In This Issue

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

Special Issue: Neurobiology of Resilience

Resilience can be defined as an organism's ability to adapt to adversity and is a vital concept in advancing our understanding of the mechanisms of stress responding. Here, **Cathomas *et al.*** (pages 410–420) review recent advances in our understanding of the neurobiological mechanisms of stress resilience, with a focus on preclinical models of major depressive disorder and posttraumatic stress disorder. Multiple central and peripheral body systems are implicated, including brain circuitry, gut microbiota, the immune system, and the blood-brain barrier, indicating that resilience to stress is a multifaceted, complex process.

Resilience is a multifaceted concept that applies to humans as well as animals and varies by sex across the lifespan. In this review, **Hodes and Epperson** (pages 421–432) examine risk and resilience mechanisms discovered through preclinical and clinical research that impact sex differences in the proximal and distal effects of stress across developmental epochs, from the prenatal period through late-life hormonal changes. The authors identify interacting, complex effects of sex with epigenetic regulation of stress physiology that contribute to the timing and type of stress effects that are manifested.

The identification and understanding of resilience mechanisms holds potential for the development of mechanistically informed prevention and interventions in psychiatry. In this review, **Elbau *et al.*** (pages 433–442) discuss how gene-by-environment interaction studies may help to unravel resilience mechanisms through both top-down designs (i.e., disease phenotypes) and bottom-up approaches (i.e., molecular measures). They summarize the inherent challenges of such work, along with the recent technological advances that may improve these strategies.

Here, **Feder *et al***. (pages 443–453) review recent advances in our understanding of the biology of human resilience across the lifespan, from early childhood and adolescence to adulthood and older age. Examples include studies of the heritability of resilience, the impact of early caregiving on the development of stress response systems, the neural underpinnings of psychological traits associated with resilience, and resilience-enhancing interventions, including studies of interventions that may improve developmental trajectories in high-risk youths.

Few pharmacological treatments are available for posttraumatic stress disorder, and none that promote resilience. In this review, **DePierro *et al.*** (pages 454–463) highlight two approaches to drug discovery in posttramatic stress disorder and discuss how the use of certain medications together with psychotherapy may promote symptom improvement and resilience. The first approach is based on the identification of biological targets associated with psychopathology or resilience (e.g., hypothalamic-pituitary-adrenal axis) and the development of pharmacological interventions to engage those targets. The second approach (e.g., ketamine and 3,4-methylenedioxymethamphetamine studies) encourages reverse translation to identify mechanisms underlying recovery by investigating biological changes in successful treatments.

Exposure to childhood adversity is a potent risk factor for depression and anxiety. Leveraging cognitive neuroscience to identify mechanisms that contribute to resilience in children with a history of maltreatment may provide viable intervention targets for the treatment or prevention of psychopathology. Here, **Rodman *et al.*** (pages 464–473) argue that the ability to recruit frontoparietal control networks to modulate amygdala reactivity to negative cues may be a protective factor that buffers children from developing internalizing problems following exposure to adversity. They then present findings that are consistent with this possibility, demonstrating that children who are more able to modulate amygdala reactivity and recruit prefrontal regions of the frontoparietal network during cognitive reappraisal are less likely to exhibit symptoms of depression following exposure to maltreatment, results that point to a potential neurobiological mechanism of resilience.

Peripheral inflammation has been implicated in stress-related disorders, but the underlying mechanisms have been unclear. In this work, **Pfau *et al.*** (pages 474–482) investigated the role of microRNAs, which regulate immune responses, using a repeated social defeat stress model. The authors show that there are intrinsic differences in peripheral immune cell activation following stress between susceptible and resilient mice. Further, selective genetic knockout of the microRNA cluster miR106b∼25 in peripheral immune cells promoted stress resilience, suggesting that this cluster may represent a novel therapeutic target.

Here, **Nasca *et al.*** (pages 483–491) identified interrelated predictors of susceptibility and resilience to stress that are more accurate than single risk factors to explain the complexity of individual responses to social defeat stress in mice. The susceptible phenotype was characterized by presence of anxiety, decreased hippocampal volume, and elevated systemic interleukin-6. Further, the authors provide evidence that administration of acetyl-L-carnitine, an epigenetic modulator of glutamatergic function, acts as a novel rapid-acting agent to promote resilience. These findings provide a novel framework that may be useful to study the mechanisms that lead to stress-induced neurobiological and behavioral deficits.

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