Update on Cognition

The Genetics of Cognitive Impairment in Schizophrenia

by Philip D. Harvey, PhD

Schizophrenia and other psychotic conditions have a substantial genetic component, although the patterns of heritability are clearly not consistent with standard patterns of inheritance. Heritability estimates for schizophrenia are fairly substantial, with considerable increases in risk for concordance across monozygotic as compared to dizygotic twin pairs. As a result, the study of genetics of schizophrenia and bipolar disorder has headed in the direction of attempting to identify heritable phenotypes for the illnesses. Since both of these conditions are clearly quite heterogeneous, this approach appears to have some intrinsic appeal. Thus, the search for heritable phenotypes has been ongoing for the last two to three decades.

There is an intrinsic relationship between cognitive impairments and vulnerability to schizophrenia. It has been known for decades that first-degree relatives of people with schizophrenia have cognitive impairments of the same type seen in people with schizophrenia.[1] These impairments are present even in individuals with no other evidence of behavioral abnormalities, but are often more severe in people who have additional features of psychopathology related to schizophrenia (such as schizotypal symptoms). Individuals with disorders related to schizophrenia, such as schizotypal personality disorder, also have cognitive impairments that are qualitatively similar to those seen in people with schizophrenia. These impairments are not related to global aspects of maladjustment, because they are more substantial than those seen in individuals with other severe personality disorders, such as borderline personality.[2]

Even more striking is the finding that cognitive impairments present in children whose parents have schizophrenia predicts increased risk for the illness. As reported by Cornblatt, et al.,[3] the more impaired the attentional performance of children of mothers with schizophrenia, the more likely that they would develop schizophrenia. Children with minimal attentional impairments have the smallest risk for developing schizophrenia themselves. Thus, cognitive impairments seem to be a marker of not only the presence of schizophrenia in the family, but of increased individual risk development of the illness.

Given the centrality of cognitive impairment in both the familial characteristics of schizophrenia

and in risk transmission for the illness, it is no surprise that cognitive impairments have been given consideration as potential phenotypes for the illness. One recent, large-scale, NIH-funded study, the Consortium on the Genetics of Schizophrenia (COGS)[4] project, examined the heritable nature of cognitive impairments in families with members who had schizophrenia. Cognitive performance tends to be heritable in general. This should not be a surprise as evidence has accrued for years that elements of cognitive functioning, namely intelligence, tend to be quite consistent in family members and have been shown to be heritable in studies of members of the same family who were reared apart. Further, many of the elements of cognitive functioning that are impaired in schizophrenia have been shown to be heritable in families with and without psychopathology.

The COGS study used several criteria to select specific elements of cognitive performance as potential endophenotypes. These included the following:

I. Association with illness
State independent:
(a) adequate test-retest stability
(b) adequate between-site reliability
(c) evidence that impairments in patients are not due to medications
(d) evidence that impairments are observed regardless of the illness state;
Heritability:
(a) in healthy populations
(b) in schizophrenia families;

II. A known neurobiological substrate relevant to schizophrenia

III. Practicality of task administration in a large multisite protocol.

After careful review of the literature, the COGS research team decided that the following cognitive ability areas met the above criteria:

- Attention and, in particular, vigilance
- Verbal learning and memory
- Working memory.

In addition, several subtests from a computerized cognitive assessment battery were examined, including face memory and affect recognition, spatial memory, spatial reasoning, and problem solving.

The review of the literature on these tests revealed very important findings.[5] For instance, across these different cognitive ability domains, heritability estimates for performance on most tests was in the range of h=0.50, with higher estimates in populations with more variance in scores, such as older adults. These data indicate that, in general, cognitive abilities share considerable variance across family members and the correlation within family members in terms of cognitive performance is much closer than many other traits.

All of these cognitive potential endophenotypes were tested in a preliminary study.[6] The study was based on 183 nuclear families ascertained by the presence of a schizophrenic member. Each family was required to have both parents available for assessment, the index case, and at least one unaffected full sibling. All of the cases in the study were tested with an assessment battery based on the cognitive domains described above.

As might be expected from a systematic, large-scale study, the estimates of heritability were slightly lower than the smaller studies that preceded it. The range of heritabilites was 0.24 to 0.55 for performance-based cognitive measures and lower for putative psychophysiological measures (0.10 for p50 suppression and 0.32 for prepulse inhibition). That said, these data still suggest substantial levels of genetic influence on various aspects of cognitive functioning. The conclusion from the first stage of COGS is that the classical cognitive impairments seen in schizophrenia manifest substantial heritability.

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These findings are even more interesting because of the nature of the assessments performed. The tests with higher heritabilities were standard neuropsychological measures, not specialized neuroscience tests. As we described in a previous column, the NIH is very interested in the translation of experimental cognitive science procedures into repeatable measures suitable for use in clinical trials. It is not clear if the higher heritability of the standard measures is because of their standardization or because they measure content that is inherently more heritable. Later research will clearly be focused on identification of genetic variation in experimental procedures as well as clinical neuropsychological tests.

An even more clinically relevant point is related to the idea of treatment of cognitive impairments and the contributions of genetic variation to cognitive treatment response. With the advent of

genome wide association studies, there will be attempts to identify specific genetic loci that are quantitatively linked to specific cognitive abilities. With more efforts to treat cognitive impairments and the promise of eventual successes in pharmacological and remediation interventions, identification of genetic predictors of treatment response to cognitively oriented treatments will be a goal of genomics research. As soon as genetic factors that predict cognitive impairments are detected, they can then be used to predict treatment response.

In conclusion, cognitive performance is a highly heritable trait. The most common cognitive impairments seen in schizophrenia manifest considerable heritability and clearly meet criteria for genetically mediated endophenotypes. These cognitive impairments are present across the schizophrenia spectrum and across the course of illness in people with schizophrenia. They also show evidence of being associated with increased risk for schizophrenia in people who are related to people with the illness. The detection of patterns of genetic variation that are associated with cognitive impairments may also hold promise for the prediction of treatment response, when treatments for cognitive impairment are developed and commonly available.

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REFERENCES

1. Harvey PD, Walker E, Wielgus M. Psychological markers of vulnerability to schizophrenia. In: Maher BH, Maher WB (eds). *Progress in Experimental Personality Research, Volume 14.* New York: Academic Press, 1986:231–267.
2. Mitropoulou V, Harvey PD, Maldari M, et al. Neuropsychological performance in schizotypal personality disorder: evidence regarding diagnostic specificity. *Biol Psychiat.* 2002;52:1175–1182.
3. Cornblatt B, Obuchowski M, Roberts S, et al. Cognitive and behavioral precursors of schizophrenia. *Dev Psychopathol.* 1999;11:487–508.
4. Calkins ME, Dobie DJ, Cadenhead KS, et al. The Consortium on the Genetics of Endophenotypes in Schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration. *Schizophr Bull.* 2007;33:33–48.
5. Gur RE, Calkins ME, Gur RC, et al. The Consortium on the Genetics of Schizophrenia: neurocognitive endophenotypes. *Schizophr Bull.* 2007;33:49–68.
6. Greenwood TA, Braff DL, Light GA, et al. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia *Arch Gen Psychiatry.* 2007;64(11):1242–1250.

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