In This Issue

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A brief summary of the articles in this issue of *Biological Psychiatry: Global Open Science*.

Clinical and Circuit Neuroscience Crosstalk

Emerging evidence highlights the importance of developmental trajectories in determining early psychiatric outcomes. However, effective communication and translation between domains of rodent and human basic neuroscience and clinical practice remains limited. In this review, **Meyer *et al.*** (pages 169–178) highlight avenues by which research investigating neural circuit development in adolescence can support ongoing clinical practice, with the goal of encouraging back-and-forth dialogue to advance both research and practice in this domain. The authors highlight two examples, safety cues and incentives, that leverage insights from neural circuit development and may have great promise for augmenting existing behavioral treatments for anxiety disorders during adolescence.

Review: Dopamine in Cost-Benefit Processing

Dopamine contributes to weighing the benefits against the costs (e.g., effort required to obtain a reward) of actions. However, there is no consensus on dopamine's precise role in cost-benefit weighing. Here, based on a review of dopaminergic manipulations in humans, **Soutschek *et al.*** (pages 179–186) argue that the empirical findings can best be explained by assuming that dopamine both promotes the pursuit of psychologically close rewards and computes the costs that are considered as acceptable for a reward.

Glutamatergic Synaptic Transmission in Depression

Pharmacological and anatomical evidence suggests that abnormal glutamate neurotransmission may be associated with the pathophysiology of depression. Here, **He *et al.*** (pages 187–196) discuss the dysfunction of glutamatergic synaptic transmission in depression with an emphasis on AMPA receptors (AMPARs). The authors suggest that modulating the functions of AMPARs via targeting AMPAR trafficking–associated proteins may provide a more selective pharmacology and may be of value for the development of novel drugs for depression.

Inflammation: Psychiatric Illness and Stress

During the global COVID-19 crisis, studies reported that over one-third of COVID-19 patients presented with neuropsychiatric manifestations. This raises a crucial question of whether the psychiatric patient population exposed to SARS-CoV-2 may be more vulnerable to having a severe COVID-19 phenotype. Using data from published meta-analyses, **Duong *et al.*** (pages 197–203) report that increased systemic C-reactive protein and interleukin 6 are common biomarkers of both severe COVID-19 and DSM-5–defined disorders. These findings highlight a potential biological process that may explain the clinically observed link.

Discrimination is associated with poor mental and physical health outcomes. Here, **Chen *et al.*** (pages 204–212) examined links between discrimination and inflammation—a key biological pathway in mental and physical illnesses—across two samples of adolescents of color. Greater experiences with discrimination were associated cross-sectionally with a more proinflammatory phenotype, and longitudinally with increasing trajectories of low-grade inflammation over time, in males but not females. These data suggest that adolescent males of color may be more vulnerable to discrimination-related inflammatory processes that are implicated in many psychiatric disorders and physical conditions.

Early-life adversity is linked to increased depression risk and increased inflammation. Here, **Kuhlman *et al.*** (pages 213–221) characterized the intracellular and circulating innate immune response to acute social stress in an adolescent sample. Results implicated increased activity of CREB transcription factors as a potential mechanism for enhanced immune responses to stress among youth exposed to early-life adversity.

Substance Exposure and Outcomes in Youth

Most adolescents who use marijuana do so sporadically. With highly potent forms of marijuana now widely available, understanding the effects of recreational use on brain maturation is critically important. Based on two complementary longitudinal studies, **Ho *et al.*** (pages 222–232) found that recreational marijuana use disrupted adolescent cognitive maturation, with those at high familial risk especially affected. These results highlight the deleterious impact of recreational marijuana use during this vulnerable period of brain development.

Exposure to secondhand smoke is associated with numerous adverse effects in children, but the majority of research has focused on tobacco smoke, despite the rising prevalence of cannabis use. Analyzing data from a large cohort, **Wade *et al.*** (pages 233–242) report that secondhand exposure to tobacco smoke was related to poorer visual memory in adolescents, whereas secondhand exposure to cannabis smoke showed no relationships with cognition. Further, environmental exposure to tobacco was associated with poorer visuospatial and language performance, while environmental cannabis exposure was associated with better reading. These results emphasize the importance of reducing secondhand tobacco exposure in youth.

Whether prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) is associated with adverse outcomes remains unclear, as evidence has been inconsistent. **Moreau *et al.*** (pages 243–254) report that prenatal SSRI exposure was not associated with depression among 9- to 10-year-old children after accounting for recent maternal depression but was associated with small differences in two brain regions, which

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were not associated with depression. These data suggest that concerns about depression during middle childhood should not discourage SSRI use during pregnancy, but that further research is needed to evaluate other outcomes.

Normative Trajectories of Cognition

Adolescence hosts a sharp increase in the diagnosis of mental disorders. Prior to receiving a diagnosis, many report cognitive symptoms. Using a modeling approach with cognitive data from a large cohort of youths, **Kjelkenes *et al.*** (pages 255–263) estimated normative trajectories of cognitive performance and found that deviations from the estimated trajectories were associated with general and specific domains of psychopathology. These data support the close links between emerging psychopathology and cognitive function in youth.

Gray Matter Development and Psychotic Experiences

Gray matter abnormalities are observed across the psychosis spectrum. In this longitudinal study, **O'Neill *et al.*** (pages 264–273) found that adolescents who reported subthreshold psychotic experiences displayed impaired right hippocampal development, compared with control adolescents. These results reflect findings in established psychosis, implicating hippocampal volumetric abnormalities in the pathophysiology underlying psychotic experiences.

Mechanisms of Resilience After Adolescent Stress

Resilience to stress is still not well understood. Using an animal model, **Cotella *et al.*** (pages 274–282) report that chronic variable stress during adolescence protected against the behavioral effects of single prolonged stress, a combination of stressors used to model symptoms of posttraumatic stress disorder, in adulthood. Further, the authors found that changes in brain regions such as the prefrontal cortex (in males) and amygdala (in females) were responsible for this resilience effect following adolescent stress. These data indicate that stress during adolescence may evoke a beneficial resilient phenotype in adulthood.

Altered Microbiome in Schizophrenia

Gut health and brain health are known to be linked, although much is not known. Here, **Thirion *et al.*** (pages 283–291) report that gut microbiota from patients with schizophrenia differed significantly from those of healthy individuals in terms of richness and global microbial composition, with enrichment in *Flavonifractor plautii* and depletion in *Faecalibacterium prausnitzii*. Furthermore, functional potential of the gut microbiota was related to cognitive scores of patients with schizophrenia, particularly the module for synthesizing tyrosine, a precursor for dopamine. These data suggest that the gut microbiome may be a potential target for intervention in schizophrenia.

Cognitive Control in Pedophilic Disorder

Pedophilic disorder, a risk factor for committing child sexual abuse, is associated with cognitive deficits. Compared with healthy control individuals, help-seeking individuals with pedophilic disorder showed altered brain activity and response times during presentation of sexually salient child images in a functional magnetic resonance imaging paradigm designed to probe behavioral control. Sexual preferences and stimuli sex had no effect on response time. These findings by **Mannfolk *et al.*** (pages 292–300) contribute to our understanding of the neurocognitive mechanisms of impaired cognitive control in pedophilic disorder.

Brain Stimulation for Alcohol Use Disorder

A common cause of relapse in alcohol use disorder is elevated brain response to alcohol cues. Previous work has shown that a single session of continuous theta-burst stimulation (cTBS), a form of noninvasive stimulation, can decrease brain reactivity to such cues. In this work, **McCalley *et al.*** (pages 301–310) report that individuals with alcohol use disorder who received 10 sessions of cTBS, compared with sham TBS, showed reductions in alcohol drinking, craving, and brain reactivity to alcohol cues that persisted up to 3 months. These results provide support for further investigation of noninvasive brain stimulation treatment options for alcohol use disorder.