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Brain Network Disturbance Related to Posttraumatic Stress and Traumatic Brain Injury in Veterans

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ABSTRACT

BACKGROUND: Understanding the neural causes and consequences of posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) is a high research priority, given the high rates of associated disability and suicide. Despite remarkable progress in elucidating the brain mechanisms of PTSD and mTBI, a comprehensive understanding of these conditions at the level of brain networks has yet to be achieved. The present study sought to identify functional brain networks and topological properties (measures of network organization and function) related to current PTSD severity and mTBI.

METHODS: Graph theoretic tools were used to analyze resting-state functional magnetic resonance imaging data from 208 veterans of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn, all of whom had experienced a traumatic event qualifying for PTSD criterion A. Analyses identified brain networks and topological network properties linked to current PTSD symptom severity, mTBI, and the interaction between PTSD and mTBI.

RESULTS: Two brain networks were identified in which weaker connectivity was linked to higher PTSD re-experiencing symptoms, one of which was present only in veterans with comorbid mTBI. Re-experiencing was also linked to worse functional segregation (necessary for specialized processing) and diminished influence of key regions on the network, including the hippocampus.

CONCLUSIONS: Findings of this study demonstrate that PTSD re-experiencing symptoms are linked to weakened connectivity in a network involved in providing contextual information. A similar relationship was found in a separate network typically engaged in the gating of working memory, but only in veterans with mTBI.

Keywords: Posttraumatic stress disorder, Traumatic brain injury, Brain network, Graph theory, Hippocampus, fMRI

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The psychological and physical consequences of trauma can be devastating to affected individuals and their families. U.S. veterans of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn experience particularly high rates of trauma-related conditions, such as posttraumatic stress disorder (PTSD) (1) and traumatic brain injury (TBI) (2). Understanding the neural causes and consequences of these conditions has been labeled a high research priority (3), owing to the high rates of disability (4) and suicide associated with trauma (5,6).

Despite remarkable progress in elucidating the brain mechanisms of PTSD and TBI, a comprehensive understanding of these conditions at the level of brain networks has yet to be achieved. Mapping interactions between brain regions, as opposed to solely activity within regions, is crucial for precisely modeling the neural pathology of PTSD and TBI (7,8). Prominent theoretical models of the brain networks involved in PTSD propose that top-down control over the amygdala by the medial prefrontal cortex (PFC) structures is deficient, allowing amygdala responses (e.g., to threat cues) to remain unregulated (9–11). Suvak and Barrett (12) posited that this amygdala dysregulation is linked specifically to the hyperarousal PTSD symptom cluster. These researchers also proposed that the re-experiencing symptom cluster is related to hippocampus hypoactivation (13), which is thought to contribute to a failure to construct contextually nuanced memories. These models suggest specificity in the functional pathology associated with different sets of PTSD symptoms.

To date, no models have been proposed regarding the brain networks disrupted in mild traumatic brain injury (mTBI) or in the interaction between mTBI and PTSD, making this a research area particularly in need of exploration. However, extant evidence indicates that mTBI increases the incidence and severity of PTSD (14). Thus, the presence of mTBI may exacerbate PTSD-related network disruption.

Although research has begun to test models of PTSD-related network disruption (15,16), the methods used to date examined coupling only between pairs of regions, without taking into account the role of that connection within the greater network. In addition, these methods examined connectivity only with a set of a priori "seed" regions, which can lead to important connections being missed (i.e., connections that do not include a seed region). A missed connection is particularly likely to occur when only a few seed regions are examined, as has been the case in existing studies. As a consequence, our understanding of

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trauma-related disturbance in brain networks is limited. For example, although research has found support for disturbed top-down PFC↔amygdala coupling (16), it is unclear whether this aberrant coupling is accompanied by disruption within the top-down control network itself. Disruption in top-down PFC networks would suggest that disturbed amygdala coupling is due to a difficulty engaging top-down control rather than (or in addition to) the amygdala being hyperactive to such a degree that top-down control is deficient.

More recent methodologic advances, in particular, graph theory (17,18), allow for an increasingly sophisticated analysis of brain networks at a level of complexity that was impossible in previous work. Specifically, graph theory examines all possible network connections and elucidates key topological properties of the overall network and subnetworks and the function of regions within local and global networks (19). Categories of topological properties include the following: functional segregation—how optimized the network is for specialized processing; functional integration—how well the network can combine specialized information across distributed regions; and centrality—how well a particular region facilitates network intercommunication (19). These properties can delineate the functional mechanisms by which altered network structure contributes to PTSD and TBI pathology. For example, measures of functional segregation can be used to assess the integrity of network function in PFC top-down control networks, providing insight into the mechanism leading to disrupted regulation of subcortical structures (e.g., amygdala). Similarly, measures of centrality can be used to assess the influence of the hippocampus on the overall network, providing insight into whether hippocampal hypoactivation is accompanied by a disruption in the importance of the hippocampus for network functioning.

To address these critical gaps, we applied graph theoretic tools to resting-state functional magnetic resonance imaging (fMRI) to identify functional networks and topological properties related to current PTSD severity and mTBI in 208 veterans of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn, all of whom experienced at least one traumatic event. Resting-state fMRI was used (vs. diffusion magnetic resonance imaging, which indexes white matter tracts) because it assays the functional relationship between regions. To our knowledge, this sample is the largest used to date to study trauma-related brain networks. In contrast to most research in this area (15,16,20), we examined the interplay between PTSD severity and mTBI, owing to their high comorbidity, overlap in symptoms, and evidence that TBI increases the incidence and severity of PTSD (14). In addition to overall PTSD severity, we examined the constituent symptom clusters (re-experiencing, avoidance, hyperarousal) to capture potentially important heterogeneity in brain networks related to these phenotypes (12,16).

Based on theoretical and empirical work regarding the impact of PTSD on network function (9–12), we predicted that PTSD severity would be linked to disturbed amygdala connectivity with the medial PFC, decreased integrity of PFC networks (i.e., worse functional segregation), and decreased overall hippocampal coupling (i.e., worse centrality). Given evidence that TBI increases the incidence and severity of PTSD (14), we also predicted that mTBI would exacerbate PTSD-related network disturbances.

METHODS AND MATERIALS

Supplement 1 contains details regarding participants, assessment measures, and first-level processing.

Identification of Trauma-Related Network Connections

To identify network connections that varied with PTSD and mTBI, connectivity matrices were entered as dependent variables into the Network-Based Statistic (NBS) tool, version 1.2 (21). The first set of models focused on total current PTSD severity score (summed across symptom clusters). The first model in this set contained total current PTSD and mTBI as predictors, and the total PTSD × mTBI interaction was added in a second model. The second set of models focused on the three PTSD symptom clusters (re-experiencing, avoidance, hyperarousal). The first model in this set contained the three symptom clusters and mTBI as predictors, and symptom cluster × mTBI interactions were added in a second model. All models contained age and ethnicity nuisance covariates. An individual connection level threshold of $t = 2.9$ was used with intensity-based correction for multiple comparisons, 5000 permutations, and an overall corrected $\alpha < .05$.

The pairwise LiNGAM method (22) was used to gain initial insight into the overall direction of influence of the connections observed in NBS analyses. Given that this method requires nongaussian information to be retained in the time series (23), preprocessing was repeated substituting in the FMRIB Software Library nonlinear filter. For each connection, a pairwise LiNGAM coefficient was estimated for each participant, and a one-sample t test was computed with significance determined via permutation (5000 permutations).

Identification of Trauma-Related Graph Theoretic Properties

To identify graph theoretic properties that varied with PTSD and mTBI, connectivity matrices were entered into the Graph Theory GLM tool (www.nitrc.org/projects/metalab_gtg), which computes properties for each participant using the Brain Connectivity Toolbox (19). Properties for thresholded networks were computed across a range of density thresholds, and the area under the curve was computed for use in group-level analyses. Minimum density was chosen as the lowest value at which paths between all regions of interest (ROI) remained in a set of mean networks (mean across sample, networks created by stratifying across variables of interest). This procedure reduces potential bias introduced by choice of minimum density because the density threshold is more likely to be appropriate for all levels of variables of interest. Minimum density was .19 for positive connections and .16 for negative connections, and density step (increment used for computing different thresholds) was .01. Maximum density was specified as .6.

The following four graph theoretic properties were calculated for thresholded networks (19): 1) density—overall network connectivity (one value computed for entire network); 2) degree (indexing centrality)—the influence of a specific region on the overall network (one value computed per ROI); 3) global efficiency (indexing functional integration)—the efficiency of overall network communication (one value computed for entire network); and 4) local efficiency (indexing functional