include blunted emotional responses, withdrawal from social interaction, impoverished content of thought and speech, and loss of motivation. Psychotic symptoms include hallucinations, delusions, and disordered thought such as loosening of association (Box 60–1). Psychotic symptoms of schizophrenia are responsive to antipsychotic drugs. These drugs also reduce psychotic symptoms that

Box 60–1 Thought Disorder

The structure of a psychotic person's speech may range from wandering to incoherence, a symptom commonly referred to as loosening of association. Other examples of schizophrenic 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 types of loosening of association have been described (eg, 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.

occur in other neuropsychiatric disorders, including bipolar disorder, severe depression, and neurodegenerative disorders such as Parkinson disease, Huntington disease, and Alzheimer disease.

Schizophrenia Has a Characteristic Course of Illness With Onset During the Second and Third Decades of Life

Schizophrenia affects 0.25% to 0.75% of the population worldwide, with only modest regional differences. Males are more commonly affected than females, with the sex ratio estimated to be 3:2, and onset is often earlier in males. Schizophrenia typically begins during the late teen years or the early to mid-twenties. Enduring cognitive and deficit symptoms generally begin months and sometimes years prior to the onset of psychotic symptoms. This period is referred to as the ultra-high-risk state by some researchers and as the schizophrenia prodrome by others.

Individuals in this risk state generally have measurable declines in cognitive functioning accompanied by such symptoms as social isolation, suspiciousness, and decreased motivation to engage in school work or other tasks. Attenuated psychotic symptoms often follow, including transient and mild hallucinations. Not every teen with such symptoms progresses to develop the full spectrum of symptoms warranting a diagnosis of schizophrenia. A small fraction recovers; others develop serious psychiatric conditions other than schizophrenia. Antipsychotic medications do not appear to benefit individuals in the risk state, nor do they delay the onset of schizophrenia. However, talk therapies and therapies delivered via computer-based approaches aimed at cognitive remediation show promise in delaying the onset of psychosis.

The Psychotic Symptoms of Schizophrenia Tend to Be Episodic

Psychotic symptoms, including hallucinations and delusions, are the most dramatic manifestations of schizophrenia. Hallucinations are percepts that occur in the absence of appropriate sensory stimuli, and they may occur in any sensory modality. In schizophrenia, the most common hallucinations are auditory. Typically, an affected person hears voices, but noises and music are also common. Sometimes, the voices will carry on a dialog and frequently are experienced as derogatory or bullying. Occasionally, voices will issue commands to the affected individual that can create a high risk of harm to self or others.

Delusions are firm beliefs that have no realistic basis and are not explained by the patient's culture, nor are they amenable to change by argument or evidence. Delusions may be quite varied in form. For some affected individuals, reality is significantly distorted: The world is full of hidden signs meant only for the affected person (ideas of reference), or the person believes that he is being closely watched, followed, or persecuted (paranoid delusions). Others may experience bizarre delusions; for example, they may believe that someone is inserting thoughts into or extracting thoughts from their minds or that their close relatives have been replaced by aliens from another planet. In addition to the person's enduring cognitive impairments, psychotic episodes are frequently accompanied by disordered thought and odd patterns of speech (Box 60–1).

Psychotic symptoms may also occur in other neuropsychiatric disorders, such as bipolar disorder, major (unipolar) depression, various neurodegenerative disorders, and drug-induced states. However, these other conditions can usually be distinguished from schizophrenia by associated symptoms and age of onset. Once schizophrenia has become fully manifest, psychotic symptoms tend to be episodic. Periods of florid psychosis accompanied by markedly disordered thinking, emotion, and behavior are interspersed with periods in which psychotic symptoms are milder or even absent. Psychotic episodes typically require hospitalization; the severity and duration of such episodes are markedly shortened by antipsychotic drugs. First and second episodes of psychosis often respond fully to antipsychotic drugs, but cognitive impairments and deficit symptoms typically persist. After the first few psychotic relapses, people with schizophrenia typically suffer residual psychotic symptoms even between their acute relapses and suffer these symptoms despite treatment with antipsychotic drugs. Cognitive and social functioning typically continue to deteriorate over several years until they reach a plateau well below the person's premorbid level of functioning.

The Risk of Schizophrenia Is Highly Influenced by Genes

As early as 1930, Franz Kalman in Germany studied familial patterns of schizophrenia and concluded that genes contribute significantly. To separate genetic from environmental influences more clearly, Seymour Kety, David Rosenthal, and Paul Wender examined children who were adopted at or shortly after birth in Denmark. They found that the rate of schizophrenia in the biological family of the adoptee was much more strongly

predictive of schizophrenia than the rate of schizophrenia in the adoptive family.

Kety and his colleagues also observed that some of the biological relatives of adoptees with schizophrenia exhibited milder symptoms related to schizophrenia, such as social isolation, suspiciousness, eccentric beliefs, and magical thinking, but not frank hallucinations or delusions. Since Kety's time, it has been observed that such relatives may also exhibit cognitive impairments that are intermediate between unaffected individuals and those with schizophrenia. They also may exhibit thinning of the cerebral cortex observed by magnetic resonance imaging (MRI) that is also intermediate between healthy individuals and those with schizophrenia. (Cortical thinning in schizophrenia is discussed below.) Such individuals are now diagnosed with schizotypal disorder, which appears to be the milder end of the schizophrenia spectrum of psychotic disorders. The severity and nature of symptoms appear to be influenced by the individual's overall burden of risk-associated genetic variants as well as exposure to environmental risk factors.

Irving Gottesman's studies of extended pedigrees of Danish patients with schizophrenia supported the importance of genes. Gottesman noted the correlations between the risk of schizophrenia in relatives and the degree to which they shared DNA sequences with an affected person. He found a greater lifetime risk of schizophrenia among first-degree relatives (including parents, siblings, and children, who share 50% of DNA sequences with the patient) than among second-degree relatives (including aunts, uncles, nieces, nephews, and grandchildren, who share 25% of their DNA sequences). Even third-degree relatives (who share only 12.5% of the patient's DNA sequences) were at higher risk for schizophrenia than the approximately 1% of the general population at risk for this disease (Figure 60–1).

Based on the differences in levels of risk Gottesman measured in these pedigrees, he recognized that schizophrenia risk was not transmitted within families as Mendelian dominant or recessive traits (ie, it was not caused by a single genetic locus). He predicted correctly that schizophrenia is a polygenic trait, involving a large number of loci throughout the human genome. This genetic architecture underlies many human phenotypes, including disease phenotypes, and may involve many hundreds of loci within the genome. In polygenic traits, variants at each disease-associated locus contribute small, additive effects to the phenotype. Genetic risk variants act together with environmental factors to produce the schizophrenia phenotype.

In 2014, a large global consortium reported on a genome-wide association study of more than 35,000 individuals with schizophrenia. The study identified 108 genome-wide significant loci associated with schizophrenia that were distributed across the genome. The research continues, and the number of known loci is already greater than 250. Each of these loci represents a segment of DNA identified by a single

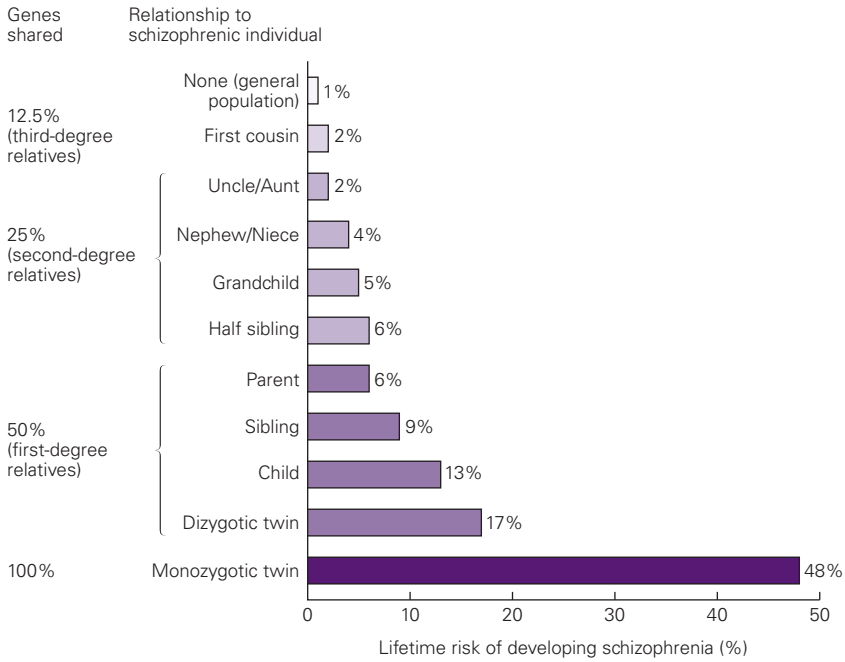

Figure 60–1 **The lifetime risk of schizophrenia increases as a function of genetic relatedness to a person with schizophrenia.** The risk of schizophrenia rises with genetic relatedness to an affected individual and, therefore, with increased sharing of DNA sequences. However, the pattern of segregation in families does not follow simple Mendelian ratios; rather, inheritance reflects genetic complexity. In addition, risk varies within categories of relatedness (first- and second-degree relatives), suggesting a role for unshared developmental or environmental effects. (Reproduced, with permission, from Gottesman 1991.)

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