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# Using Brain-Based Phenotyping to Improve Discovery in Psychiatry

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**Many lines of evidence** from different laboratories are now joining the same chorus: that conventional psychiatric diagnoses of serious mental illness (SMI), when tested, do not show a common biology. The article by Wolfers et al[1] notes that SMI diagnoses do not have strong biomarkers similar to those that are already increasingly valued in the rest of medicine and that could help define disease groups, select treatments, and mark clinical outcomes. The authors used innovative regional brain structure mapping on an individual basis in people with schizophrenia and bipolar disorder and developed voxel-by-voxel measures of individual brain structure deviations from a normative model. They calculated group-level volume values for brain regions in a usual fashion, and then they derived deviations from the normative model, voxelwise, for each participant and each diagnostic group. Their calculations of individualized voxel-wise maps of deviance from the normative model allow the comparison of this individual deviance within and across diagnostic groups.

First, Wolfers et al[1] report typical group-level outcomes, which show the usual kinds of changes reported in SMI: gray matter reductions in frontal, temporal, and cerebellar regions in people with schizophrenia and gray matter reductions in the frontal cortex in individuals with bipolar disorder. However, in a section that is to our knowledge unique to their analysis, the authors also demonstrated localizations of extreme individual deviations by voxel and by group. This study shows that, despite the mean disease-associated deviations, there are many individual volumetric deviations unmasked by these analyses that are not consistent within or across conventional diagnoses. The authors conclude that, based on this extreme heterogeneity, the *DSM*-defined categories of SMI are not useful for clustering biologically similar disorders. The authors suggest applying clustering algorithms to these deviations to find subtypes of disorders based on biology, a suggestion they have left to future researchers. The authors report being disappointed by the insufficiency of conventional diagnoses for disease characterization. This study is a clear portrayal of extreme neurobiological heterogeneity across individuals within conventional SMI diagnoses.

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**Additional Contributions:** We recognize the contribution of all Bipolar-Schizophrenia Network for Intermediate Phenotypes collaborators in the development of these concepts and their application to psychotic disorders, including Brett Clementz, PhD, Department of Psychology, University of Georgia, Matcheri Keshavan, MD, Harvard Medical School and Beth Israel Deaconess Medical Center, Godfrey Pearlson, MBBS, MA, Departments of Psychiatry and Neuroscience, Yale University School of Medicine, and Elliot Gershon, MD, Department of Psychiatry and Behavioral Neuroscience, University of Chicago. Their contributions to the Bipolar-Schizophrenia Network for Intermediate Phenotypes were supported by grants from the National Institute of Mental Health.

We have all seen this before, albeit not with either the localized individual analyses nor with the individual estimates of brain volume deviation calculated this precisely or individually. The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) Consortium has used a broad biomarker battery and has noted extensive heterogeneity across all biomarkers. But even such a broad approach has been insufficient to find even 1 informative biomarker to specify conventional psychosis diagnoses.[2] Similarly to the suggestion of Wolfers et al,[1] the B-SNIP Consortium went on to apply clustering algorithms to the data to identify neurobiologically driven disease subtypes. The B-SNIP Consortium has previously reported these subtype clusters, called *Biotypes*, and shown that in these novel groups biological markers fall not on conventional diagnoses but rather on the Biotypes. Yet, asking the obvious, we question whether these Biotype structures represent disease groups as opposed to mere brain biomarker clusters. We would like to think that brain biomarker homogeneity in a cluster of individuals with SMI could be founded on a common, explanatory, targetable pathophysiology. In this context, a question exists: what evidence would we need about biologically based subgroups to accept them as disease subtypes, or even different brain disorders, and advocate for their clinically applicable use?

Certainly, defining disease groups based on clinical signs and symptoms is an approach that has failed throughout medicine. No one uses the diagnosis of a condition called *dropsy* anymore, now that many diseases characterized by morbid edema (the phenomenon to which dropsy once referred) have emerged. Indeed, treatments for the underlying pathophysiology generating edema now usually forestall the diagnosis of dropsy. Conversely, taking a widely accepted genetic disorder as a prototypical biological disease, we can see that the clinical phenomenology within this kind of disorder is highly varied. An example would be the 22q11 deletion syndrome, where the psychiatric phenotype includes psychosis, anxiety, depression, and degrees of cognitive dysfunction, just at the behavioral level. Nonetheless, psychiatry has spent more than a century and considerable guild effort to design disease entities based on clinical presentation and course, with the need now to revise these to gain biological disease definitions. What kind of evidence from practical experiments is necessary to identify clinical relevance for such disease entities?

To frame the question: we start with a biomarker battery to complexly classify a dimension such as psychosis with biomarkers selected to reflect important brain characteristics in the disorder, as speculated by Wolfers et al.[1] In sum, we create clusters of individuals with common biological indicators rather than a common set of symptom manifestations. These new entities could be like other biological disease examples in medicine in which multiple biomarkers collectively define a disease entity (eg, diabetes). The operant question of this kind of a novel subtype, however biologically homogeneous, is whether it is a disease category and tied to a common pathophysiology. How to answer this question? First, one could seek a characteristic genetic fingerprint, either genetic or epigenetic. This kind of a finding would implicate a causal molecular system, altered in the brain, that could generate symptoms of the disorder. Moreover, it would allow the experimental demonstration of whether or not a group defined by this genetic fingerprint would demonstrate the defining biomarker profile. Having a genetic definition for a SMI disorder would be an aspirational goal.

A disorder clustered by biological features might also show a distinctive pharmacological profile. Some dimensional disorders, such as congestive heart failure, are clearly biologically heterogeneous, while they respond to a common treatment (eg, digitalis). It would be most useful to generate more specific disease constructs that have a unique pathophysiology and can be targeted to develop specific novel therapies. In the case of psychotic disorders, clinical guidelines would suggest that some patients would benefit not only from antipsychotic drugs, but also mood stabilizers, neuromodulation, and even antianxiety drugs. It would be a leap in clinical care to be able to establish this clinical response a priori from a biomarker profile in early treatment, rather than to test out treatments by trial and error.

As case-specific neuronal cultures are developed, transformed from an individual's own cell samples, cellular characteristics (whether deviations in function or structure) can theoretically help inform the individual biology of the person. Certainly, we need to explore whether the pharmacological response of case-specific neuronal populations will prognosticate a patient's pharmacological responses. Early studies are only teasingly promising, and there is a long way to go to demonstrate their usefulness, but the promise of individualized medicine is so compelling and clinically indicated, especially in psychiatry, that study in this domain is also indicated. It could be that some aspects of brain-based biomarkers will overlap individual cellular characteristics, and this will allow us to simplify the individual biological profiling process. Individualized medicine is the overall goal that psychiatry needs to pursue.

The task that psychiatry researchers have today is to make SMI and other disorders into diagnoses with known biological bases that can be characterized by broad array of biomarkers and for which treatments can be determined by biomarker characteristics. It will be a revolution in our ability to understand and treat complex brain disorders. This is not an idle exercise, but one which will establish molecular disease targets and rational treatments for intractable psychiatric disorders. It will give us diagnoses that we can rationally treat. It is the advances in basic neurobiology and in our understanding of disease that makes these expectations, although understandably challenging, within the realm of possibility.

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