Schizophrenia Bulletin vol. 46 no. 6 pp. 1337–1338, 2020
doi:10.1093/schbul/sbaa122
Advance Access publication 9 September 2020

INVITED EDITORIAL

Embracing the Complexity of Heterogeneity in Schizophrenia: A New Perspective From Latent Clinical-Anatomical Dimensions

Caterina Gratton* and Vijay A. Mittal

Department of Psychology, Northwestern University, Evanston, IL

*To whom correspondence should be addressed; Swift Hall 102, 2029 Sheridan Rd., Evanston, IL 60208, US; tel: 847-467-3480; e-mail: cgratton@northwestern.edu

Support continues to grow for the idea that schizophrenia, as we know it, is not a discrete illness but rather a generalized symptom of brain dysfunction. Distinct groups of individuals, sharing some common symptoms, may be affected by different underlying pathophysiology. This idea is driven by a number of factors, including clinical observations suggesting a wide variation in patient phenomenology, course, demographics, and prognosis (eg, deficit syndrome[1]). Further support comes from a series of new studies that have adopted unsupervised machine learning approaches and generated compelling evidence to suggest biological and clinically relevant discrete biotypes[2] as well as clinical high-risk (CHR) subtypes.[3] Of course, as noted above, there are common symptom phenotypes across schizophrenia, irrespective of any subgroups, and there is a reasonable argument to be made that these are central to diagnostic systems and in communicating the clinical experience. A range of brain abnormalities is also widely observed in psychosis, and the extent to which these map on to specific symptoms or functions, or give rise to broader constellations of clinical features, remains an open question. Clouding this picture, findings may also relate to compensatory mechanisms or to any number of confounds that separate schizophrenia from neurotypical controls. It is presently unclear whether particular brain abnormalities contribute to particular subtypes, or reflect or contribute to dimensions that cut across the schizophrenia spectrum. The truth is that this is all very complicated and that these possibilities are not mutually exclusive; in all likelihood each is probably correct and revealing. But how then can we embrace this complexity and move forward?

As a field, we have continued to be limited by our available tools and approaches. For example, while biotyping has many benefits, it forces discrete categories at the expense of any shared symptoms and components (mechanisms) that run dimensionally across subgroups. Essentially, while this method holds enormous potential for promoting applications such as precision medicine, it also necessitates that we lose an important part of the bigger picture. An approach (or series of complementary strategies) that embraces the full complexity of schizophrenia must facilitate subtyping but also allow for the presence of continuous variables (latent or otherwise). In this context, the present work by Matthias Kirschner and colleagues (in this issue) holds tremendous promise as it represents one of the first major efforts to test the feasibility and clinical utility of a clinical-anatomical dimension approach.

The authors began by examining the relationship between clinical and brain measures in a large sample of 133 individuals with schizophrenia and 113 neurotypical controls from a publicly available dataset. Anatomical variation was measured with deformation-based morphometry (DBM), a technique that quantifies the deviation of gray matter locations relative to a normative template, interpreted as a signature of tissue loss. These anatomical deviations were then related (via partial least squares) to behavioral measures, including clinical symptoms (positive, negative, and extrapyramidal motor symptoms), cognitive functioning, and demographic features. Partial least squares is able to identify features that covary across measurements types[4] rather than relying only on either behavioral or anatomical measures to identify relevant dimensions, making it a powerful method for uncovering brain-behavior relationships. Using this technique, the authors found evidence for 3 latent dimensions that explained 55% of the variance in the original dataset.

Matthias and colleagues then confirmed their findings in an independent dataset from the Douglas Institute (108 schizophrenia, 69 neurotypical controls). This is a critical step (in order for findings to be clinically useful, they must translate to other scanners and individuals), but is all too rarely conducted in studies searching for neurobiological markers.[5] The first and strongest latent dimension replicated across datasets and became the major focus of study. This dimension highlighted a connection between

cognitive impairments, negative symptom severity, and anatomical abnormalities in the default mode and visual networks. This suggests that cognitive/negative symptoms in association with these anatomical features may cut a major swath in explaining heterogeneity in schizophrenia. Interestingly, a mediation analysis also suggested that the anatomical deviations of this dimension mediated the connection between socioeconomic status and clinical symptoms. Thus, these anatomical features may help explain the well-documented relationship between socioeconomic status and poor outcomes in schizophrenia.[6]

This work is an important early step in moving the field towards managing the complexity of heterogeneity across serious mental illnesses. The integrative analysis allowed for a large number of clinical, cognitive, and anatomical features to be considered in a single model, and then parsed down to a smaller set of informative and potentially useful latent dimensions. The findings suggest that this approach is an invaluable tool for examining continuous latent variables, allowing researchers to evaluate cross-cutting dimensions, while also leaving room for the possibility of subtypes. For example, the authors suggested that the replicated latent negative-cognitive dimension might help to draw ties across 2 well-documented biotypes.[2] What is particularly exciting about this work is the foundation it lays for what comes next. We would like to see mainstream adoption of the out-of-sample prediction used here. Notably, only one dimension replicated in the external dataset, and in our minds, this restricted replication serves as an invaluable cautionary note for studies adopting similar approaches without external validation. Further, we believe that incorporating the general approach in larger heterogeneous datasets (including additional clinical as well motor and thought disorder variables; incorporating other imaging domains including resting-state connectivity; including additional disorders) will expand our understanding of clinical-neural relationships that can cross classical domain divisions. In addition, our hope is the field continues to experiment with existing methods (eg, Meehl's cut coherent kinetics)[7] and to develop new approaches that free the nature of outcomes from a given statistical approach. In addition, longitudinal studies will be integral for determining causality, and relatedly, applying these findings to treatment decisions. Mapping latent clinical-anatomical dimensions in the psychosis risk period has tremendous promise for complementing subtyping as well as for better highlighting mechanisms, improving identification, and informing novel interventions. Excitingly, examining many of these questions, including through the lens of development, is well within reach given the impressive growth in publically available data (eg, Adolescent Brain and Cognitive Development and Human Connectome-Development studies).

Acknowledgments

The authors report no conflicts of interest related to this manuscript.

References

1. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT Jr. A separate disease within the syndrome of schizophrenia. *Arch Gen Psychiatry.* 2001;58(2):165–171.
2. Clementz BA, Trotti RL, Pearlson GD, et al. Testing psychosis phenotypes from bipolar-schizophrenia network for intermediate phenotypes for clinical application: biotype characteristics and targets. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2020;5(8):808–818.
3. Gupta T, Cowan H, Strauss G, Walker EF, Mittal VA. Deconstructing negative symptoms in individuals at clinical high-risk for psychosis: evidence for volitional and diminished emotionality subgroups that predict clinical presentation and functional outcome. *Schizophr Bull.* In press.
4. McIntosh AR, Mišić B. Multivariate statistical analyses for neuroimaging data. *Annu Rev Psychol.* 2013;64:499–525.
5. Poldrack RA, Huckins G, Varoquaux G. Establishment of best practices for evidence for prediction: a review. *JAMA Psychiatry.* 2020;77(5):534–540.
6. Werner S, Malaspina D, Rabinowitz J. Socioeconomic status at birth is associated with risk of schizophrenia: population-based multilevel study. *Schizophr Bull.* 2007;33(6):1373–1378.
7. Meehl PE. 1995. Bootstraps taxometrics: solving the classification problem in psychopathology. *Am Psychol.* 50(4):266.