In This Issue

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

Neuroplasticity and Stress

Synaptic plasticity in the prefrontal cortex (PFC) is critical for the regulation of emotion and behavior. Muscarinic acetylcholine receptors (mAChRs) play a role in fear extinction learning. Recent work has found that activation of the M_1 subtype induces a form of long-term depression in the rodent prelimbic PFC. **Maksymetz *et al.*** (pages 989–1000) further this work by reporting that M_1 mAChR activation induced input-specific long-term depression at fear-related limbic inputs to the PFC and is required for contextual fear extinction in rodents. Potentiating M_1 function with a positive allosteric modulator enhanced fear extinction in a mouse model of posttraumatic stress disorder (PTSD), highlighting a mechanism by which M_1 receptors modulate fear-related circuitry.

Stress induces changes in nucleus accumbens D_1-expressing medium spiny neurons. Reduction in nucleus accumbens dendritic complexity due to stress has been shown to be dependent on RhoA activation. Here, **Francis *et al.*** (pages 1001–1010) demonstrate that administration of Rhosin, a RhoA-specific inhibitor, prevents stress-induced D1-medium spiny neuron hyperexcitability and electrophysiological changes that drive depression-like behavior in stressed mice. These data provide insight into the mechanisms by which RhoA inhibition promotes stress resilience.

Cumulative childhood stress is a risk factor for the development of anxiety disorders and attention-deficit/hyperactivity disorder in adulthood. The ventral hippocampus is associated with the regulation of anxiety. **Murthy *et al.*** (pages 1011–1020) explored the influence of repeated early life stress in a mouse model and found increased rhythmic firing of neurons as well as enhanced perineuronal nets, the structures surrounding neurons that regulate plasticity, in the ventral hippocampus. These findings indicate that early life adversity may produce altered neuronal oscillations in the hippocampus along with cellular changes in interneurons that may be causally linked to the electrophysiological and behavioral alterations.

Mechanisms of Anxiety-Related Behavior

Chronic pain is hypothesized to predispose an individual to anxiety by provoking plasticity in neural circuits that regulate emotions. **Llorca-Torralba *et al.*** (pages 1021–1035) combined immunohistochemistry with chemogenetic and behavioral approaches in a rat model of neuropathic pain. They report that inhibition of the locus coeruleus neurons that project to the basolateral amygdala, or blockade of beta-adrenergic receptors, reversed pain-induced anxiety, suggesting novel targets for the comorbidity of pain and anxiety.

Endocannabinoids and neurosteroids regulate emotions and stress responses. Activation of peroxisome proliferator-activated receptor (PPAR)-α by the endocannabinoid *N*-palmitoylethanolamine regulates inflammation, but the effects on emotions are unclear. In a rodent model of PTSD, **Locci and Pinna** (pages 1036–1045) report that *N*-palmitoylethanolamine reduced fear- and anxiety-like behaviors via increased allopregnanolone levels. This evidence supports a role for PPAR-α in behavior regulation and suggests novel strategies that may be investigated to treat stress-related disorders.

The lateral septum is a subcortical brain region that has been implicated in the regulation of anxiety. The gene that codes for neuroligin-2, *Nlgn2*, has been associated with anxiety-related behavior in both humans and animals. Here, **Troyano-Rodriguez *et al.*** (pages 1046–1055) report that conditional deletion of *Nlgn2* in the lateral septum of male and female mice selectively reduced inhibitory synaptic transmission, produced impairments in the responsiveness of local and target neurons to stress, and altered anxiety-related behavior. These findings provide insight into the role of excitation-inhibition balance in the lateral septum.

Nociceptin Receptors in Sexual Violence

Nociceptin is an antistress neuropeptide in the brain that promotes resilience in animal models of PTSD, but its effects in humans are not clear. Using [^{11}C]NOP-1A positron emission tomography, **Narendran *et al.*** (pages 1056–1064) measured in vivo binding to nociceptin receptors in college women who had experienced sexual violence and control women with no history of sexual violence. There were no binding differences between the two groups. However, decreased midbrain and cerebellum nociceptin receptors were associated with less severe PTSD symptoms after sexual violence, suggesting that the role of nociceptin receptors in resilience and recovery following trauma should be investigated.

Rare Deletions in Major Depressive Disorder

Two prior genome-wide association studies of rare copy number variants in major depressive disorder (MDD) found no associations. **Zhang *et al.*** (pages 1065–1073) conducted a meta-analysis of four cohorts to study the association of MDD with genomic deletions and duplications. Genome-wide, patients with MDD had more rare short deletions, particularly in intergenic regions, compared with control subjects. However, no copy number variants met criteria for genome-wide significance after correction. These data suggest that rare deletions of regulatory sequences may contribute to genetic risk of MDD, but larger sample sizes are needed.

Challenges to Study Fear Extinction Retention

Significant research in the last 2 decades has been conducted on the neurobiology of fear extinction and its maintenance (i.e., retention). A systematic literature search by **Lonsdorf *et al.***

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(pages 1074–1082) identified 16 different operationalizations of the extinction retention index, a widely used cross-species translational tool, illustrating that it has evolved into a poorly defined and heterogeneous measure. The authors then reanalyzed four datasets, providing evidence that the extinction retention index does not provide an adequate operationalization of the construct of extinction retention. The authors discuss concerns about replicability and the need for standardization in the field, and close by providing specific recommendations for future work.