Biological Psychiatry: Celebrating 50 Years

Commentary

The Neurobiology of Resilience: Complexity and Hope

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The societal burden of stress-related neuropsychiatric disorders is staggering. Major mental health sequelae of maladaptive responses to stress in humans include major depressive disorder and posttraumatic stress disorder (PTSD), although the risk of developing nearly every psychiatric condition is increased as a result of stress exposure (1). A driving hope for this field is that new insights into the mechanisms of stress resilience will lead to novel therapeutic discoveries. Over the past decade it has become increasingly apparent that the tendency to resist development of negative psychiatric consequences following extreme or prolonged stress is in fact a highly adaptive process. From this perspective, the most salient features of resilience in the face of stress likely reflect active regulation of key neurobehavioral systems aimed at the maintenance of homeostasis, rather than simply the absence of stress-related maladaptive changes (2). Moreover, individual differences in coping strategies mediated by sex and developmental factors play crucial roles in resilience (3). The neurobiological mechanisms of stress resilience are exceedingly complex. Detailed investigations of resilience mechanisms have implicated alterations in specific neurocircuits, epigenetic mechanisms, immune pathways, and microbiota-related pathways. Such studies are beginning to illuminate some consistent themes but in many cases are yielding more questions than answers. Perhaps this is to be expected given the nature of the topic, the inherent complexity of brain-behavior relationships, and the relative youth of the field. Still, patients are waiting for new treatments and the field is growing impatient. When will basic insights into the mechanisms of resilience yield therapeutic results for patients suffering from disorders such as major depressive disorder or PTSD? Or better yet, when will we be able to prevent the onset of these disabling disorders? In this special issue of *Biological Psychiatry*, the selected articles from basic, clinical, and translational perspectives address the topic of neurobiology of resilience; together these articles summarize the essential components of our knowledgebase concerning this important and rapidly expanding topic.

Cathomas *et al.* (4) provide an overview of the current understanding of neurobiological and neuroimmune mechanisms of resilience, informed primarily from work in rodents. The review begins with a discussion of key roles of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis in coordinating neurobehavioral responses to threat and other forms of stress, and it introduces the concepts of allostasis and allostatic load, originally described by McEwen *et al.* (5). Allostasis is an adaptive process designed to maintain homeostasis, while allostatic load refers to the “wear and tear” on neurobehavioral systems resulting from repeated stressors that outstrip the body’s homeostatic processes. The concepts of allostasis and allostatic load are helpful for the study of resilience because they provide a framework to understand how and why individuals’ responses to stress can differ markedly. Resilience can be understood as arising from the particular allostatic responses that are generated in an individual following stress. Within this context, Cathomas *et al.* (4) consider the concept of resilience as a process that requires integration of multiple central and peripheral systems, ranging from specific brain circuits to humoral factors of the immune system and changes at the interface between the brain and the periphery (the blood-brain barrier). Many of these key insights require further study as well as validation in humans.

Continuing with the theme of inflammation in the context of resilience, Pfau *et al.* (6) studied the role of microRNAs in mediating inflammatory and behavioral responses to stress in the social defeat model. Previous work showed preexisting differences in leukocyte release of interleukin-6 that predicted whether an individual animal will develop a susceptible or resilient phenotype (7). Because this suggests that intrinsic mechanisms within leukocytes play an important role in regulating the stress response, Pfau *et al.* (6) focused on epigenetic regulation by microRNAs as a mediator of individual differences in response to social defeat stress. Using isolated Ly6c^{high} monocytes from the blood of susceptible and resilient mice, the investigators examined microRNA expression via quantitative real-time polymerase chain reaction. They provide several lines of evidence causally linking miR-25-3p, a member of the miR-106b$\sim$25 cluster, in Ly6c^{high} monocytes to stress vulnerability. This early finding on the potential role of microRNAs in stress resilience should encourage substantially more work in this area.

One of the most powerful factors influencing vulnerability is that of childhood trauma and maltreatment, yet even under these extreme situations, we find subsets of resilient individuals. Rodman *et al.* (8) consider a powerful conceptual model of such resilience centered on the role of neural systems that underpin the cognitive control of emotion. Their model suggests that individual differences in the capacity to recruit prefrontal cortical control systems to regulate affective processing by the amygdala and related structures mediates a child’s response to maltreatment. To achieve this, they examined data from a longitudinal sample of 151 children 8 to 17 years of age (79 with and 72 without childhood maltreatment) who completed a cognitive reappraisal procedure while undergoing functional magnetic resonance imaging.

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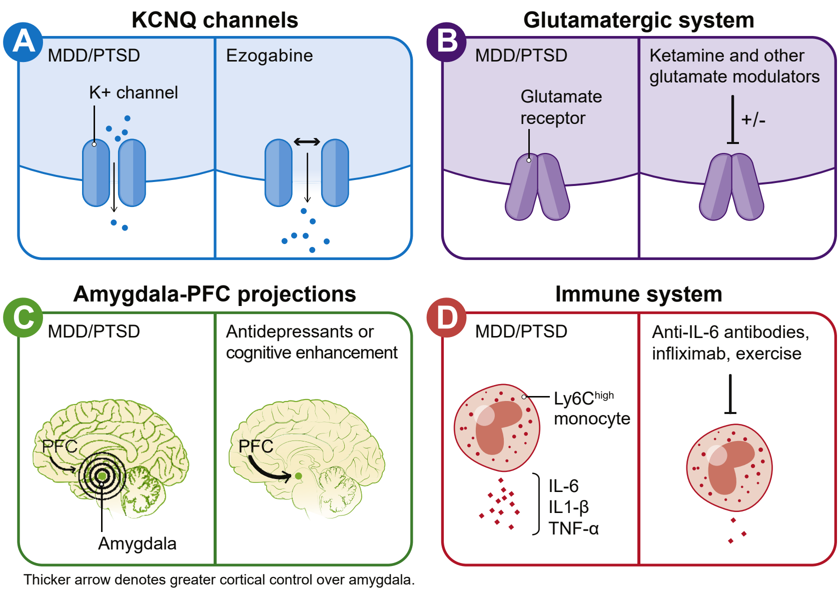

Figure 1. Novel therapeutic targets to promote stress resilience. **(A)** Drugs, such as the KCNQ (Kv7) voltage-gated potassium channel opener ezogabine, show antidepressant efficacy in a mouse social defeat model and potentially in patients with depression. Pharmacological approaches such as this may help treat stress-related disorders via enhancement of the brain's natural pro-resilience systems. **(B)** Drugs targeting glutamate receptors have shown the potential for rapid and robust antidepressant efficacy. The glutamate system is a key contributor to neuroplastic responses to stress and offers a rich array of targets for novel treatment discovery. **(C)** Resilience to stress is associated with greater cortical control over emotion-generating systems including the amygdala. Standard antidepressants and cognitive training have been shown to promote resilience by enhancing prefrontal cortical control of the amygdala. **(D)** Resilience to stress is associated with reduced activation of monocytes and lower levels of proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α. Anti-inflammatory drugs and physical exercise may promote resilience by reducing expression or function of these cytokines. MDD, major depressive disorder; PFC, prefrontal cortex; PTSD, posttraumatic stress disorder.

Compellingly, children who experienced maltreatment yet were able to regulate their amygdala responses to emotional stimuli were relatively protected from developing depression compared with maltreated children who were less able to regulate their amygdala responses to such stimuli. This suggests that strategies designed to enhance these systems may represent novel approaches either to protect individuals from the development of maladaptive responses to trauma or to treat individuals that have already developed depression or some other trauma-related sequelae.

Expanding these ideas further, Feder *et al.* (9) provide an authoritative review of neurobehavioral factors related to stress resilience in humans across the life span. The investigators work from a core assumption that resilience reflects stress responses that are "sufficient but not excessive" and "rapid and efficient psychobiological recovery" following stress. Consistent with the work of Rodman *et al.* (8), Feder *et al.* (9) review data supporting a model wherein manageable levels of stress exposure early in life may actually enhance the development of neural circuits that regulate emotion, thereby protecting individuals from the development of maladaptive consequences of stress later in life. They consider differing parenting styles and argue that a proresilience caregiving style is neither neglectful nor overprotective. Feder *et al.* (9) also review factors associated with resilience in adulthood and older age, including higher levels of dispositional optimism, greater cognitive reappraisal capacity, and the ability to develop and strengthen social support. What becomes clear is that resilience emerges from a complex ensemble of interrelated factors that ultimately arise from the interplay of distributed neural systems that include the anterior cingulate and prefrontal cortices, amygdala, and neuromodulatory systems. Importantly, the investigators conclude with a detailed consideration of resilience-based novel interventions targeting these systems. While still preliminary, the extant research encourages further pursuit of targeting neuropeptide Y, glutamate, and gamma-aminobutyric acid, as well as a class of potassium channels known as KCNQ channels (10). Ultimately, these molecular targets are hoped to regulate and optimize essential neural circuits that promote resilience and recovery from stress-related disorders.

While clearly much progress has been made to understand neurobiological mechanisms of risk versus resilience to stress, far less is known about the genetic contributions to resilience. Elbau *et al.* (11) argue that determining genetic variations that modify disease risk in the face of adversity may help identify fundamental mechanisms and pathways that promote resilience, thereby identifying new treatment targets. They specifically explore how human studies that investigate gene-by-environment interactions can illuminate resilience mechanisms. They base their discussion around recent conceptual frameworks for understanding gene-by-environment interactions such as the "match-mismatch" or "differential susceptibility" theories that strive to understand these interactions within the context of a unifying theory of general programming of susceptibility to environmental influences, no matter the valence. These conceptual models may address limitations of the common stress-diathesis model and identify new research directions.

One of the major goals of current psychiatric research is to define bona fide biomarkers of illness that will aid in diagnosis, treatment, or prevention. To this end, Nasca *et al.* (12) present original work considering multidimensional predictors of susceptibility and resilience in the context of the preclinical social defeat stress model using computational and molecular approaches. They find that the coexistence of anxiety, reduced hippocampal volume, and elevated interleukin-6 in mice prior to social stress predicted whether mice would develop a susceptible phenotype. Critically, the investigators were able to use this information to begin early treatment of susceptible mice with L-acetyl carnitine during social defeat to promote resilience behavior. The implication of these findings are quite profound given that the investigators used genetically identical inbred C57BL/6J mice. Their findings suggest that environmental factors alter developmental trajectories to determine stress vulnerability in adulthood and that one might predict such vulnerability in an unbiased way to enhance treatment outcomes. If this computational, predictive approach can be translated to clinical populations, the result on diagnosis and patient care would be tremendous.

The article by Hodes and Epperson (13) takes the perspective that resilience to trauma is a dynamic process shaped by both when the exposure occurs and the sex of an individual. They discuss overlapping end points from clinical and preclinical literature to examine how hormonal and epigenetic regulation of stress physiology changes across the life span in male and female individuals. Remarkably, responses to stress that occur during the same time period as the stressor (proximal) and responses occurring in a different time period than the stressor (distal) yield distinct behavioral and physiological outcomes. Within this context, the investigators discuss compelling evidence to suggest that male individuals more affected proximally to gestational and early life stress than female individuals. Female individuals are also affected by some gestational and early life stress, but the consequences generally emerge later in life, often following periods of gonadal hormonal changes such as puberty, pregnancy, and menopause. This work suggests that an integrated life span approach should have advantages for future research. This work also underscores the striking complexity of differential responses to stress.

Finally, DePierro *et al.* (14) address both the opportunities and considerable challenges associated with translating neurobiological findings related to resilience or PTSD to novel therapies for stress-related disorders. They discuss advances in pharmacological approaches to PTSD based on basic knowledge of the hypothalamic-pituitary-adrenal axis, the sympathoadrenal medullary system, and neuropeptide Y, among other systems. In particular, promising new advances related to the use of ketamine treatment (15) and 3,4-methylenedioxymethamphetamine–assisted psychotherapy in PTSD are described. While progress has been made, the reality is that fundamentally new, more effective treatments for PTSD continue to be elusive and the scope of approved pharmacotherapy treatment for PTSD is currently quite limited. In this context, the investigators strike a cautionary note concerning the near-term potential of "rational pharmacotherapy" in PTSD. Conversely, a case is made for "reverse-translation" based on the observations of the preliminary efficacy of novel, repurposed compounds. Clues from clinical observations are hoped to fuel a greater understanding of mechanisms of resilience and, ultimately, to yield novel targets for PTSD and related disorders.

Resilience is undeniably complex and multidetermined. As highlighted throughout this special issue, however, significant progress has been made in defining the genetic and neurobiological underpinnings of resilience. New clinical trials of novel therapeutics to harness the body's own natural resilience mechanisms are underway and some show early promise. Figure 1 shows some of the most promising treatment targets now under investigation. There are also a number of ongoing studies aimed at predicting susceptibility versus resilience in humans that will be a major step toward early detection and prevention in some cases. We hope that this issue has provided a roadmap for the future of resilience research. Though still in its infancy, resilience research holds great promise in defining new strategies to combat mental illness by promoting better psychological health in patients suffering from a range of stress-related disorders.

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