In This Issue

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

Review: Synapse-to-Nucleus Signaling in Brain Diseases

The brain's adaptability to experiences and daily activities depends on the ability to modify neuronal circuits through changes of synaptic connections (i.e., synaptic plasticity). Synapse-to-nucleus signaling is an essential mechanism for converting synaptic signals into gene changes mediating synapse plasticity. **Parra-Damas and Saura** (pages 87–96) review this process, which is mediated by synaptic factors that have been linked to neuropsychiatric, neurodevelopmental, and neurodegenerative disorders and that may be relevant for novel clinical and therapeutic strategies in these brain diseases.

Review: Polygenic Risk of Psychiatric Disorders

With the growing scale of genetic studies, polygenic risk scores are increasingly being used in research and are being discussed for their clinical potential as a biomarker in psychiatry. In this review, **Martin *et al.*** (pages 97–109) discuss the fundamental concepts for calculating these scores, strengths and weaknesses of various methods, limitations and misunderstandings, examples of previous applications in psychiatry, and potential future directions. The authors also provide guidelines for evaluating the utility and rigor of genetic prediction studies.

Copy Number Variation in Bipolar Disorder

Many common alleles contribute to genetic risk for bipolar disorder (BD), but the role for rare copy number variants (CNVs) is less clear. **Charney *et al.*** (pages 110–119) assessed rare CNVs in a genome-wide study of cases with BD and unaffected controls. CNV burden did not differ when BD was analyzed as a single diagnosis. However, when analyzed by subtype, schizoaffective cases showed increased CNV burden compared with controls, cases with BD I, and cases with BD II. These data suggest a role for rare CNV burden in individuals with psychotic symptoms, which is consistent with the known CNV burden in individuals with schizophrenia.

NT5C2 Regulates Protein Translation

An important extension of genome-wide association studies is to translate these findings into a neurobiological understanding of psychiatric disorders. Here, **Duarte *et al.*** (pages 120–130) investigated the neuronal function of *NT5C2*, a gene implicated in schizophrenia risk, using human neural progenitor cells, postmortem tissue, and a model system. Their data reveal that *NT5C2* plays a role in the regulation of adenosine monophosphate-activated protein kinase signaling and protein translation in neural stem cells and is associated with motility behavior in *Drosophila melanogaster*. This study reveals the molecular mechanisms associated with *NT5C2*.

Protein Signaling Complex in Depression

Synaptic plasticity is disrupted in stress-related disorders. A-kinase anchoring protein 150 (AKAP150) directs kinases and phosphatases to synaptic glutamate receptors, controlling synaptic transmission and plasticity. **Zhou *et al.*** (pages 131–142) focus on the role of AKAP150 in the basolateral amygdala, a brain region implicated in the pathophysiology of major depressive disorder. The authors report that the AKAP150-PKA-GluA1 signaling complex is responsible for chronic stress–induced depressive-like behaviors in mice, providing a novel target for therapeutic interventions in depression.

BDNF–VEGF Interplay in Antidepressant Actions

Ketamine produces rapid antidepressant effects that requires both brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) release in the medial prefrontal cortex, but the relationship between these factors is not clear. Here, **Deyama *et al.*** (pages 143–152) report that the neurotrophic and antidepressant actions of BDNF and VEGF in the medial prefrontal cortex are interdependent, suggesting that BDNF–VEGF interplay may also be crucial for the actions of rapid-acting antidepressants.

Resting-State Connectivity and Inflammation

Growing evidence documents bidirectional signaling between the brain and immune system in the pathogenesis of emotional and physical health problems. Extending this work using two independent samples of youths and young adults, **Nusslock *et al.*** (pages 153–162) report that higher peripheral inflammation is associated with lower resting-state functional connectivity in large-scale brain networks involved in emotion regulation and executive control. These results may help lead to the generation of novel neuroimmunological treatments for mental and physical illnesses.

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