

# Neurobiology of Schizophrenia

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Schizophrenia is a common chronic and disabling brain disease of unknown etiology, pathogenesis, and mechanism. Whether schizophrenia represents a single disorder of markedly variable expression or a family of clinically related disorders is unclear. Genetic factors, most likely multiple genes of modest effect, play a major role in its etiology, but an environmental "second hit" may be necessary for clinical expression. The inherited biological susceptibility to schizophrenia is probably expressed clinically as nonpsychotic abnormal personality traits, plus numerous biological markers (cognitive, anatomical, and psychophysiological) that are all found significantly more commonly in the population than is schizophrenia. Neuropathological studies suggest that schizophrenia may be a neurodevelopmental disorder, characterized by reduced neuropil, with no evidence for ongoing cell death. A hypothesized mechanism for these changes involves cell migrational abnormalities occurring in the fetal brain. Schizophrenia is also distinguished by biochemical abnormalities involving the dopamine, GABA, and glutamate systems, and NMDA and nicotinic receptors. Structural and functional brain imaging studies suggest both global and regional abnormalities as well as "disconnections" of specific cerebral circuits. Despite the lack of knowledge regarding pathophysiology, there are reasonably effective treatments for schizophrenia. As the neurobiology of the disorder is unraveled, more effective, targeted treatments will become available.

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## Clinical and Diagnostic Features

A clinical diagnosis of schizophrenia is based on behavioral observations and self-reported abnormal mental experiences. Because schizophrenia has neither pathognomonic symptoms nor biological markers, the diagnosis is determined by ruling out the possibility of other psychiatric and neurological disorders. Defined in this manner, diagnosis is reliable but of unclear validity. Following Hughlings Jackson's suggestion for neurological disorders, symptoms of schizophrenia are conventionally divided cross-sectionally into "positive" and "negative" types. Positive symptoms cause acute problems but may persist. They include delusions (fixed false beliefs that are idiosyncratic to the person's culture and impervious to rational refutation), hallucinations (realistic sensory perceptions that are not generated by stimuli outside of the subject experiencing them), "thought disorder" (difficulties generating coherent verbal expression), and bizarre behavior (eg, wearing an aluminum foil helmet to prevent theft of one's thoughts). Secondary depressive symptoms are not uncommon. "Negative" symptoms include emotional flattening; social withdrawal; apathy; impaired judgment; poor initiative, motivation, and drive; lack of insight; difficulty in planning; impaired problem solving and abstract reasoning; and decreased concern for personal hygiene. "Deficit" symptoms constitute se-

vere, primary, enduring negative symptoms. Diagnosis requires a history of longitudinal deterioration in function (work, interpersonal relationships, or self-care). A duration criterion of at least 6 months is required in DSM-IV.<sup>1</sup>

Traditional clinical subtypes are constructed by identifying symptoms that commonly co-occur. The current DSM-IV classification includes five subtypes: paranoid, disorganized (hebephrenic), catatonic, undifferentiated, and residual, defined by predominant cross-sectional symptoms. However, the longitudinal stability of these subtypes is poor.

The disorder has marked gender differences in risk and clinical expression that remain unexplained. Women are more likely to have an affected family member, to experience more positive and affective symptoms, and to have better treatment response. Men have more negative symptoms, earlier onset, and worse long-term outcome.<sup>2</sup>

Some evidence for the boundaries of the schizophrenia spectrum comes from studies of Kendler, who concluded that schizophrenia shares a familial predisposition with several clinical syndromes, including schizoaffective disorder, schizotypal personality disorder, and probably psychotic affective illness.<sup>3</sup> This suggests the possibility of clinical and perhaps genetic overlap between certain forms of affective illness and schizophrenia.

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## Epidemiology

Schizophrenia has about 1% population prevalence and occurs in all cultures and socioeconomic groups.<sup>4</sup> Developing nations may have slightly higher incidence remission rates,<sup>5,6</sup> but the latter may be an artifact of lesser environmental complexity or more social support. It usually manifests clinically in the late teens or early adult life. There is a slightly increased population prevalence of schizophrenia in individuals born in urban environments. The peak onset age in males is between 15 and 25 years, onset in women being delayed by approximately 3 to 5 years, with ultimate equal male/female prevalence. Up to 50% of patients with schizophrenia attempt suicide, and 10% ultimately succeed. This is an expensive mental disorder, because onset is in early adulthood and it is often chronic and disabling but not fatal. Comorbid substance abuse is common.

## Long-Term Outcome

A small percentage of patients have a single episode with no residual impairment.<sup>7</sup> Reviews of long-term outcome studies suggest that about 30% of patients have a good outcome, represented by one or several episodes of acute positive symptoms with minimal or no residual impairment. Approximately 30% of patients have moderate but stable impairment (due to deficit symptoms) after their first episode of acute illness but without a progressive increase in deficit symptoms. Unfortunately, the remaining third of patients have persisting, progressive deficit symptoms causing increasing impairment, without return to baseline. Previously, these patients were most likely to have remained in chronic state hospital facilities. With deinstitutionalization, however, they are more likely to become homeless or to be jailed.

As patients with schizophrenia age, cognitive deficits (see later) may accumulate; in some studies, more than 50% of aged patients meet criteria for dementia.<sup>8,9</sup> The cause of such severe cognitive impairment remains unknown, but the overall cognitive profile, neuropathological and biochemical features of Alzheimer's disease or vascular dementia, is not seen in elderly schizophrenic patients. There is no increased risk for Alzheimer's disease in elderly schizophrenic patients.

## Neurological Abnormalities

Despite the extrapyramidal side effects resulting from drugs used to treat schizophrenia, it is now clear that nonfocal, so-called soft neurological signs (eg, spontaneous dyskinesias) as well as focal abnormalities are evident in many untreated first-episode individuals, as well as a proportion of those at-risk for schizophrenia.<sup>10,11</sup>

## Cognitive Abnormalities

Cognitive function in schizophrenia is characterized by a background of generalized impairment (IQ is gener-

ally a standard deviation lower than expected), with poorer performance on attentional, memory, abstraction, spatial working memory, and executive functions.<sup>12</sup> Functioning on tasks that require complex contextual information to be held on-line and used consistently is especially impaired.

These deficits are present at the onset of illness, persist despite clinical improvement, and are not confounds of emotional or motivational problems, drug-induced sedation, or prior institutionalization.<sup>13</sup> Some prominent cognitive deficits seem related to abnormal frontotemporal interactions.<sup>12</sup> Supportive evidence is the fact that frontal lobe injuries (particularly of the dorsolateral prefrontal cortex [DLPFC]) in adult life can mimic the "deficit syndrome" of schizophrenia and impair cognitive tasks involving working memory and set-shifting.

## Neuropathology

Both nonspecific and focal neuropathological changes are seen in schizophrenia. Cortical thickness and overall brain weight are approximately 5% less on average in patients with schizophrenia, with modest ventricular enlargement. No whole-brain survey has been carried out using any pathological technique; thus, generalizability of locally identified abnormalities is poorly documented. The neuropathology of schizophrenia is one of subtle changes in cellular architecture and brain circuitry, none of which is diagnostically specific. Neuropathological studies provide strong evidence against a neurodegenerative pathogenesis of schizophrenia and some support for prenatal development abnormalities.<sup>14</sup>

Akbarian and colleagues examined glial guideposts that help guide neurons migrating to the fetal cortex, leaving detectable traces in the white and gray matter of the adult cortex.<sup>15</sup> In cadaver brain samples taken from subjects with and without schizophrenia, specialized staining revealed that these glial remnants were distributed differently in schizophrenia, with an excess number in white matter and a paucity in cortex, for the frontal and temporal areas examined. Akbarian's group interpreted these data as consistent with a developmental subplate disturbance, in which the normal pattern of programmed cell death is disrupted and accompanied by defective neuronal migration toward the cortical plate.

Normally, local circuit neurons in the prefrontal cortex that contain the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) differentially regulate the activity of pyramidal cells, the principal type of excitatory output neurons, and receive direct input from dopamine neurons. Lewis showed that a subclass of prefrontal GABA axon terminals (from chandelier cells) is selectively altered in patients with schizophrenia.<sup>16</sup> Parallel studies from the same group show that prefrontal cortical neu-

ronal connectivity of these cells is substantially refined during adolescence.

The prefrontal cortex (and likely other cortical areas) in schizophrenia are characterized by modest thinning, a downward shift in neuronal sizes accompanied by an increase in small neuron density, without change in overall neuron number.<sup>17</sup> Synaptic connections either are reduced in number or abnormal.<sup>14</sup>

As noted by Johnstone and associates, potential problems arise with neuropathological studies in schizophrenia because the disease occurs early in life but is not fatal, so patients are likely to be old and perhaps chronically institutionalized at death. This leads to difficulties with retrospective clinical characterization and incidental age-related findings obscuring the essential illness pathology.<sup>18</sup> Artifacts could result from years of poor diet, self-neglect, concomitant substance abuse, and effects of medication treatment. Newer brain imaging techniques (see later), particularly those used at the time of onset of illness, can help overcome some of these difficulties.

### Psychophysiological Changes

Eye-tracking dysfunction occurs in about 50% of patients with schizophrenia and is not an artifact of psychotic state, inattention, or treatment with antipsychotic drugs.<sup>19,20</sup> It involves primarily an impairment of smooth pursuit eye movements, with additional saccadic problems. These changes are not localizable to any single brain region but are believed to represent abnormal interactions between the frontal eye fields and the temporal and posterior parietal regions.

Event-related potential (ERP) abnormalities in schizophrenia are a robust finding, particularly in the auditory modality, consistent with severe disruption of temporal cortex auditory processing from the earliest stages through higher-order language processing. Several basic ERP paradigms have been used to explore patients with schizophrenia, including the P50 and P300.<sup>21,22</sup> Abnormalities of the P50 represent a failure of inhibition at very early stages of auditory processing. This sensory gating takes place in medial temporal lobe structures and is enhanced by nicotinic cholinergic mechanisms. There are claims that the abnormal P50 in schizophrenia may be linked to the  $\alpha 7$  nicotinic receptor.<sup>23</sup> The P300 ERP is a late-occurring "surprise wave" obtained in response to infrequent, task-relevant stimuli. It is abnormal in first-episode schizophrenic patients, those withdrawn from medication, and those who have had a clinical improvement. The auditory P300 wave in schizophrenia is reduced in amplitude and abnormal in topographic asymmetry, with the latter finding differing from that in psychotic bipolar patients.<sup>22</sup> Severity of the P300 abnormality is linked to the degree of reduction of gray matter volume, specifically in the left posterior superior temporal gyrus,

which is disproportionately smaller in schizophrenia and likely related to fundamental symptoms of auditory hallucinations and language disorder.<sup>22</sup>

### Functional and Structural Brain Changes

#### *Structural Changes*

Modern neuroimaging techniques have shown that virtually every brain region is affected in schizophrenia.<sup>24</sup> Both chronic and first-episode, unmedicated patients show widespread, if small, alterations in ventricular size and cortical gray matter. Such global brain changes do not appear to be bimodally distributed within schizophrenia, suggesting a graded phenomenon affecting all patients rather than subtypes. Compared with the approximately 5% overall gray matter alterations, schizophrenic patients manifest more disproportionate local brain changes, generally in the range of 15%, in the mesial temporal, temporal neocortical, prefrontal, and parietal regions, with possible alterations in thalamus, basal ganglia, and cerebellum.<sup>24</sup>

Many of the prominent volume changes and asymmetry disturbances in schizophrenia may lie within the heteromodal association neocortex, a highly organized and interconnected neocortical system that includes the planum temporale (PT), DLPFC, Broca's area, and inferior parietal lobule (IPL).<sup>25</sup>

#### *Functional Changes*

Functional imaging data with positron emission tomography (PET) and functional magnetic resonance imaging (MRI) activation with a variety of cognitive probes suggest that the pathophysiology of schizophrenia reflects aberrant activity in, and integration of, the components of distributed circuits involving various neocortical, limbic, and subcortical structures, especially in coordination of heteromodal association cortical circuits that play a major role in the selection, initiation, and monitoring of self-generated mental activity.<sup>26</sup> For example, regional cerebral blood flow studies carried out during performance of a set-shifting task reveal that patients with schizophrenia have problems in properly activating a fronto-hippocampoparietal circuit normally accessed by healthy controls in performing this task.

Functional imaging studies employing different designs have examined cerebral activity associated with the occurrence of auditory hallucinations.<sup>26,27</sup> The agreement between these various studies is low, with reports of pathological activity in left Broca's area, medial temporal lobe, superior or middle temporal gyrus, orbitofrontal cortex, ventral striatum, and thalamus. Deficit symptoms appear to be more correlated with abnormal (reduced) activity in frontal and parietal cortex.

Few direct schizophrenia/bipolar comparisons of structural brain change have been carried out to assess

specificity of changes. Specific regional changes associated with schizophrenia may include disturbed brain asymmetries and changes in entorhinal/parahippocampal cortex.<sup>28</sup>

### Neurochemical Abnormalities

Neurochemical studies in schizophrenia have focused on several major neurotransmitter systems—dopamine, serotonin, GABA, and glutamate.

#### *Dopamine and Serotonin Systems*

The dopamine hypothesis of schizophrenia is based primarily on pharmacological evidence, that dopamine agonists provoke or exacerbate positive symptoms and that all known drugs used to treat schizophrenia are dopamine antagonists. Also, for conventional neuroleptics, there is a proportional relationship between the average clinical antipsychotic dose and the *in vitro* dissociation constant at the dopamine D2 receptor.<sup>29</sup> Dopamine abnormalities in schizophrenia likely involve the mesolimbic and mesocortical rather than the nigrostriatal dopamine system, which is more relevant to extrapyramidal side effects inadvertently caused by dopamine receptor-blocking drugs.

Postmortem chemical data document increased numbers of basal ganglia dopamine receptors in schizophrenia, but it was unclear whether these were effects of illness or merely artifactual, treatment-related homeostatic changes caused by neuroleptic-induced dopamine receptor blockade. *In vivo* neuroreceptor PET studies in first-episode, never-treated individuals have addressed this question. Laruelle reviewed the results of 15 brain imaging studies comparing indices of dopaminergic function in drug-naïve or drug-free patients with schizophrenia compared with healthy controls and concluded that schizophrenic patients possess a significant but mild and variable elevation of D2 receptor density parameters.<sup>30</sup> SPECT studies of presynaptic activity reveal an increase in dopaminergic transmission in response to amphetamine challenge. It has been suggested that neurocognitive difficulties in schizophrenia may be related to reduced dopaminergic activity in prefrontal cortex. Dopamine systems in the temporal lobe and in most neocortical areas are poorly explored in schizophrenia. It is feasible that schizophrenia is associated with dopamine dysregulation—subcortical dopamine overactivity coexisting with frontal dopamine underactivity. There are at least five known types of dopamine receptors, with varied cortical and subcortical distributions. The genes coding for these receptors are candidate genes both for schizophrenia and for drug treatment response variability.

The involvement of serotonin (5-hydroxytryptamine [5-HT]) dysfunction in the pathophysiology of schizophrenia has been the focus of much research in the past decade, especially since atypical/novel neuroleptic

drugs are high-affinity antagonists for the serotonin 5-HT<sub>2A</sub> receptor. Serotonin inhibits dopamine function at both midbrain nuclei and terminal dopaminergic fields, so that serotonergically active drugs may act secondarily by modulating dopaminergic activity.<sup>31</sup>

#### *NMDA and Glutamate*

Alterations of *N*-methyl-D-aspartate (NMDA)/glutamate function may be relevant to the pathophysiology of the disease.<sup>32,33</sup> The NMDA receptor, a subtype of excitatory amino acid receptor, has been implicated in crucial physiological processes such as synaptogenesis, learning, and memory. The NMDA hypothesis derives from actions of NMDA antagonists such as phencyclidine and ketamine that can reproduce some symptoms of schizophrenia in normal individuals, while NMDA receptor coagonists (eg, the glycinergic agents, glycine, serine, and cycloserine) may provide modest improvement of deficit symptoms.

#### *GABA*

GABA, an inhibitory neurotransmitter, may play a role in schizophrenia, and functional links may exist between GABA-ergic and dopaminergic neural systems.<sup>34,35</sup> Some studies have found abnormal GABA-ergic activity in the anterior cingulate and hippocampus in schizophrenia, while postmortem studies have shown an increased number of GABA receptors in the brains of schizophrenic patients.

### Schizophrenia as a Developmental Disorder

Despite its clinical onset in young adulthood, the neural abnormalities of schizophrenia are hypothesized to occur early in brain development for the following reasons: epidemiological evidence of an association with pregnancy, obstetrical, and prenatal abnormalities; evidence of childhood behavioral and neurological abnormalities prior to adult onset of the disorder; pathological and neuroimaging evidence consistent with early developmental brain defects (disturbed brain asymmetries and abnormalities of sulcogyral patterns); and developmental defects in associated structures (eg, craniofacial) of ectodermal origin.<sup>36</sup> There is also an absence of evidence of neurodegeneration, in that gliosis is not identifiable.

According to Weinberger's influential conceptualization, schizophrenia is a neurodevelopmental disorder in which a fixed brain lesion acquired early in life interacts with normal maturational events that occur much later: "The lesion itself is static but its effects on neurologic function change. . . . If a lesion affects the brain structure or region that has yet to mature functionally, the effect of the lesion may remain silent until that structure or system matures."<sup>37</sup> Addenda to this concept are, first, that the lesion may be evident in subtle form before the onset of obvious clinical illness, and,

second, that because brain development occurs over a much more protracted period than previously realized (especially heteromodal in regions), with extensive remodeling and pruning of neural connections occurring through adolescence and into early adult life, schizophrenia may become clinically obvious only as these processes continue.

Several recent studies have revealed subtle abnormalities in the behavior of children who were diagnosed as suffering from schizophrenia as adults. One retrospective study revealed social and neurological abnormalities in subjects with adult-onset schizophrenia, from home movies taken when they and their siblings were children.<sup>38</sup>

#### *Perspective Studies*

Whole-population longitudinal cohort developmental studies address many of the retrospective and sampling biases inherent in cross-sectional and retrospective studies.<sup>39–41</sup> Crow and Done followed up on all of the more than 15,000 children born in the United Kingdom in 1 week in March 1958. Subjects were tracked from their mother's pregnancies up until the present time, by health visitors, school nurses, doctors, teachers, mothers, and self-ratings. Socially, individuals (especially boys) who experienced schizophrenia as adults were already rated by teachers at age 7 years as manifesting more maladjustment than peers; preschizophrenic girls were rated as more withdrawn and depressed at age 11.<sup>40</sup> IQ was 5 to 10 points lower than expected, and the children were reading impaired at ages 7, 11, and 16 years. Neurologically, these children showed delayed development of handedness preference at age 11.<sup>41</sup>

A complementary approach is to focus longitudinal studies on persons at increased genetic risk for the disorder. Neurocognitive deficits (especially impaired attention) are the best-identified candidates for susceptibility markers for schizophrenia, with oculomotor dysfunction also showing promise, although relatively few eye movement dysfunction studies have been carried out in children.<sup>36</sup>

Although multiple neurodevelopmental processes could be responsible, including neuronal formation and migration, axon formation, dendritic proliferation, synapse formation, myelination, and pruning, the relevant pathological developmental processes for schizophrenia remain obscure.

#### **Schizophrenia as a Degenerative Disorder**

DeLisi and others have claimed that clinical onset of schizophrenia is followed by a continuing, active neurodegenerative process in either all patients or a significant subgroup.<sup>42</sup> It is possible that deterioration occurs only in a subgroup of schizophrenic patients. The few relevant neuroimaging studies do not provide un-

equivocal evidence for this hypothesis, since many are cross-sectional and not all employ suitable controls. The timing of neurodegeneration, if present, is unknown.

A progressive developmental mechanism active into adult life can reconcile the neuropathological and imaging data while being compatible with both early onset and late deterioration in schizophrenia.<sup>43</sup> Thus, schizophrenia may be both "neurodevelopmental" and "progressive" without necessarily being degenerative.

#### **Schizophrenia as a Genetic Disorder**

Schizophrenia is clearly in part a genetic disorder in that it "runs in families." Family, twin, and adoption studies show that relatives of schizophrenic patients have a higher risk of illness compared with the 1% general population rate, correlating with their degree of genetic relationship, and that there is an excess of schizophrenia in adopted-away offspring of schizophrenic parents. There is also higher concordance for schizophrenia in monozygotic (MZ) compared with dizygotic (DZ) twins, with respective rates being approximately 50% and 15%.

It is also clear that classic mendelian genetic models fail to fit the disorder. For example, concordance is neither 100% for MZ twins nor 50% for DZ twins, and, as noted by Tsuang, the concordance rate in DZ twins is not half of that in MZ.<sup>44</sup> Additionally, the offspring of unaffected discordant MZ twins have the same (15%) risk of transmitting the disorder to their children as affected MZ twins, and the risk for a child with two schizophrenic parents approximates 45% rather than 100%.<sup>45</sup> A single major locus model for the inheritance of schizophrenia is not tenable, and complex segregation analysis, pedigree analysis, and path analytic approaches have not been able to resolve this. Despite several promising leads, there has not yet been a definitive association of a gene variant with the illness. As reviewed by Pulver, genetic linkage analysis or association studies comprising large family datasets, multiple genetic markers, and sophisticated statistical marker analysis will be required to unravel the underlying genetic picture.<sup>46</sup>

#### *What Are the Risks of Genes?*

Lack of success of traditional genetic models has encouraged new perspectives on what might constitute schizophrenia risk genes. Proposals include no gene of major effect but multiple genetic loci of modest effect, which are epistatic (interactive), in combination yielding a true cumulative risk for the disorder. Whereas the disease alleles in single gene disorders such as cystic fibrosis and Huntington's disease increase the risk of illness by 500 and 5,000 times, respectively, susceptibility alleles in schizophrenia may increase risk by as little as 2 or 3 times. Other proposed etiological models in-

clude a genetic predisposition, “psychosis proneness” interacting with one or several environmental factors acting during brain development.<sup>44,46</sup> As in Alzheimer’s disease, differing susceptibility genes among sample populations (multiple genetic paths) may converge on a common phenotype.

While these examples may appear unduly intricate, it is helpful to bear in mind that similar complex inheritance models are hypothesized for type 2 diabetes, hypertension, and obesity.

The inheritance of schizophrenia is also possibly complicated by incomplete penetrance, etiological heterogeneity (with the probability of phenocopies), and pleiotropic effects (eg, a single genotype with multiple expressed phenotypes, such as in Marfan’s syndrome or osteogenesis imperfecta).<sup>44,46,47</sup> The likelihood of phenotypic heterogeneity, with many mild, “spectrum,” nonpsychotic carriers of the involved genes, has motivated a fresh look at the boundaries of the clinical disorder.

#### *Phenotypic Definition*

One major stumbling block for researchers may be the definition of disease phenotype. One tendency has been to further subtype schizophrenia, such as to separate out that 15 to 20% of schizophrenics (80–90% of whom are male) who have pronounced deficit symptoms.<sup>47</sup> This approach is useful, but it may select one extreme of severity of a particular cluster of symptoms. Another approach has been to widen the phenotypic definition considerably. It is possible that the number of individual risk genes in schizophrenia must exceed a threshold level for full clinical expression and that subclinical expression is common, resulting in clinical phenomena such as schizotypal personality disorder. Thus, although the classic clinical picture of schizophrenia with delusions and hallucinations can be vivid, one contributing factor to the failure to identify a schizophrenia susceptibility gene may be that the classic symptom-based disease phenotype is too narrowly defined and too heterogeneous and, as noted earlier, that clinical subtypes are not stable over time.

An analogy might be that hypothetical clinicians attempting to define the phenotype of type 2 diabetes, who include as “diabetic” only those severely affected individuals with the characteristic nephropathy and retinopathy, while missing both many mildly affected cases of the disorder and the underlying concept of insulin resistance.

#### *Biological Markers*

Such caveats have led multiple researchers to propose the employment of heritable physiological or neurobiological traits correlated with the disease as the phenotype. Such intermediate or “endophenotypes,” sometimes referred to as “epigenetic” phenomena or

“biomarkers,” are proposed to have the utility of simplicity, higher penetrance, improved operational definition, and more objective diagnosis.<sup>44,48</sup> Ideally, too, they exhibit greater reliability and validity and represent features closer to the relevant genes of interest. Specific endophenotypes may implicate candidate genes (those genes suspected to be involved on prior physiological grounds). Redefinition of the phenotype may be furnished by certain of the biological abnormalities reviewed below, features that may be more closely allied to the relevant underlying pathophysiology and genetic etiology than to clinical phenomenology.

Given the number of biological abnormalities identified in relatives of patients with schizophrenia who themselves do not have the chronic illness, it is likely that a proportion of relatives classified as unaffected in fact carry one or more pathogenic genes.<sup>48,49</sup> Extending the earlier analogy, just as nondiabetic first-degree relatives of diabetics are more likely than average to demonstrate elevated fasting blood glucoses and steroid or pregnancy-related hyperglycemia, multiple studies show a higher than expected prevalence of several biological and personality abnormalities in nonschizophrenic first-degree relatives of schizophrenia patients.

These abnormalities include the same or milder forms of alterations seen in patients. For example, Holzman, Levy, and others have investigated the proportion of eye tracking dysfunction, which they identify as a “cofamilial” or “enriched” trait.<sup>19,20,48,50,51</sup> This finding occurs in approximately 50% of schizophrenics, a large proportion of unaffected first-degree relatives, and discordant identical twins. Hence, researchers have begun to define biological markers that “may be more reliably related to the genotype than the clinical features.”<sup>48,52,53</sup>

An emerging consensus among investigators is that the most useful candidate biological markers for schizophrenia are those that are more frequent in patients than control populations; that are stable over time and insensitive to age, gender, and medication status; that are more frequent in nonschizophrenic members of multiply affected families than control populations (and in high-risk individuals); and that tend to segregate with schizophrenia and spectrum disorders in multiply affected families.

Possible candidates for biological markers (Table) include abnormalities on structural neuroimaging, cognition (especially impairment in sustained attention), neurological examination, eye-tracking, event-related potentials, and minor physical anomalies,<sup>10,12,24,49–51,54,55</sup> traits that apart from the last mentioned appear to normally be under genetic control (eg, in twin studies).

Other recent studies have focused on presumed “obligate carriers,” individuals who appear to be transmitting the liability to schizophrenia without themselves

Table. Major Candidates for Biological Markers in Schizophrenia

Finding	Abnormal in		
	Schizophrenia	First-Degree Relatives <sup>a</sup>	Persons at High Risk or Preschizophrenics
Brain neurochemical abnormalities (seen on PET/SPECT, MRS, or in vitro)	24, 30	56, 57	
Abnormal functional brain activation patterns	26, 56	58	
Structural neuroimaging differences	24, 28	49, 59	24, 55
Schizotypal or schizoid personality features <sup>b</sup>	N/A	3, 60	61
Peculiar word use, language abnormalities <sup>b</sup>	N/A	62, 63, 64	39
Cognitive abnormalities (eg, spatial working memory, attention)	12	65, 66, 67	36, 40, 61
Neurological abnormalities	10, 11, 13	68, 69	38
Eye-tracking differences	20, 50	19, 20, 21, 51	36
Event-related potential changes (P50, P300)	22, 23, 70	21, 23	

Although not an exhaustive listing, most of the measures listed here are reported to be significantly more prevalent in patients with schizophrenia, their nonschizophrenic first-degree relatives, and young persons genetically at high risk for schizophrenia, than in the general population.

<sup>a</sup>Includes discordant twins and obligate carriers.

<sup>b</sup>May represent intermediate, subdiagnostic variant of a symptom that occurs in schizophrenia.

manifesting the full-blown clinical disorder. An example is the parent of a child with schizophrenia, who does not have the disorder himself or herself but who has a schizophrenic parent or sibling. Compared with their remaining relatives and normal controls, such presumed obligate carriers have lateral ventricular enlargement on brain MRI scans that is similar to that of patients with schizophrenia and similar reversals of normal cerebral asymmetries.

A higher than expected proportion of relatives of patients with schizophrenia suffer from schizotypal, schizoid, and paranoid personality disorders. Personality disorders in general are defined as enduring patterns of experience and behavior that deviate markedly from cultural expectations. Schizotypal personality disorder (SPD), the condition most studied by schizophrenia researchers, is defined by DSM-IV as a pervasive pattern of social and interpersonal deficits marked by discomfort and difficulty with close relationships, cognitive or perceptual distortions, behavioral eccentricities, ideas of reference (excluding delusions), odd beliefs (eg, in telepathy) and unusual perceptual experiences.<sup>1</sup> Although several elements of SPD overlap with schizophrenia (Fig), these individuals lack hallucinations, delusions, or disordered speech. SPD also occurs outside of families containing schizophrenic individuals, with an overall population prevalence of 5 to 10%. Individuals with SPD, like first-degree relatives of schizophrenics (only some of whom have SPD), have a high prevalence of the biological abnormalities noted earlier. For example, like schizophrenic patients, SPD subjects show increased rates of asymmetrical P300 topography with smaller left temporal amplitudes, as well as ventricular enlargement on MRI scans and deviant eye tracking.<sup>20,21</sup> Thus, they likely represent either a

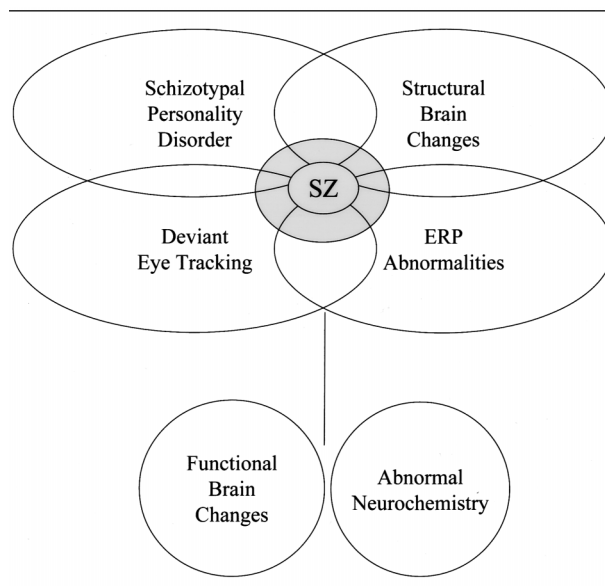


Fig. Clinical schizophrenia (SZ) is depicted as the result of an accumulation of associated biological vulnerability factors (plus environmental risks; not shown). Schizotypal personality disorder (SPD) is known to share several biological vulnerability markers with schizophrenia, as shown. The extent of such overlap between schizophrenia and SPD is not known for the functional imaging and neurochemical abnormalities found in the former. For schizophrenia, the association of the latter two markers with each other is also unknown. ERP = event-related potential.

partially penetrant form of the disorder or the result of an aggregation of risk genes insufficient for clinical schizophrenia to be expressed in the absence of a “second hit.”<sup>69</sup>

Interestingly, SPD may also represent one example

of a “bridge” between continuous phenomena, such as personalities and their associated traits, and “all or none” categories such as schizophrenia.

An obvious question is the clustering of these various hypothesized biological vulnerability markers for schizophrenia in schizophrenic patients, in their first-degree relatives, and in other family members. As noted by Murray and co-workers, if the disorder were transmitted by a single or dominant gene, one would expect biomarker uniformity.<sup>48,52</sup> Several studies to date have examined the relationship between eye movement abnormalities and P300 latency in schizophrenic probands and have found no clear associations.<sup>20</sup>

Some endophenotypes have already been linked to possible gene markers. Abnormal P50 auditory-evoked potential gating, found in about 50% of the first-degree relatives of schizophrenic patients, may be linked to a region of chromosome 15, coding for the  $\alpha 7$  nicotinic receptor.<sup>23</sup> Eye-tracking abnormalities may be linked to a region of chromosome 6.<sup>49,51</sup>

Thus, observations in first-degree relatives are also supportive of a multigene defect model, where various genes of modest to low effect need to combine with environmental factors for schizophrenia to emerge.<sup>44,46</sup>

### Environmental Factors

The search for environmental risk factors has focused mainly on perinatal complications and prenatal exposure to the influenza virus. As reviewed by Cannon, since genetic factors are estimated to account for roughly 50 to 80% of liability, the magnitude of unique environmental contributions is unlikely to be large. If schizophrenia is a “two-hit” disorder, obstetric and perinatal factors are the best candidates for the second, nongenetic “hit.”<sup>71</sup> The best candidates for pregnancy complications include maternal influenza infection and rhesus hemolytic disease. Obstetric influences may be relevant only in association with an existing genetic predisposition to schizophrenia, perhaps leaving the at-risk fetus more vulnerable to neurotoxicological consequences of oxygen deprivation as a final common path for these events.

The *viral hypothesis* of schizophrenia has been around for many decades.<sup>72</sup> Rubella studies illustrate that intrauterine viral infections can cause seasonal birth patterns and can have damaging effects on fetal development. In general, results of epidemiological studies have been inconsistent. There is a modest effect of season of birth: Kinney and others reviewed multiple studies and concluded that they are consistent with an approximately 5% excess birth of patients with schizophrenia during December to May.<sup>73</sup>

Susser and associates studied effects of the Dutch “Hunger Winter” of 1944–1945, when the population of the western Netherlands underwent a severe famine. As well as periconceptional nutritional deficiencies (cal-

ories, vitamins), women pregnant at this time also ingested possibly toxic food substitutes (eg, tulip bulbs). Males so exposed had a double relative risk of spina bifida. Subsequent follow-up reveals the relative risk for both schizophrenia and schizoid personality disorder in young adults whose mothers were pregnant during this time is also double that expected in both males and females compared with matched unexposed birth cohorts.<sup>74</sup>

### Treatments for Schizophrenia

Kane underlined the point that despite an unclear etiology, there are fairly effective treatments for schizophrenia.<sup>75</sup> There is a need for a more fundamental understanding of the neuroscience of schizophrenia so that new, specifically targeted medications can be designed.

For “classic” neuroleptic drugs that mainly block dopamine D2 receptors, antipsychotic efficacy requires approximately 75% D2 blockade. At higher drug doses, at which receptor occupancy exceeds around 85%, patients generally show signs of extrapyramidal side effects, including parkinsonism.<sup>29</sup> These drugs increase prolactin levels and can cause tardive dyskinesia, a syndrome best conceptualized as late-occurring, sometimes irreversible, involuntary movement disorder, likely due to chronic blockade-induced dopamine receptor supersensitivity.

### Atypical Neuroleptics

Atypical antipsychotics, typified by clozapine, are more powerful blockers of dopamine D4 receptors than D2, and have more propensity to block serotonin 5HT2 receptors. Maximum D2 dopamine blockade, even at high doses of clozapine, is approximately 35%. Clozapine is the only drug that has consistently demonstrated superiority in treatment of schizophrenic patients who have not adequately responded to conventional antipsychotic drugs.<sup>75</sup> However, clozapine has its own adverse side effects, most notably an incidence of agranulocytosis of around 1%. Newer atypical drugs, such as risperidone and olanzapine are now being vigorously promoted as first-line treatment in schizophrenic patients, since, they have a much lower prevalence of extrapyramidal side effects and appear to be less likely to cause tardive dyskinesia. Intramuscularly administered slow-release forms of some typical neuroleptics are available for individuals who are more likely to comply with biweekly or monthly injections than to take daily oral medications. Psychosocial rehabilitation is a useful adjunct to medication treatment.

### Conclusions

#### *What’s Still Unknown?*

Schizophrenia is a common and frequently debilitating disorder that is a significant burden in terms of cost as

well as individual and family suffering. Despite its apparent onset in young adulthood, it is now apparent that schizophrenia has earlier behavioral antecedents and there is suggestive evidence for its being a neurodevelopmental disorder. Recent data emphasize a failure of brain *systems* or circuits rather than isolated regions. Although much research has focused on a single region, the dorsolateral prefrontal cortex, the true regional specificity (if any) of the neuropathology identified there, remains unclear.

Despite multiple biological abnormalities associated with the disorder, a coherent picture that unifies the disparate puzzle pieces into a generalized pathophysiological abnormality has yet to emerge. Evidence is consistent with a neurodevelopmental disorder resulting in a subtle neuropathology that may interact with normal brain development.

Despite many investigations, we have not as yet identified a gene, a gene product, or even an undisputed, unique genetic locus associated with schizophrenia. However, the biological susceptibility to schizophrenia is likely genetically transmitted and expressed clinically as nonpsychotic schizotypal, paranoid, or schizoid personality traits plus numerous biological markers that represent modest defects (eg, deviant eye-tracking, abnormal P300, enlarged ventricles). These occur significantly more commonly in the general population than does schizophrenia. The underlying physiological nature, extent of coinheritance, and association of these biological markers, as well as their overall population prevalence, remain only partly documented. Which combinations of these genes and traits are sufficient to lead to schizophrenia and which require an additional, environmental “second hit” to do so requires elucidation. We may, however, be left with a picture of schizophrenia as conventionally defined as the most severe tip of a much larger iceberg.

#### *Psychosis Proneness and Specificity*

Whether the same gene combinations leading to “psychosis proneness” can confer vulnerability to the development of affective disorders may challenge the specificity of schizophrenia. Studies from several large data sets have considered the issue of overlap between schizophrenia and psychotic affective disorder, and reported higher than expected rates of psychotic affective disorder in relatives of schizophrenic probands and vice versa. Twin studies (although not adoption) provide some indication of overlap between psychotic affective disorder and schizophrenia. Linkage studies of schizophrenia and bipolar disorder implicate overlapping chromosomal regions.<sup>46,76,77</sup> One of the two groups reporting significant linkage to chromosome 13 has found the evidence was strongest in the subgroup of families in which relatives had psychotic affective disorder.<sup>46</sup> Evidence for linkage in the same region of

chromosome 13 has also been reported in bipolar disorder for 22 families, 15 of which contained subjects with schizophrenia or schizoaffective disorder (an intermediate diagnosis). Another group found evidence for linkage in a subset of bipolar disorder families that are heavily psychotic.<sup>77</sup> Similar evidence for overlap, though less strong, has been found on 22q.<sup>76</sup>

The disparities in the illness between men and women provide us with important research directions, including the study of interactions between the pathophysiology and normal sexual dimorphisms in male and female brains and the role of sex hormones in normal fetal and preadult brain development and regulation of dopamine receptors.<sup>78</sup>

As stressed by Murray, there is general agreement that schizophrenia represents a group of illnesses, but how to split these apart defies any easy classification scheme. Ultimately, we may depend on genetic mechanisms to aid in this regard, as in fact has happened recently in both Alzheimer’s disease and triplet-repeat disorders. Analogous interlocked biological processes may underlie schizophrenia. We need to determine when and where in development risk genes are expressed, as we need to for “second hits” or cofactors.

It is also possible that each distinct clinical feature or endophenotype (eg, deficit syndrome, eye-tracking abnormalities) is associated with a separate genetic mutation<sup>47</sup> or variant. Determining how alleles increase risk would be aided by a large-scale examination (ie, a population-wide study) to examine both intraindividual prevalence and clustering of biomarkers such as those in the Table. Estimates of clustering of these measures within particular kindreds would be similarly illuminating, while clarifying patterns of inheritance of the endophenotypes themselves.

It is possible that the susceptibility alleles (eg, single-nucleotide polymorphism [SNP]) associated with the biomarkers are common variants rather than mutations that disrupt the gene. These “risk factors” may be common variants that may be benign or even advantageous in other combinations (James Joyce and Albert Einstein both fathered children with schizophrenia).

The way forward for schizophrenia research over the next decade is to identify vulnerability genes by focusing on more clearly defined phenotypes in large-scale collaborations. The National Institutes of Health have a role in fostering this type of research.<sup>79</sup> The role of genes in central nervous system development needs to be clarified, as does the question of whether defined genes are associated with particular clinical features. Such gene development will lead to novel, targeted treatments through joint industry–academic partnerships. Dynamic brain imaging studies and diffusion tensor imaging will be able to characterize the aberrant connectivity in a manner that links clinical symptoms more clearly to pathological brain states.<sup>80</sup> Links be-

tween the various, seemingly disparate “puzzle pieces” (eg, the discovery of dopamine/GABA-A coupling) will ultimately lead to a coherent unified view of this devastating illness.<sup>81,82</sup> The development of rationally based animal models, more effective treatment approaches, and improved preventive interventions for this complex disease will follow.

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## References

- Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994
- Goldstein JM. Sex differences in schizophrenia: epidemiology, genetics and the brain. *Int Rev Psych* 1997;9:399–408
- Kendler KS, Neale MC, Walsh D. Evaluating the spectrum concept of schizophrenia in the Roscommon family study. *Am J Psych* 1995;152:749–754
- Jablensky A, Sartorius N, Ernberg G, et al. Schizophrenia: manifestations, incidence and course in different cultures: a World Health Organization ten country study. *Psychol Med* 1992; (Suppl 20):1–97
- Goater N, King M, Cole E, et al. Ethnicity and outcome of psychosis. *Br J Psych* 1999;175:34–42
- Sartorius N, Jablensky A, Korten A, et al. Early manifestations and first-contact incidence of schizophrenia in different cultures. *Psychol Med* 1986;16:909–928
- Harding C, Hall GM. Long-term outcome studies of schizophrenia: do females continue to display better outcome as expected? *Int Rev Psych* 1997;9:409–418
- Barak Y, Swartz M, Davidson M. Dementia in elderly schizophrenic patients: reviewing the reviews. *Int Rev Psych* 1997;9: 459–463
- Purohit DP, Davidson M, Perl DP, et al. Severe cognitive impairments in elderly schizophrenic patients: a clinicopathological study. *Biol Psych* 1993;33:255–260
- Arango C, Bartko JJ, Gold JM, et al. Prediction of neuropsychological performance by neurological signs in schizophrenia. *Am J Psych* 1999;156:1349–1357
- Sanders RD, Keshaven MS, Schooler NR. Neurological examination abnormalities in neuroleptic-naïve patients with first-break schizophrenia: preliminary results. *Am J Psych* 1994;151: 1231–1233
- Gur RC, Ragland JD, Gur RE. Cognitive changes in schizophrenia: a critical look. *Int Rev Psych* 1997;9:449–457
- Saykin AJ, Shtasel DL, Gur RE, et al. Neuropsychological deficits in neuroleptic naïve, first episode schizophrenic patients. *Arch Gen Psych* 1994;51:124–131
- Harrison PJ. The neuropathology of schizophrenia: a critical review of the data and their interpretation. *Brain* 1999;122: 593–624
- Akbarian S, Vinuela A, Kim JJ, et al. Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. *Arch Gen Psych* 1993;50:178–187
- Lewis DA. Chandelier cells: shedding light on altered cortical circuitry in schizophrenia. *Mol Psych* 1998;3:466–471
- Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol Psych* 1999;45:17–25
- Johnstone EC, Bruton CJ, Crow TJ, et al. Clinical correlates of postmortem brain changes in schizophrenia: decreased weight and length correlate with indices of early impairment. *J Neurol Neurosurg Psych* 1994;57:474–479
- Holzman PS, Kringlen E, Matthyse S, et al. A single dominant gene can account for eye tracking dysfunction and schizophrenia in offspring of discordant twins. *Arch Gen Psych* 1988;45: 641–647
- Levy DL, Holzman PS. Eye tracking dysfunction and schizophrenia: an overview with special reference to the genetics of schizophrenia. *Int Rev Psych* 1997;9:365–371
- Blackwood DHR, St Clair DM, Muir WJ, et al. Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. *Arch Gen Psych* 1991;48:899–909
- McCarley RW, O'Donnell BF, Niznikiewicz MA, et al. Update on electrophysiology in schizophrenia. *Int J Psych* 1997;9:373–386
- Freedman R, Coon H, Worsley H, et al. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci* 1997;94:587–592
- Pearlson GD, Marsh L. Structural brain imaging in schizophrenia: a selective review. *Biol Psych* 1999;46:627
- Ross CA, Pearlson GD. Schizophrenia, the heteromodal association neocortex and development: potential for a neurogenetic approach. *Trends Neurosci* 1996;19:171–176
- Liddle PF. Dynamic neuroimaging with PET, SPET or fMRI. *Int Rev Psych* 1997;9:331–337
- Silbersweig DA, Stern E, Frith CD, et al. A functional neuroanatomy of hallucinations in schizophrenia. *Nature* 1995;378: 176–179
- Pearlson GD, Barta PE, Powers RE, et al. Ziskind-Somerfeld Research Award 1996: medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. *Biol Psych* 1997;41:1–14
- Kapur S, Remington G, Jones C, et al. High levels of dopamine D<sub>2</sub> receptor occupancy with low dose haloperidol treatment: a PET study. *Am J Psych* 1996;153:948–950
- Laruelle M. Imaging dopamine transmission in schizophrenia: a review and meta-analysis. *Q J Nucl Med* 1998;42:211
- Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. *Am J Psych* 1996;153:466–476
- Coyle JT. The glutamatergic dysfunction hypothesis for schizophrenia. *Harv Rev Psych* 1996;3:241–253
- Heresco-Levy U, Javitt DC. The role of *N*-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in the pathophysiology and therapeutics of psychiatric syndromes. *Eur Neuropsychopharmacol* 1998;8:141–152
- Garbutt JC, van Kamm DP. The interaction between GABA and dopamine: implications for schizophrenia. *Schizophr Bull* 1983;9:36–53
- Liu F, Wan Q, Pristupa ZB, et al. Direct protein coupling enables cross-talk between dopamine D5 and  $\gamma$ -aminobutyric acid A receptors. *Nature* 2000;403:274–280.
- Cornblatt B, Obuchowski M. Update of high-risk research: 1987–1997. *Int Rev Psych* 1997;9:437–447
- Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 1987; 44:660–669
- Walker E, Lewine RJ. Prediction of adult-onset schizophrenia from childhood home movies of the patients. *Am J Psych* 147: 1052–1056
- Crow TJ, Done DJ, Sacker A. Childhood precursors of psychosis as clues to its evolutionary origins. *Eur Arch Psychiatry Clin Neurosci* 1995;245:61–69

40. Done DJ, Crow TJ, Johnstone EC, et al. Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *Br Med J* 1994;309:699–703
41. Crow TJ, Done DJ, Sacker A. Cerebral lateralization is delayed in children who later develop schizophrenia. *Schizophr Res* 1996;22:181–185
42. DeLisi LE, Sakuma M, Tew W, et al. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psych Res* 1997;74:129–140
43. Woods BT. Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. *Am J Psych* 1998;155:1661–1670
44. Tsuang M. Schizophrenia: genes and environment. *Biol Psych* 2000;47:210–220
45. Kringlen E, Cramer G. Offspring of monozygotic twins discordant for schizophrenia. *Arch Gen Psych* 1989;46:873–877
46. Pulver AE. Search for schizophrenia susceptibility genes. *Biol Psych* 2000;47:221–230
47. Carpenter WT, Arango C, Buchanan RW, et al. Deficit psychopathology and a paradigm shift in schizophrenia research. *Biol Psych* 1999;46:352–360
48. Wickham H, Murray RM. Can biological markers identify endophenotypes predisposing to schizophrenia? *Int Rev Psych* 1997;9:355–364
49. Sharma T, Lancaster E, Sigmundsson T, et al. Lack of normal pattern of cerebral asymmetry in familial schizophrenic patients and their relatives: the Maudsley family study. *Schizophr Res* 1999;40:111–120
50. Levy DH, Holzman PS, Matthyse S, et al. Eye tracking and schizophrenia: a selective review. *Schizophr Bull* 1994;20:47–62
51. Arolt V, Lencer R, Nolte A, et al. Eye tracking dysfunction is a putative phenotypic susceptibility marker of schizophrenia and maps to a locus on chromosome 6p in families with multiple occurrence of the disease. *Am J Med Genet* 1996;67:564
52. Murray RM, O'Callaghan E, Castle DJ, et al. A neurodevelopmental approach to the classification of schizophrenia. *Schizophr Bull* 1992;18:319–332
53. Lander ES. Splitting schizophrenia. *Nature* 1998;336:105–106
54. Woodruff PWR, Murray RM. The aetiology of brain abnormalities in schizophrenia. In: Ancill R, ed. *Schizophrenia: exploring the spectrum of psychosis*. Chichester, UK: John Wiley & Sons, 1994:94–155
55. Cannon TD, Mednick SA, Parnas J, et al. Developmental brain abnormalities in the offspring of schizophrenic mothers. *Arch Gen Psychiatry* 1993;50:551–563
56. Callicott JH, Ramsey NF, Tallent K, et al. Functional magnetic resonance imaging brain mapping in psychiatry: methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* 1998;18:186–195
57. Callicott JH, Egan MF, Bertolino A, et al. Hippocampal *N*-acetyl aspartate in unaffected siblings of patients with schizophrenia: a possible intermediate neurobiological phenotype. *Biol Psych* 1998;44:941–950
58. Blackwood DH, Glabus MF, Dunan J, et al. Altered cerebral perfusion measured by SPECT in relatives of patients with schizophrenia: correlations with memory and P300. *Br J Psych* 1999;175:357–366
59. Staal WG, Hulshoff Pol HE, Schnack HG, et al. Structural brain abnormalities in patients with schizophrenia and their healthy siblings. *Am J Psych* 2000;157:416–421
60. Fogelson DL, Nuechterlein KH, Asarnow RF, et al. The factor structure of schizophrenia spectrum personality disorders: signs and symptoms in relatives of psychotic patients from the UCLA family members study. *Psych Res* 1999;87:137–146
61. Cornblatt BA, Lenzenweger MF, Dworkin RH, et al. Childhood attentional dysfunctions predict social deficits in unaffected adults at risk for schizophrenia. *Br J Psychiatry* 1992;161(Suppl 18):59–64
62. Nieznanski M. Disorders in cognition and language vs. communication deviances in families of schizophrenics. *Psychiatr Pol* 1999;33:399–406
63. Docherty NM, Gordinier SW, Hall MJ, Cutting LP. Communication disturbances in relatives beyond the age of risk for schizophrenia and their associations with symptoms in patients. *Schizophr Bull* 1999;25:851–862
64. Shenton ME, Solovay MR, Holzman PS, et al. Thought disorder in the relatives of psychotic patients. *Arch Gen Psychiatry* 1989;46:897–901
65. Chen WJ, Faraone SV. Sustained attention deficits as markers of genetic susceptibility to schizophrenia. *Am J Med Genet* 2000;97:52–57
66. Laurent A, Saoud M, Bougerol T, et al. Attentional deficits in patients with schizophrenia and in their non-psychotic first-degree relatives. *Psychiatry Res* 1999;89:147–159
67. Park S, Holzman PS, Goldman-Rakic P. Spatial working memory deficits in the relatives of schizophrenic patients. *Arch Gen Psychiatry* 1995;52:821–828
68. Flyckt L, Sydow O, Bjerkenstedt L, et al. Neurological signs and psychomotor performance in patients with schizophrenia, their relatives and healthy controls. *Psychiatry Res* 1999;86:113–129
69. Kinney DK, Yurgelun-Todd DA, Woods BT. Neurologic signs of cerebellar and cortical sensory dysfunction in schizophrenics and their relatives. *Schizophr Res* 1999;35:99–104
70. Kathmann N, Wagner M, Rendtorff N, et al. Delayed peak latency of the mismatch negativity in schizophrenics and alcoholics. *Biol Psych* 1995;37:754–757
71. Cannon TD. On the nature and mechanisms of obstetric influences in schizophrenia: a review and synthesis of epidemiologic studies. *Int Rev Psych* 1997;9:387–397
72. Torrey FE, Peterson MR. The viral hypothesis of schizophrenia. *Schizophr Bull* 1976;2:36–146
73. Kinney DK, Levy DL, Yurgelun-Todd DA, et al. Season of birth and obstetrical complications in schizophrenics. *J Psychiatr Res* 1994;28:499–500
74. Susser E, Neugebauer R, Hoek HW, et al. Schizophrenia after prenatal famine. Further evidence. *Arch Gen Psych* 1996;53:25–31
75. Kane JM. Update on treatment strategies. *Int Rev Psych* 1997;9:419–427
76. Wildenauer DB, Schwab SG, Maier W, Detera-Wadleigh SD. Do schizophrenia and affective disorder share susceptibility genes? *Schizophr Res* 1999;39:107–111
77. Berrettini WH. Susceptibility loci for bipolar disorder: overlap with inherited vulnerability to schizophrenia. *Biol Psych* 2000;47:245–251
78. Pearlson GD, Pulver AE. Sex, schizophrenia and the cerebral cortex. In: Ancill EJ, Holliday S, Higenbottam J, eds. *Schizophrenia: exploring the spectrum of psychosis*. Chichester, UK: John Wiley & Sons, 1994:345–362
79. Hyman SE. The NIMH perspective: next steps in schizophrenia research. *Biol Psych* 2000;47:1–7
80. Andreasen NC. Bleuler's "fragmented phrene" as schizencephaly. *Arch Gen Psych* 1999;56:781–787
81. Carlsson A, Waters N, Waters S, Carlsson ML. Network interactions in schizophrenia: therapeutic implications. *Brain Res Rev* 2000;31:342–349
82. Goodman AB. Congenital anomalies in relatives of schizophrenic probands may indicate a retinoid pathology. *Schizophr Res* 1996;19:163–170