

## Introduction to Special Theme Issue

The last 2 decades have witnessed a relative explosion of research on cognition in schizophrenia, using a variety of approaches that range from the use of large neuropsychological batteries to focused cognitive experimental techniques. There are several reasons for this surge of research on cognitive function in schizophrenia. One reason is the growing body of research suggesting that cognitive function in schizophrenia is one of the most critical determinants of quality of life in schizophrenia, potentially more so than the severity of other aspects/symptoms of schizophrenia such as hallucinations, delusions, or even negative symptoms.<sup>1</sup> A second reason is the hope that understanding the nature of cognitive dysfunction in schizophrenia will give us insight into the neurobiological mechanisms that contribute to the development of this disorder, spurred by the advances made in understanding the neural mechanisms supporting intact cognitive function. A third reason is the hope that cognitive deficits will serve as endophenotypic markers that will help identify genetic or environmental risk factors for the development of schizophrenia. A fourth reason is the hope that understanding the mechanisms leading to cognitive dysfunction in schizophrenia will spur novel drug development and discoveries that may improve cognitive and life function in this illness. As articulated by Gottesman and Hanson,<sup>2</sup> the clinical traits used to diagnose schizophrenia, or the subclinical phenomena often used to identify those at risk for schizophrenia, have little biological reality, making it difficult to link them to genetic mechanisms. If at least some cognitive functions have an identifiable link to neurobiological and genetic mechanisms (as recent cognitive neuroscience and functional genomics research suggests), then cognitive deficits may serve as promising endophenotypic markers in the search for the etiology of schizophrenia.<sup>3-5</sup>

Gottesman and Hanson<sup>2</sup> have laid out 5 requirements for a construct to qualify as an endophenotypic marker of schizophrenia, including (1) an association between the endophenotype and schizophrenia (or at least symptoms of schizophrenia) in the population; (2) higher rates of the endophenotype even in unaffected family members of

individuals with schizophrenia as compared with the general population; (3) the presence of the endophenotype even when manifest schizophrenia is not present; (4) cosegregation of the endophenotype and schizophrenia in families; and (5) the endophenotype is heritable. This special theme issue of *Schizophrenia Bulletin* seeks to provide additional empirical data and review articles that provide evidence on the degree to which cognitive deficits in specific domains meet the first 4 of these criteria for endophenotypic marker status and to point to critical directions for future research on cognitive endophenotypes.

Although there is variability across the studies and reviews in regard to the specific cognitive domain under study, there is a primary focus on the constructs of working memory, episodic memory, and executive function. Numerous studies document deficits in these cognitive domains among individuals with schizophrenia. This provides evidence for an association between these endophenotypes and schizophrenia in the general population, though the specificity of such cognitive deficits to schizophrenia is debatable. The articles in this special theme issue provide further documentation of an association between cognitive deficits and the presence of (1) subclinical symptoms of schizophrenia (Delawalla et al.); (2) schizophrenia spectrum disorders such as schizotypal personality disorder (SPD) in both adolescents and adults (Trotman et al., Saperstein et al); or (3) individuals who meet various criteria for the prodromal phase of schizophrenia (Brewer et al.). However, the Saperstein et al. article raises some potential caveats to the consistency of the relationship between SPD and working memory deficits in the general population. These authors find that schizophrenia spectrum disorders in the first-degree relatives of individuals with schizophrenia were clearly associated with working memory impairment, but that this association was less clear in individuals who did not have a first-degree relative with schizophrenia. Although this finding requires replication, it suggests a potentially complex relationship between the presence of schizophrenia spectrum disorders, genetic risk for schizophrenia, and cognitive deficits.

The articles in this special theme issue also speak to the second of Gottesman and Hanson's<sup>2</sup> criteria for an endophenotypic marker: higher rates of the endophenotype in even unaffected family members of individuals with schizophrenia as compared with the general population.

<sup>1</sup>To whom correspondence should be addressed; e-mail: dbarch@artsci.wustl.edu.

Consistent with a number of prior reports (see reviews<sup>4,5</sup>), these studies provide data that demonstrate that there are higher rates of dysfunction in working memory (Delawalla et al., Saperstein et al.), executive function (Delawalla et al., Seidman et al.), and episodic memory (Delawalla et al.) among unaffected relatives of individuals with schizophrenia. Further, these studies provide evidence for Gottesman and Hanson's third criterion, which is that the endophenotype is present even when manifest illness is not, in that these relatives did not have diagnosable psychotic disorders. However, the Delawalla et al. and Seidman et al. studies herein are of adolescent and young adult relatives who have not yet passed the period of risk. Thus, some of these adolescents may go on to develop manifest schizophrenia. The Saperstein study includes adults past the period of risk who did not have even spectrum disorder, providing clear evidence for this third criterion.

This research also provides evidence at least indirectly consistent with Gottesman and Hanson's<sup>2</sup> fourth criterion, cosegregation of the endophenotype and schizophrenia in families, in that they address the association between the severity of cognitive deficits and the severity of subclinical symptoms of schizophrenia. For example, Saperstein et al. find that working memory deficits were more severe in first-degree relatives with schizophrenia spectrum disorders as compared with those without. In addition, the Delawalla et al. and Trotman et al. articles both find that the severity of cognitive deficits in working memory and executive function was related to the severity of negative symptoms and, to a certain extent, to the severity of disorganization symptoms. Further, the Trotman et al. article provides some evidence suggesting that cognitive deficits at baseline predict worsening of clinical symptoms among adolescents with SPD. Thus, such data provide some evidence of the association between the severity of cognitive dysfunction and the presence of at least subclinical symptoms of schizophrenia among family members of those with schizophrenia.

The studies included in this special theme issue shed additional light on the degree to which cognitive deficits in schizophrenia meet the endophenotypic criteria outlined by Gottesman and Hanson.<sup>2</sup> However, these articles also raise several additional questions about the status of cognitive deficits as endophenotypic markers of risk for schizophrenia and point to critical areas for future research. First, deficits in a number of different cognitive domains (eg, working memory, executive function, episodic memory) are discussed in these articles, and this introduction has discussed several of these domains together in a broad sense. Nonetheless, it is also important to distinguish between deficits in different cognitive domains, as the strength of evidence for endophenotypic marker status may vary across cognitive domains, and different psychological, neurobiological, and genetic mechanisms contribute to function in different domains.

Currently, it is not clear whether deficits in domains such as working memory, executive function, and/or episodic memory each represent unique or dissociable endophenotypes, though work on this question has started,<sup>6</sup> or whether there are one or more elemental processes contributing to deficits in multiple domains that is the "true" endophenotype. If these different domains represent dissociable endophenotypes, then further work is needed to understand their differential contribution to vulnerability for schizophrenia. For example, the Brewer et al. review article suggests that deficits in working memory among prodromal individuals are predictors of psychosis development, consistent with prior work,<sup>7</sup> though there was also some evidence for episodic memory deficits as predictors of psychosis development. In contrast, the Brewer review suggests that attentional deficits might be a more general indicator of schizophrenia vulnerability. Thus, although deficits in several different cognitive domains may be endophenotypic markers of schizophrenia, they may differ in their relationships to either specific aspects of schizophrenia or development of manifest illness.

Second, the articles in this special theme examine cognitive function in populations at risk for the development of schizophrenia for several different reasons, including genetic risk, the presence of a schizophrenia spectrum disorders, or the presence of phenomena meeting the definition for the prodromal phase of schizophrenia. Although there is evidence for some commonalities in the pattern of cognitive deficits found in these different populations, there is also evidence for differences in the nature and severity of deficits across studies and populations. One possibility is that this variability is theoretically important, in that it may indicate differences in the nature of cognitive endophenotypes present in different at-risk populations and thus potential differences in the neurobiological and genetic mechanisms contributing to these different risk states. Alternatively, this variability may reflect methodological differences across studies, in that researchers often use very different methods or paradigms to assess constructs labeled with the same name. In future research it will be extremely important to examine cognitive function across a range of risk states using a common set of paradigms designed to assess key cognitive processes that may operate as either common or unique markers of vulnerability for schizophrenia across populations.

Third, all of the potential cognitive endophenotypes discussed in these articles still represent fairly global assessments of complex cognitive constructs that are themselves dissociable into more basic subcomponents. For example, the construct of working memory is multi-componential, consisting of buffer systems for the maintenance of both verbal and nonverbal materials, as well as several different central executive functions that coordinate the operating of the buffer systems and operate on

their contents. Importantly, these subcomponents are themselves differentially related to neurobiological and genetic mechanisms, and deficits in some components but not others may be endophenotypic markers of risk for schizophrenia.<sup>8</sup> Thus, determining which specific elements of more global constructs meet the criteria outlined by Gottesman and Hanson<sup>2</sup> will be the most promising route to using cognitive endophenotypic markers as guideposts in the search for the genetic, neurobiological, and environmental causes of schizophrenia.

## References

1. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the “right stuff?”. *Schizophr Bull.* 2000;26:119–136.
2. Gottesman II, Hanson DR. Human development: biological and genetic processes. *Annu Rev Psychol.* 2005;56:263–286.
3. Cannon TD, van Erp TG, Glahn DC. Elucidating continuities and discontinuities between schizotypy and schizophrenia in the nervous system. *Schizophr Res.* 2002;54:151–156.
4. Snitz BE, Macdonald AW 3rd, Carter CS. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophr Bull.* 2006;32:179–194.
5. Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophr Res.* 2004;71:285–295.
6. Krabbendam L, Marcelis M, Delespaul P, Jolles J, van Os J. Single or multiple familial cognitive risk factors in schizophrenia? *Am J Med Genet.* 2001;105(2):183–188.
7. Niendam TA, Bearden CE, Rosso IM, et al. A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *Am J Psychiatry.* 2003;160:2060–2062.
8. Conklin HM, Curtis CE, Calkins ME, Iacono WG. Working memory functioning in schizophrenia patients and their first-degree relatives: cognitive functioning shedding light on etiology. *Neuropsychologia.* 2005;43(6):930–942.