Commentary

Biological Psychiatry

Biotypes: Promise and Pitfalls

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This issue of *Biological Psychiatry* contains a thought-provoking article by Ivleva *et al.* (1) reporting on data generated as part of the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) project. The B-SNIP project is an important effort that was started to help identify the similarities and differences across individuals with a spectrum of psychotic disorders, including schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis. In addition, the B-SNIP project also recruited the first-degree relatives of these individuals to provide further information about what characteristics might be "endophenotypic" markers of risk for psychosis compared with characteristics present only among individuals with manifest illness. The B-SNIP project assessed a variety of measures in their sample that were motivated by previous research in psychosis, including in-depth clinical assessments, measures of a range of cognitive functions (including cognitive control), electrophysiological measures of sensorimotor reactivity, and both structural and functional neuroimaging (resting-state functional connectivity).

One of the key goals of the B-SNIP project was to directly assess the neurobiological validity of the traditional categorical distinctions between schizophrenia, schizoaffective disorder, and psychotic bipolar disorder. In addition, they wished to determine whether they might be able to identify other ways of understanding the structure or organization of psychopathology among such individuals with psychosis. Accordingly, in previous work (2), B-SNIP used cognitive and electrophysiological data along with clustering techniques to identify three subgroups of individuals, or Biotypes. These Biotypes showed evidence of within-group homogeneity in terms of cognitive control and electrophysiological function, but differences between groups. The three Biotypes showed graded impairment in cognitive control compared to healthy controls, with individuals in Biotype1 showing the most impairment, individuals in Biotype2 showing less impairment but still significantly worse than control subjects, and individuals in Biotype3 not differing from control subjects. In contrast, in terms of sensorimotor reactivity, individuals in Biotype1 and Biotype3 showed significant reductions compared to controls (with a larger difference in Biotype1 than Biotype3), while individuals in Biotype2 showed significantly enhanced reactivity. Most importantly, diagnoses were not evenly distributed across Biotypes, because all three diagnoses were clearly represented across all three Biotypes, although there were more individuals with schizophrenia in Biotype1 and more individuals with bipolar disorder in Biotype3. In addition, Ivleva *et al.* also found that the level of impairment in the relatives of the probands also sorted more strongly as a function of Biotype than it did by diagnosis.

In the original paper reporting on the creation and validation of the Biotypes (2), Clementz *et al.* used analyses of gray matter volume to provide evidence about the validation of the Biotype distinctions, showing differences in gray matter volume that appeared to be more dissociable as a function of Biotype than as a function of DSM-IV diagnosis. Ivleva *et al.* (1) report on analyses of gray matter density (GMD) in the same participants using a similar analytic approach as their first report, with similar results. In the probands with manifest illness, they found that overall GMD was more strongly predicted by Biotype category than by diagnostic category, using regression analyses that directly pitted the two types of classification approaches against each other. In other words, when both Biotype and DSM-IV-TR diagnosis were in the same regression model, Biotype predicted overall GMD reduction and DSM-IV-TR diagnosis did not. The Biotypes showed a graded effect of GMD. Individuals in Biotype1, the Biotype with the most impaired cognitive control and reduced sensorimotor reactivity, showed the greatest reduction. Individuals in Biotype3, those with no significant impairment in cognition and a relatively minor reduction in sensorimotor reactivity, showed the least reduction (though still significantly different than control subjects). This same pattern was echoed in many of the regional analyses, with graded reductions in GMD in frontal, cingulate, insular, temporal, parietal, and occipital regions. Interestingly, individuals with Biotype3 did not differ from controls in subcortical, thalamic, or cerebellar GMD, while individuals in both Biotype1 and Biotype2 did, with more similar effect sizes to each other than in other brain regions. Intriguingly, in the relatives, both Biotype and diagnosis accounted for independent variance, a result that was different from the findings in the probands.

The approach taken by the B-SNIP project in trying to understand and validate a classification of individuals with psychotic disorders is an important step forward in attempting to define a more neurobiologically based way to understand the structure of psychosis. As noted by the authors, this goal is consistent with a Research Domain Criteria initiative approach. However, a key question raised by these results and other attempts at novel classification systems is the degree to which the premise that there are categories shapes the resulting outcomes. The B-SNIP project used a clustering approach to identify Biotypes that will identify clusters even if the underlying structure of the data is at least in part dimensional. In addition, the B-SNIP project did not explicitly test whether a categorical representation better fit the data than a dimensional or even a hybrid categorical–dimensional approach. In part, they may not have performed such an analysis because the Biotypes did not show the same graded effect across both the cognitive control and sensorimotor dimensions. More specifically, individuals in Biotype2 showed an impairment in cognitive control that was intermediate between individuals in Biotype1 and Biotype3. In contrast,

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individuals in Biotype2 showed enhanced sensorimotor reactivity compared to control subjects, while both Biotype1 and Biotype3 showed reduced sensorimotor reactivity. Thus one could argue that individuals in Biotype2 showed a qualitatively different pattern of impairments across the two dimensions (e.g., not intermediate on both) compared with individuals in Biotype1 and Biotype3, rather than only a quantitative difference with the same pattern on both dimensions. However, this configuration does not rule out the possibility that there are two dimensions: cognitive control impairment and sensorimotor reactivity alterations. In fact, the structural data analyses presented by both Clementz *et al.* and Ivleva *et al.* seem consistent with a dimension of severity across Biotypes (Biotype1 $<$ Biotype2 $<$ Biotype3), with little evidence for a qualitatively distinct pattern among either the Biotype2 probands or their relatives compared with the other Biotypes. Questions about dimensional versus categorical representations of psychopathology are especially salient given the growing body of data providing support for core dimensions of psychopathology that do not seem to follow categorical boundaries (3,4), including dimensions that capture thought disorder (5,6).

There are statistical methods that allow one to explicitly compare assumptions about categorical versus continuous representations of the underlying data. For example, there are hybrid approaches that allow a researcher to test for both dimensional facets (e.g., cognitive control impairments and/or sensorimotor alterations) and categories or kinds (e.g., Biotypes) in the same model (7–10). Critically, in such models, continuous and categorical latent structures can be directly compared with each other, and the models can help determine whether the underlying data reflect dimensional, categorical, or hybrid latent constructs (7–10). Alternatively (or in addition), one could use a variation of the regression approach used by Ivleva *et al.*, and whether the density data are better captured by one or more dimensions (either or both cognitive control or sensorimotor reactivity) and whether the use of additional categorical predictors—either Biotype- or DSM-based—accounts for any additional variance over and above the dimension(s).

The results originally presented by Clements *et al.* (2) on gray matter volume, and replicated in the same sample in Ivleva *et al.* (1) with GMD, are an important step in identifying a potential alternative structure to the organization of psychotic disorders. Such efforts are a critical endeavor, because the field needs approaches that provide enhancements to pathophysiological validity and hopefully also clinical validity in terms of more effective treatment and or prevention approach. However, it is also necessary that such efforts explicitly test assumptions about the structure of psychopathology (e.g., categorical, dimensional, and hybrid) by comparing alternative models. By directly pitting different model types against each other across many levels of analysis, we will be able to move the field forward in terms of developing robust, replicable, and hopefully practically useful novel organizations of the structure of psychopathology.

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