Schizophrenia is an illness where the clinical signs and symptoms, course, and cognitive characteristics are well described. Successful pharmacological treatments do exist, even though they are likely palliative. However, this broad knowledge base has not yet led to the identification of its pathophysiology or etiology. The risk factors for schizophrenia are most prominently genetic, and scientists anticipate that contributions from the new genetic information in the human genome will help progress towards discovering a disease mechanism. Brain-imaging techniques have opened up the schizophrenic brain for direct inquiries, in terms of structure, neurochemistry, and function. New proposals for diagnosis include grouping schizophrenia together with schizophrenia-related personality disorders into the same disease entity, and calling this schizophrenia spectrum disorder. New hypotheses of pathophysiology do not overlook dopamine as playing a major role, but do emphasize the participation of integrative neural systems in the expression of the illness and of the limbic system in generating symptoms. Critical observations for future discovery are likely to arise from molecular genetics, combined with hypothesis-generating experiments using brain imaging and human post-mortem tissue.

Schizophrenia is a chronic recurring psychotic illness that characteristically begins in young adult years and lasts a lifetime. Prodromal symptoms often precede the acute psychosis, including cognitive dysfunction and negative symptoms. Whether schizophrenia represents a single illness or is a syndromal diagnosis is still unknown, and data indicating how we should define disease subgroups are still required. Because the disease has affected humans for millennia, clinicians know a considerable amount about the clinical characteristics, onset, response to interventions, and tissue response characteristics of persons with the illness. Here, we will review what is known about schizophrenia and speculate on the potential meaning of this constellation of observations.

Schizophrenia: the clinical condition

Psychosis

The defining features of a schizophrenia diagnosis are hallucinations, delusions, paranoia, and thought disorder; these experiences are manifest in multiple sensory modalities and include abnormalities in all aspects of thought, cognition, and emotion (Table I, see next page). The psychotic symptoms often have an insidious onset, and are characterized by a failure of logic, customary associations, intent, and the organization that usually accompanies human thought. It is not the loss but rather the malfunction of these functions that characterizes psychosis. Moreover, these features can fluctuate in intensity and across sensory substrates throughout the illness.

Keywords: clinical presentation; dopamine; glutamate; pathophysiology; schizophrenia

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Other disease features

The advent of antipsychotic drugs that are effective in the treatment of psychosis has exposed aspects of schizophrenia that were often overlooked when the florid presentation was untreated. These aspects include cognitive dysfunction and primary negative symptoms.\textsuperscript{1,12-14} Cognitive symptoms will be discussed later in their own section. Primary negative symptoms include manifestations of alogia, anhedonia, and asociality, and are seen as part of the illness complex in many persons with schizophrenia.\textsuperscript{4} Whether these symptoms are generated in the central nervous system (CNS) along with the process that results in the psychosis, or whether they have their own pathophysiology, is not yet known and opinions differ widely as to the answer. In optimally treated outpatient populations in which psychosis is at least partially controlled, analyses show that negative symptoms and cognitive dysfunction contribute more strongly to overall psychosocial disability than do residual positive symptoms.\textsuperscript{15} Therefore, targeting these symptomatic dysfunctions for treatment could powerfully improve outcome for affected individuals.

Course

Schizophrenia characteristically begins in young adult years and lasts throughout life, with only occasional recovery.\textsuperscript{11,16} It is the case, however, that childhood-onset and adult/elderly-onset cases occur. The initial years of illness are often the most symptomatic and include severe psychosocial deterioration. Middle-aged years are more benign; and in the elderly, frank symptom recovery has been described.\textsuperscript{17-19} Within this simplistic framework, episodes of psychosis regularly occur. One can formulate schizophrenia as a disease of childbearing years, even though elderly persons with the illness still retain symptoms. Differing interactions between schizophrenia and aging have been reported. Some clinical samples show symptom improvement accompanied by psychosocial stability with aging, whereas other clinical samples show a precipitous age-related deterioration with loss of cognitive function and frank dementia.\textsuperscript{20} Questions of late-life outcome in schizophrenia remain to be addressed.

Risk factors for schizophrenia

Genetics

A risk for schizophrenia is inherited.\textsuperscript{21} Twin studies have been pivotal in verifying a genetic predisposition.\textsuperscript{22,23} The more closely one is related to an individual with schizophrenia, the greater the risk of contracting the illness (Table II). The prevalence in the general population is 1%. The disease occurs in all cultures and people around the world (with rare exceptions), and with similar genetic risk

| Table II. Genetic risk for schizophrenia in terms of prevalence estimates. |
|----------------------------------|------------------|
| General population               | 1%               |
| Second-degree relative           | 2.5%             |
| Parent                           | 3.8%             |
| Sibling                          | 8.7%             |
| Child, 1 parent                  | 12%              |
| Child, 2 parents                 | 30%–40%          |
| Twin, monozygotic                | 40%–50%          |
estimates. The monozygotic twin of a person with schizophrenia, who shares the same genome, has a 40% to 50% risk of contracting the illness; this number represents not only a 50% genetic risk, but also a 50% nongenetic risk, each operating in the manifestations of the illness. Association studies in schizophrenia suggest that schizophrenia is a complex multigenetic disorder. Many genes associated with the illness have been identified in the different studies. Each risk factor confers a small risk, with the genetic factors being the most potent. Risk factors are thought to be multiplicative.24,27

Pre- or perinatal events

Catastrophic pre- or perinatal events, like exposure to famine, radiation, or a maternal viral illness, especially during the second trimester, are significant risk factors for schizophrenia. These early events do not have as much predictive power as the genetic factors, but can nonetheless explain significant variance.25 Perinatal events like toxemia and hypoxia at birth are risk factors for schizophrenia,26 as is a winter birth.28 It should be emphasized that most individuals who experience pre- or perinatal events of this sort or a winter birth do not ultimately contract schizophrenia. So the neural consequences that derive from these pre- or perinatal conditions do not inevitably lead to schizophrenia. These conditions, however, may combine with other precipitating factors to facilitate illness onset.

Factors during childhood and adolescence

Environmental factors have also been suggested as risks for schizophrenia. These most prominently include the use of marijuana (and possibly other forms of drug dependence, although this is less rigorously documented). Trauma is often mentioned as a proximal risk factor for the illness, although the actual documentation for this is soft. The rearing environment characterized by emotion and stress is also often identified as a precipitant for schizophrenia.

Psychological and electrophysiologic characteristics of schizophrenia

Cognitive dysfunction

Patients with schizophrenia characteristically perform more poorly on neuropsychological tasks than normal subjects.31 No cognitive domain is entirely spared and abnormalities are highly intercorrelated within a single individual.32 This performance defect is explained as both (i) a consequence of ongoing psychotic symptoms, early disease onset, and/or chronic institutionalization; and (ii) a set of specific deficits associated with the pathophysiology of schizophrenia.12,13,33,34 Persons with the illness show particular inabilities when performing tasks associated with attention, memory, and executive function.36 In monozygotic twins discordant for schizophrenia, the schizophrenic twin inevitably performs more poorly on tests of intelligence, memory, attention, verbal fluency, and pattern recognition than the nonschizophrenic twin.37 When tested, the nonschizophrenic twin only differs from normal individuals on the basis of a reduction in “logical memory,” as measured on the Wechsler scale and in Trails A performance. In addition, persons with schizophrenia consistently perform poorly on tasks that require sustained attention, sometimes called vigilance.38 Also, “working memory” or the mechanism by which task-relevant information is kept active for brief periods (ready for quick retrieval) is deficient in schizophrenia.39 Cognitive scientists have suggested that the widespread disturbances in attention, memory, and language are associated with a change in the “internal representation” of contextual information.40 They also have speculated that it is the CNS connection between “cognitive modules” (ie, the circuitry) that may be altered in schizophrenia, but not the internal organization of the module itself.41 Whatever the model turns out to be, the cognitive defects of schizophrenia are consistent with a widespread disruption in cerebral function and cognition. Also notable is the observation that in any single individual with the illness, symptoms fluctuate and change over time, making it hard to invoke permanent cerebral changes in neuronal function or circuitry as the basis of these cerebral abnormalities.

Neurophysiological dysfunction

Measures of brain response to graded external stimuli have been characterized in schizophrenia and used to postulate its pathophysiology. These measures include primary eye movements in response to a smooth pursuit stimulus and electroencephalography (EEG) wave characteristics in response to a sensory stimulus. Smooth pursuit movements are slow eye movements used to
track a small moving object. Normal subjects locate the moving target on their retinal fovea and move their eye with the target, following its smooth rate. The normal eye and brain use predictive smooth pursuit movements with occasional predictive saccades to follow a moving target efficiently. Persons with schizophrenia have abnormal smooth pursuit eye movements, and these are not explained by psychosis or medication. Moreover, many nonpsychotic family members of schizophrenics also show abnormal smooth pursuit movements, especially if they have a diagnosis of schizophrenia spectrum disorder. It has been hypothesized that the cerebral defect underlying abnormal eye tracking in schizophrenia is one of motion processing, in the link between motion information and eye movements or in the holding of the motion information in short-term memory. The latter formulation implicates the posterior parietal cortex and/or the middle frontal cortex in abnormal eye movements. In addition to smooth pursuit movements, saccadic eye movements have also been noted to be abnormal in schizophrenia. The nature of this abnormality also implicates frontal cortical dysfunction in the illness. Signal-averaged EEG changes that are time-locked to sensory or cognitive events (evoked potentials) represent measures of individual information processing, independent of a behavioral response. Elements of these evoked potentials are abnormal in schizophrenia, specifically the P300 element and the P50 wave. The P300 amplitude is consistently reduced in schizophrenia. The P50 wave after a second auditory stimulus in schizophrenia is also abnormal, insofar as its amplitude is the same after the second as after the first auditory stimulus (instead of diminished). Investigators have used these kinds of measurements to support the concept of abnormal sensory gating in schizophrenia and its genetic association.

**Schizophrenia spectrum disorders**

There is an emerging formulation from several laboratories that schizophrenia is part of a larger set of disorders called schizophrenia spectrum disorders or schizotaxia; these disorders are related to each other in terms of genetics, symptom expression, cognitive characteristics, and, potentially, pathophysiology. Schizophrenia itself may be the most severe manifestation of the class and characterized by the most flagrant psychosis and the worst psychosocial function (Figure 1). But impairment at multiple levels and schizophrenia-like symptoms span the entire spectrum group. Approximately 20% of family members of an individual with schizophrenia have spectrum manifestations. Moreover, approximately 20% of persons with spectrum manifestations have symptoms that are severe enough to impair work function and may benefit from antipsychotic treatment (G. Thaker, personal communication).

First-degree relatives of schizophrenic probands may display many of the cognitive symptoms characteristic of schizophrenia, only without the florid psychosis. These include task-related impairments in attention, language comprehension, verbal fluency, verbal memory, and spatial working memory. It is suspected that these cognitive disturbances in relatives occur predominantly in those with spectrum symptoms, however more study is required. Some adjustments in the criteria for spectrum disorder (ie, loosening) may be required for that diagnosis to capture all affected persons. Considering spectrum disorders as a relevant diagnostic category adds 5% to the prevalence of the schizophrenia diagnosis. Perhaps up to 20% of the spectrum group is impaired enough to require treatment. These observations may serve to broaden our concepts of schizophrenia, its manifestations, and beneficial treatment opportunities.

**Figure 1.** Schizophrenia spectrum disorders. The prevalences of schizophrenia and schizophrenia-related personality disorders in the general population are 1% and 5%, respectively; the prevalence of both together is 6%.
Brain structure and function in schizophrenia

Brain structure

One of the first discoveries in schizophrenia using modern imaging technologies was structural, first with computerized axial tomography (CAT) scanning and later with magnetic resonance imaging (MRI). Johnstone and Crow then Weinberger described enlarged cerebral ventricles in persons with the illness. Over time, an overwhelming number of confirmations have accumulated. Ventricular size is a crude and nonspecific indication of cerebral dysfunction, and possibly only an epiphenomenon of this illness. However, this observation has served to redirect interest toward examining the brain for abnormal characteristics in persons with the illness.

As structural imaging techniques have developed higher resolution, additional volumetric differences in the schizophrenic brain have been identified. Several laboratories focusing on the superior temporal gyrus have reported volume decreases in schizophrenia and a correlation between the volume changes and clinical characteristics of the illness. The medial temporal cortex, including parahippocampal, entorhinal, and hippocampal cortex, is also reduced in size in schizophrenia. This size reduction is only of the order of 5%, but is consistent across laboratories and subject populations. Csernansky has gone on to identify hippocampal shape irregularities in schizophrenia. Some laboratories note middle frontal cortical volume reductions in negative-symptom schizophrenia and volume alterations in the pulvinar region of the posterior thalamus in persons with the illness. These alterations are thought to be in vivo reflections of regional cellular pathology in the illness.

Brain function

When functional techniques for studying human brain became available, they were quickly applied to schizophrenia. Ingvar was the first to note reduced prefrontal cortical blood flow in schizophrenia. Subsequent early studies served to focus scientific interest on the frontal cortex; this was a great advantage to the scientists who later followed up these ideas. Subsequent functional imaging studies have noted an antipsychotic drug effect in prefrontal regions (reduced neuronal activity) and an influence of negative symptoms in prefrontal and inferior parietal cortex. Current imaging approaches in schizophrenia utilize both structural scanning and neurochemical (see Laruelle in this issue) and functional methodologies. The functional approaches are based on advances in the understanding of normal cognition also derived from functional imaging data. Since the introduction of functional imaging techniques over 20 years ago, using either glucose metabolism or blood flow as the functional end points, several technical methodological principles have developed. Functional "stimulation" using either a psychological task or a centrally active drug adds an important parameter to such an examination. Drug effects, especially antipsychotic compounds, are recognized as potentially informative in deciding on disease-related (compared with drug-related) differences between schizophrenia and normal test populations. Studies with this focus, in addition to functional increases in the basal ganglia, also noted alterations in delimited cerebral areas, especially reductions in metabolism or regional cerebral blood flow (rCBF) in the frontal cortex (anterior cingulate and middle frontal gyri). Since the effect of psychological tasks on rCBF has been particularly informative in exploring normal brain function, hierarchical subtraction techniques are now being applied to schizophrenia. This approach has been problematic because of the altered performance levels between persons with schizophrenia and normal controls, which introduce a potential confounding element into the functional assessment during performance. Recent utilization of variable performance tasks have contributed to a solution here. rCBF studies in schizophrenia have been used to identify CNS regions of abnormal function in the illness. While no single region has been identified in all laboratories, several distinct abnormalities are prominent and suggest, above all, the possibility that an abnormality of several systems in the brain underlies the illness. Initially, the middle frontal cortex (dorsolateral prefrontal region) was identified as abnormal in schizophrenia and has subsequently been tied to manifestations of primary negative symptoms in the illness. More recently, laboratories have focused on the anterior cingulate cortex (ACC) and the hippocampus as being potentially primarily involved in the psychotic process. A role of the basal ganglia cannot be ruled out. Functional magnetic resonance imaging (fMRI) studies...
of rCBF have produced a variety of results, often with conflicting data, possibly because of the augmented spatial resolution of this methodology. For example, during studies involving performance of a motor task in three different laboratories, subjects with schizophrenia were found to show no differences from normal subjects in rCBF, or increased rCBF, or decreased rCBF in the sensorimotor cortex. Each of these studies suggested the potential of an interactive effect with previous or current antipsychotic medication. Tasks demanding higher-order cognitive functions, such as attention or working memory, have also resulted in conflicting data. For example, one study found an increase in frontal cortical rCBF in schizophrenia compared with healthy persons with a working memory task, whereas two other laboratories reported decreases in this area with a similar task. Additional studies in this area will hopefully define the subject variables, performance demands, or the illness phase contribution(s) that are important for an explanation of these discrepancies. Use of fMRI is rapidly increasing in all academic centers, and so progress will not lag in this area.

The functional imaging studies from our laboratory have compared persons with schizophrenia with matched healthy individuals while performing an auditory recognition task in an overlearned, practiced condition, with normals with a similar task performance. The two groups of volunteers performed similarly on accuracy and tone interval. In this situation, the volunteers with schizophrenia showed rCBF differences from the normals only in the ACC/medial frontal cortex. Those schizophrenic volunteers who had a similar performance to normal subjects on the basis of accuracy, but required wide tone disparities to do so, had not only rCBF reductions in the ACC, but also flow reductions in the middle frontal and inferior frontal cortex (Figure 2). These observations invoke the concept of a circuit failure, possibly of limbic cortex, and affect those areas of prefrontal cortex whose functions are highly influenced by the ACC.

Some of our functional imaging studies have focused on the hippocampus. Because statistical parametric mapping (SPM) analytic techniques rely on group average data and because the hippocampus is both small and variably located in humans, magnetic resonance–guided hand sampling producing volumes of interest (VOIs) is necessary to adequately represent the structure. We used magnetic resonance–guided individual VOI image sampling and made several interesting observations about hippocampal function. First, in a practiced, overlearned auditory recognition task, the hippocampus remains uninvolved with task performance with respect to changes in rCBF, in both normal volunteers and those with schizophrenia. This confirms that novelty and/or learning is necessary for hippocampal activation. Second, rCBF in the schizophrenic hippocampus is greater than in the normal hippocampus bilaterally, and across different task conditions. Third, the noncompetitive N-methyl-D-aspartate (NMDA) antagonist ketamine reduces rCBF in the schizophrenic hippocampus, but not in the normal hippocampus, over a 30-min time course. This last observation suggests that the affected hippocampus, which already evidences elevated rCBF in the medication-free state, is more sensitive to glutamatergic inhibition. This observation is consistent with some of our other postmortem findings showing reduced NMDA receptor NR1 subunits in schizophrenia, and hence potential reductions in the number of functional NMDA receptors.
Theories of schizophrenia

Dopamine
Hypotheses to explain the manifestations of schizophrenia have been posited for centuries. The finding a half century ago that antipsychotic drugs block dopamine receptors in brain\(^8\) and thereby reduce psychotic symptoms strongly supported the idea that an overactive dopaminergic system causes schizophrenia. Many years and many experiments later, evidence to support this idea has now been generated using modern imaging tools.\(^8\) Yet while increased dopamine release may be associated with the psychotic manifestations of schizophrenia, there is slim evidence that dopaminergic abnormalities may be more broadly influential in cognitive or negative manifestations or in a broader schizophrenia process.

Neural systems
As knowledge of normal brain function has revealed intricate and complexly interacting neural systems, so these ideas have also been applied to schizophrenia. The work of DeLong\(^8\) has suggested that there are long-tract pathways between the frontal cortex and subcortical areas through which the basal ganglia and thalamus influence the function of the frontal cortex. Since many of the cognitive and functional abnormalities in schizophrenia involve the frontal cortex and its functions, an alteration in these feedback systems offers strong face validity to explain certain symptoms in schizophrenia. Regions of the frontal cortex project to the caudate or putamen in segregated, parallel neuronal pathways. Within the basal ganglia, these projections are propagated to related downstream structures, including specific thalamic nuclei, and then project back to the discrete frontal cortex regions. Since the basal ganglia have a diversity of neurotransmitters and modulators, and are richly innervated by diverse brain structures, there is ample opportunity within these pathways to capture significant regional influence and to subsequently modulate frontal cortical function. Any abnormality in the dopaminergic dynamics,\(^8\) the balance of neurotransmitter function in the basal ganglia,\(^8\) or the influence of the thalamus\(^8\) could alter frontal cortical function through these pathways.

Neurodevelopmental factors
The idea that schizophrenia is a neurodevelopmental illness, whose pathology is already set at birth and only expresses itself as psychosis later, has become popular. This formulation of illness onset explains the influence of pre- or perinatal events and the evidence of premorbid cognitive predictors of illness onset. Nonetheless, the course of schizophrenia does not conform to that of a traditional neurodevelopmental illness, like mental retardation, whose symptoms appear at birth. However, it has been argued that the neural apparatus subserving schizophrenia does not mature until late teens, and cannot fully express its dysfunction before this. Another caveat is that there is actually scant biological evidence to support the neurodevelopmental formulation. Also, it is not the case that all forms of schizophrenia need to be based on the same etiology, even if they involve the same pathophysiology. Hence, neurodevelopmental aspects may be important in some, but not all, forms of schizophrenia.

Limbic cortex
Experimental modalities beyond brain imaging have advanced our understanding of the pathophysiology of schizophrenia. These include postmortem tissue studies and animal model experiments. Findings from postmortem brain studies in schizophrenia are reviewed in this issue by Harrison et al.\(^85\) From the substantial body of postmortem work reviewed, several guiding formulations emerge: (i) the limbic system has been consistently identified as affected in schizophrenia; and (ii) although the examination of postmortem transmitter systems has been skewed toward the monoamines and dopamine in particular, it is clear that many chemical systems are affected in schizophrenia.\(^86\) In accounting for a demonstrated abnormality, separating cause and effect of the psychotic condition is always critical and, at present, a matter of hypothesis. In normal persons, phencyclidine (PCP) causes psychotomimetic symptoms purportedly reminiscent of schizophrenia. PCP causes changes in experimental animals in regional expression of immediate early genes (IEGs), a marker of regional neuronal response to the drug. This IEG response is interesting in that it is most potent in the limbic cortex (hippocampus and anterior cingulate), and it is long lasting, extending far beyond the drug half-life in brain. To understand the underlying neurochemistry, we have studied glutamate receptor response as a marker of...
glutamate-mediated transmission. In response to PCP, the NR2 subunit of the NMDA-sensitive glutamate receptor shows a significant and sustained elevation in rat hippocampus, especially in CA1, the last hippocampal subfield of the perforant pathway, suggesting reduced glutamatergic transmission at this synapse in response to PCP. We interpreted these data to mean that a psychotomimetic compound like PCP can decrease glutamatergic transmission in hippocampus, thus critically interfering with hippocampal function. Since the hippocampus is a brain region already known from post-mortem studies in schizophrenia to be abnormal, these conclusions seemed plausible. Our own postmortem findings, most importantly including a decrease in NR2 expression in the schizophrenic hippocampus, are consistent with this current formulation. Moreover, our examination of the human hippocampus in schizophrenia using functional imaging techniques is largely consistent with this formulation of abnormal hippocampal function drawn from these animal and postmortem data.

**Working hypothesis**

We would like to suggest a working hypothesis of reduced glutamatergic transmission at the NMDA receptor in the hippocampus in schizophrenia, of greatest degree in the CA1 area at the end of the perforant pathway and feeding into the efferent structures of the subiculum. As a consequence, one might expect a failure of both feed-forward excitation and feed-forward inhibition, each in distinct situations. One might interpret the high resting rCBF in the hippocampus as a failure of feed-forward inhibition (ie, a lack of glutamatergic excitation of the inhibitory gamma-aminobutyric acid [GABA]-ergic systems), while the heightened sensitivity of hippocampal rCBF to ketamine inhibition could be due to the abnormal composition of the NMDA receptor in the illness and an overinhibition of the feed-forward excitation.

**Future**

The availability of the very new resource of the sequenced human genome is challenging our field to take advantage of this critical genetic information. Tracking the genetic basis of the cerebral mechanisms that might express a particular genetic defect in psychosis or in a disease like schizophrenia will require specific information about the human schizophrenic brain. Disease formulations will be testable as models for the genetic changes we will find in this illness.

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