In this Issue

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

Neurobiological Responses to Stress

Telomeres are protective caps on the ends of chromosomes, shortening each time a cell divides, and thereby related to the age of the cell. Several studies have shown that telomeres shorten with chronic somatic illness, and recent work suggests that a similar process might occur with some kinds of psychiatric disorders and psychosocial stressors. Here, **Price *et al.*** (pages 15–23) review emerging work suggesting a robust, and perhaps dose-dependent, association between reduced telomere length and early-life stress. These findings highlight the complex relationships between experience, physical and psychiatric illness, and aging.

Toll-like receptors (TLR) may be a mechanism through which the brain monitors peripheral immune responses to stress. Using a stress model in mice, **Gárate *et al.*** (pages 32–43) report an activation of the TLR pathway triggering inflammation and cellular oxidative damage in prefrontal cortex tissue. Experiments also showed a role of bacterial translocation on TLR-4 signaling pathway activation after stress exposure. Together, these data suggest a key stress-related role for TLR in brain neuroinflammation and in the regulation of gut barrier dysfunction.

Chronic stress increases the vulnerability to anxiety disorders and depression. Here, **Saavedra-Rodríguez and Feig** (pages 44–53) show in mice that exposure to an unstable social environment while young promotes anxiety and dysfunctional social interactions in their future progeny, independent of the interactions of parents with their offspring. This suggests that psychiatric disorder susceptibility is related not only to one's own genetics and environment, but also parental experiences.

Chronic pain is associated with a high risk for mood or anxiety disorders, but the underlying disturbances in brain circuitry are still poorly understood. **Alba-Delgado *et al.*** (pages 54–62) found that neuropathic pain in rats produced behaviors resembling anxiety and depression that were more prominent than the fear of pain itself. These emotional changes temporally coincided with marked modifications in noradrenaline-releasing nerve cells in the locus coeruleus. These changes are consistent with alterations in noradrenaline messaging in the brain associated with anxiety disorders and depression.

Most rodent stress models involve the physical experience of a traumatic event. Here, **Warren *et al.*** (pages 7–14) show that when a mouse watches another mouse undergo a stressful experience, in this case defeat by a more dominant animal, it can induce long-lasting anxiety- and depression-like behaviors. The authors found that the behaviors and changes in gene expression produced by witnessing a stressful event resembled the changes produced by experiencing that stressful event. Chronic fluoxetine administration reduced the impact of observing the stressful event, as it does with the direct effects of stress. Together, these findings indicate that for rodents, as for humans, witnessing another creature undergo a stressful event has many consequences that resemble the actual experience of that stress.

Review: Neurochemical Abnormalities in Obsessive-Compulsive Disorder

Magnetic resonance spectroscopy has been used extensively to investigate neurochemical abnormalities in patients with obsessive-compulsive disorder, but studies have reported diverse and seemingly inconsistent findings. In this review, **Brennan *et al.*** (pages 24–31) summarize these findings. Overall they report that there is initial evidence of 1) reduced *N*-acetylaspartate levels in the anterior cingulate cortex and caudate, 2) reduced glutamate + glutamine levels in anterior cingulate cortex, 3) increased glutamate + glutamine in caudate, and 4) increased choline levels in thalamus, parietal white matter, and hippocampus. The authors also highlight a number of methodological issues that would enable this research area to move forward productively.

Circadian Rhythm Sleep Disorder

Little is known about the pathophysiology of drifting sleep patterns in circadian rhythm sleep disorder, free-running type (FRT). **Kitamura *et al.*** (pages 63–69) detected a prolonged circadian rhythm period (τ) in sighted patients with FRT compared to controls with normal sleep habits, using a forced desynchrony protocol that disrupted normal daily routines and light/dark cycles. However, the prolonged τ was also observed in a subset of controls with evening chronotypes, suggesting that the pathophysiology of FRT is not solely explained by the abnormal τ.

Gray Matter Abnormalities in Stress Disorders

In their meta-analysis, **Kühn and Gallinat** (pages 70–74) investigated overlap of brain structural alterations in trauma-exposed individuals without or without posttraumatic stress disorder (PTSD). Their study identified a number of brain regions where PTSD was associated with reductions in gray matter volume, including the anterior cingulate cortex, ventromedial prefrontal cortex, left temporal pole/middle temporal gyrus, and left hippocampus. This deficit profile is consistent with brain networks thought to be affected functionally in PTSD.

Talati *et al.* (pages 75–84) used magnetic resonance imaging to investigate the neuroanatomical abnormalities associated with social anxiety disorder. Compared to controls, they identified abnormalities in the cerebellum, parahippocampal gyrus, and temporal pole, findings which they replicated in an independent sample. These differences were not observed in a separate group of subjects with panic disorder, suggesting that these structural changes might be a distinctive feature of social anxiety disorder, among the anxiety disorders.

Anxiety and Functional Connectivity

In their study of healthy individuals, **Baur *et al.*** (pages 85–92) report that connectivity between the insula and the amygdala, two key regions for emotional behavior, is linked to anxiety levels. Patterns of resting-state functional connectivity within a pathway between anterior insula and basolateral amygdala predicted state anxiety, whereas a measure of axonal organization reflecting structural connectivity was related to trait anxiety. These findings highlight network-related aspects within limbic/paralimbic circuits underlying anxious behavior and identify a potential candidate biomarker for anxiety.

Cognitive behavioral therapy is an effective treatment for panic disorder, but the neural mechanisms underlying its effects are unknown. In their imaging study, **Kircher *et al.*** (pages 93–101) found increased left inferior frontal gyrus activation during fear conditioning in panic disorder patients that was normalized after therapy. Analyses also revealed increased connectivity of the inferior frontal gyrus with regions of the fear network in panic disorder patients compared to a control group, which was unchanged over time. These data suggest an increased association of cognitive and emotional processes within panic disorder.

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