In This Issue

Volume 93, Number 1, January 1, 2023

A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Review: Machine Learning in Psychiatry

The primary focus of machine learning in psychiatry has been the development and optimization of diagnostic classifiers. In this review, **Chen *et al.*** (pages 18–28) summarize the developing, complementary perspective of leveraging machine learning approaches to gain insights into the pathophysiology and nosology of mental illness. The authors highlight key areas and approaches, including those that may advance insights into the neurobiological hallmarks of individual disorders, relationships among diagnostic groups, and potential heterogeneities within them.

Genetic Variation and Lithium

Genetic background influences clinical response to lithium treatment in bipolar disorder. Lithium exposure influences neural progenitor cell proliferation. Here, **Wolter *et al.*** (pages 8–17) discovered genetic variation associated with lithium-induced proliferation in a population of cultured primary human neural progenitor cells. The authors also identified a gene, *GNL3*, that mediates differences in the proliferative response to lithium. These results demonstrate the potential of cell culture–based genome-wide association study (GWAS) approaches to identify context-specific pharmacogenomic effects.

Correcting Bias in Heritability Estimates

It is standard practice to report the single nucleotide polymorphism (SNP)-based heritability for a GWAS of human complex traits. For case-control GWASs, these SNP-based heritability estimates are converted to the liability scale to produce an estimate that is unbiased by ascertainment and that accounts for the theoretical distribution of continuous risk in the population. Here, **Grotzinger *et al.*** (pages 29–36) demonstrate that the standard approach for performing the liability conversion produces a downward bias in heritability estimates, and they describe a simple solution that can be applied to produce more accurate estimates.

Genetic Effects in ADHD Risk

Attention-deficit/hyperactivity disorder (ADHD) is heritable, but the relative influence of direct genetic risk factors that are transmitted from parents to offspring and of nontransmitted (indirect) factors on offspring ADHD is unclear. Analyzing polygenic risk scores, **Martin *et al.*** (pages 37–44) found evidence of directly transmitted polygenic liability for ADHD and cognitive ability from parents to offspring with ADHD. The authors also found evidence that nontransmitted parental risk alleles do not contribute indirectly to offspring ADHD risk. These data provide novel insight into the direct versus indirect genetic effects related to ADHD risk.

Polygenicity and Brain Connectivity

The effects of psychiatric genomic risk factors on brain connectivity are not clear. **Moreau *et al.*** (pages 45–58) compared the effects of copy number variants and polygenic risk scores on functional brain connectivity across multiple disorders, traits, and conditions. The authors found that genetic risks affect functional brain connectivity, but with large differences in effect sizes. Effect sizes decreased for genomic variants with increasing levels of multigenicity. These data suggest that genetic heterogeneity and polygenicity may lead to diverse brain connectivity patterns underlying psychiatric conditions.

GWAS of Executive Functioning

Executive functions (EFs) are cognitive control processes involved in goal-directed behaviors and are associated with psychiatric disorders. Using data from a large biobank, **Hatoum *et al.*** (pages 59–70) performed a GWAS on a common EF factor score derived from multiple cognitive tasks. The authors found that the common EF factor is associated with GABA-mediated processes. Further, common EF and intelligence showed genetic correlation, but were differentially associated with psychiatric disorders. These results suggest that a factor of EF may be relevant for understanding the genetic variance in psychiatric disorders.

FXS Neurons in the Mouse Brain

Fragile X syndrome (FXS) is the most commonly inherited form of developmental and intellectual disability. Here, **Krzisch *et al.*** (pages 71–81) transplanted neural precursor cells derived from FXS patients into the mouse brain to mimic human neuron development. The authors report that the transplanted FXS neurons showed accelerated maturation after an initial delay, providing new insights into the in vivo development of FXS neurons.

Protein Targets for Psychiatric Disorders

Circulating proteins are potential candidates for targeted drug development because they are relatively easy to measure and modulate and also play important roles in signaling. Using data from proteomic and GWA studies, **Lu *et al.*** (pages 82–91) estimated associations between circulating protein abundances and risk for 10 psychiatric disorders. The authors report several protein-disease associations, including proteins related to risk for anorexia nervosa, bipolar disorder, and schizophrenia. These data identified proteins that may be viable candidates for therapeutic development.

Sensory Over-responsivity in Childhood

Children who have strong negative responses to everyday sensory stimuli such as clothing tags are more likely to experience psychiatric illness. Studying a large community sample of early adolescents, **Schwarzlose *et al.*** (pages 92–101) report that sensory over-responsivity is associated with greater psychiatric symptom burden, predicted later development of psychiatric conditions, and is associated with functional connectivity differences in brain networks that support tactile processing. These findings implicate sensory over-responsivity as a sensory-based risk factor for psychiatric illness.

ISSN: 0006-3223