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Commentary

Post-trauma brain: A commentary on functional brain alterations after trauma and implications to posttraumatic stress disorder

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Posttraumatic stress disorder (PTSD) is a highly debilitating psychiatric condition that develops in a subset of individuals following a traumatic event, such as a threat of death, serious injury or sexual assault [1]. Over the past two decades, substantial body of research has focused on key neural regions and circuits that play a role in pathogenesis and maintenance of PTSD symptoms [2,3]. More specifically, hyper-activation of amygdala, insula, and dorsal anterior cingulate cortex, as well as hypo-activation in ventral medial prefrontal cortex and altered function of hippocampus have been repeatedly reported [4,5]. Moreover, PTSD has been consistently found to be associated with increased functional connectivity within Salience Network (SN; linked to threat and salience detection with key nodes in dorsal anterior cingulate cortex, insula/operculum and amygdala) [3,6], decreased connectivity within Default-Mode Network (DMN; linked to mind wandering, autobiographical memory and self-referential processes and comprised of posterior cingulate cortex, ventral medial/subgenual prefrontal cortex and hippocampus) [3,7], as well as with functional SN-DMN desegregation (i.e., greater inter-network connectivity) [3,8,9]. Alterations in connectivity patterns of SN and DMN with other networks such as Frontoparietal Network (FPN) and attention networks, have also been reported in PTSD. Specifically, increased connectivity between SN and ventral and dorsal attention networks (VAN and DAN, respectively) [8], decreased connectivity between DMN and Frontoparietal Network [10,11], as well as increased connectivity between SN and Frontoparietal Network [9] (Table 1).

Notably, much of the literature is based on a comparison of PTSD patients to non-trauma-exposed controls, which raises the question of the effect of trauma exposure itself on the reported neural patterns. Studies that did include trauma-exposed controls and compared them to PTSD patients, have been mainly utilizing a two-group design, without analyzing non-trauma-exposed controls [12-15]. As such, findings from these studies contribute to the knowledge of PTSD mechanisms, but not to the understanding of the neural correlates of trauma exposure per se. In the next paragraphs of the commentary, we will summarize the existing literature on effects of trauma on functional neural patterns, discuss it in relation to the alterations reported in the PTSD literature, and focus on a recent study from our group which included a three-group design (PTSD patients, trauma-exposed and non-exposed controls). We will then discuss the significance of these findings, what they could teach us about vulnerability and resilience mechanisms and how they could guide research design and treatment approaches.

To date, empirical evidence of functional neural changes associated with traumatic exposure is rather limited. Several studies demonstrated elevated activity of regions of SN (insula, dorsal anterior cingulate cortex and amygdala), as well as greater within-SN connectivity (between amygdala and insula), as linked to experiencing trauma [16-19]. In this context, van Marle et al. [20] and our group [3] proposed that greater within-SN connectivity following acute psychological stress may underline the sustained state of hypervigilance. Studies that investigated acute stress and related changes in functional connectivity patterns showed that stress-induction is associated with increased within-SN connectivity and decreased within-DMN connectivity [21]. Interestingly, trauma-exposed controls were found to exhibit altered within-DMN connectivity compared to non-trauma-exposed controls, a connectivity which was also associated with dissociation symptoms after trauma [19,22].

Table 1: Summary of dysregulations of large-scale networks in PTSD.

	FPN dLPFC, vLPFC	VAN IFG, TPJ	DAN MFG, PPC, FEF	SN Amy, Insula, dACC	DMN vmPFC, PCC, Hpc
DMN Autobiographical memory Mind wandering Self-referential processing	↓ [10,11]	-	-	↑ [3,8,9]	↓ [3,7]
SN Threat detection	↑ [9]	↑ [8]	↑ [8]	↑ [3,6]	
DAN Top-down voluntary orienting	-	-	-		
VAN Alerting Reorienting attention to unexpected stimuli	-	-			
FPN Top-down control emotional regulation	-				

Arrows illustrate increased or decreased within or between-network connectivity in individuals with PTSD compared to healthy controls. Dashes illustrate lack of consistent findings on PTSD-related alterations in connectivity patterns within and between specific large-scale networks. Amy: Amygdala; dACC: Dorsal Anterior Cingulate; FEF: Frontal Eyes Fields; Hpc: Hippocampus; IFG: Inferior Frontal Gyrus, MFG: Middle Frontal Gyrus; PCC: Posterior Cingulate Cortex; PPC: Posterior Parietal Cortex; TPJ: Temporal Parietal Junction; vmPFC, dlPFC, vlPFC: ventromedial, dorsolateral, ventrolateral Prefrontal Cortex.

Furthermore, trauma-exposed controls displayed increased activity in regions of the prefrontal cortex (part of DMN), relative to both non-trauma-exposed and PTSD groups [23,24], although lower activity in both trauma-exposed controls and PTSD groups compared to a non-trauma-exposed group was also shown [24,25]. Trauma-exposed controls were also found to be associated with greater connectivity between regions of prefrontal cortex and ventral striatum, which has been linked to anhedonia symptoms [26,27]. Further research is needed to clarify effects of trauma exposure on DMN and other networks, as well as on symptoms and behavioral responses that occur in the aftermath of trauma. Notably, a three-group design, involving a group of trauma-unexposed healthy controls is particularly useful, as it allows to distinguish between effects of trauma exposure per se, from those associated with PTSD development.

A recent study by our group utilized a three-group design, examining the neural correlates of trauma exposure in a non-treatment seeking adolescent population during resting-state functional MRI [28]. There, we indeed replicated some of the findings previously reported in PTSD patients (e.g., lower within-DMN and greater SN-DMN connectivity), but also highlighted the effect of trauma exposure on neural function. Specifically, trauma-exposed controls exhibited greater within-SN connectivity, compared to non-trauma-exposed controls. The trauma-exposed group also showed greater connectivity between SN and DAN (specifically, between amygdala and superior parietal lobule), as well as lower connectivity between DMN and DAN (between hippocampus and middle frontal gyrus). Interestingly, these patterns were not different between adolescents with PTSD symptoms and the trauma-exposed non-PTSD group, suggesting that these altered connectivities are likely the result of a traumatic exposure itself. The altered connectivity with DAN similarly suggests that trauma exposure may drive some of the altered connectivity with attention networks reported in PTSD [29].

Alterations that are found in both trauma-exposed individuals and in PTSD patients could represent vulnerability factors, which increase risk to develop symptomatology, in conjunction with other factors that are absent in the trauma-exposed group alone. Such is the greater within-SN connectivity [3,6,30-32]. Greater within-SN connectivity after a stressful event is also consistent with prior trauma literature [20,33], and could represent a state of hypervigilance that could increase risk to develop PTSD after subsequent trauma. Similarly, the finding of greater SN-DAN connectivity after trauma [28] is consistent with a neural alteration reported in PTSD patients and could relate to disrupted attention reported in these patients [29]. Interestingly, trauma exposure in this study was associated with lower DMN-DAN connectivity [28], a pattern not seen in PTSD patients. It is possible that this represents a better segregation of the DMN and DAN, that could serve as a protective factor or mechanism of resilience, protecting trauma-exposed individuals from PTSD development. Further research of PTSD patients and trauma-exposed individuals is needed to better understand both the pathophysiologic and the adaptive processes involved in PTSD development.

Importantly, while the Sheynin et al. study utilized a cross-sectional design [28], ideally, future research will also utilize a prospective longitudinal approach. If participants could be recruited at the time or even before the trauma (identifying high-risk population), it will help to pinpoint the pre-existing vulnerability factors, isolating them from trauma and disorder-related underlying

mechanisms. Longitudinal assessments at multiple time points would be beneficial not only to better understand the process of PTSD development, but also to establish causative links that are not possible based on cross-sectional data alone. For instance, by studying individuals pre and post exposure to stressful events during a military service, Admon et al. found that lower within-DMN connectivity (between hippocampus and ventromedial prefrontal cortex) is a consequence of trauma that might contribute to PTSD symptoms, while greater activation in SN (amygdala) before traumatic exposure could put individuals in higher risk to develop PTSD symptoms later [34,35]. If the identification of "high-risk" is not feasible, assessment in the early aftermath of trauma (before PTSD is established and early in pathophysiologic process) will help to capture early emerging symptoms, and to discriminate them from transient changes [36]. Importantly, fluctuation in clinical picture within first six months following the trauma had been observed by us and colleagues [36], suggesting that more stable clinical picture might emerge later on. In this case, final assessment in longitudinal studies should be conducted within 9-12 months from trauma, or sometime after the 1-year period (to avoid 1-year "anniversary" that has been shown to be associated with exacerbation of traumatic symptoms [37]).

Finally, understanding of neural correlates of trauma per se (distinct from underlying mechanisms of PTSD) not only contributes to existing knowledge on resilience and PTSD pathogenesis, but might be able to assist in guiding the choice of treatment approaches. If consistent patterns of functional connectivity and activation associated with trauma exposure can be established, it could have a prognostic value, identifying cases when secondary prevention could be helpful. If these patterns also lead to better understanding of PTSD pathophysiology, this would assist with mechanistic understanding of PTSD and the development of mechanism-based treatments. In sum, this commentary highlighted the importance of studying trauma-exposed healthy controls, to better understand effects of trauma alone, as well as in the larger context of the neural alterations reported in PTSD patients. Its importance lies not only in the greater understanding of symptoms development in PTSD, but also in its potential to inform decisions made by researchers and clinicians in the field.

Conflict of Interests

No conflict of interest reported by authors.

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