Psychosis Endophenotypes in Schizophrenia and Bipolar Disorder

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Recent studies provide considerable evidence that schizophrenia and bipolar disorder may share overlapping etiologic determinants. Identifying disease-related genetic effects is a major focus in schizophrenia and bipolar disorder research, with implications for clarifying diagnosis and developing specific treatments for various impairments in these 2 disorders. Efforts have been multifaceted, with the ultimate goal of describing causal paths from specific genetic variants, to changes in neuronal functioning, and to behavioral and functional impairments. Parallel efforts have identified and refined several alternative phenotypes that are stable, heritable, some with known biological substrates, and are associated with psychosis liability. These alternative phenotypes are likely to aid search for liability genes in schizophrenia and bipolar disorders and likely to be informative regarding the extent to which the 2 disorders share etio-pathophysiology.

The search for genes that confer psychosis liability has been extremely difficult even though many of the psychotic disorders are known to be highly heritable. There are several reasons for this lack of substantial progress in the gene hunt. Major obstacles are the complexity of psychotic disorders that are heterogeneous, lack clear boundaries, and overlap with other diagnostic categories. Today’s classification system has entirely depended on the presence of clinical symptoms to categorize psychotic disorders. These symptoms are rated on several dimensions that include reality distortions, disorganization in thought and behavior, anhedonia and related pathology, and mood disturbance (such as irritability, agitation, anxiety, depression, and euphoria). Some of the associated features such as age of onset, whether certain symptoms co-occur, the course of the illness, sleep disturbance, appetite disturbance, and functional outcomes are taken in to account in order to categorize the disorder into a clinical diagnosis such as schizophrenia or bipolar disorder. This tradition dates back to times of Morel and Kraepelin, who made the initial distinctions between organic, affective and poor outcome psychosis.1,2 Results from family studies in large, epidemiological samples generally validated these distinctions, although some overlap in familial risks across these 2 major psychotic disorders were noted.3 Interestingly, subsequent linkage studies found some common chromosomal loci, and candidate genes, whose associations were observed both in schizophrenia and bipolar disorder.

The findings from genetic studies raise several interesting fundamental questions regarding the diagnostic categorization of psychotic disorders into bipolar disorder and schizophrenia. Unlike the overlap in clinical phenomenon and in familial risk, which can be explained by errors or the lack of finesse of the clinical diagnosis, the genetic studies point to a shared neurobiology across the 2 disorders. While the first part of the last century focused on clinical phenomenon, the advances in cognitive neuroscience, electrophysiology, and imaging techniques have allowed investigators over the past few decades to examine the neurobiology of these psychotic disorders. The initial neurobiological studies were conducted in probands, where confounding effects of state-dependent factors including medications became an issue. Subsequent studies focused on at-risk groups which provided an added advantage of identifying deficits that were not only associated with the illness but were also familial suggesting that they were associated with heritability of the illness. These were the beginnings of endophenotypic studies in schizophrenia, which examined the “soft neurology” of schizophrenia liability that were nearer to the effects of genes.4 Gottesman and Shield were first to coin the term “endophenotype” in this context, borrowing the phrase from entomology, arguing that assessing endophenotypes has an advantage since they identify aberrant genetic effects even when such effects are not discernable at the clinical level.5 In contrast to the complex clinical phenomenon that define psychotic disorders such as schizophrenia and bipolar, endophenotypes represent neuronal deficits nearer to the genetic effects. As phenotypes, these are much more simple. The extensive research in schizophrenia of the past decades, and to a lesser extent in bipolar illness, has yielded several potential endophenotypes. Emerging data suggest that many of these

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endophenotypes are uncorrelated, marking different aspects of disease risk. Akin to the clinical and genetic findings, there is some overlap in findings of neuronal deficits marked by the endophenotypes across bipolar disorder and schizophrenia patients. However, there is meager data in the first-degree relatives of bipolar patients.

Several investigators have made a compelling argument for the use of endophenotypes in the search for schizophrenia and bipolar disorder genes. There is an obvious advantage for the use of a much simpler phenotype than the complex clinical syndrome in genetic studies. In addition, animal models are available for many of the endophenotypes, and the underlying neurobiology is well understood thus better providing clues to the etiopathophysiologic pathways. As is reviewed by several articles in this issue, parallel studies of endophenotypes in schizophrenia and bipolar disorder, and examination of endophenotype-genotype relationships, are likely to be informative regarding the extent to which the 2 disorders share etio-pathophysiology. Such studies inform on how and where the 2 disorders diverge. It will clarify to what extent unique genes or etiological factors associated with each of the disorders modulate their pathophysiology.

The first article of the theme raises an interesting question: Do some of these heritable phenotypes associated with the psychotic disorders confer an adaptive advantage? Psychosis, in spite of the negative impact on evolutionary fitness, has persisted. Studies suggest that during recent evolution, certain variations in the genome are positively selected, and some of these overlap with the genes implicated in schizophrenia. The second article examines the extent to which schizophrenia and bipolar disorder overlap in their clinical phenomena and familial and genetic risks. The next 3 articles examine the similarity and differences in the pattern of cognitive, neurophysiological, and brain structural impairments in schizophrenia and bipolar disorders. These articles review the findings in the relatives on these measures, arguing that similar findings in the 2 relative groups may be the result of the effects of common genetic factors. The last article in the theme discusses approaches to studying shared genetic liabilities across disorders.

References