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Finding the Neural Basis of Pediatric Posttraumatic Stress Disorder

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What is the neural basis of the DSM-5–defined pediatric posttraumatic stress disorder (PTSD)? The DSM-5 defines PTSD as a maladaptive response to at least one severe, threatening event (1). The symptoms that arise ostensibly involve neural systems underlying threat learning, the stress response, and emotion regulation. In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Heyn *et al.* (2) demonstrate a disciplined approach to identifying major neural systems associated with pediatric PTSD. Their approach has three major aspects: a well-defined PTSD phenotype, an exploratory, whole-brain analysis, and a longitudinal design. The importance of this work is in its empirical implication of prefrontal and affective regions supporting emerging theories of affective dysfunction in pediatric PTSD.

With regard to phenotyping, Heyn *et al.* (2) use a combination of the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (3) supplemented with Clinician-Administered PTSD Scale (4). Common to both, a severe traumatic event is established, and symptoms are linked to that event. Thus, all individuals in the PTSD group experienced at least one severe traumatic event, and PTSD-associated symptoms were linked to that event. Such clarity in clinical phenotyping improves reproducibility and comparisons with other studies, such as the effect of increasing exposure to Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version–style traumatic events to social and executive cognitive dysfunction (5).

Moreover, defining PTSD by a reaction to a traumatic event allows Heyn *et al.* (2) to invoke a promising theory based on a substantial basic literature on the neural basis of threat-learning to explain their results (6). In this formulation, PTSD represents a set of threat associations that produce a maladaptive response. The response is a defensive state induced by associations, e.g., "triggers," that do not represent a presently valid threat. Of course, a first step is to establish that this system is related to pediatric PTSD. The significance of doing so has direct implications for treatment development. Widely used exposure-based treatments target this system to reduce maladaptive responses to threat associations, and so it may be that exposure-based therapies for PTSD may be improved when considering this theory (7).

While this phenotype does establish a threatening event and associated symptoms, it does not address the degree of sustained stress. Often a point of confusion, it cannot be assumed that the pathophysiology of PTSD described here is same for maladaptive behavior and distress following chronic deprivation or chronic stress (e.g., toxic stress). Keeping focused on a clearly defined clinical phenotype may be a way of reducing the confusion among clinicians and investigators as to what comprises PTSD. The current Research Domain Criteria divides "acute threat" and "sustained threat" as separable systems that differentiate the two for future research.

With regard to an exploratory approach, the study maps brain differences between youth with PTSD and typically developing youth with no psychopathology (TD). It uses established, exploratory techniques surveying PTSD-TD differences in structure via voxel-based morphometry and function via resting-state functional connectivity. Both techniques are ideal for in vivo exploration, demonstrating the utility of magnetic resonance imaging to implicate regions in the pathophysiology of mental illness. The reliance on exploratory work is critical when we know little of the system in which any future theory will operate—here, the neural basis of PTSD symptoms.

Heyn *et al.* (2) have a two-staged approach, using volume changes found by morphometry as a localizer for functional connectivity. Averaged across time, PTSD-TD volume differences were found in four prefrontal regions, the precentral gyrus, and the posterior cingulate cortex. Over the course of a year, decreases in dorsolateral prefrontal cortex volumes found in the TD were not observed in the PTSD group. In the second stage, Heyn *et al.* (2) lean on theory a bit to constrain their analyses to search for PTSD-TD differences in functional connectivity between the prefrontal regions found in morphometry stage and the bilateral amygdala and hippocampus. These regions are critical mediators of associative learning for threat (described above) as well as emotion regulation, described by a complementary theory in affective neuroscience that is also relevant for PTSD. This theory describes prefrontal–subcortical circuitry involvement in context-sensitive regulation of emotions (8). Here the PTSD-TD differences in connectivity involving three prefrontal regions were largely driven by changes in prefrontal–amygdala/hippocampal connectivity over time.

Overall, these techniques implicate these regions in the pathophysiology of PTSD or something related to having PTSD, e.g., a general mental illness factor, treatment effects, and symptom changes. The addition of a functional connectivity arm provides some external validation for the morphometry results. It provides evidence that this relationship has something to do with prefrontal–amygdala/hippocampal connectivity predicted by major theories in affective neuroscience. As Heyn *et al.* (2) are careful to note, the functional significance of these findings cannot be known from their data. Regardless, empirical evidence implicating these regions with PTSD and their striking correspondence with emerging theory is an advance.

Another important aspect of this study is the longitudinal approach. The adolescent brain changes. Failing to capture

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this change would have clearly cost Heyn *et al.* (2) important findings in connectivity. It also makes the study more demanding from a technical standpoint. In clinical research, establishing safety and following individuals' treatments substantially increases the effort to conduct the study. As part of the nature of clinical studies, no interference in standard treatment is acceptable. While it is encouraging to see symptom improvement and treatment, this complicates any interpretation of the results. Indeed, the authors discuss the implications of medication use on type II error. However, it is critical to appreciate that mechanisms of treatment and recovery are of as much clinical interest as pathophysiology. Heyn *et al.* (2) have a limited sample but do attempt preliminary analyses that only a longitudinal design would allow.

In sum, longitudinal pediatric neuroimaging studies involving careful clinical phenotyping are of high value. Heyn *et al.* (2) advance our knowledge of pediatric PTSD by linking it with neural systems underlying threat learning and context-sensitive emotion regulation.

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Article Information

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