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Introduction to Recent Advances in Understanding and Treatment of Posttraumatic Stress and Trauma-Related Disorders:

Special Issue on PTSD

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Post-traumatic stress disorder (PTSD) is a maladaptive and debilitating psychiatric syndrome with significant risk for impaired functioning, comorbidity, and suicide. It is characterized by an extreme sense of fear at the time of trauma occurrence, with characteristic re-experiencing, avoidance, and hyperarousal symptoms in the months and years following the trauma. PTSD has a prevalence of approximately 6%, but can occur in a much higher percentage of subjects who have experienced severe psychological trauma, such as combat veterans, refugees, and assault victims.¹ The differential risk determining those who do vs. those who do not develop PTSD is multi-factorial. It is in part genetic, with at least 30–40% risk heritability for PTSD following trauma; and in part depends on past personal history, including adult and childhood trauma and psychological factors which may differentially mediate fear and emotion regulation.² Therefore, PTSD is among the most likely of psychiatric disorders to be understood from the perspective of environmental influences interacting with biological vulnerability, because diagnosis requires a specific, highly traumatizing experience. By combining biomarker approaches with a mechanistic understanding of fear- and stress-related neural circuitry, great progress is possible in the understanding, diagnosis, and development of new treatments for PTSD.

This edition of *Harvard Review of Psychiatry*, 'Special Issue on PTSD,' focuses on recent advances in understanding and treatment of posttraumatic stress and trauma-related disorders. Given the increased awareness of trauma in civilian populations, with interpersonal violence and assault, and in military cohorts and war-torn regions, we feel that this is a particularly timely topic in Mental Health. Furthermore, there are currently a number of reasonably effective pharmacotherapies and psychotherapies, and recent advances in understanding its underlying neurobiology suggest that rational, neurobiologically-informed, targeted therapies may not be far off.³ This edition will review the

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Disclosures:

Dr. Ressler is on the Scientific Advisory Boards for Resilience Therapeutics, Sheppard Pratt-Lieber Research Institute, Laureate Institute for Brain Research, The Army STARRS Project, and the UCSD VA Center of Excellence for Stress and Mental Health – CESAMH. He holds patents for use of D-cycloserine and psychotherapy, targeting PAC1 receptor for extinction, targeting tachykinin 2 for prevention of fear, targeting angiotensin to improve extinction of fear. Dr. Ressler is also founding member of Extinction Pharmaceuticals to develop d-Cycloserine to augment the effectiveness of psychotherapy. He has received no income within the last 3 years from any of the above intellectual property. He also provides fee-for-service consultation for Biogen and Resilience Therapeutics. He receives or has received research funding from NIMH, HHMI, NARSAD, and the Burroughs Wellcome Foundation.

neurophysiology of PTSD, particularly related to the dysregulated fear and threat response that is so pervasive in PTSD. We then examine the neuroimaging findings associated with PTSD, as well as the interaction of the stress pathways on hippocampal structure and function. The special issue includes an examination of how an understanding of stress resilience may protect from and prevent PTSD following trauma exposure, and ends with an updated review of empirically validated psychotherapeutic and pharmacological approaches to treating PTSD.

In the first manuscript by Jovanovic and Norrholm, “Fear Processing, Psychophysiology, and PTSD,” they provide a comprehensive review of possibly the best understood quantitative phenotypes underlying PTSD.⁴ This review examines the different aspects of fear and threat processing in mammals, pointing out how this evolutionarily conserved survival reflex provides a unique and powerful window into understanding PTSD. As detailed by the authors, these studies have revealed that impairments in fear overexpression, overgeneralization, inhibition, and extinction represent a fundamental component of PTSD biology and treatment targeting. In fact, the most empirically validated treatments for PTSD – exposure and related therapy methods – are widely viewed as utilizing the neural mechanisms of fear extinction. The combination of technologies to provide clinicians with real-time physiology, along with our rapidly expanding understanding of these phenotypes in PTSD, may provide for exciting and important new approaches to intervening in posttraumatic stress.

In their manuscript, “Functional Neuroanatomy of Emotion and Its Regulation in PTSD,” Fitzgerald and colleagues examine another critical component of PTSD – emotion dysregulation – and how this may be represented at the level of brain function.⁵ The authors note that emotion dysregulation, arising from exaggerated response to threat and/or inability to regulate negative emotional states, plays a defining role in the pathophysiology of PTSD. This fascinating review examines the neural biomarkers of emotional responding and symptom provocation, as well as implicit and explicit emotion regulation, using modern neuroimaging tools. In addition to reviewing the well-established observation of increased activation in amygdala and insula in response to negative stimuli, the authors also document the roles of anterior cingulate and prefrontal cortex during emotion regulation processes. Overall this review helps to clarify some of the known intermediate phenotypes related to PTSD, and how they can also be addressed with neural biomarkers, further contributing to our understanding of the different components of this syndrome.

Szezko and colleagues discuss two additional well-established biomarkers of PTSD, stress axis dysregulation and hippocampal dysfunction, in their manuscript, “Glucocorticoids and Hippocampal Functioning in PTSD.”⁶ Observations of cortisol-mediated enhanced sensitivity of the hypothalamic-pituitary-adrenal axis have long been associated with PTSD. Furthermore, smaller hippocampal volumes have been repeatedly identified as associated with PTSD, and this finding was recently replicated in a large multisite analysis.⁷ Notably, previous reports suggested that hippocampal volume and function may be a risk factor, instead of a result of, trauma exposure.⁸ Szezko and colleagues nicely review these findings, spanning the HPA axis and its regulation by hippocampal function, providing a more clear

understanding of these critical endocrine and neural pathways in mediating information processing and stress regulation after trauma.

PTSD is one of the few psychiatric disorders in which a critical, and possibly the most important, causal component is understood and identifiable - that of the traumatic incident. While averting the occurrence of the trauma would be the ideal prevention, that is generally beyond the scope of the medical field. However, secondary prevention – with early intervention to disrupt the development of PTSD following trauma exposure, as well as enhancing resilience in advance for those who experience trauma, may be within reach. Feder and Horn examine these components in their article, “Understanding Resilience and Preventing and Treating PTSD.”⁹ As stated by the authors, translating our expanding knowledge of the neurobiology of resilience additionally promises to yield novel preventions and therapeutic strategies for the treatment of PTSD.

Charney and colleagues present current best practices in their manuscript, “Evidenced-based Treatment of Posttraumatic Stress Disorder (PTSD): An Updated Review of Validated Psychotherapeutic and Pharmacological Approaches.”¹⁰ This review provides a concise overview of the empirical literature examining current treatment approaches. The authors examine the evidence for a variety of psychotherapies, which have the strongest evidence base in treating PTSD. Many of these treatments build upon improving fear extinction and emotion regulation, outlined above, as critical dysfunctions in the syndrome. They then review the evidence for pharmacotherapy, noting that to-date the only FDA approved medications for PTSD remain selective serotonin reuptake inhibitors; but a large number of off-label medications are also utilized for symptom improvement. This excellent and timely review reminds us that while there are many relatively good treatments available for those suffering from PTSD, a further understanding of the different subtypes of the syndrome and what treatments are best for them, is critical to progress.

Posttraumatic stress and trauma-related disorders are debilitating and common. Current treatments can be quite beneficial in some patients, and identifying untreated PTSD among its comorbid and similar conditions is critical to helping those in need.¹¹ However, many patients do not recover or remain symptomatic, and improvements in prevention and treatment are much needed. Advances in neurobiology and behavioral science are needed for truly targeted, innovative, robust treatments and preventions. The conserved biology of fear processing and emotion regulation provide particularly tractable targets for intervention. PTSD, while one of the most recently defined syndromes in psychiatry, may also be one of the earliest to benefit from progress in neurobiology and advances in translational approaches to brain function and behavior.

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