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Intrinsic Connectivity Networks in Posttraumatic Stress Disorder: A Systematic Graph Theory Approach

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Abstract

The Methodological Question Being Addressed: Can fMRI-derived restricted-network metrics serve as a robust biomarker of PTSD symptomatology? Can these network-analyses identify abnormalities that can be targeted using circuit-based therapeutics?

Introduction: Circuit-based abnormalities have long been proposed in PTSD and the need for circuit-based treatment is increasingly recognized in the field. Yet, the majority of PTSD neuroimaging literature to date has been region based evidence, that is speculated to reflect circuit/network level disturbances. Disruption in the default mode network (DMN) has been implicated in numerous neuropsychiatric disorders, including posttraumatic stress disorder (PTSD). Furthermore, unlike other intrinsic connectivity networks (ICNs), the DMN is active at rest during internally-focused tasks, and suppressed during goal-directed tasks. This makes the DMN a prime target for biomarker development, since the resting-state functional paradigm is convenient to recreate, and likely to be consistent, across studies. Despite its apparent importance, the DMN has not been fully investigated in PTSD, where previous studies are either limited to a small number of seeds or are not ICN-specific. Recent advances in neuroimaging and graph theory now permit the systematic exploration of intrinsic brain networks.

Methods: We used resting-state functional magnetic resonance imaging (fMRI), diffusion MRI, and graph theoretical analyses to systematically examine the DMN connectivity and its relationship with PTSD severity in a cohort of 65 combat-exposed US Veterans. We employed metrics that index overall connectivity strength, network integration (global efficiency), and network segregation (clustering coefficient). Then, we conducted a modularity and network-based statistical analysis to identify DMN regions of particular importance in PTSD. Salience and central executive networks as well as ICN-to-ICN connectivity was also studied in an exploratory analysis. Finally, structural connectivity analyses were used to probe whether white matter abnormalities are associated with (i.e., potentially underlie) the identified functional DMN changes.

Results: We found decreased DMN functional connectivity strength to be associated with increased PTSD symptom severity. Further topological characterization revealed decreased functional integration and increased segregation in subjects with severe PTSD. Modularity and network-based statistical analyses revealed a medial prefrontal dysmodularity. Analysis of the diffusion networks revealed no alterations in medial prefrontal structural connectivity.

Conclusions: DMN abnormalities in patients with severe PTSD symptoms are characterized by decreased overall interconnections. Particularly affected are long-range integrative connections, along with increased segregation in the medial prefrontal cortex. These findings in PTSD contrast with prior evidence in major depressive disorder where an opposite pattern of DMN functional connectivity, i.e., increased within-DMN connectivity strength has been described. This may indicate a potential for specificity in DMN-based functional connectivity biomarkers. The DMN measures established in this study may serve as a biomarker of disease severity and could have potential utility in developing circuit-based therapeutics.

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