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Parsing Psychiatric Heterogeneity Through Common and Unique Circuit-Level Deficits

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It is increasingly recognized that progress in psychiatry is hindered by the heterogeneity of clinical diagnoses as codified by the DSM. Progress in other fields of medicine has in large part been predicated upon parsing clinical phenomena that appear similar into biologically homogeneous subtypes that align with prognosis and treatment response. At present, psychiatric diagnostic entities remain defined by clinical signs and symptoms and are likely to be composed of multiple distinct circuit- and system-level biological abnormalities. Similarly, it is recognized that there may be common circuit-level deficits (e.g., reward system abnormalities) that are present in many disorders. Identifying common mechanisms across disorders and parsing heterogeneity within clinical diagnoses has the potential to accelerate efforts in precision medicine where diagnosis, prognosis, and therapeutics can be tailored to the individual.

This special issue of Biological Psychiatry provides a synthesis of approaches to defining common circuit-level abnormalities and dissecting heterogeneity in psychopathology. Specifically, this issue includes articles that examine new methods for understanding heterogeneity, review recent evidence of heterogeneous patterns of evolution associated with mental illness across the lifespan, and describe advances in understanding heterogeneity within specific disorders. Taken together, this issue assembles leaders in the field with a broad array of perspectives to provide a timely and rigorous evaluation of this important topic.

Methodological Considerations in Delineating Heterogeneity

Methodological advances provide new abilities to integrate high-dimensional data and parse heterogeneity in psychiatry; in this special issue, three articles review several particularly promising approaches. First, the review by Feczko and Fair (1) focuses on strategies for

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tackling two key problems: diagnostic comorbidity and biological heterogeneity. These two problems are distinct but highly related, as patients frequently carry more than one diagnosis, but each diagnosis likely encompasses many distinct biological mechanisms. The authors highlight promising approaches for each, including emerging machine learning methods. Next, Bornovalova et al. (2) focus specifically on bifactor models, which allow one to model both common and unique dimensions of psychopathology. Importantly, this article provides a balanced appraisal of the strengths and limits of a method that shows great promise. Finally, the review by Gratton et al. (3) introduces recently developed "precision functional mapping" techniques, which allow large-scale functional neuroanatomy to be delineated in individuals using functional magnetic resonance imaging. This emerging technique is particularly exciting because it provides a way to move beyond a group average representation of the brain and potentially understand heterogeneity through individual variability of brain organization.

Neurobiological Heterogeneity Across the Lifespan

Many psychiatric illnesses are increasingly understood as disorders of brain development. Within this paradigm, clinical symptoms are a relatively late manifestation of abnormal developmental processes. As such, understanding heterogeneity of both normal and abnormal brain maturation across the lifespan is a critical task. Four reviews in this special issue delve into different facets of this problem. First, Thomason (4) focuses on noninvasive techniques for studying heterogeneous development in utero. Accumulating evidence from both animals and humans suggests that this period of peak plasticity is particularly important for psychiatric illnesses. In her review, Thomason (4) outlines the many significant methodological challenges for conducting such work, highlights recent progress, and proposes important next steps. Second, Kaczkurkin et al. (5) examine another critical period of development—adolescence. This review emphasizes the promise of how new data-driven methods may help identify both common and dissociable developmental deficits in youths with psychopathology. Third, Becht and Mills (6) build upon this discussion by providing an overview highlighting the importance of developmental trajectories. They emphasize that many of the constructs we use to examine longitudinal development assume that development is homogeneous, and therefore tools that relax this assumption are critical to studying child mental health and brain development. Fourth, Habes et al. (7) examine the other end of the lifespan, focusing on heterogeneity in brain aging. Specifically, they describe emerging evidence that suggests the presence of nested dementia subtypes and also highlight methodological obstacles including the need for harmonization of measurement and analysis.

Heterogeneity Within Psychiatric Syndromes

Finally, four articles in this special issue provide an overview of recent advances for understanding heterogeneity within specific clinical syndromes. Each of these articles starts from the premise that each major diagnostic category encompasses multiple disparate circuit-level deficits. As such, a crucial research task is to identify biologically heterogeneous clusters of patients (e.g., "biotypes") who have similar clinical presentations. First, Lynch et al. (8) provide an overview and discussion of heterogeneity in depressive

disorders. In particular, this article highlights the exciting potential of prognostic biomarkers for informing treatment decisions in depression. Second, Voineskos et al. (9) examine recent progress in using data-driven techniques for parsing heterogeneity in psychosis. Recent studies incorporate a wealth of clinical, cognitive, genomic, and imaging data and are increasingly being linked to clinical trials. Third, Karalunas and Nigg (10) focus on person-centered computational approaches for identifying attention-deficit/hyperactivity disorder subtypes using cognitive, emotion-related, and other features. Notably, the authors suggest that these features may be integrated to create personalized risk scores for use in clinical practice. Finally, Hong et al. (11) give an overview of neurosubtypes in autism spectrum disorder, which is the focus of rapidly accelerating research. These reviews demonstrate the potential utility of subtyping specific diagnostic categories using data-driven approaches.

Conclusions

Taken together, the reviews in this special issue emphasize that a deeper understanding of biological heterogeneity in psychiatric syndromes may be necessary for advances in diagnostics, prognostics, and therapeutics. Several elements may be particularly important for progress. For example, even when case-control designs are used, investigators and sponsors should be cognizant that samples do not represent homogeneous entities but are instead drawn from populations that exhibit a large array of heterogeneous characteristics across multiple dimensions. The challenge for the field is to 1) identify and characterize this population variance and 2) link this variance to clinically relevant outcomes. On this front, the work reviewed by articles in this issue provides some optimism. Importantly, analytic methods for parsing heterogeneity are rapidly evolving. While the approaches reviewed in this issue—bifactor models, semisupervised learning, and multiview learning—are exciting and have provided new insights with regard to heterogeneity, they are unlikely to be sufficient to fully explain the complex structure that underlies typical and atypical populations.

Finally, progress is predicated upon large, well-annotated training datasets that are publicly available. While large data resources are increasingly present, those that include clinically meaningful outcomes—such as longitudinal prognosis or treatment response—remain scarce. Some large efforts currently in progress, such as the Adolescent Brain and Cognitive Development study, could change this landscape considerably. However, such research programs will likely need to be complemented by efforts within and across health systems, which remain nascent at present. Overall, the articles in this special issue highlight exciting recent advances, gaps in our current knowledge, and critical next steps for understanding heterogeneous psychiatric syndromes according to their underlying biology.

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