In This Issue

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

Anxious Temperament in Primates

Anxious temperament (AT) in early life is a risk factor for the later development of anxiety and depressive disorders, but the molecular substrates remain unclear. Here, **Fox *et al.*** (pages 881–889) sequenced dorsal amygdala RNA in a primate model and identified a growth factor receptor, *NTRK3*, that is associated with variation in AT and AT-related brain metabolism. The authors then used viral-vector gene manipulation to overexpress *NTF3*, the ligand of NTRK3, which resulted in reduced AT and altered AT-related neural circuitry. These findings reveal a neurotrophic pathway linked to a high-risk early-life behavioral phenotype and identify potential molecular targets that may be useful in guiding the development of targeted interventions.

Altered uncinate fasciculus (UF) microstructure has been linked with anxiety disorders in boys, but not girls. Using diffusion tensor imaging, **Tromp *et al.*** (pages 890–898) report that the UF is associated with AT in male, but not female, rhesus monkeys, with higher AT levels linked to lower UF fractional anisotropy values. These findings provide evidence that the relationship between UF alterations and early-life anxiety are evolutionarily conserved and male specific, suggesting the potential need to develop sex-specific treatments for anxiety.

Role of Angiotensin II Receptors in Fear

The renin-angiotensin system has recently been identified as a potential therapeutic target for fear and anxiety disorders, but little is known about the functional role of angiotensin II receptors within regions of the brain that mediate defensive responses. Here, **Yu *et al.*** (pages 899–909) used multiple approaches in mice to characterize a novel role for angiotensin II type 2 receptors (AT_2R) in the central amygdala in modulating the expression of learned fear. Specifically, the authors identified localization to gamma-aminobutyric acidergic projection neurons and found that AT_2R activation in the central amygdala attenuated freezing behavior in response to conditioned fear. These data expand our neurobiological understanding of brain angiotensin receptors.

Extinction learning is a core process underlying exposure therapy for anxiety disorders, and evidence from animal work suggests that the renin-angiotensin system plays an important role. In this pharmacologic functional magnetic resonance imaging study, **Zhou *et al.*** (pages 910–920) demonstrated that losartan, an angiotensin II type 1 receptor used to treat hypertension, accelerates extinction learning in healthy male subjects via effects on brain regions that are critically engaged in threat regulation (ventromedial prefrontal cortex) and threat reactivity (amygdala). These data suggest that adjunct losartan administration should be further investigated for its potential to facilitate the efficacy of exposure-based interventions.

Socioeconomic Status, Stress, and Brain Structure in Children

Socioeconomic factors have been linked to brain structure in children, but whether stress mediates this association is unclear. **Merz *et al.*** (pages 921–929) conducted magnetic resonance imaging and measured hair cortisol, as an index of chronic stress, in children from socioeconomically diverse families. The authors report that greater stress (i.e., higher cortisol concentration) was associated with smaller CA3 and dentate gyrus hippocampal subfield volume. Hair cortisol mediated associations between parental education and CA3 and dentate gyrus volume. These data indicate that chronic physiologic stress may represent a mechanism through which socioeconomic disadvantage leads to reductions in hippocampal volume.

Amygdala Habituation to Threatening Stimuli in Borderline Personality Disorder

A deficit in the ability to reduce brain activity after exposure to repeated threatening cues has been observed in borderline personality disorder, but the biological underpinnings remain incompletely understood. **Bilek *et al.*** (pages 930–938) used a functional magnetic resonance imaging emotion processing task to examine this neural phenotype in patients with borderline personality disorder and healthy control subjects. The results revealed no phenotypic association with symptom severity or diagnostic status, but did show an association with exposure to childhood adversity, a well-established risk factor for emotion dysregulation and psychiatric illness. These data provide insight into reduced amygdala habituation in borderline personality disorder.

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