Biological Psychiatry

Commentary

Stress and Cognition: From Bench to Bedside?

Lars Schwabe and Nikolaos P. Daskalakis

Stressful events are ubiquitous in everyday life and can significantly impact mental health. In fact, there is hardly any mental disorder in which stress is not considered to be a major factor in the pathogenesis, maintenance, or relapse. This impact of stress on mental health is at least partly driven by stress-induced changes in cognitive processes, such as learning, memory, or decision making—and, in turn, alterations in these cognitive processes can influence the long-term effects of stress. Accordingly, the effects of stress on cognition, as well as the underlying mechanisms, have been the subject of intense scientific inquiry for decades (1–4). This research has been driven by the hope that a better mechanistic understanding could lead to improved interventions for stress-related mental disorders. Yet, to date, examples of successful translation of basic science findings on stress-induced changes in cognition into clinical practice remain scarce. Why is this translation so difficult? What are the main obstacles, and how might they be overcome?

This special issue of *Biological Psychiatry*—Stress and Cognition: From Bench to Bedside?—provides a state-of-the-art review of how stressful events impact the brain, cognition, and mental health. It covers recent advances, key neural and molecular mechanisms, and potential clinical applications, offering a foundation for renewed efforts to enhance treatments for stress-related mental disorders based on research on stress and cognition. The first section of this special issue summarizes recent insights into how stress-induced changes in the brain and cognition may promote resilience and adaptation to stressful events, as well as how these adaptive changes may become maladaptive, potentially contributing to stress-related psychopathologies. The second section reviews molecular, cellular, and neural mechanisms thought to underlie the detrimental effects of stress on cognition, stress-induced impairments of prefrontal cortex (PFC)–dependent cognitive functions, and the role of stress in age-related cognitive decline. The final section discusses potential treatment approaches for posttraumatic stress disorder (PTSD) that are derived from basic research on stress and cognition, along with the challenges that may impede the translation of basic science findings on stress and cognition into clinical practice—and opportunities to overcome these challenges.

Stress-Induced Changes in the Brain and Cognition: Tuned Toward Adaptation. When exposed to stressful events, the body initiates a coordinated cascade of physiological responses that involves numerous neurotransmitters, peptides, and hormones (5,6). Among the many stress response systems, two are particularly prominent: the rapidly acting autonomic nervous system, which triggers the release of adrenaline and noradrenaline, and the slower hypothalamic-pituitary-adrenal axis, which leads to the secretion of glucocorticoids. Through these mediators, stressful events can influence brain areas that are essential for cognitive processing. Importantly, the neural and cognitive changes in response to stressful events are not merely byproducts or detrimental but serve as integral components of an adaptive response to stressors.

The first review of this special issue, by Hermans *et al.* (7), highlights the adaptive nature of the acute stress response. In particular, the authors propose that the neurotransmitter and hormonal changes triggered by acute stress activate neural and cognitive resilience mechanisms that enable the organism to effectively cope with current and future stressors. For example, these responses are thought to promote predictions of potential threats and facilitate the storage of effective coping strategies, leading to memories of controllability and safety that support coping with stressors.

Similarly, Schwabe (8), in the second review, emphasizes that acute stress responses tune cognitive processing toward adaptation to ongoing and future stressors. Recent research shows that acute stressors enhance memory formation while reducing memory retrieval, mnemonic flexibility, and memory contextualization. Such changes are argued to facilitate adaptation by promoting efficient responding under stress and by enhancing storage of successful coping strategies. In addition, decontextualized memories can be integrated into more abstract conceptual knowledge structures that are essential for coping with novel threats (9). Schwabe argues that, while being generally adaptive, the exact same cognitive changes may become maladaptive, contributing to rigid behavior or generalized fear responding seen in stress-related psychopathologies. The transition from adaptive to maladaptive cognitive changes is thought to hinge on the interplay of stressor characteristics and individual predispositions.

Mechanisms of Stress-Related Mental Disorders. Methodological advances and the rise of new technologies, including single-cell genomics, have significantly improved our understanding of the molecular, cellular, and neural mechanisms by which stress affects cognition and mental health. The most recent discoveries at the molecular level are summarized in the review by Lugenbühl *et al.* (10). The authors discuss how genetic and epigenetic changes in noradrenaline and glucocorticoid signaling pathways alter brain function. These alterations include altered neuroplasticity, neurogenesis, and balance between excitatory and inhibitory neurons. Based on these insights, the authors discuss (epi)genetic risk factors for stress-related disorders, such as genetic variants in the locus

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of the corticotropin-releasing hormone receptor 1, which have been linked to increased vulnerability to PTSD.

A crucial region for stress effects on cognition is the PFC. Highly sensitive to catecholamines and glucocorticoids (11,12), the PFC is critically implicated in a broad range of cognitive functions, including working memory, cognitive control, memory retrieval, and control of emotional responses (13,14). In their review, Joyce *et al.* (15) summarize the cellular mechanisms by which stress and inflammation impair prefrontal functions. For instance, they argue that stress weakens dorsolateral PFC layer III connectivity by driving feedforward calcium cyclic adenosine phosphate opening of potassium channels, which is regulated by postsynaptic noradrenergic α_{2A}-adrenergic receptors and could be a treatment target.

Stress-induced dysfunction in limbic brain areas, including the amygdala and hippocampus (16,17), has been the predominant focus of stress research and may also contribute to cognitive impairment and Alzheimer's disease. While stress research has traditionally focused on mood- and anxiety-related disorders, accumulating evidence suggests that stress may also influence age-related cognitive decline and Alzheimer's disease. Lucassen *et al.* (18) discuss recent preclinical and clinical findings showing how stress during critical periods of brain development may increase the risk of Alzheimer's disease. In particular, the authors underscore that early-life stress can affect the brain's capacity to resist amyloid-β accumulation, a hallmark of Alzheimer's disease neuropathology. Collectively, these mechanistic insights could help to develop new strategies to prevent or treat stress-related mental disorders.

Toward Basic Science–Informed Treatment Approaches for Stress-Related Mental Disorders: Challenges and Future Perspectives. Several attempts have been made to translate basic science findings on stress and cognition into clinical interventions. For example, based on evidence that glucocorticoids can impair memory retrieval (19,20), studies have administered glucocorticoids to interfere with fear memory retrieval, showing beneficial effects on anxiety or PTSD symptoms (21). Maples-Keller *et al.* (22) provide a comprehensive overview of the multitude of basic science–based intervention approaches for PTSD, which range from specific behavioral strategies, such as precisely timed exposure therapy, to pharmacological approaches targeting glucocorticoid, noradrenergic, or glutamatergic activity, as well as device-based strategies including brain stimulation or virtual reality. These strategies may be used to modulate the initial consolidation of trauma memories or their proposed reconsolidation—a process thought to be triggered by memory retrieval that could offer a window of opportunity to retrospectively alter unwanted memories (23,24). In addition, such intervention strategies may be directed at augmenting outcomes of exposure therapy. Maples-Keller *et al.* acknowledge that findings related to these intervention strategies have been mixed. Indeed, effective and robust interventions informed by research on stress and cognition have yet to be fully established.

Why is clinical translation so challenging? In his commentary, Liberzon (25) outlines specific challenges for successful translation in this area, which can be categorized into 3 main types: conceptual, methodological, and individual variability–related. Conceptual challenges involve the precise definition of stress and the specific cognitive process targeted. This is closely linked to methodological challenges, particularly those associated with species differences. For instance, distinguishing between memory and performance in animal models can be difficult, and certain stressors may be unique to humans. Another methodological issue involves a lack of statistical power or general methodological rigor. Finally, translation is complicated by significant interindividual variability in background or vulnerability and in stressor characteristics, such as duration or type of stressor.

How might these challenges be addressed to facilitate translation? Beyond clearly defining what is meant by stress and the specific stress response system under investigation, greater methodological rigor and the implementation of open science principles may be essential to successful translation, as these can help to identify the most robust effects and mechanisms—those most likely to translate across levels of research and ultimately into clinical practice. Moreover, translation may be more successful if it follows incremental steps—from molecular to cellular levels, cellular to systems levels, systems to animal behavior and human cognition, and healthy individuals to patients. Importantly, this translational ladder is not a one-way street. In addition to bench-to-bedside translation, bedside-to-bench reverse translation is also essential, starting with clinical symptoms that are then examined at the cognitive, systems, cellular, and molecular levels (Figure 1). This bidirectional process of translation across levels of investigation, with rigorous methodological standards, could enhance translational success and hopefully pave the way to more effective treatments for stress-related mental disorders.

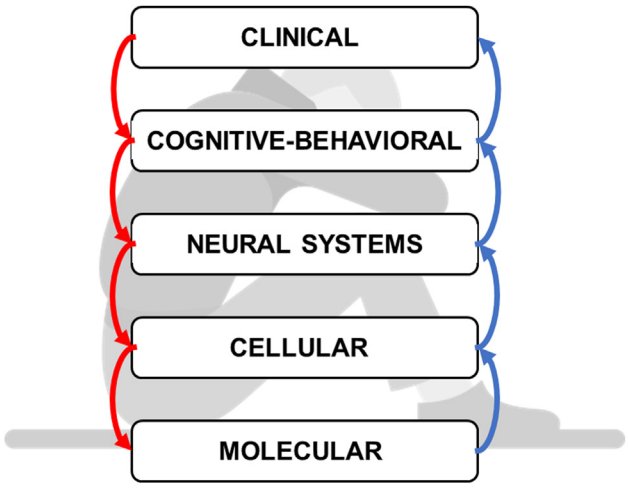

Figure 1. Iterative process of translation across levels of investigation. Successful translation requires incremental steps, from molecular to cellular levels, cellular to systems levels, systems to animal behavior and human cognition, and human behavior to clinical symptoms—and vice versa. (Background image designed by Afian Rochmah Afif from flaticons.com.)

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Article Information

From the Department of Cognitive Psychology, Institute of Psychology, University of Hamburg, Hamburg, Germany (LS); Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, Massachusetts (NPD); and Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts (NPD).

Address correspondence to Lars Schwabe, Ph.D., at lars.schwabe@uni-hamburg.de.

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