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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

segregation)—the efficiency of communication in the local network surrounding a region (one value computed per ROI). An additional ROI-specific property was calculated on unthresholded networks: participation coefficient (indexing centrality)—the extent to which a region is connected with regions in different modules (one value computed per ROI). Modules are sets of regions having more within-module than between-module coupling, and modularity was computed on the mean (across sample) network using the Louvain algorithm followed by the Kernighan-Lin fine-tuning algorithm (10,000 repetitions, modularization with highest modularity chosen) (see Table S2 in Supplement 1 for module structure). Supplement 1 contains further information regarding the calculation and interpretation of the properties. Table S1 in Supplement 1 presents means and standard deviations.

The ROI-specific properties were examined only for ROIs found in the equivalent NBS analyses to have three or more differential connections. Properties were computed for positive and negative connections separately. Properties were entered as dependent variables in robust regressions in the Graph Theory GLM toolbox. Predictor models were the same as the NBS analyses; however, relationships were tested only for the predictor that was significant in the equivalent NBS analysis. Significance was determined via permutation tests (5000 repetitions). In addition to calculating significance for each test, permutation-based correction was used to correct for multiple comparisons across ROIs.

Relationship to Functional Disability

To determine the impact that differences in connections/graph properties may have on day-to-day functioning, significant dependent variables were correlated with World Health Organization Disability Assessment Schedule II. For NBS networks, all or a subset of connections in the network were averaged to create one variable. For connections/properties associated with the main effect of PTSD/clusters/mTBI, Pearson correlations were computed. For connections/properties associated with PTSD/clusters × mTBI interactions in which both mTBI groups exhibited effects, univariate analyses of variance were computed testing the interaction between connections/properties and mTBI. For interactions in which only one mTBI group exhibited an effect, Pearson correlations were computed within that group. Only significant analyses are reported.

RESULTS

Trauma-Related Network Connections

Total PTSD severity and mTBI were not associated with brain networks. When PTSD symptom clusters were examined, a network emerged in which higher levels of re-experiencing were linked to less connectivity among regions (order 15, size 15, corrected $p = .045$) (Figure 1), including several right hippocampal↔right PFC connections. Three of these connections evidenced a significant pairwise LiNGAM coefficient, providing insight into the mean direction of influence. Specifically, the sign of a significant pairwise LiNGAM coefficient indicates whether region A is influencing region B or vice versa. Significant pairwise LiNGAM coefficients were found for right caudal anterior cingulate cortex→right hippocampus ($\Lambda = .003$, $p = .026$), right caudal middle frontal gyrus (MFG)→right hippocampus ($\Lambda = .002$, $p = .042$), and right superior frontal gyrus→right hippocampus ($\Lambda = .002$, $p = .042$). Thus, it appears that right PFC regions significant influence the hippocampus.

Decreased right hippocampal↔right PFC coupling was related to worse daily functioning on the World Health Organization Disability Assessment Schedule II, underscoring the functional importance of this network. Specifically, mean connection correlated with the number of days that veterans reported being totally unable to carry out usual activities ($r = -.151$, $p = .036$) and the number of days veterans reported having to reduce usual activities ($r = -.161$, $p = .025$).

When interactions between PTSD symptom clusters and mTBI were examined, we discovered a (nonoverlapping) network in which coupling was negatively related to re-experiencing severity, but only in veterans with mTBI (order 10, size 11, corrected $p = .025$) (Figure 2). One connection evidenced a significant pairwise LiNGAM coefficient: left putamen→right insula ($\Lambda = .003$, $p = .028$), suggesting that the left putamen functionally influences the right insula.

Trauma-Related Graph Theoretic Properties

Re-experiencing severity predicted lower density (p for positive connections = .047), indicating that higher re-experiencing was associated with fewer network connections overall. The ROI-specific graph theoretic properties were examined only for ROIs found in the equivalent NBS analyses to have three or more differential connections; for re-experiencing analyses, we examined properties for the right hippocampus, rostral MFG, and posterior cingulate cortex (PCC). Multiple comparison–corrected p values are in brackets. Re-experiencing predicted three ROI-specific properties: 1) lower degree for right hippocampus, rostral MFG, and PCC (positive $p = .002$ [.003], .020 [.026], .033 [.045], negative $p = .002$ [.005], .036 [.050], .027 [.039]); 2) worse local efficiency for right rostral MFG and PCC (negative $p = .027$ [.041], .009 [.017]); and 3) decreased participation coefficient for right hippocampus (positive $p = .044$ [.067]). Lower degree indicates that the right hippocampus, rostral MFG, and PCC evidenced a weaker influence on the overall network in veterans with high levels of re-experiencing. Similarly, worse local efficiency suggests greater inefficiency of communication in the networks surrounding the right rostral MFG and PCC in high re-experiencing. Finally, decreased participation coefficient indicates that the right hippocampus interacts with fewer functional modules in high re-experiencing. Lower right hippocampus degree was linked to a greater number of days that veterans had to reduce usual activities (World Health Organization Disability Assessment Schedule II, $r = -.150$, $p = .037$), underscoring the functional impact of disrupted hippocampal networks.

For interaction analyses, we examined properties for the right insula and right and left caudate. The interaction between re-experiencing and mTBI was linked to right and left caudate local efficiency (positive $p = .038$ [.056], .007 [.009]) and right insula participation coefficient (positive $p = .020$ [.020]). Specifically, re-experiencing predicted lower efficiency and participation in veterans with mTBI, whereas the opposite emerged for veterans

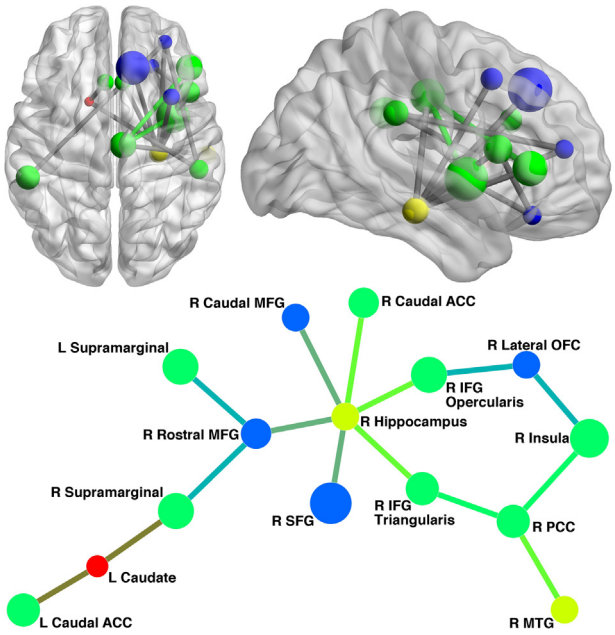

Figure 1. Network coupling negatively associated with posttraumatic stress disorder re-experiencing symptoms. Color of circles reflects module, and size represents degree. Stick/ball figure was created using the Kamada-Kawai spring embedder algorithm. ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; L, left; MFG, middle frontal gyrus; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; R, right; SFG, superior frontal gyrus.

with no mTBI (Figure 3). Worse local efficiency in the right and left caudate interacted with mTBI to predict the number of days veterans reported having to reduce usual activities (right, $F = 4.38$, $p = .038$; left, $F = 4.69$, $p = .032$) (Figure 4). In veterans with no mTBI, local efficiency was positively correlated (right, $r = .153$; left, $r = .201$), whereas a negative correlation was found for veterans with mTBI (right, $r = -.172$; left, $r = -.137$). Worse local efficiency in the right and left caudate also interacted with mTBI to predict the number of days veterans reported being totally unable to carry out usual activities (right, $F = 6.59$, $p = .011$; left, $F = 8.28$, $p = .004$). In veterans with no mTBI, local efficiency was positively correlated (right, $r = .297$; left, $r = .308$), whereas a negative correlation was found for veterans with mTBI (right, $r = -.128$; left, $r = -.092$). These findings highlight the necessity of considering PTSD networks in a TBI context. Supplement 1 contains analyses to isolate which specific symptoms contributed to cluster findings.

DISCUSSION

PTSD and mTBI can be extremely debilitating, and a comprehensive understanding of the neural networks involved in these conditions has yet to be achieved. We identified two networks linked to current PTSD re-experiencing severity, but we did not observe effects for total PTSD, avoidance, or hyperarousal.

Re-experiencing-Related Network Disturbance

The first network (Figure 1) evidenced decoupling at higher levels of re-experiencing. Consistent with hypotheses, the hippocampus had the largest number of weakened connections, all of which were with regions of the right PFC linked to top-down control (24). Hippocampal↔PFC decoupling may be related to weaker downregulation of trauma-related hippocampal associations, potentially leading to intrusion by trauma memories. However, the hippocampus plays a primary role in relational memory, including linking events to appropriate contexts (25). Re-experiencing-related reduction in hippocampal coupling (degree), particularly with regions in multiple modules (participation coefficient, although the finding became marginal after correction for multiple comparisons), may reflect a failure by the hippocampus to contextualize trauma memories properly, which may promote overgeneralization of such memories (26).

The PFC may fail to recruit the hippocampus appropriately to propagate contextual information to other functional modules, and our findings hint at a potential mechanism for this failure. Specifically, re-experiencing-related decreases in rostral MFG local efficiency indicate that processing in that module is less coherent, which may reflect a disruption in top-down control processes instantiated therein. Preliminary tests of the direction of influence also support the hypothesis that the right PFC is engaged in top-down regulation of hippocampal processes, which may be disrupted in re-experiencing. Specifically, the direction of influence for three regions of the right PFC (caudal MFG, caudal anterior cingulate cortex, superior frontal gyrus) was found to be PFC→hippocampus.

Re-experiencing was also linked to inefficiency in the network surrounding the PCC, a critical hub for interregional transmission (27). Hippocampal↔PCC decoupling may reflect one mechanism by which the hippocampus fails to propagate appropriate contextual information. At the present time, these are speculative interpretations that require formal testing using sensitive cognitive paradigms. However, the hippocampal network disruptions demonstrated here were related to worse real-world function, suggesting that these disruptions contribute significantly to PTSD-related impairment.

When individual re-experiencing symptoms were investigated, "physiologic reactivity on exposure to trauma cues" contributed significant unique variance to most of these findings; this is consistent with the idea that the hippocampus is failing to propagate appropriate contextual information when trauma-related memories are cued. For example, in veterans without high levels of re-experiencing, the hippocampus may signal that the current context is safe. Cues that could be interpreted as trauma related are instead processed as "safe," whereas this fails to occur in individuals with high levels of re-experiencing.

Interactive Impact of PTSD and Mild TBI

We discovered a second network that included regions of the basal ganglia (caudate/putamen) and the PFC (Figure 2). Re-experiencing-related network decoupling was observed only in veterans with mTBI, indicating that mTBI facilitates the relationship between re-experiencing symptoms and decoupling. Given research indicating that the basal ganglia and PFC interactively gate access to working memory in a

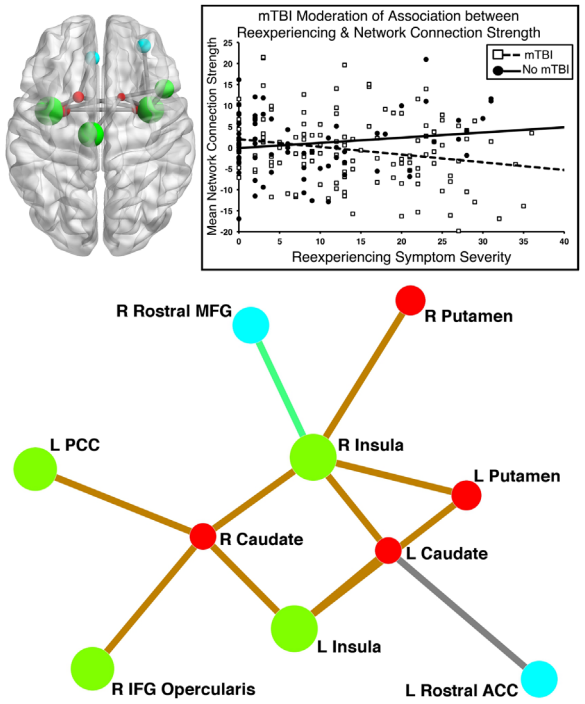

Figure 2. Mild traumatic brain injury moderating association between posttraumatic stress disorder re-experiencing symptoms and network coupling. Color of circles reflects module, and size represents degree. Stick/ball figure was created using the Kamada-Kawai spring embedder algorithm. ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; L, left; Mean Network Connection Strength, mean strength of re-experiencing × mTBI connections; MFG, middle frontal gyrus; mTBI, mild traumatic brain injury; PCC, posterior cingulate cortex; R, right.

context-dependent manner (28), decoupling in this network may be associated with weakened protection against trauma associations inappropriately entering working memory (e.g., in safe contexts). Our finding in mTBI that re-experiencing severity was associated with worse local efficiency in the network surrounding the caudate supports this interpretation, particularly because worse caudate local efficiency was also linked to greater functional disability.

Given the role of the insula in assessing salience (29), insula decoupling in the second network may reflect disrupted salience determination for currently relevant stimuli, which would allow associations with previously salient (i.e., trauma-related) stimuli to interrupt ongoing activities. The influence of the insula appears to be less widespread in mTBI, given that re-experiencing severity predicted reduced insula participation coefficient (Figure 3) in mTBI. Resting-state fMRI data cannot support direct inferences about specific processes occurring in the identified networks. Future research should examine trauma-related pathology in these networks using tasks that recruit the processes discussed earlier.

When individual re-experiencing symptoms were investigated, the interaction between mTBI and "physiologic reactivity on exposure to trauma cues" contributed significant unique variance to mean connection strength in the identified network. However, no specific symptoms were found to contribute unique variance to caudate local efficiency or right insula participation coefficient, suggesting that these findings are related to the larger re-experiencing construct.

The mechanism behind the specificity of the second network to veterans with mTBI requires further investigation. Individuals with mTBI show no gross brain damage on conventional structural magnetic resonance imaging, suggesting that network disruption occurs at a finer neural scale. Given the nonspecific regional impact of mTBI, it likely disrupts many networks, and we observed networks particular to re-experiencing. Regardless, our findings highlight the importance of examining PTSD and TBI in tandem and provide a potential brain mechanism by which TBI increases the incidence and severity of PTSD symptoms (14). Given high levels of comorbidity, exploring the interactive impact of PTSD and TBI is critical.

Relationship to Anatomic Connectivity

It is important to note that fMRI coupling does not imply direct anatomic connection, given that these analyses are not strictly bounded by the presence of such connections. Functional connections can be detected that might otherwise be missed

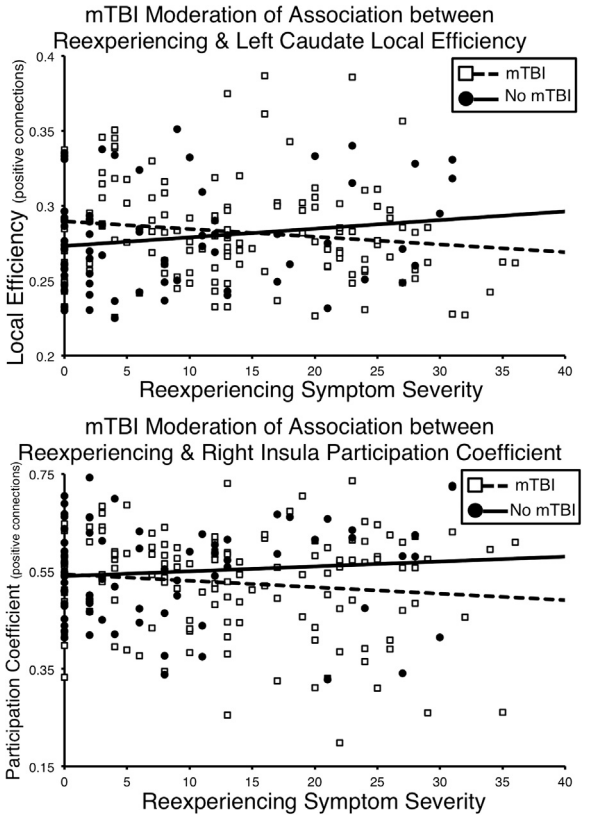

Figure 3. Mild traumatic brain injury moderating association between posttraumatic stress disorder re-experiencing symptoms and graph theoretic properties. Local Efficiency, local efficiency for left caudate calculated using positive weights; mTBI, mild traumatic brain injury; Participation Coefficient, participation coefficient for right insula calculated using positive weights. Graph for right caudate local efficiency is extremely similar to graph for the left caudate.

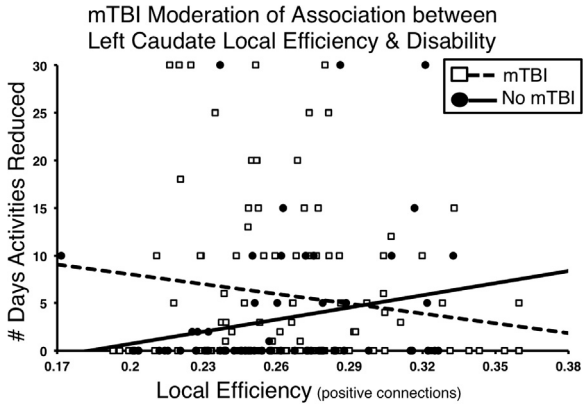

Figure 4. Mild traumatic brain injury moderation of association between local efficiency for left caudate and World Health Organization Disability Assessment Schedule II disability. mTBI, mild traumatic brain injury; Local Efficiency (positive connections), local efficiency values for left caudate calculated using positive weights; Days Activities Reduced, number of days (in last 30) that participants reported having to reduce their typical daily activities, indexed by World Health Organization Disability Assessment Schedule II. Graphs for right caudate and for number of days totally unable to carry out usual activities are extremely similar to the graph depicted here.

(e.g., when anatomically mediated via the thalamus, an intermediary for many connections and unlikely to have a functional time course reflective of any particular link). Potential anatomic mediators for the observed network related to the main effect of re-experiencing include the cingulum bundle or thalamostriatal loops (via the anterior column of the fornix) mediating connections between the hippocampus and right PFC. The right PFC has direct connections to the supramarginal gyrus (via the superior longitudinal fasciculus), and the PCC has direct connections to the insula, inferior frontal gyrus, and middle temporal gyrus (via the cingulum).

With regard to the network related to the re-experiencing × mTBI interaction, the insula has direct connections with the putamen and caudate, and the caudate is connected with the PCC via the cingulum bundle. The caudate receives direct projections from the ACC and inferior frontal gyrus and projects back via pallidum→thalamus. Future research is needed to determine exact anatomic pathways and whether trauma-related network disturbance is due to differences in functional or anatomic pathways. Specifically, combining fMRI with measures of anatomic connectivity (e.g., diffusion) is likely needed to best identify pathology-related disturbance in brain networks.

Implications

Overall, graph theoretic analyses indicate that re-experiencing is linked to worse functional segregation (local efficiency), suggesting that some forms of specialized processing (e.g., protection against intrusion) are less effective. We did not find differences in functional integration, suggesting that combining specialized information across distal regions may be intact in PTSD and mTBI. We also did not find associations with avoidance or hyperarousal severity, suggesting that our study context is particularly relevant for re-experiencing. Although resting fMRI coupling is thought to be relatively stable (29), the absence of an external task may increase the likelihood of trauma re-experiencing during the scan. Active/directed tasks (e.g., encountering threat-related stimuli) may be required to engage avoidance/hyperarousal-related networks.

Contrary to our hypothesis, we did not observe trauma-related disturbances in amygdala coupling. Given that disturbed amygdala↔PFC coupling has been linked to the hyperarousal symptom cluster (16), it is possible that an active/directed task is also required for amygdala-related disturbances to manifest. Methods to apply graph theory tools to such functional tasks are currently being developed (J.M. Spielberg, Ph.D., *et al.*, unpublished data, 2015). Future research can employ these tools to more fully elucidate trauma-related disturbances in the topological role of the amygdala.

It is unclear whether the network disturbances observed in the present study were present before trauma or are a consequence of trauma exposure itself. For example, research indicates that stress leads to a decrease in the expression of brain-derived neurotrophic factor, which promotes hippocampal and PFC atrophy (30). This pathway could explain our finding of decreased connectivity between these structures, along with observed decreases in the general influence of these regions on the network (i.e., density). It is also possible that weaker hippocampal↔PFC connectivity represents a risk factor for the development of re-experiencing symptoms after trauma, such that reductions in the propagation of contextual information from the hippocampus allow traumatic memories to be triggered in a wider array of contexts. An interaction between these pathways is possible as well, with atrophy driven by brain-derived neurotrophic factor diminishing hippocampal↔PFC coupling to the point of dysfunction in individuals for whom coupling was already weakened.

With regard to the interaction between re-experiencing and TBI, it is likely that these findings are at least partly a consequence of the TBI event, given that it is unlikely for the network disturbances to have led in some way to the TBI event. However, it is unclear whether observed disturbances reflect an exacerbation of previously weakened connections between PFC, basal ganglia, and insula or are a consequence of the traumatic event. Further research examining at-risk individuals (e.g., relatives of affected persons) or shifts in brain networks before and after trauma (e.g., before and after military deployment) is needed to elucidate specific causal pathways associated with the observed network disturbances.

Although not a limitation per se, the present findings cannot be directly applied to clinical practice. Rather, our findings further delineate the specific network disruptions that characterize trauma-related pathology. If replicated, one clinical use for the present findings is to inform the creation of multivariate algorithms that use information from multiple domains (e.g., brain networks, genetic markers, self-report, clinical interviews) to guide diagnosis and treatment selection. Although such algorithms are not yet available, the barriers to their implementation are currently being identified and addressed (31,32).

In conclusion, we demonstrate in a large sample of veterans that trauma-related pathology has important and heterogeneous effects on brain networks and related graph theoretic topological properties. These results move us closer to understanding the precise networks disturbed by trauma and

highlight the importance of taking into account the interactive effects of different manifestations of trauma pathology.

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ARTICLE INFORMATION

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