In This Issue

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

Special Issue: Synaptic Mechanisms of Prefrontal Circuit Failure in Schizophrenia: Crossing a Developmental Threshold

Large-scale neuroimaging and microarray genotyping studies have identified altered glutamatergic function, impaired synaptic plasticity, and abnormal brain development as core pathogenic factors in schizophrenia. Here, **Girdhar *et al.*** (pages 443–449) take an epigenomics perspective, reviewing how changes in epigenetic marks, and the packaging of DNA in the brains of individuals with schizophrenia provides insights into altered synaptic plasticity in neurons during the early stages of brain development, which leads to impairment of neuronal function in adulthood.

Cognitive dysfunction in individuals with schizophrenia may emerge from altered development of excitatory and inhibitory components of a local circuit in the dorsolateral prefrontal cortex (DLPFC). Here, **Dienel *et al.*** (pages 450–459) review studies investigating the postnatal developmental trajectory of this DLPFC circuit and its alterations in schizophrenia. These findings suggest a model in which early alterations in excitatory signaling evoke homeostatic responses in inhibitory signaling that are insufficient to compensate for further impairments in excitatory signaling during adolescence.

The maternal immune activation model has emerged as an important translational tool to evaluate the association between maternal infections during pregnancy and increased risk for offspring neurodevelopmental disorders. This review by **Hanson *et al.*** (pages 460–469) highlights the translational utility of the nonhuman primate as a model species closely related to humans to explore PFC vulnerabilities associated with the maternal immune activation model.

Recent genomic and neuropathological observations suggest that microglia, the resident immune cells of the brain, contribute to aberrant neurodevelopment in schizophrenia. In this review, **Sheridan *et al.*** (pages 470–479) discuss efforts to develop and validate patient-derived cellular models of microglia function. Such models may be applied to characterize microglia-neuronal interaction, investigate disease pathophysiology, and facilitate identification of novel therapeutics and biomarkers for more targeted interventions in neurodevelopmental disease.

Schizophrenia is associated with impairments and alterations in DLPFC functioning. In this work, **Arnsten *et al.*** (pages 480–490) describe how circuits in the DLPFC that subserve higher cognition have unusual molecular requirements that may render these neurons especially vulnerable to atrophy and dysfunction in schizophrenia. In particular, inflammation and genetic insults may interact to weaken connections and lead to symptoms such as cognitive deficits and thought disorder.

Adolescence is a period of increased vulnerability for the development of psychiatric disorders, including schizophrenia. Thalamic abnormalities have been observed during adolescence, early in the progression of schizophrenia. In this review, **Benoit *et al.*** (pages 491–500) discuss the involvement of neuronal activity in the thalamus in PFC maturation. The authors hypothesize that adolescent thalamic dysfunction may have long-lasting consequences for PFC function and cognition in patients with schizophrenia.

The neurodevelopmental and dopamine hypotheses are leading theories of schizophrenia pathoetiology. Using updated evidence from genetic, neuroimaging, in vitro, and in vivo studies, **Howes and Shatalina** (pages 501–513) propose a novel unified framework that ties together dopamine abnormalities, aberrant synaptic trajectories during neurodevelopment, and excitation-inhibition imbalance in schizophrenia. The authors highlight outstanding questions and discuss the implications for treating and preventing schizophrenia.

In this review, **Vinogradov *et al.*** (pages 514–522) describe and discuss 4 features of psychosis spectrum illnesses: 1) the bidirectionality of the causes of psychosis; 2) the catastrophic clinical threshold that happens during the first episode of psychosis; 3) varied observations of people with the same diagnosis versus different diagnoses; and 4) understanding how dopamine affects brain circuit function. The authors argue that theoretical computational perspectives are needed to reduce this complexity and variability of psychosis spectrum illnesses in order to advance treatment innovations.

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