Endophenotypic Studies in Schizophrenia: Promise and Challenges

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The hunt for disease-related genes has proven more difficult than initially appreciated and is successful mostly in disorders that are clearly defined and homogenous. Psychotic disorders have posed a particularly difficult problem due to a lack of preciseness in defining the boundaries of the clinical phenotype and the absence of objective, biological tests that confirm diagnostic categorization. Clinical heterogeneity and the complex nature of schizophrenia and other psychotic disorders have further confounded the search for culprit genes. Previous efforts to address the problem of classification of psychotic disorders have included careful operationalizing of diagnostic criteria and attempting to refine clinical methods to reliably identify valid clinical subsyndromes. In addition, investigators focused their efforts on identifying biological or psychobiological tests that could sensitively and specifically mark schizophrenia. Initial studies looked for measures that differentiated patients from appropriate comparison groups. These efforts generally failed because the effects of medications and other secondary factors associated with having serious mental illness could not be separated from the neurobiology of the disease. Based on findings that many first-degree relatives of schizophrenia patients show schizophrenia-like characteristics, the search for biological markers of schizophrenia shifted to first-degree relative cohorts, where the usual confounds associated with having a chronic illness are absent. This was a significant paradigm shift; the results of these studies not only identified biological markers of the disease but also captured measures that are familial, perhaps heritable, and related to the etiology of schizophrenia. These family studies were the beginning of the endophenotypic studies in schizophrenia with the aims of exploring the neuronal mechanisms underlying schizophrenia-related deficits and using these deficits as alternative phenotypes in genetic analysis to identify associated genes.1

The field has made remarkable theoretical and empirical progress in recent decades, identifying several putative endophenotypes and using these measures as phenotypes in genetic studies of schizophrenia.2,3 One theme in this issue is “The Use of Endophenotypes to Deconstruct and Understand the Genetic Architecture, Neurobiology, and Guide Future Treatments of The Group of Schizophrenias,” organized by David Braff. The theme issue includes interesting articles illustrating the advantages of using endophenotypes for deconstructing the complex schizophrenia phenotype in genetic studies. However, several challenges remain. Many of the endophenotypes remain complex, thereby decreasing the utility in a genetic study. An endophenotype that indexes a specific physiological dysfunction, which occurs or can be modeled at a cellular level, has a tremendous advantage in the search for a molecular basis of the disorder.4 Identifying a specific phenotype at a cellular level remains a challenge for psychiatric disorders. Future studies that combine a neurophysiological or neurocognitive measurement with imaging techniques, thereby localizing the deficit to a particular neural circuit, will further refine the endophenotype.

The success of the previous work in identifying several schizophrenia endophenotypes, many overlapping in function or construct, raises the question of the extent to which these measures mark the same or independent psychosis risk. Large sample studies are needed to examine how different biomarkers map on to psychosis risk within and across various psychotic disorders and to develop multivariate statistical methods that are able to identify clusters of measures that coaggregate within families.

Theoretical groundwork and preliminary data presented in this issue, as well as the future findings from the Consortium on the Genetics of Schizophrenia, will provide new direction to the field. There is overlap among major psychotic disorders sharing clinical manifestation, pathophysiology, and, as suggested by recent studies, genetic factors. Future studies that establish similarities and differences in the endophenotypic signatures of schizophrenia, bipolar disorder, and other psychotic disorders will improve concepts about the common and distinct aspects of pathophysiology, about heterogeneity, and about clinical boundaries of psychotic disorders. Better understanding of the genetic mechanisms underlying endophenotypes will identify novel targets for drug development with relevance not only for schizophrenia but also other psychotic disorders with similar endophenotypic signature. Because the neuronal deficits indexed by the endophenotype often precede first psychotic episode, such treatments may also have relevance for early intervention and preventive strategies.
References


