In This Issue

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

Mechanisms of Fear

MicroRNAs orchestrate the pattern of gene expression in the brain and thus have emerged as potential biomarkers and treatment targets for anxiety disorders. Using a mouse model of impaired fear extinction, **Murphy *et al.*** (pages 979–989) report that increasing the expression levels of a particular microRNA, miR-144-3p, in the amygdala rescues the capacity for fear extinction. Their work also implicates genes that are regulated by miR-144-3p, including *Pten*, *Spred1*, and *Notch1*, in this process. These findings suggest that miR-144-3p may be a specific target for the development of effective therapeutics for anxiety disorders.

Synaptic gamma-aminobutyric acid type A ($GABA_A$) receptors mediate amygdala inhibition and prevent inappropriate expression of fear, but the role of extrasynaptic $GABA_A$ receptors is largely unknown. Here, **Liu *et al***. (pages 990–1002) report that the δ subunit-containing $GABA_A$ receptor, which is exclusively situated in extrasynaptic space, acts to disinhibit lateral amygdala and facilitate the expression of learned fear in mice. The disinhibition produced by the $GABA_A(\delta)$ receptor may protect against excessive amygdala inhibition and put the amygdala in a state of "preparedness" for the expression of fear-based emotions.

Ghrelin, a hormone that regulates appetite and metabolism, plays a role in fear memory, but findings have been contradictory. Here, **Harmatz *et al.*** (pages 1003–1013) show that ghrelin, through actions in the amygdala, inhibits the formation of fear memories in unstressed rodents. Higher ghrelin levels were related to weaker fear memories, which were not related to appetitive behavior. In contrast, chronic stress increased ghrelin levels, increased the formation of fear memories, and promoted loss of ghrelin binding sites in the amygdala. These data suggest that chronic stress may induce ghrelin resistance in the brain, which in turn enhances vulnerability to excessive fear memory formation.

Risk and Loss Aversion in Anxiety

Pathological anxiety is strongly associated with avoidance behaviors, which may result from a combination of aversion to uncertainty (risk aversion) and fear of losing (loss aversion). Using computational modeling of a gambling task, **Charpentier *et al.*** (pages 1014–1022) show that pathologically anxious individuals exhibit increased risk aversion relative to healthy controls, but equivalent levels of loss aversion. This suggests that hypersensitivity to risk may be a unique feature of pathological anxiety, indicating that successful interventions may work by increasing risk tolerance rather than by reducing the psychological impact of negative outcomes.

After Trauma: Identifying Risk and Recovery

The amygdala regulates emotion and shows heightened responses to threat in posttraumatic stress disorder (PTSD). To investigate whether amygdala function predicts later PTSD, **Stevens *et al.*** (pages 1023–1029) conducted a prospective neuroimaging study in individuals admitted to the emergency department after experiencing trauma. Greater amygdala reactivity to emotional stimuli 1 month after trauma predicted poorer recovery from PTSD symptoms over the following year. Amygdala hyperreactivity may serve as a neural signature of risk for the maintenance of PTSD symptoms and may help identify individuals at greatest risk following trauma.

In a randomized, double-blind trial, **van Zuiden *et al.*** (pages 1030–1040) investigated whether intranasal oxytocin administration early posttrauma would reduce PTSD symptom development in emergency department patients. Relative to placebo, oxytocin administration did not result in subsequent lower PTSD symptoms in the entire group. However, participants with high acute PTSD symptoms who received oxytocin, relative to those who received placebo, had significantly lower PTSD symptoms across follow-up. If replicated, these data would suggest that oxytocin administration may have value as an acute treatment for a subgroup of patients with high levels of PTSD symptoms.

Role of Rostromedial Tegmental Nucleus in Punishment

The decisions one makes in daily life often rely on a delicate balance between the positive and negative consequences of one's actions. While evidence suggests a role for midbrain dopamine in reinforcement and motivation, the mechanisms underlying impulse inhibition are less well known. **Vento *et al.*** (pages 1041–1049) show that lesions of the rostromedial tegmental nucleus (RMTg) induced resistance to the behavioral consequences of punishment in adult rats. Using optogenetic techniques, the authors discovered that this deficit is related to the role of RMTg projections to the ventral tegmental area at the time of punishment, which produce changes in dopaminergic activity that are consistent with an aversive "teaching signal." Similarly, RMTg inactivation immediately prior to the retrieval of punishment-associated memories released behaviors suppressed by the fear of that punishment. These findings suggest that the RMTg plays two roles in decision-making, one related to learning and one related to the expression of punished behavior.

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