In This Issue

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

Female Aggression and Chronic Defeat Stress

Despite the twofold higher prevalence of mood disorders in females compared with males, most clinical and preclinical research focuses on male subjects. In this work, **Newman *et al.*** (pages 657–668) report that female mice chronically defeated by aggressive female rivals later show increases in corticosterone and c-Fos activation in brain regions associated with defense and social impairments, including the medial amygdala and ventromedial hypothalamus. Furthermore, the defeated female mice showed social interaction deficits, which improved with a single dose of ketamine. This work introduces a female model of social defeat stress that may be used to advance the study of sex differences in stress-induced psychopathologies.

The Role of Prefrontal Interneurons in Stress

The medial prefrontal cortex (mPFC) receives information regarding stimuli and then directs appropriate behavioral and physiological responses to stress. Output of the mPFC is mediated by glutamatergic pyramidal neurons, whose activity is coordinated by an intricate network of interneurons. In this review, **McKlveen *et al.*** (pages 669–681) discuss the interplay between interneurons, stress, and the PFC, illustrating the importance of interneurons in the transition between stress adaptation and stress-induced pathology.

Adolescence is a period characterized by a high incidence of psychiatric disorders and a correspondingly diminished ability to suppress fear memory, which has been linked to reduced infralimbic mPFC plasticity. Here, **Koppensteiner *et al.*** (pages 682–692) studied the involvement of gamma-aminobutyric acidergic (GABAergic) neurons on fear extinction suppression during the transition from preadolescence to adulthood in mice. The authors found an enhancement of adolescence-specific plasticity in somatostatin-positive interneurons, but not parvalbumin-positive interneurons, which may play a role in diminished fear extinction during adolescence.

Enhancing Extinction Learning

Mindfulness meditation is believed to foster the ability to recall that a stimulus is no longer associated with threat, but the neural mechanisms associated with mindfulness-enhanced extinction learning remain unclear. Here, **Sevinc *et al.*** (pages 693–702) studied healthy volunteers randomly assigned to a mindfulness-based or exercise-based stress management program. Functional magnetic resonance imaging revealed differential engagement of the supramarginal gyrus following mindfulness training as well as increased connectivity between the hippocampus and the primary sensory cortex for the mindfulness group. These data demonstrate hippocampal-dependent changes in extinction learning, specifically in the retrieval of extinction, as a potential mechanism through which mindfulness-based interventions enhance fear extinction and foster stress resilience.

Return of fear following exposure therapy for anxiety disorders may be explained by context specificity of extinction. In rodents, context specificity is attenuated by systemic administration of scopolamine, a muscarinic cholinergic receptor antagonist. In a double-blind, randomized, controlled trial, **Craske *et al.*** (pages 703–711) evaluated scopolamine for attenuating context renewal of phobic fear in humans with social anxiety disorder and observed augmentation of extinction during exposure therapy. Participants also showed partial attenuation of fear when tested in a new context and 1 month later, under drug-free conditions. Scopolamine also disrupted hippocampal processes. These data offer a proof of concept that scopolamine may be a viable approach for the augmentation of exposure therapy.

Immunomodulatory Cell Therapy for Stress-Based Disorders

Stress-based disorders, such as major depressive disorder, are associated with neuroinflammation. Mesenchymal stromal cells (MSCs) show the ability to regulate inflammatory processes. Using a preclinical model of repeated defeat stress, **Gallagher *et al.*** (pages 712–724) report that injection of MSCs reduced inflammation and also depressive- and anxiety-like behaviors. Further work showed that these MSC effects occurred via peripheral actions that trigger a cellular cascade leading to resolution of inflammation, rather than via direct effects in the brain. These data indicate that targeting inflammation for stress-based disorders may hold promise as a potential treatment approach.

Effect of Physician Training on Telomere Length

Stress is a key precipitant for many common diseases, but established biomarkers are lacking. Here, **Ridout *et al.*** (pages 725–730) utilized a cohort of U.S.-based interns (first-year residents) to prospectively assess the impact of physician residency training on telomere length, a measure of cellular aging that has previously been correlated with stress exposure. The authors found that telomere length shortened over the course of the internship year, with longer work hours correlating with greater telomere shortening. This work suggests that telomere attrition may serve as an objective biomarker of stress.

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