Recent studies into the etiology of schizophrenia have yielded both promising leads and disappointing dead ends, indicating the multifactored and complex nature of the disorder. The focus has subsequently shifted back to refining the phenotype and identifying clinical and biological subtypes. Recent technological breakthroughs in genomics and proteomics hold promise for advancing our understanding of the molecular pathophysiology of schizophrenia.

Advances in schizophrenia

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After the spirochete-caused insanity of late stage syphilis was distinguished from other forms of madness, in 1919 Kraepelin described two major endogenous psychoses: manic-depressive psychoses and dementia praecox[1]. Bleuler substituted the term schizophrenia for the latter, emphasizing that the disorder was not a dementia and did not always begin during youth[2]. Now, almost 100 years later, much is known about the course of disease in the schizophrenic disorders. A more informed picture of the neuroanatomy and pathophysiology associated with the disease is emerging, particularly anomalies in neuronal connectivity and the associated neurochemistry. Several risk factors have been identified, and the search for genes endowing vulnerability to schizophrenia is in full swing. Due to the complex nature of schizophrenia, however, gaining a complete understanding of disease pathogenesis and developing effective therapeutics might take time.

Clinical presentation

Schizophrenia affects almost 1% of the world's population with similar prevalence throughout diverse cultures and geographic areas. The financial burden of schizophrenia exceeds that of all cancers in the United States, and the World Health Organization finds this disease the world's fourth leading cause of disability. Suffering is substantial, and death by suicide occurs in about 10% of cases. Forty years ago, schizophrenia was by far the leading cause of hospital utilization in industrialized nations, and the results of deinstitutionalization are often observed in homeless and jailed populations.

Schizophrenia is a clinical syndrome comprising several discrete clinical features with extensive variation between individuals. No single symptom is unique to schizophrenia or evident in every case. The central features include what are known as 'positive' psychotic symptoms, such as hallucinations, delusions, disorganization of thought, bizarre behavior and incongruity of affect. 'Negative' symptoms include loss of motivation, restricted range of emotional experience and expression, alogia and reduced hedonic capacity. These negative symptoms are present in some but not all cases. Cognitive impairments are also observed in most cases, involving deficits in a broad range of information processing tasks. Cognitive dysfunction usually precedes psychosis and might reflect early signs of the illness or define susceptibility. Patients often experience depression and anxiety, express hostility and become demoralized.

Little is known about what triggers the disease. The development of symptoms does not fit a picture of progressive neurodegeneration; instead, the course is variable, ranging from acute to insidious in onset, involving continuous or episodic psychosis, and the presence or absence of clinical deterioration over the lifetime. To the extent that schizophrenia is a progressive illness, deterioration is observed in the pre-psychotic and early course phases, reaching a plateau within a few years. Late-life improvement is often observed, although there is not a single outcome that is typical for this group of disorders.

A current view of the illness typology calls attention to five epochs in the life span. First, some people appear to be born with subtle motor and emotional impairments. Second, during later childhood and adolescence, many cases display a range of cognitive impairments in psychological tests of attention, memory, executive function and physiologic tests of information processing. Negative symptoms also tend to be present during the developmental years. The cognitive and negative pathologies tend to be long-lasting traits. Third, the onset of psychosis usually occurs at ages 17–27 in males and 20–37 in females. Fourth, the initial psychotic break is followed by a variable course of illness. The course of subsequent psychosis is episodic in most cases with variable intervals of partial or full remission. It is unremitting in some individuals and complete remission is rare. Fifth, during later life, some patients improve—many are stable with continued symptoms, while some experience rapid cognitive decline. The development of psychosis only modestly predicts outcome (level of functional capability, social and occupational ability and quality of life), whereas cognitive impairments and negative symptoms are better prognostic factors for the long-term effects of the disease.

Pathophysiology

Over the past 40 years, most schizophrenia studies have been based on the 'hyperdopaminergic hypothesis', which implicates excess dopamine production in schizophrenia pathogenesis. This hypothesis was based on the observed ability of a dopamine agonist to induce paranoia, whereas dopamine antagonists reduced psychosis. This theory has recently received its first direct validation with the demonstration that schizophrenic subjects release more dopamine at the synaptic junction in response to amphetamine stimulation than non-schizophrenic subjects. This increase in dopamine release is associated with worsening of positive psychotic symptoms in schizophrenic subjects[3,4]. Although excessive production of dopamine can explain the psychosis observed in these patients, it cannot account for the negative symptoms of the disease. It is likely that changes in the dopaminergic system are region-specific and a hypodopaminergic explanation for negative symptoms is viable.

Recent studies have focused on glutamatergic physiology, spawned by the observed effects of chronic phencyclidine (PCP) treatment. In humans, PCP causes a broader range of schizophrenic symptoms than dopamine agonists, which only induce paranoia. In addition to inducing psychosis, PCP produces negative symptoms and cognitive impairment[5]. This drug is believed to block the ion channel in the NMDA (*N*-methyl-D-aspartate) receptor complex, resulting in diminished glutamatergic neurotransmission at this receptor complex. Recent data show that both dopaminergic and glutamatergic terminals converge on the spines of pyramidal neurons in cor-

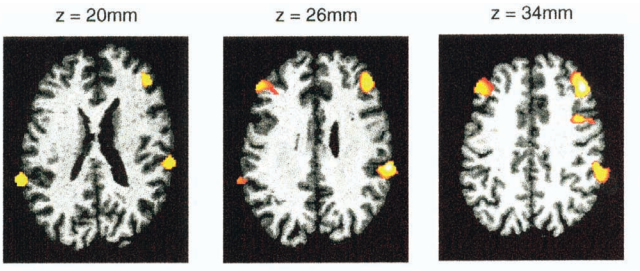

Fig. 1 Statistical parametric maps derived from ^{15}0-labeled water positron emission tomography scans obtained when nondeficit schizophrenic patients (n = 10) were contrasted to deficit patients (n = 8). Both groups were drug-free and performed an effortful tone discrimination task at the same level of performance during scanning. The transverse brain slices show the location of differences in activation between the two groups during performance of the task (Decision-Rest). Deficit patients showed significant less activation in middle frontal cortex, bilaterally and in inferior parietal cortex, bilaterally (A.C. Lahti, pers. comm.).

tex, indicating a common site of action for both dopamine agonists and PCP (refs. 6,7). Although there are complex presynaptic and postsynaptic interactions among the two neurotransmitter systems[8,9], modulation of glutamate release by D1 receptors might mediate some of the effects of dopamine on psychosis[10].

Earlier histopathological examination of postmortem brains of schizophrenic patients showed slight reductions in neocortical gray-matter volumes, decreased neuronal size and neuronal disarray in several corticolimbic structures[11–13]. These histopathological findings, however, have not been consistently reproduced. A neurodegenerative basis of schizophrenia has been all but ruled out because massive cell loss and/or gliosis have not been observed in these patients. More recent investigations have focused on changes in neuronal connectivity or microcircuitry within the cortical layers. These studies report an increase in cell-packing density without a change in neuronal number, indicating a decrease in neuropil density and a reduction in dendritic spine density in the pyramidal neurons of the prefrontal cortex[14,15]. However, we must interpret these findings with caution, because chronic treatment with antipsychotic drugs can alter expression of neuronal cytoskeleton and spine-associated proteins[16]. Using cDNA microarray analysis, Mirnics *et al.* reported a decrease in the expression of several genes involved in glutamate and GABA transmission, and in the regulation of presynaptic function and signal termination in the prefrontal cortex of individuals with schizophrenia[17]. Together, these findings suggest a decrease in cortical and/or thalamic excitatory synaptic inputs to the pyramidal neurons.

Search for causes

Although the precise causative agents of schizophrenia remain elusive, several environmental risk factors have been identified. These include maternal malnutrition and viral infections during critical periods of fetal development, fetal hypoxia, other birth and obstetric complications, winter birth and use of psychoactive drugs[18,19]. The lifetime morbidity risk for schizophrenia in the general population is about 0.8%. This risk increases to about 3–5% in second degree relatives or in half-siblings, 9–12% in siblings and dizygotic twins, and 40–50% in monozygotic twins of schizophrenic patients or in children of two schizophrenia parents, suggesting a strong genetic basis to the disease[20]. Indeed, several investigators have calculated the heritability of schizophrenia to be around 80% (ref. 1). However, the identification of disease susceptibility genes has proven difficult.

One of the first genetic studies of schizophrenia reported the linkage of a broadly defined schizophrenia phenotype to chromosome 5q11-q13 with a log odds ratio (LOD score) of 6.49 in seven families of British and Icelandic origin(Table 1). Attempts to replicate these findings have been unsuccessful. Since then there have been several other positive linkage results (Table 1). Many of the initial findings, however, have not been fully reproduced. Even in cases where initial observations were confirmed, the LOD scores have been much lower than the initial report[22,23].

The hunt for schizophrenia genes is particularly challenging, as the syndrome seems to encompass several diseases that have not yet been completely defined. Different genetic vulnerability profiles are likely to lead to different disease phenotypes. Furthermore, each disease entity may be a complex disorder caused by multiple genetic factors. Each disease susceptibility gene may have only a modest individual effect that might also depend on specific environmental conditions.

A diagnosis of schizophrenia is therefore inadequate as a phenotypic definition[24], and more specific phenotypes must be defined if we are to uncover the true schizophrenia susceptibility genes. There have been two broad lines of investigation aimed at reducing phenotype heterogeneity. The first is at the clinical level. The observation that the occurrence of core symptoms (psychosis and negative symptoms) are relatively independent indicates that each might have distinctive etiopathophysiologic and pharmacologic response attributes[25]. The amount of heterogeneity in the schizophrenia phenotype can be reduced by dividing patients into cohorts based on whether they manifest primary and enduring negative symptoms. It is this form of negative pathology, in contrast to secondary and transitory negative symptoms, which defines the deficit subgroup of schizophrenia. Studies indicate large differences in these two schizophrenia subgroups, although they share symptoms such as reality distortion, disorganization and certain aspects of cognitive pathologies. The deficit-pathology patients can be distinguished by their poor outcome on functional measures but good outcome on measures of substance abuse, dysphoric mood and suicidal behavior and thoughts[26]. Deficit symptoms are also associated with higher prevalence rates of Borna disease virus antibodies and summer birth excess[27,28].

There is also a genetic basis for these schizophrenia subgroups. The risk for deficit schizophrenia is increased threefold if a sibling has this type of the disease[29]. Neuropsychological data, ocular motor physiology, functional and structural neuroimaging data and post-mortem neuropathology implicate alterations in the dorsolateral prefrontal basal-ganglia–thalamocortical circuit in this type of schizophrenia[30] (Fig. 1). In contrast, abnormalities in anterior cingulate basal-ganglia–thalamocortical circuit are associated with psychosis, which is shared by all schizophrenic patients whether or not they manifest deficit symptoms[30,31].

Researchers are hunting for other biological markers of schizophrenia, known as 'alternative phenotypes', which may eventually lead to schizophrenia genes. Holzman *et al.* reported an association between abnormal eye tracking and schizophrenia, and documented an increased prevalence of

Table 1 Linkage studies in schizophrenia

Chromosome locus	Study sample source	LOD score (L) or NPLZ (N)	Comment
1q32-q44	Finland	3.82 (L)	Initial interest was stimulated by a finding of 1:11 translocation segregating with serious psychotic ill ness in a Scottish pedigree. Mirnics *et al.* found a decresssion of a regulator of G-protein signaling 4 (RGS4) in prefrontal cortex of schizophrenic patients[43]. RGS4 maps to locus 1q22,the region linked to schizophrenia in the Canadian pedgrees[44].
1q21-22q	Canada	6.50 (L)	
5q11-q13	UK and Iceland	6.49 (L)	Numerous replication failures of the first linkage study by Sherrington *et al.*[45]. Interest in chromosome 5 was renewed by several recent findings suggestive of linkage in region distinct from the first linkage finding.
5q22-q31	Ireland	3.35 (L)	
6p24-p22	Ireland	3.9 (L)	Replication efforts yielded mixed results with 2 negative LOD scores and 2 positive LOD scores (strongest score was 2.2 near D6S274). Arolt *et al.* reported linkage with eye-tracking phenotype in this region of interest[46].
6q21-q22	US and Australia	3.82 (L)	Initial evidence suggestive of a susceptibility locus on chromosome was derived from an ethnically mixed US sample, and was replicated in an other sample. Combined analysis of these and an Australian sample yielded a significant LOD score.
8p22-p21	Maryland (US)	3.64 (N)	Another replication with LOD score of 2.2. Stratification of the genome scan data based on the schizophrenia related personality disorders in the non-schizophrenic relatives yielded a strong genome-wide linkage support for the 8p21 region (NPL of 5.04) in the Maryland sample[47].
8p22-p21	Canada	3.49 (L)	
13q14-q32*	Maryland (US)	4.18 (N)	Area of interest because of the presence of 5HT2A receptor gene in the region. 4 other studies report positive LOD scores suggestive of linkage and 2 studies report negative LOD scores excluding linkage. Studies suggest a bipolar-disorder susceptibility locus on 13q32 region[48]
13q14-q32*	Canada	4.42 (N)	
15q13-q14	Utah (US)	5.3 (L)	Evoked potential P50-gating abnormality was used as a phenotype. The genetic marker is 0.5 cM distant from α-7 nicotinic-cholinergic receptor gene. Using schizophrenia diagnosis as a phenotype, 4 studies in indepen dent samples report some evidence in support of the findings and 2 failed to replicate.
22 q11-13	Maryland (US)	2.82 (L)	Several reports suggestive of linkage in this region were followed by a finding of significant linkage using a composite inhibitory neurophysiological phenotype[49]. This is an area of interest because of the presence of the velocardiofacial syndrome locus nearby. About 1/3 of VCFS cases experience psychosis[50]. A positive linkage with bipolar disorder has also been observed in this region[51]. A recent study finds an association of working memory with catechol-o-methyltransferase (COMT) gene located at this site. The working memory test is sensitive to schizophrenia impairment, and a significant allelic difference was reported between schizophrenia and control subjects[53].
22 q11-13	Utah (US)	3.55 (L)	

See refs. 22, 23 and 52 for review. *, In addition to the findings on chromosomes 13q and 22q, there is evidence suggestive of linkage of both schizophrenia and bipolar disorder to chromosome 18p11 and 10p14 in independent samples[54].

this feature in patients' relatives[32]. A preliminary study has also linked abnormal eye tracking to a chromosome 6q in schizophrenia probands[33]. Other markers include impairments in attention, language and memory, as well as deficits in expression levels of the neuronal marker N-acetyl-aspartate in the hippocampal region[34,35]. Freedman *et al*. used electrophysiological measurements to identify a linkage between a sensory gating defect and a locus at chromosome 15q14 in schizophrenic patients[36,37]. There have been several recent replications of this linkage finding at 15q14 locus using diagnosis of schizophrenia as a phenotype[38]. This locus has been reported to contain the gene encoding an α-7 nicotinic-cholinergic receptor subunit gene, which is involved in sensory gating. Although these studies represent compelling translational research accomplishments, no genetic mutation in this region has been associated with schizophrenia[36].

New drug targets and therapeutic approaches are desperately needed for this incurable disease. There are many components to comprehensive treatment, including psychological therapy based on psychoanalytic theory and psychogenic etiology, which have not proven efficacious. Patients also receive psychosocial therapy involving education about the disease and its treatment, stress reduction, and coping strategies; these have proven efficacious in reducing psychotic symptoms and relapse rates. However, the effects of this treatment approach on negative symptoms, cognitive impairments, and functional outcome is minimal, with the strongest results often seen in the second or third year.

Although there are some pharmacotherapies for schizophrenia, none are completely effective. The 2000 Nobel Prize in medicine was awarded, in part, to Arvid Carlsson for discovering dopamine and the dopamine antagonist mode of action of antipsychotic drugs, thus initiating the study of dopamine physiology in schizophrenia[39]. Reserpine, which reduces dopamine and other catecholamine release, was an early drug used in schizophrenia with limited effectiveness. More robust effects were observed with chlorpromazine, introduced in 1952, which blocks the dopamine receptors. The antipsychotic effects of dopamine antagonists have been observed across disease boundaries, and are not specific to the treatment of schizophrenia. Although they are effective in reducing reality distortion and disorganization symptom complexes in patients, they have little effect on cognitive impairments and negative symptoms of schizophrenia.

New generation antipsychotic drugs such as clozapine and olanzapine have a similar profile of effects. These drugs, which are less potent in blocking dopamine D2 receptors than older generation drugs, also block serotonergic receptors, are associated with fewer motor side effects, and are more effective in reducing secondary negative symptoms (such as depressive anhedonia and neuroleptic akinesia). In addition, clozapine is shown to have superior efficacy for psychotic symptoms in treatment-resistant patients[40]. Compared with older antipsychotic drugs, the claims of superior efficacy of the new drugs on cognitive impairments are controversial. Although the ability of these drugs to reduce psychotic symptoms and relapse rates has greatly facilitated schizophrenia therapy, effective treatment of negative symptoms and cognitive impairments remains the central therapeutic challenge. The most promising lead at present involves enhancing glutamatergic transmission using agonists or partial agonists of the glycine modulatory site of the glutamatergic NMDA receptor. Activation of this receptor complex requires simultaneous occupancy of the glycine and glutamate receptor sites. Early reports suggest that this drug is effective in reducing negative symptoms in schizophrenic patients[41,42].

The genomic era has already begun to alter the course of schizophrenia research. Advances in proteomics and genomics will provide more powerful approaches to identifying the gene products involved in schizophrenia pathogenesis. Drug discovery techniques used by the pharmaceutical industries will identify additional therapeutic targets. Clinical trials and post-mortem studies will uncover more compelling definitions of disease phenotypes within the schizophrenia syndrome. Together, these three approaches should lead to better therapies for schizophrenia.

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