In This Issue

Volume 85, Number 7, April 1, 2019

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

Early Mechanisms in Autism

Many symptoms of autism spectrum disorder (ASD), including social deficits and repetitive behaviors, are present early in life, but little is known about early pathophysiological mechanisms. **Chung *et al.*** (pages 534–543) demonstrate that young preweaned mice lacking SHANK2, an excitatory postsynaptic protein, display abnormally enhanced *N*-methyl-D-aspartate receptor (NMDAR) function. This phenotype rapidly shifts to suppressed NMDAR function in juvenile and adult mice. In addition, early correction of the NMDAR hyperfunction showed long-lasting effects by preventing NMDAR hypofunction and social deficits at later developmental stages. These results highlight the importance of early pathophysiological mechanisms and the potential of early intervention in ASD.

Genetic Approaches to Schizophrenia Risk and Pathogenesis

Many small genetic effects cumulatively contribute to neurodevelopmental disorders such as schizophrenia and ASD, but translating that complex genetic knowledge into the study of the underlying biological mechanisms has remained a significant challenge. Here, **Ori *et al.*** (pages 544–553) integrated information from large-scale genetic studies with in vitro stem cell–based gene expression profiles of human neuronal differentiation. They found an association between polygenic disease risk and upregulated genes during differentiation in schizophrenia, with strong aggregation in a gene cluster linked to synaptic function. These data demonstrate that the polygenic architecture of schizophrenia translates to biologically relevant pathways that can be modeled in an experimental system.

Sequencing studies have started to provide insights into the genetic architecture and etiology of schizophrenia, a highly polygenic disorder. **Rees *et al.*** (pages 554–562) sequenced the coding regions of 187 schizophrenia candidate genes in a large case-control sample. They provide evidence that rare variants in ARC (activity-regulated cytoskeleton-associated protein) and NMDAR complexes contribute to the risk for schizophrenia, consistent with prior findings. In addition, they found evidence implicating multiple voltage-gated sodium channels in schizophrenia pathogenesis.

15q11.2 BP1-BP2 Variation and White Matter

Copy number variations at 15q11.2 BP1-BP2, a region that includes the CYFIP1 protein, have been associated with learning and motor delays, ASD, and schizophrenia. Using diffusion tensor imaging data, **Silva *et al.*** (pages 563–572) found a reciprocal effect of 15q11.2 BP1-BP2 on white matter microstructure in healthy individuals, with the deletion group showing widespread increased fractional anisotropy compared with the duplication group. Further, findings in the deletion group showed overlap with prior findings in patients with fragile X syndrome, suggesting that there may be a common pathogenic mechanism derived from disruptions of CYFIP1-FMRP complexes.

Specific Dysconnectivity in Schizophrenia

Schizophrenia is associated with numerous brain alterations. To address whether these changes are specific to schizophrenia, **Brandl *et al.*** (pages 573–583) conducted a transdiagnostic multimodal meta-analysis of resting-state functional and structural magnetic resonance imaging studies. Analyses revealed that changes of intrinsic functional connectivity in multiple networks are specific to patients with schizophrenia, compared with patients with major depressive disorder, bipolar disorder, addiction, and anxiety. Further, these changes showed overlap with gray matter volume reductions in insula, lateral postcentral cortex, striatum, and thalamus.

Altered Cerebral Blood Flow in ASD

Altered brain metabolism has been reported in ASD, but findings using positron emission tomography have been inconsistent. **Peterson *et al.*** (pages 584–595) used arterial spin labeling to measure regional cerebral blood flow (rCBF) in children and adults with ASD. Compared with typically developing control subjects, ASD participants showed higher rCBF throughout frontal lobe white matter and gray matter nuclei, which correlated with social deficits. Greater rCBF in frontal white matter was associated with lower *N*-acetylaspartate metabolite levels in ASD. Further, rCBF was inversely associated with IQ, but only in typically developing subjects. Together, these findings suggest that axonal functioning processes may be disrupted in ASD, which then trigger partial compensatory responses from glial cells.

Glutamate in Treatment-Resistant Schizophrenia

Evidence suggests that glutamatergic neurometabolites may be elevated in schizophrenia and may be linked to treatment resistance. **Iwata *et al.*** (pages 596–605) used proton magnetic resonance spectroscopy to further investigate this relationship in patients classified into three groups by their antipsychotic treatment response. The authors found higher glutamate+glutamine levels in the dorsal anterior cingulate cortex of patients with clozapine-resistant schizophrenia compared with healthy control subjects, suggesting that higher glutamatergic levels may be among the shared biological characteristics of treatment resistance to antipsychotics.

Computational Modeling of the Dot-Probe Task

Altered attentional patterns are a key transdiagnostic feature of many conditions and may be modified through automated treatment interventions. However, widely used measures of biased attentional patterns suffer from psychometric issues including poor reliability. Here, **Price *et al.*** (pages 606–612) applied computational modeling to behavioral data from clinically anxious patients who completed the dot-probe task before and after treatment. The authors show that this computational approach improves the reliability and sensitivity of conventional attentional bias indices and yields novel insights into neural correlates and the changes that accompany treatment.

ISSN: 0006-3223