Schizophrenia: A Complex Disorder That Has Stymied Research Efforts to Uncover Its Origin

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Schizophrenia is a disabling mental disorder that affects close to 1% of the general population. From a societal perspective, a large sector of the population is affected, worldwide. Currently there is no laboratory test to diagnose this disorder. Instead, a myriad of symptoms are used to define the illness, and treatment is based primarily on symptom profile. A more rational approach is to group patients based on variables that are more closely associated with the presumed etiology of the disorder, including neurobiological indicators or markers such as brain abnormalities and cognitive dysfunctions, which are also likely to reflect, or be associated with, variations in gene expression. The latter foci might serve to define more homogeneous groupings, which, in turn, might lead to both earlier and more targeted treatments, as well as to better long-term outcome, reduced healthcare and societal costs, and to unraveling the etiology of this enigmatic and devastating disorder.

Defining Schizophrenia

Schizophrenia is a serious, often chronic and disabling mental disorder that affects approximately 1% of the population worldwide. With a low incidence, or base rate, and no laboratory tests to diagnose schizophrenia, progress has been hampered in effectively treating or preventing this disorder. Particularly troublesome is the myriad of symptoms used to diagnosis schizophrenia, with no one symptom being either necessary or sufficient for a diagnosis of schizophrenia. In addition, not all symptoms are observed in every patient, nor are the same symptoms observed over time in the same patient. Instead, symptoms tend to wax and wane over the course of the illness. These symptoms include overt or positive symptoms such as auditory hallucinations, disordered thinking, and delusions; and more covert or negative symptoms such as avolition, anhedonia, blunted affect, and apathy.

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Of further note, patients with schizophrenia frequently show a deteriorating course, with an estimated 40 to 60% suffering lifelong impairments. Additionally, there are often devastating effects on the psychological and financial resources of the patient, family, and larger community. Patients with schizophrenia also tend to have major impairments in social, occupational, and cognitive functioning, which represent a significant health care burden. More specifically, the economic burden for excess direct healthcare costs has been estimated at 22.7 billion in the United States in 2002, with an addition 7.6 billion in excess direct non-healthcare costs, and an additional 32.4 billion in excess total indirect costs, for a total excess economic burden of 62.7 billion for schizophrenia.

Efforts have been made to rethink and reformulate how to treat severe mental illnesses in order to lessen the economic, social, and family burden, not to mention the burden on the person diagnosed with schizophrenia. For example, positive steps have now been taken to identify early indicators of psychosis, and to begin the treatment of psychosis as early as possible. The race to intervene early is based on evidence which suggests that delays in treatment lead to unnecessary distress for the patient, greater risk of relapse, as well as adversely effecting the long-term course of the illness. There is also evidence to suggest that changes in brain volume occur in the first year to year and a half of first hospitalization, thus highlighting still further the importance of the early identification of indicators of psychosis and early intervention.

Finally, one of the main obstacles to understanding the etiology of schizophrenia is that the presenting symptoms may or may not be related to the disorder’s pathophysiology and/or etiology. This suggests that defining patients by symptoms alone may not be an optimal way of grouping them, as this approach likely includes a heterogeneous grouping of patients. A more careful delineation based on neurobiological indicators or markers such as brain abnormalities, cognitive dysfunctions, and/or variations in gene expression, etc., might serve to define more homogeneous groupings. This may ultimately lead to more targeted psychopharmacological and cognitive-behavioral treatments, and ultimately to unraveling the etiology of this devastating disorder. Additionally, by focusing on neurobiological indicators of brain and cognitive dysfunction in schizophrenia, we may be better able to identify individuals who are at risk for developing schizophrenia, which will likely lead to earlier intervention, and perhaps, in the future, to preventative measures. At present, however, and as described below, we are currently far from understanding the etiology of schizophrenia.

In fact, after more than 100 years of research, the etiology of schizophrenia is still unknown. What we do know is that schizophrenia is a complex brain disorder with clinical symptoms, cognitive distortions, and course of illness largely determined by neural substrates, which, in turn, are likely influenced by the weak effects of multiple genes, with environmental factors playing a secondary or contributory role. Moreover, and perhaps one of the most distressful facts about schizophrenia, is that it typically afflicts individuals in late adolescence or early adulthood, a time when most people are on the thresh-
old of entering the most productive years of their lives. There are also likely several interacting biological (e.g., genetic and neurodevelopmental) and environmental factors (e.g., viral infection, fetal insult, drug abuse) that predispose an individual to schizophrenia.

The strongest evidence for the role of genetics in schizophrenia comes from twin studies, which have reported higher concordance rates for schizophrenia in monozygotic (identical) twins compared with the concordance rates for schizophrenia in dizygotic (fraternal) twins (about 10%).

Evidence for the role of genetics also comes from adoption studies which have shown a higher incidence of schizophrenia in the offspring of mothers with schizophrenia who were raised in adopted homes (about 13%), compared with the incidence of schizophrenia in the offspring of mothers without schizophrenia who were raised in adoptive homes (about 2%). As concordance rates for monozygotic twins are not 100%, as would be expected for identical twins, it is evident that there are likely important environmental risk factors that are also involved. Nonetheless, twin and adoption studies, taken together, demonstrate that genes influence the susceptibility to schizophrenia, although the mode of inheritance is not known. It is likely, however, to be complex and not related to one gene (e.g., Mendelian autosomal transmission), but instead the result of the effect of multiple weak genes that, in concert with environmental risk factors, exert their influence on the susceptibility, or predisposition, to developing schizophrenia.

### The Role of the Brain in Schizophrenia

Although, as noted above, the etiology of schizophrenia is not known, both Kraepelin and Bleuler, who first described “dementia praecox” and “the schizophrenias”, believed that brain abnormalities would ultimately be linked to the etiology of schizophrenia. This conviction was fueled during the late 19th and early 20th century by important inroads that were being made into the neuropathology of Alzheimer’s disease, Huntington’s Chorea, Pick’s disease, tertiary syphilis, and some forms of epilepsy. Given the importance of brain abnormalities in these other diseases, researchers were hopeful to discover similar abnormalities in the postmortem brains of patients diagnosed with schizophrenia. The results, however, were disappointing and often conflicting, largely due to the crude measurement tools that were employed, and the expectation that large abnormalities would be discovered, when in fact such abnormalities are small and subtle. Consequently, progress, as well as interest, waned, and the general consensus, voiced in 1972 by Plum, was that “schizophrenia is the graveyard of neuropathologists”.

Interest was rekindled in 1976 with the first computer-assisted tomography (CT) study that showed enlarged lateral ventricles in schizophrenia. This study was pivotal in that CT was seen as a new window on the brain that would enable investigators to revisit old theories about the role of brain abnormalities in schizophrenia. With the introduction of magnetic resonance imaging (MRI) studies, the first MRI study of schizophrenia was conducted in 1984. Since that time there have been
many improvements in MR acquisition and image processing, including the introduction of positron emission tomography (PET), followed by functional MR (fMRI) and diffusion tensor imaging (DTI), all of which have enabled us to exploit more fully information contained in MR and other medical images. These advances have led to an important appreciation of the critical role that brain abnormalities play in schizophrenia. Moreover, an important question has also been answered in the affirmative – brain abnormalities are indeed observed in schizophrenia.

The implications of these findings, reviewed below (MRI and Schizophrenia), remain to be determined, particularly in the context of how they pertain to the presence of brain abnormalities in at-risk individuals, in prodromal states (i.e., prior to the actual onset of illness but where indicators of illness are present such as brain abnormalities, cognitive deficits, etc.), at time of first episode of illness, in the well relatives of patients diagnosed with schizophrenia, as well as in association with cognitive dysfunctions, clinical symptoms, and genetic variations. These areas are currently being investigated and early findings suggest that the unaffected first-degree relatives of patients with schizophrenia show similar brain abnormalities, as do individuals at high-risk for developing schizophrenia.\textsuperscript{20,21} Importantly, identifying early indicators of illness will assist in treating at-risk individuals early, with the outcome hopefully being one of lowering recidivism rates and ameliorating or even preventing the chronic course of the illness, a course often seen in patients diagnosed with schizophrenia.

MRI and Schizophrenia

Described as “The Decade of the Brain”, the 1990s witnessed unparalleled progress in what we know about the brain, largely the result of new in vivo medical imaging tools. More progress was made during this period in documenting brain abnormalities in schizophrenia, than had occurred in the previous history of schizophrenia research. Of particular note, advances in imaging led to the identification of a number of small subtle brain abnormalities, including ventricular enlargement, preferential involvement of medial temporal lobe structures, including the amygdala-hippocampal complex, parahippocampal gyrus, and superior temporal gyrus, as well as moderate evidence for frontal and parietal lobe abnormalities and subcortical abnormalities.\textsuperscript{16} Findings were more equivocal for cerebellar abnormalities. Thus several discrete brain regions seem to be involved in the neuropathology of schizophrenia, and these likely involve neural circuitry abnormalities that affect brain regions that are not necessarily proximal to each other but which are nonetheless functionally related.

For example, our research group has focused on gray matter temporal lobe abnormalities, including the amygdala-hippocampal complex, parahippocampal gyrus, and superior temporal gyrus, which we reported to be reduced in volume in patients diagnosed with schizophrenia compared with healthy controls. The volume reduction was left lateralized and associated with formal thought disorder, one of the cardinal symptoms of schizophrenia. We concluded that there was damage to an in-
terconnected neural network that is functionally important for language and associative links in memory, which we believed was a fundamental deficit in schizophrenia. Andreasen and colleagues proposed an alternative hypothesis: that the observed abnormalities were part of a neural circuit involving the thalamus and its connections with the cortex and cerebellum, which she termed “cognitive dysmetria”, and which she believed reflected the primary deficit in schizophrenia. Others have focused on abnormalities in the frontal lobes, basal ganglia and temporal lobe connections, or in alterations in the temporal lobe that interrupt connections between temporolimbic and prefrontal regions, and vice versa. Of note, all of these theories evolved from earlier theories of brain abnormalities in schizophrenia, though confirmation was not possible until the application of in vivo neuroimaging techniques.

More recently, functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) have been added to the arsenal of tools available to investigate brain abnormalities in schizophrenia. Functional MRI enables a more direct examination of interconnected neural networks, which is not possible with structural MRI alone, while DTI enables the examination of white matter fiber tracts, which connect gray matter regions in the brain.

To understand further the nature of schizophrenia, we now need to integrate and to synthesize what is known about brain abnormalities in schizophrenia, gleaned primarily from in vivo neuroimaging studies conducted over the past fifteen years. We need to combine this knowledge with approaches and advances from the new frontier of molecular genetics. Specifically, we need to combine neuroimaging tools, including structural magnetic resonance imaging (MRI), functional MRI (fMRI) and diffusion tensor imaging (DTI), as a powerful approach to evaluate the in vivo effects of genetic variation, an approach heretofore not possible. (The National Institute of Mental Health recognizes the importance of bringing together knowledge from neuroimaging studies and the new frontier of genetics as is clear from the focus of the intramural program as well as the new organization of NIMH on October 1, 2005 with a focus to accelerate both translational and interdisciplinary sciences to identify brain and behavior pathophysiology in mental illness.)

For example, we are now well poised to characterize and to quantify physiological aspects of the disorder, such as an abnormal neural circuit involving verbal memory. While this may be associated with susceptibility to schizophrenia, it may be more directly quantifiable using neuroimaging tools, as well as more directly associated with a gene such as the Brain-Derived Neurotrophic Factor (BDNF). A focus on the abnormal neural circuitry involved in verbal memory, and/or a focus on BDNF, would be used instead of more distantly associated or indirect indicators of language/memory deficits, such as a clinical symptom, or a cognitive phenotype, e.g., poor performance on a neuropsychological test.

Tsuang and Faraone, in fact, observe that a focus on neurobiological dysfunctions instead of diagnostic classifications in schizophrenia “may reflect relatively more proximal effects” of genes, as opposed to diagnosis and symptoms, which “reflect relatively distal and variable effects of genes.” Of interest here, approaches to mapping
susceptibility genes for complex disorders such as schizophrenia have begun, making it a real possibility that molecular genetics studies will identify susceptibility genes in schizophrenia. It is also quite likely that it is not “schizophrenia” per se that is inherited but instead multiple alleles that are “disadvantageous for cognitive processes.” Thus, future studies need to evaluate carefully the weak effects that one or more genes have on cognitive impairments commonly observed in schizophrenia, and these need to be investigated in conjunction with neuroimaging measures of the brain regions involved in these processes.

The focus on more neurobiological and cognitive dysfunctions, along with their association with genetic variation, is also a common approach in medicine. For example, it was not until patients with Alzheimer’s disease were separated into early and late onset that the apolipoprotein E gene was discovered and shown to increase the risk of late-onset Alzheimer’s disease, while the epsilon 2 variant was found to be protective. That is, by further delineating more homogeneous groupings in schizophrenia, the hope is that “endophenotypic markers”, or “intermediate phenotypes”, will enable us to move to more “proximal effects”, and thus closer to the etiology, or to perhaps several different etiologies, where “schizophrenia”, defined currently primarily by the symptoms evinced, is the final common pathway. Furthermore, with new advances and tools available for gene profiling, this area of research is ripe for exploring the impact of genetic variation on cognitive processes and their associated neural circuits.

Criteria for selecting such “intermediate phenotypes”, or “endophenotypes”, have a long history in schizophrenia research and include that the characteristic or trait being measured should: 1) be associated with the disease or disorder that is being studied; 2) that it be heritable; 3) that it not be state-dependent; and, 4) that it be observed in the unaffected family members at a higher rate than is observed in the general population.

Some candidate endophenotypes for schizophrenia include eye tracking dysfunction, fMRI measures of working memory deficits, as well as neurophysiological measures of P50, which indexes the ability to inhibit prepotent responses. What makes these endophenotypes most promising is that they have a much higher prevalence than schizophrenia in the relatives of schizophrenics.

Finally, and reviewed further below, evaluating the impact that genes have on biological intermediate phenotypes, in conjunction with cognitive processes, is an important new frontier for making schizophrenia more tractable, as well as for shedding new light on the etiology of this devastating disorder.

**Imaging Genomics and Future Challenges**

It is noteworthy that there are now novel methods for searching for schizophrenia susceptibility genes that have only become available in the last several years, including micro-array analyses of polymorphisms (SNPs). Accordingly, evaluating the weak effects of multiple genes, including their effect on cognition and brain abnormalities, is now at hand.

Also of note, several genes that have been implicated in the susceptibility to
schizophrenia are associated with memory impairments, a common finding in schizophrenia. These genes include the BDNF gene, described above, as well as the catecholamine-O-methyl transferase (COMT) gene, the latter important for the catabolism of dopamine. Briefly, BDNF has figured in both bipolar disorder and schizophrenia, and has also been shown to be associated with declarative memory impairments in schizophrenia. The COMT gene, importantly, has been associated with frontal impairments in the dorsal lateral prefrontal cortex as well as with working memory impairments in schizophrenia.

This gene has also been linked to bipolar disorder and to velocardiofacial syndrome (VCFS or DiGeorge syndrome). Of particular interest here, in 90% of VCFS cases there is a deletion on chromosome 22 (del22q11.2) that is 3Mb long and the COMT gene maps onto this region. Moreover, up to 30% of these individuals will develop schizophrenia during adolescence or early adulthood. For this reason, Bassett and Chow describe VCFS as a model for “a genetically mediated subtype of schizophrenia.” A promising approach to investigate schizophrenia at the genetic level is thus to study VCFS, where the COMT gene may be involved in both disorders, and may account for the 30% of VCFS patients who develop schizophrenia.

In summary, as the classification of psychiatric diagnoses and clinical symptoms are not based on underlying genetic or biological considerations, by linking genetic abnormalities to cognitive disruptions, as they are reflected in brain structure and function, we may be in a better position to observe more robust findings, as the associations being made will be based on measures that are closer to biology. Hariri and Weinberger describe this new area of scientific inquiry as “imaging genomics.” This is the next important frontier in schizophrenia research, for if we can identify even a subset of the genes that influence cognition and brain function and structure, we may be able to develop treatments that enhance or block the effects of these genes, thereby effecting the course and treatment of the illness, as well as lead us to preventative measures.

Findings from such a program of research may also lead us to a new understanding of the impact of multiple weak genes on cognition and brain structure and function in schizophrenia as well as possibly serve as reliable markers for identifying individuals at risk for schizophrenia (i.e., as yet unaffected relatives, individuals with VCFS, individuals with prodromal symptoms and/or first episode patients), so that intervention can begin early. The implications here for early intervention and ameliorating and even preventing a debilitating, often chronic illness, as well as reducing the psychological and economic burden to the patient, family, and to society, is immeasurable.

References


*Note: Many of the ideas and concepts for this paper were derived and adapted from: Shenton ME, et al. A review of MRI findings in schizophrenia. Schizophr Res 2001;49:1-52.