Snipping at the Endophenotypic Space

Currently, psychiatric diagnoses are based on categorical syndromes derived from observed and self-reported clinical signs and symptoms. These syndromes are supported by their empirical clinical utility (1) but are severely limited because they are poorly aligned with pathogenetic and pathophysiological mechanisms (2). Therefore, there is general agreement that a more biologically informed approach is necessary to identify and stratify psychiatric patients (1, 2).

Over the last decade, innovations in genomics and bioinformatics have led to significant advances in the characterization of the genetic architecture of medical disorders, with cancer (3) and type 2 diabetes (4) being two notable examples. Similar efforts in psychiatric genetics, although not unsuccessful (5, 6), have faced greater challenges. Common variants for psychiatric disorders identified by genome-wide association studies have a small effect on population risk. It is possible that this pattern is characteristic of psychiatric disorders. Alternatively, it may reflect extensive phenotypic heterogeneity, in which case the power of genetic association studies could be enhanced if biologically informed phenotypes were available.

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A dominant strategy to reduce phenotypic heterogeneity is based on the concept of the endophenotype (also known as intermediate phenotype) (7). Endophenotypes are defined as quantifiable, state-independent traits that are genetically correlated with disease liability and can be expressed in unaffected family members. The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) (www.b-snip.org) is one of the most systematic, rigorous, and productive initiatives to implement the endophenotype approach in the study of psychotic disorders. B-SNIP is a multisite consortium led by Carol Tamminga (University of Texas Southwestern Medical Center), Godfrey Pearlson (Yale University School of Medicine and the Institute of Living), John Sweeney (University of Illinois at Chicago), Matcheri Keshavan (Harvard Medical School), and Gunvant Thaker (Maryland Psychiatric Research Center). The value of the consortium is exemplified by three B-SNIP reports published in the *Journal,* each focusing on different potential endophenotypes related to psychosis.

The study by Hill et al. (8) in this issue focused on cognitive endophenotypes. The Brief Assessment of Cognition in Schizophrenia (BACS) was used to evaluate memory, working memory, motor speed, attention, executive functions, and verbal fluency. The study group comprised 293 individuals with schizophrenia and 316 of their first-degree relatives, 227 with psychotic bipolar disorder and 259 of their relatives, 165 with schizoaffective disorder and 197 of their relatives, and 295 healthy comparison individuals. Cognitive task performance was compromised in patients and their relatives. No diagnosis-related qualitative differences were found in the composite or domain-specific BACS scores. The degree of impairment was

influenced by psychopathology; more prominent affective symptoms and less persistent psychotic features were associated with less cognitive impairment. Cognitive impairment was associated with subthreshold psychoticism in relatives, as captured by the presence of cluster A personality disorders. Symptomatic expression and cognitive dysfunction were closely linked only in families with bipolar disorder. Cognitive dysfunction segregated with subthreshold psychoticism in the relatives of bipolar patients, while in the relatives of patients with schizophrenia it was present independent of symptoms.

The study by Skudlarski et al. (9) published in the August issue examined white matter integrity as indexed by fractional anisotropy in diffusion tensor imaging (DTI) data acquired from 109 individuals with schizophrenia and 95 of their relatives, 63 with psychotic bipolar disorder and 64 of their relatives, 35 with schizoaffective disorder and 43 of their relatives, and 104 healthy individuals. Patients with either schizophrenia or bipolar disorder showed overlapping white matter deficits in several regions, most consistently within the genu and body of the corpus callosum. Patients with schizophrenia and their relatives showed qualitatively similar patterns of white matter deficits. In contrast, there was little evidence of white matter involvement in relatives of patients with bipolar disorder. Also of interest, white matter abnormalities in the genu of the corpus callosum seemed to track clinical expression of psychoticism, as they were also present in all relatives with cluster A personality disorders regardless of family history.

The third study, by Ivleva et al. (10) and appearing in this issue, also used neuroimaging data, but the emphasis was on gray matter volume estimates obtained from structural magnetic resonance imaging (MRI) data from 146 individuals with schizophrenia and 134 of their relatives, 115 with psychotic bipolar disorder and 129 of their relatives, 90 with schizoaffective disorder and 106 of their relatives, and 200 healthy individuals. Widespread gray matter volume reductions in cortical and subcortical regions were observed. These segregated with psychoticism regardless of diagnostic status (including relatives with cluster A personality disorders). This dimensional approach was complemented by a more traditional diagnosis-based analysis, which showed incremental gray matter deficits among patients from bipolar disorder to schizophrenia, while both relatives' groups did not differ from healthy comparison participants.

The findings of these three studies underscore the importance of symptom dimensions, psychoticism in this case, over syndromal classifications in attempts to map the underlying biological mechanisms. They also provide strong evidence for considering subthreshold psychotic symptoms on the same pathophysiological continuum with syndromal psychotic presentations. This supports the inclusion of schizotypal disorder within the schizophrenia spectrum in DSM-5. Several inferences can be drawn regarding the relative strength and usefulness of the different endophenotypes presented. The study by Hill et al. (8) showed little differentiation between domain and composite BACS scores in terms of their usefulness as endophenotypes. This is consistent with existing literature suggesting that composite measures capture most of the variance accounted for by cognition on a range of outcomes (11, 12). This observation suggests that cognitive assessments, when used to yield endophenotypic measures, could be simplified and harmonized through the use of brief standardized tests. Additionally, cognitive profiling appeared to fit the classic definition of an endophenotype better than either neuroimaging measure. Cross-sectional DTI and structural MRI provide information about the static configuration of the brain. In contrast, cognitive test

performance is an expression of the dynamic configuration of neural networks engaged by the task. It is therefore likely that measures of functional and effective connectivity may prove more promising than other neuroimaging-derived endophenotypes.

Perhaps the most significant contribution of the B-SNIP consortium is that it provides a framework for the evaluation of the different endophenotypes proposed for psychoses. The number of traits that can potentially be tested is enormous, and this poses conceptual, logistical, and computational problems. The availability of uniform assessments based on standardized (and thus independently replicable) measures of cognition and brain structure in a substantial number of patients and relatives across a range of diagnoses is a unique strength of the B-SNIP consortium. This is because these data can be used to test, validate, and rank potential endophenotypes, thus rationalizing the endophenotypic space for future genetic studies. Additionally, the data available to the consortium are suitable for the combined investigation of quantitative neuroimaging, cognitive, and clinical measures with genetic risk factors. Such a development holds the promise of identifying multimodal markers for a biologically informed classification of psychotic disorders.

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