In This Issue

Volume 81, Number 6, March 15, 2017

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

Review: Functional Genomic Annotations

Functional genomic annotations, through their regulation of gene function, contribute to particular psychiatric and neurological phenotypes. However, the ability to study and utilize such information has been limited by the difficulty of accessing the relevant brain tissue. This review by **Gagliano** (pages 478–483) serves as a resource to investigators by summarizing the availability and accessibility of brain epigenetic and functional genomic data, which include the ENCODE, Roadmap Epigenomics, PsychENCODE, and GTEx projects. The use of such brain data is key to gaining further insight into the epigenetic factors that contribute to psychiatric and other brain disorders.

Polygenic Risk Score Prediction in Psychosis

Polygenic risk scores (PRSs) produce a summary estimate of an individual's total genetic burden for complex disorders based on all the common genetic variants. They have been shown to improve the performance of predictive risk models aimed at identifying individuals at elevated risk for a disorder. Here, in a clinical sample of first-episode psychosis patients, **Vassos *et al.*** (pages 470–477) show that PRSs can effectively discriminate between case-control status in individuals of European ancestry, but not in those of African ancestry. In addition, PRSs distinguished case subjects who developed schizophrenia from those who did not, but not at a level high enough for clinical utility.

Data-Driven Psychiatric Phenotypes

Current diagnostic categories are unable to capture behavioral and biological variation, and such limitations hinder the further characterization of brain-behavior relationships. Assessing a community-based sample, **Van Dam *et al.*** (pages 484–494) used data-driven clustering to identify phenotypic groups, which were best differentiated by behavioral/lifestyle variables although they also exhibited meaningful differences in psychopathology. Psychiatric diagnoses were a poor indicator of group membership. Functional brain connectivity varied by group membership, with differences in somatomotor, thalamic, basal ganglia, and limbic networks at the highest grouping level. These findings support the value of using data-driven phenotypic categorization to explore the neurobiology of mental illness.

Genetics, Imaging, and Behavior in Schizophrenia

Schizophrenia is extensively investigated in the fields of genetics and neuroimaging, but the relationship between schizophrenia risk genes and the consistent findings of white matter disconnectivity in patients remains unclear. In this cross-modal study, **Romme *et al.*** (pages 495–502) combined cortical gene expression data with brain connectivity data in patients with schizophrenia. Their findings show that the expression patterns of genes related to schizophrenia correlate with the disease-related pattern of brain disconnectivity, providing insight into the underlying pathogenetic mechanisms of macroscale brain connectome changes in schizophrenia.

Biomarkers have yet to be identified for the prodromal symptoms that often precede the diagnosis of schizophrenia. Using multimodal imaging methods, **Kaneko *et al.*** (pages 503–513) identified two potential brain biomarkers of early schizophrenia in a rat model: hypofrontality and posterior hyperactivity. In the behavioral tests, hypofrontality was associated with altered decision making and increased sensitivity to reward, which may reflect the vulnerability of prodromal patients to substance abuse. These biomarkers have translatable potential to contribute to the early diagnosis of schizophrenia.

NMDA Receptor Model of Schizophrenia: Predictive Coding and Altered Metabolites

N-methyl-D-aspartate receptor (NMDAR) hypofunction has been implicated in the pathophysiology of schizophrenia and theorized to underlie predictive coding deficits in the disorder. Analyzing auditory event-related brain potentials in a randomized, placebo-controlled, crossover study design, **Kort *et al.*** (pages 514–524) demonstrate that transient NMDAR blockade via administration of ketamine disrupts predictive coding during vocalization in healthy volunteers. In a separate case-control study, they show that this disruption mimics the pattern of deficits observed in patients with schizophrenia. This work provides additional evidence implicating reduced NMDAR functioning in the pathophysiology of schizophrenia.

Using 7T magnetic resonance spectroscopy in schizophrenia patients, unaffected siblings of patients, and unaffected nonrelatives, **Thakkar *et al.*** (pages 525–535) measured brain concentrations of metabolites implicated in schizophrenia. Consistent with prior work, they found reduced cortical gamma-aminobutyric acid (GABA) and glutamate in patients. Siblings also showed reduced glutamate but unaltered GABA concentrations. These findings shed light on illness mechanisms and suggest that while altered glutamatergic functioning is related to illness vulnerability, altered GABA is related to disease state.

Somatostatin in Schizophrenia and Bipolar Disorder

Circadian dysfunction is associated with bipolar disorder, but how this relates to neural circuits regulating anxiety remains unclear. Examining postmortem amygdala tissue, **Pantazopoulos *et al.*** (pages 536–547) report that somatostatin (SST), involved in the regulation of anxiety and stress, is decreased in subjects

ISSN: 0006-3223

with bipolar disorder or schizophrenia. The authors also studied the relationship between time of death and SST levels by constructing a daily pattern of SST levels across individuals. They found a circadian rhythm in the number of neurons staining positive for SST in tissue from people who did not have bipolar disorder, which was altered in tissue from subjects with bipolar disorder. In particular, individuals with bipolar disorder showed a marked decrease in neurons staining positive for SST in the morning. These findings suggest that dysregulation of circadian SST levels in the amygdala may contribute to the morning peaks of anxiety often reported in individuals with bipolar disorder.