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# High-Fidelity Measures of Whole-Brain Functional Connectivity and White Matter Integrity Mediate Relationships between Traumatic Brain Injury and Post-Traumatic Stress Disorder Symptoms

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## Abstract

Traumatic brain injury (TBI) disrupts brain communication and increases risk for post-traumatic stress disorder (PTSD). However, mechanisms by which TBI-related disruption of brain communication confers PTSD risk have not been successfully elucidated in humans. This may be in part because functional MRI (fMRI), the most common technique for measuring functional brain communication, is unreliable for characterizing individual patients. However, this unreliability can be overcome with sufficient within-individual data. Here, we examined whether relationships could be observed among TBI, structural and functional brain connectivity, and PTSD severity by collecting ~3.5 hours of resting-state fMRI and diffusion tensor imaging (DTI) data in each of 26 United States military veterans. We observed that a TBI history was associated with decreased whole-brain resting-state functional connectivity (RSFC), while the number of lifetime TBIs was associated with reduced whole-brain fractional anisotropy (FA). Both RSFC and FA explained independent variance in PTSD severity, with RSFC mediating the TBI–PTSD relationship. Finally, we showed that large amounts of per-individual data produced highly reliable RSFC measures, and that relationships among TBI, RSFC/FA, and PTSD could not be observed with typical data quantities. These results demonstrate links among TBI, brain connectivity, and PTSD severity, and illustrate the need for precise characterization of individual patients using high-data fMRI scanning.

**Keywords:** FC; high-data MRI; PTSD; TBI; white matter integrity

## Introduction

Traumatic brain injury (TBI) is the signature wound of United States military personnel who fought in Iraq and Afghanistan,[1] and accounted for ~2,800,000 emergency department visits, hospitalizations, and deaths in the civilian population in 2013 alone.[2] Whereas mild TBI is associated primarily with immediate cognitive deficits that resolve without intervention,[3–5] ~ 6–15% of patients experience persistent, long-term sequelae,[6–10] including problems with learning and memory, anxiety and mood issues, and executive function deficits.[11–17] The common persistence of these symptoms means that >5,000,000 people are currently living with some form of TBI-induced disability.[18]

When TBI-related symptoms persist, it is likely related to the presence of diffuse axonal injury, which is believed to be the most prevalent cause of TBI.[19,20] In this type of injury, the long-range axonal projections that connect distant regions of the brain are damaged by shearing forces induced by a head impact or blast wave. The prevalence of such axonal injuries in humans has been supported by a large number of *in vivo* diffusion tensor imaging (DTI) MRI studies, which commonly find reduced integrity of many different large white matter tracts in TBI patients.[21,22]

The axonal fibers making up large white matter tracts represent the structural scaffolding used to convey neural impulses long distances between distributed, networked brain regions.[23,24] The brain does not function as a collection of brain regions independently

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processing information. Rather, cognition and behavior require the complex integration of multiple networked brain regions.[25] TBI-related damage to long-range axonal tracts likely impairs this networked communication. A growing body of work has used resting-state functional connectivity (RSFC) functional MRI (fMRI) to demonstrate disrupted brain network communication in TBI.[26–40] Such disrupted brain network communication is associated with cognitive and behavioral symptoms.[28,34,41] Together, these disruptions of structural and functional connectivity, and the resulting association with behavioral symptoms, suggest that TBI may be primarily conceptualized as a disorder of brain communication, in which diffuse axonal injuries disrupt networked communication between brain regions.[22,42]

A history of TBI is also strongly associated with the presence of post-traumatic stress disorder (PTSD). The two diagnoses have many overlapping symptoms (e.g., insomnia, amnesia, concentration problems, irritability[43]), leading to apparent comorbidity in a large percentage of cases.[44–47] The TBI–PTSD relationship appears to be even stronger in veterans, in whom a history of TBI can double or triple the risk of developing PTSD symptoms.[48,49] This increased risk for PTSD has been linked to the presence of persistent TBI-induced post-concussive symptoms.[50]

The neurobiological mechanisms by which TBI confers increased risk of PTSD are only beginning to be explored.[22] Conceptually, damage that alters the function of PTSD-relevant brain regions is likely to increase the risk of developing PTSD.[51] The primary neurological correlate of PTSD appears to be amygdala hyper-responsiveness coupled with reduced activity in the ventromedial prefrontal cortex (vmPFC), suggesting reduced inhibitory control over the amygdala and related medial temporal lobe structures.[52,53] TBIs are likely to disrupt communication within emotion-regulation circuits[54]; indeed, individuals with comorbid TBI/PTSD were shown to exhibit a particularly severe decoupling of the PFC and hippocampus.[55] In practice, however, PTSD symptoms have been associated with altered function in many brain regions, including cortical networks in the medial and lateral parietal and prefrontal cortex, which may influence amygdala/vmPFC function.[56] There is a need to establish explicit links among (1) TBI, (2) structural brain damage/functional brain impairment across many networked regions, and (3) PTSD symptoms.[57]

One reason such links have been elusive may be that MRI- and especially fMRI-based measures are relatively noisy,[58] and, therefore, may be unreliable for characterizing brain function in individuals with a high degree of precision. This limitation is particularly problematic for the TBI population, in which white matter damage[59–62] and network disruption[26,29,33] are known to be diffuse and variable, because brain–behavior relationships cannot be accurately described within a variable population if the brain metric is unstable. Importantly, recent work has shown that stable measures of brain function can be achieved if a sufficient quantity of MRI data is collected.[63–66]

In the present study, we collected large quantities of DTI and fMRI data in 26 United States military veterans. We first verified that reliable measures of white matter integrity and RSFC strength could be obtained with these large data quantities. We then examined relationships among TBI history, whole-brain white matter integrity, whole-brain RSFC strength, and PTSD symptom severity. Our analysis was organized around the overarching idea that direct effects of TBIs on PTSD symptom severity are likely to be mediated by their effects on white matter damage and brain network communication. We specifically hypothesized that (1) a history of TBI would be related to reduced white matter integrity across the whole brain; (2) a history of TBI would be related to reduced RSFC strength across the whole brain, and that this effect would be mediated by white matter integrity; and (3) a history of TBI would be associated with increased PTSD symptom severity, and that this effect would be mediated by white matter integrity and RSFC. A graphical summary of this conceptual framework can be seen in Figure 1.

## Methods

### *Subjects*

Data were collected from 37 United States military veterans recruited from the areas surrounding Waco, Texas. Before beginning the study, participants were screened and excluded for MRI safety issues, any Axis I psychotic disorder, bipolar disorder, dementia, substance abuse disorder, or any substance use in the last 12 h before MRI scanning. Informed consent was obtained from all participants. This study was approved by the Central Texas Veterans Health Care System Institutional Review Board.

Each participant completed between one and five 2 h study sessions on separate days spanning <3 months. The first session included participant screening, informed consent, behavioral assessment, neuropsychological testing (not described here), and a brief initial MRI scanning session to determine whether participants could tolerate the scanning environment without excessive movement.

Participants who exhibited motion in fewer than 50% of time points in the initial fMRI scan (see ''FMRI preprocessing and analysis'' section for details) were invited back for up to four additional sessions. These additional sessions were devoted entirely to MRI scanning. In all scanning sessions, the MRI technologist performing the scanning was blind to the goals of the study and to the TBI/PTSD status of the participant.

In total, 27 participants completed the initial session and at least one scanning-only session. One participant was subsequently excluded from analyses because of outlier measures of functional connectivity believed to result from a scanner malfunction. This left 26 participants (5 females; mean ± SD age: 37.0 ± 11.8) included in the current results.

### *Behavioral assessment*

Behavioral assessment focused on determining whether individuals had a history of TBI, as well as on identifying the presence and severity of PTSD symptoms. TBI history was assessed using the Vasterling TBI assessment interview,[67] which obtains self-reports of all lifetime TBI events. Measures of interest in this study included the severity of the worst TBI event, as well as the total number of lifetime TBI events. We found that five participants had no history of TBI, whereas 17 had at least one mild TBI (but no moderate or severe TBIs) and 4 had at least one moderate TBI (but

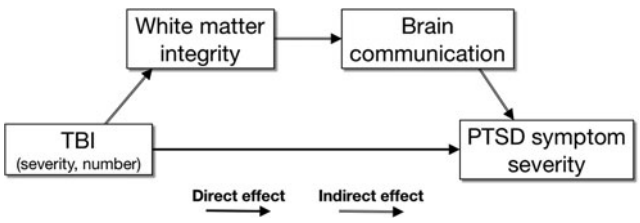


**FIG. 1.** Hypothesized model for how traumatic brain injury (TBI) increases risk for post-traumatic stress disorder (PTSD) symptoms by altering brain structure and function. In this framework, direct effects of TBI on PTSD severity (solid line) are mediated by indirect effects of TBI on white matter integrity, which reduce brain communication, which in turn increase PTSD symptoms.

no severe TBIs). No individuals with a history of severe TBI completed the scanning protocol. The mean ± SD number of lifetime TBI events experienced was 2.1 ± 1.7 (range: 0–6). The time since the most recent TBI was also recorded.

The severity of PTSD symptoms was assessed using the PTSD Check List for *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (PCL-5).[68] The measure of interest was the summed PCL-5 symptom severity score. PCL-5 scores were not available for one participant; that participant was, therefore, excluded from all analyses examining relationships with PCL-5. The mean ± SD PCL-5 score of the remaining participants was 34.2 ± 22.7 (range: 0–77).

We also assessed combat exposure using the 34 item version of the Full Combat Exposure Scale (FCES),[69] in which participants rate the frequency of their exposure to a variety of combat elements. FCES scores have previously been associated with PTSD severity.[70] Finally, we recorded the medications currently taken by each subject and grouped them into major medication categories. None of these measures except PCL-5 score differed between the TBI groups (Table 1).

### MRI image acquisition

Imaging was performed on a Philips Achieva 3T MRI scanner. Scanning in the initial session included collection of one T1-weighted magnetization prepared rapid gradient-echo (MP-RAGE) image, one DTI scan, and one T2*-weighted blood oxygen level dependent (BOLD) contrast sensitive fMRI scan. FMRI was collected during the ''resting state,'' in which participants passively viewed a white crosshair on a black background and were instructed not to fall asleep.

Scanning in subsequent sessions included collection of one MP-RAGE, one DTI scan, and as many 6.6 min resting state fMRI scans as could be collected in the rest of the 2 h session. Participants took breaks after every 30 min of scanning and were encouraged to request additional breaks whenever they felt fatigued. Breaks were allowed to be of any length but were generally ~5 min.

Scanning parameters were as follows:

T1-weighted sagittal MP-RAGE: echo time (TE) = 3.08 ms, repetition time (TR) partition = 2.4 sec, TI = 1000 ms, flip angle = 8 degrees, 176 slices, 1 × 1 × 1 mm voxels.

DTI: 32 directions with two b-values (b = 0 sec/mm$^2$ and b = 800 sec/mm$^2$), TE = 93 ms, TR = 3891 ms, anterior-posterior (AP) phase encoding, flip angle = 90 degrees, in-plane resolution = 2 × 2 mm, 60 slices, slice thickness = 2 mm.

fMRI: a gradient echo-planar imaging sequence with TE = 30 ms, flip angle = 90 degrees, in-plane resolution = 3 × 3 mm, 34 3.0 mm-thick axial slices with a 1.0 mm gap between slices, TR = 3.0 sec, 132 volumes acquired per run for 6 min and 36 sec of scan time.

Across all scanning sessions, participants underwent an average ± SD of 4.5 ± 1.2 DTI scans (range: 2–6) and an average ± SD of 24.9 ± 10.1 6.6 min resting state scans (range: 5–44).

### MRI processing and analysis

#### Structural MRI data

*T1 preprocessing.* All T1-weighted MPRAGE images were visually inspected for image quality and for potential abnormalities. The best image from each subject was corrected for magnetic field bias, skull-stripped, and linearly warped to the MNI-152 template using FSL tools.[71]

*Cortical surface generation.* Generation of cortical surfaces from the MPRAGE followed procedures described in the study by Glasser and colleagues.[72] Anatomical surfaces were generated from the native-space MPRAGE using FreeSurfer's recon-all processing pipeline (version 5.3).[73–76] The fsaverage-registered left and right hemisphere surfaces were brought into register with each other, resampled to 164,000 vertices using Caret tools,[77] and downsampled to the fs_LR 32k template space. These surfaces were then transformed into Montreal Neurological Institute (MNI) atlas volumetric space by applying the previously calculated MPRAGE-to-MNI transformation.

#### Diffusion MRI data

*DTI processing.* DTI images were processed using the Diffusion Toolbox in FSL.[71,78] All diffusion tensor images were corrected for eddy currents. In each image, a diffusion tensor model was fitted and used to calculate fractional anisotropy (FA) in each voxel. A linear rigid-body

Table 1. Demographic and Assessment Measures in Each TBI Group

| | *No TBI* | *Mild TBI* | *Moderate TBI* | *Test* |
|---|---|---|---|---|
| *n* | 5 | 17 | 4 | – |
| Number F | 0 | 3 | 1 | $p = 0.53$ |
| Age (years) | 37.4 ± 13.3 | 38.2 ± 11.8 | 35.8 ± 14.4 | $p = 0.94$ |
| fMRI data frames retained | 1848 ± 1336 | 2502 ± 1213 | 2784 ± 879 | $p = 0.46$ |
| % fMRI data lost | 26.8 ± 28.4 | 22.7 ± 15.9 | 24.1 ± 15.2 | $p = 0.91$ |
| Number TBIs | – | 2.0 ± 1.1 | 3.0 ± 1.6 | $p = 0.55$ |
| Time since last TBI (years) | – | 11.7 ± 10.6 | 7.5 ± 3.3 | $p = 0.44$ |
| Total PCL-5 | 16.2 ± 17.9 | 35.9 ± 22.0 | 54.7 ± 13.6 | ***p = 0.05** |
| Number with clinical PTSD diagnosis | 2 | 7 | 2 | $p = 0.94$ |
| Total FCES | 10.8 ± 14.5 | 30.6 ± 33.4 | 42.7 ± 7.6 | $p = 0.28$ |
| Number of participants on medications | | | | |
| Antidepressants | 3 | 8 | 1 | $p = 0.57$ |
| Antipsychotics | 0 | 2 | 0 | $p = 0.56$ |
| Benzodiazepines | 0 | 1 | 0 | $p = 0.76$ |
| Mood stabilizers | 0 | 1 | 1 | $p = 0.33$ |

The ''Test'' column shows the $p$ value from a statistical test of differences among groups. This $p$ value is variously derived from a $\chi^2$ test (gender, number with PTSD diagnosis, number on medications), a one way ANOVA (age, fMRI data retained, % fMRI data lost, PCL-5, FCES), or a two sample $t$ test between the Mild and Moderate groups (number of TBIs, time since last TBI).

TBI, traumatic brain injury; fMRI, functional MRI; PCL-5, Post-traumatic Stress Disorder (PTSD) Check List for *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5); FCES, Full Combat Exposure Scale; ANOVA, analysis of variance.

registration was computed between each B0 image and the native-space MPRAGE image, concatenated with the MPRAGE-to-MNI transformation and an interpolation into 2 mm isotropic space, and applied to the FA image. The resulting MNI-space FA images were then averaged across DTI runs for each individual (see Fig. 2A).

White matter integrity calculation. For each subject, we calculated mean FA across all of the canonical white matter tracts in the Johns Hopkins University white matter tract atlas,[79] masked by each individual subject's white matter segmentation. This atlas includes 48 discrete tracts; our DTI scans provided coverage for 38 of these tracts (the remainder being in the brainstem). We also calculated mean FA in each of these specific tracts.

### Functional MRI data

*fMRI preprocessing.* Functional data were preprocessed using FSL tools and in-house Matlab scripts. All runs underwent correction of slice timing effects and calculation of within-run correction for head movement. Linear rigid-body registrations were calculated from each run to the most representative run (calculated as the run with maximal spatial correlation to all other runs). A linear warp was calculated from the most representative mean image to the native volumetric MPRAGE using the boundary-based registration method.[80] These within-run, across-run, representative run-to-MPRAGE, and MPRAGE-to-MNI transformations were concatenated with an interpolation into 3 mm isotropic space and applied to each volume. The resulting MNI-space fMRI runs were intensity-normalized to a whole brain mode value of 1000.

Additional preprocessing steps to reduce spurious variance were executed as recommended in the studies by Ciric and colleagues and Power and colleagues.[81,82] First, temporal masks were created to flag and censor motion-contaminated frames. Motion-contaminated volumes were identified by frame-by-frame displacement (FD), which is described in the study by Power and colleagues.[83] Several subjects had a high-frequency artifact in the motion estimates, primarily in the phase encode direction, that did not appear to reflect biological movement. Similar effects have previously been observed in data from the Human Connectome Project.[84,85] We thus filtered the FD time courses to retain effects occurring below 0.1 Hz. Frames with filtered FD >0.04mm were flagged as motion contaminated, following the recommendations of Gordon and colleagues.[85] Across all subjects,

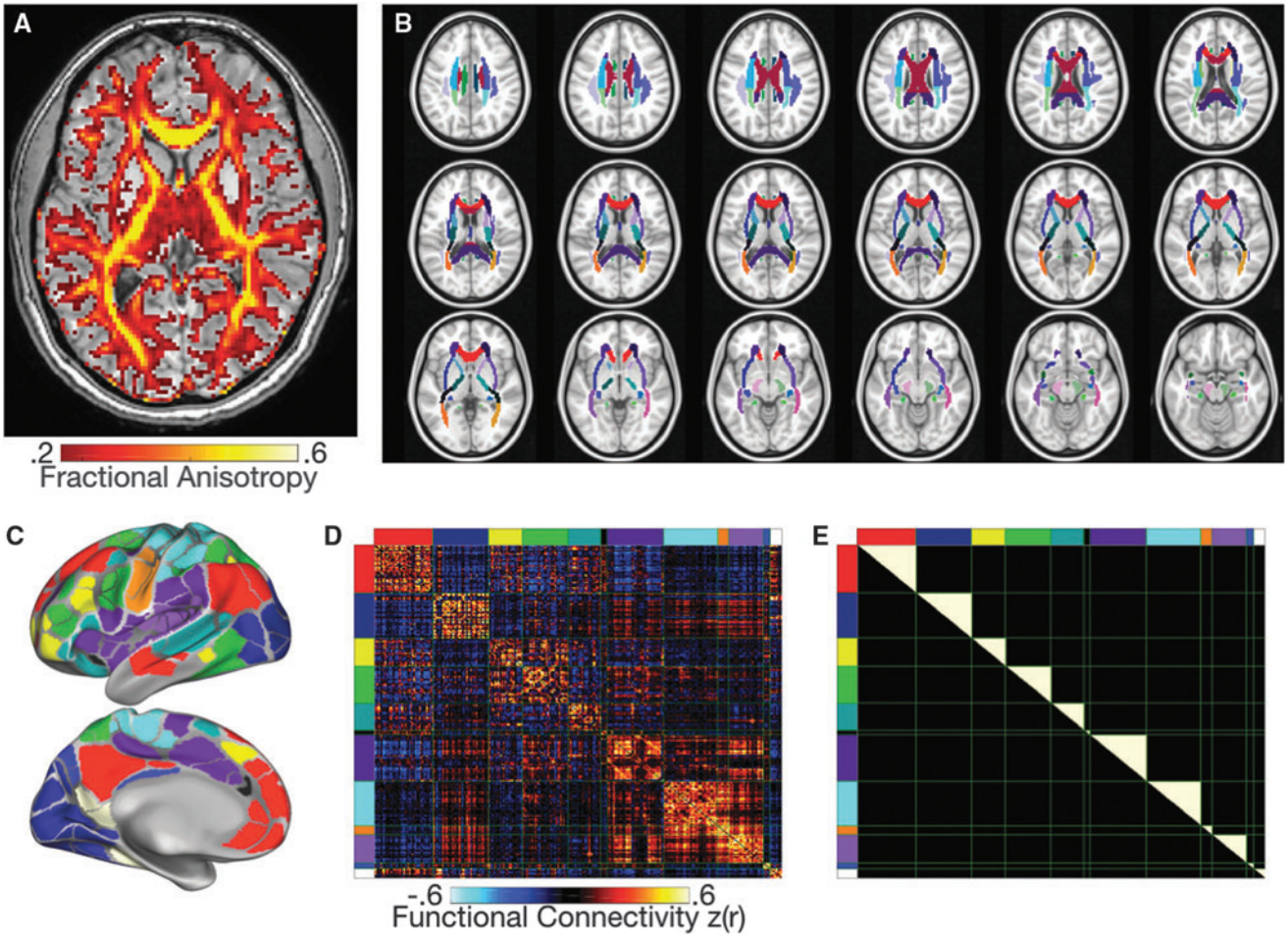


**FIG. 2.** Data collected in the present study. **(A)** Diffusion tensor imaging scans were collected in order to produce maps of fractional anisotropy (FA), a measure of white matter integrity. An FA map is shown for one example subject. **(B)** FA was assessed in each of many different *a priori* white matter tracts. Each tract is shown in a different color. **(C)** Resting-state functional MRI (fMRI) scans were collected, and data were averaged within each of 333 *a priori* parcels on the cortex. **(D)** Temporal correlations were computed between all parcel time courses to produce a functional connectivity value between each pair of parcels. A matrix illustrating the strength of functional connectivity between each parcel pair is shown for a single subject. The matrix is ordered by the known network organization of this parcel set (compare colored blocks on axes to parcel colors in **C**). **(E)** For each subject, functional connectivity values from **D** were averaged across all unique within-network connections, as illustrated here in white.

these masks censored 23.7% ± 17.9% (range: 1.5–66.8%) of the data; on average, subjects retained 2420 ± 1174 volumes (range: 515–4943). Neither the percent of data lost nor the total number of frames retained differed by TBI status (Table 1).

After computing these temporal masks, data were processed with the following steps: (1) demeaning and detrending; (2) concatenation across runs; (3) multiple regression of nuisance signals including whole brain signal, white matter signal, top principal components explaining 75% of the variance in ventricular signal, run identity, session identity, and motion regressors derived by Volterra expansion,[86] with censored data ignored during beta estimation; (4) interpolation across censored frames[83,87]; and (5) band-pass filtering ($0.009\,Hz < f < 0.08\,Hz$). Censored frames were then excised for all subsequent analyses.

To visually assess noise levels in the fMRI data, and to assess the efficacy of the motion censoring and nuisance regression procedures, we constructed ''grayplots'' of this data, following a study by Power.[84] Briefly, signal strength at every time point was calculated from a random sample of voxels within the cortical gray matter ribbon, both before and after motion censoring/nuisance regression. These strengths were plotted as a time × voxels matrix for each subject and visually examined for evidence of global artifact. This examination revealed that all subjects exhibited large global signal fluctuations, which were effectively eliminated by the motion censoring and nuisance regression procedures (see Figs. S1–S3) (see online supplementary material at http://www.liebertpub.com).

The fMRI volumetric time series were then sampled to each subject's left and right hemisphere cortical surfaces using the ribbon-constrained sampling procedure[88] in Connectome Workbench 1.0.[72] Surface-space time courses were deformed and resampled to the 32k fs_LR surface. These surface data were combined with volumetric subcortical gray matter and cerebellar data into the Connectivity Informatics Technology Initiative (CIFTI) format. Finally, the resting-state time courses were smoothed with geodesic two-dimensional (2D) (for surface data) and Euclidean three-dimensional (3D) (for volumetric data) Gaussian kernels (full width at half maximum [FWHM] = 6mm).

*RSFC) calculation.* To evaluate RSFC between brain regions, we employed a previously published parcellation of the human cortex.[89] For each subject, cortical vertex time courses were averaged within each parcel to produce a parcel average time course. Connectivity relationships between parcels were calculated by cross-correlating the time courses of all parcels against each other; the resulting correlation values were Fisher Z-transformed to improve normality. This resulted in a parcel × parcel connectivity matrix of Z(r) values for each subject (see Fig. 2D for an example).

These parcels are known to be organized into 14 discrete networks (Fig. 2C). RSFC within these networks is most likely to represent networked area-to-area brain communication. To obtain a summary RSFC measure of these strong within-network functional connections, we calculated the average functional connectivity across all within-network parcel-to-parcel connections (Fig. 2E), excluding all parcels in low-signal regions (ventral temporal and orbitofrontal cortex) that do not have known network identities (gray areas in Fig. 2C).

Notably, neither the whole-brain FA nor the within-network RSFC measures appeared to be influenced by potential residual (uncontrolled) effects of in-scanner motion, as neither the percent of frames lost to motion nor the average FD in retained frames was associated with either measure (all $ps > 0.15$; Fig. S4) (see online supplementary material at http://www.liebertpub.com).

### Reliability of FA and RSFC measures

We examined how collection of increasing amounts of data improved the within-subject reliability of FA and RSFC measures. This approach followed the iterative split-half reliability analyses described in studies by Laumann and colleagues and Gordon and colleagues.[63,65]

FA. For each subject, the DTI sessions were randomly split into two approximately equal subsets of sessions. Mean FA values were calculated in each of the 38 *a priori* tracts (see White matter integrity calculation section, above) using all data in one of the subsets (the smaller subset, if the total number of sessions was odd). A varying number of sessions (one to three, when possible) was randomly selected from the other subset, and mean FA values were calculated in each of the *a priori* tracts using these data. The split-data similarity of FA values was calculated as the correlation of tract FA values in the two data subsets. This procedure was repeated in each subject for all possible combinatorial iterations of sessions.

RSFC. For each subject, the RSFC sessions were randomly split into two equal subsets of sessions. A parcel-to-parcel connectivity matrix (see RSFC calculation section, above) was calculated from all data in one of the data subsets (the smaller subset, if the total number of sessions was odd). A varying amount of data (ranging from 2.5 min to 100 min after motion censoring, when possible) was randomly selected from the other subset. These data were contiguous within sessions, but did not necessarily include temporally adjacent sessions. A connectivity matrix was calculated for these data. The similarity of the matrices from the two subsets was calculated as the correlation of Z(r) values in the upper triangle of the matrices. To obtain robust estimates of this split-half similarity, this procedure was iterated 1000 times for each subject and for each quantity of data tested, with a different random selection of data in each iteration.

### Statistical analysis of relationships between TBI, whole-brain white matter integrity, whole-brain functional connectivity, and PTSD

We examined (1) whether TBI is related to FA, (2) whether TBI is related to RSFC, and whether that relationship is mediated by effects of FA, and (3) whether TBI is related to PTSD symptoms, and whether that effect is mediated by effects of FA and/or RSFC. To accomplish this, we conducted the following statistical tests (all two tailed, with significance criterion set at $p < 0.05$):

TBI versus PTSD. We used a one way analysis of variance (ANOVA) and a Pearson's correlation, respectively, to test whether TBI status – that is, the severity of the worst TBI event reported (none, mild, moderate) – or the total number of lifetime TBIs (in individuals with at least one TBI) is related to PCL-5 score.

TBI versus FA. We used a one way ANOVA and a Pearson's correlation, respectively, to test whether TBI status or number of lifetime TBIs is related to mean FA values across all white matter tracts.

TBI versus RSFC. We used a one way ANOVA and a Pearson's correlation, respectively, to test whether TBI status or number of lifetime TBIs influenced mean RSFC strength.

FA versus RSFC, and mediation effects of FA on TBI–RSFC relationships. We conducted a Pearson correlation to test whether mean FA was associated with mean RSFC strength. We then conducted an analysis of covariance (ANCOVA) and a partial correlation to test how TBI status and number, respectively, are related to RSFC when accounting for FA.

FA/RSFC versus PTSD, and mediation effects of FA/RSFC on TBI–PTSD relationships. We conducted Pearson's correlations to test whether mean FA and/or mean RSFC strength were each associated with PCL-5 scores, as well as a multiple regression to test whether they were associated with PCL-5 scores in combination. For each significant relationship between TBI-FA/RSFC and between FA/RSFC and PCL-5, we conducted an ANCOVA/partial correlation (as appropriate) testing how TBI status/number is related to PCL-5 when accounting for FA/RSFC.

## Results

### *Reliability of DTI data is very high after only a few scans, but RSFC requires large amounts of data to achieve high reliability*

Average within-tract FA values were highly similar across split portions of the data, indicating high reliability of the FA measure (Fig. 3A). When calculating FA from only one DTI scan, all subjects exhibited an average correlation of at least $r = 0.92$ between single scans and an average of multiple (two to three) separate scans. For the majority of subjects (21/26), this correlation was between $r = 0.97$ and $r = 0.995$. Increasing the number of DTI scans included did increase this split-half similarity, though only marginally, as could be expected for a near-ceiling measure.

By contrast, RSFC correlation matrices were much less similar when comparing split halves of data to a small quantity of data (similar to the quantity used in many other studies), indicating relatively low reliability (Fig. 3B). When calculating RSFC values from only 2.5 min of (post motion-censoring) data, subjects exhibited an average correlation of only $r = 0.54$ to the split half. This value rose to $r = 0.83$ when RSFC values were calculated using 20 min of data, and to $r = 0.91$ when values were calculated using 1 h of data. This suggests that RSFC values are not highly reliable unless a relatively large quantity of data (after motion censoring) is included in the calculation. As noted, all subjects in this study had at least 26 min of data available for RSFC calculation.

In post-hoc analyses, we also characterized these reliabilities as the average (i.e., expected) differences between split portions of data, iterated across many data splits, for the whole-brain FA and within-network RSFC measures. The results mirror the above-mentioned reliability findings (see Fig. S5) (see online supplementary material at http://www.liebertpub.com). For whole-brain FA, expected differences were quite low: $\Delta FA \sim = 0.007$ for one DTI session, decreasing only slightly to $\sim 0.005$ with additional data collection. For within-network RSFC, $\Delta RSFC \sim = 0.035$ for one fMRI session, decreasing substantially to $\sim 0.015$ with additional data. Notably, with sufficient data, these expected differences were substantially smaller than the scale of the TBI–DTI relationship or the magnitude of RSFC differences between TBI groups (see the following section).

### *Complex relationships exist among TBI, whole-brain white matter integrity, whole-brain functional connectivity, and PTSD symptoms*

**TBI status, but not number, is related to PTSD symptom severity.** We tested whether total score on the PCL-5 differed among groups with varying TBI status, taken from the severity of the worst lifetime TBI event (none/mild/moderate). We found that TBI status was related to PCL-5 score ($F[2,23] = 3.4$, $p = 0.05$; Fig. 4A). This effect appeared to be driven by parametric effects of TBI status on PCL-5 scores. Post-hoc two sample $t$ tests indicated that PCL-5 scores were significantly lower in the No TBI group than in the Moderate TBI group ($t[6] = 3.18$, $p = 0.02$), whereas differences between the Mild TBI group and the other two groups were both at trend level (No TBI vs. Mild TBI: $t[19] = 1.70$, $p = 0.10$; Mild TBI vs. Moderate TBI: $t[17] = 1.69$, $p = 0.10$).

By contrast, the total number of lifetime TBI events was not related to PCL-5 scores, either alone ($r[24] = -0.14$, $p = 0.55$; Fig. 4B) or when controlling for TBI status (partial $r[23] = -0.11$, $p = 0.60$).

**TBI number, but not status, is related to white matter integrity.** We tested whether the severity of the worst lifetime TBI event is related to average FA values within all *a priori* white matter tracts. We observed no relationship between TBI status and average FA ($F[2,23] = 0.70$, $p = 0.51$; Fig. 4C). Exploratory tests examining each *a priori* tract separately also revealed no significant effects of TBI status on FA values (all uncorrected $ps > 0.08$).

However, when examined in individuals with at least one TBI, a larger total number of lifetime TBI events was related to lower FA values ($r[20] = -0.53$, $p = 0.01$; Fig. 4D). This effect held when controlling for TBI status in all subjects (partial $r[19] = -0.51$, $p = 0.01$).

**TBI presence, but not number, is related to reduced RSFC strength within networks.** We tested whether the severity of the worst lifetime TBI event is related to RSFC strength within *a priori* networks. We observed that TBI status is related to RSFC strength within networks ($F[2,23] = 8.00$, $p = 0.002$; Fig. 4E). Post-hoc $t$ tests determined that this effect was driven by the individuals with no history of TBI exhibiting significantly stronger RSFC than individuals with a TBI history (No TBI vs. Mild TBI: $t[20] = 3.69$,

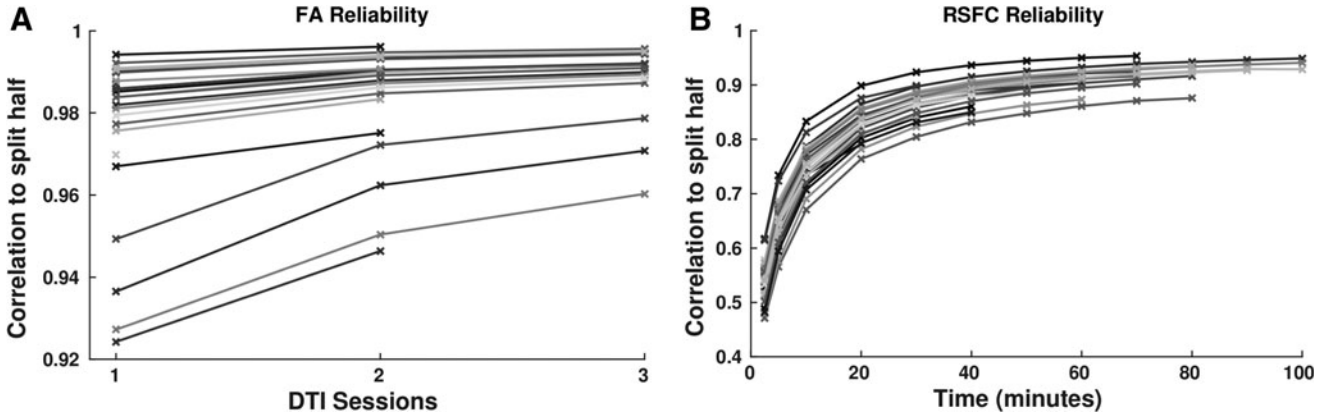


**FIG. 3.** Split-data reliability of fractional anisotropy (FA) and resting-state functional connectivity (RSFC) measures increases with the amount of data collected. **(A)** Tractwise FA measures computed from a given number of sessions (x-axis) were randomly selected and correlated against measures from an independent sample of half of the diffusion tensor imaging (DTI) sessions. This was repeated for all unique combinations of sessions. **(B)** RSFC matrices computed from a given amount of motion-censored data (x-axis) were randomly selected and compared to a random independent sample of half of the resting-state scans; this was repeated 1000 times. Lines represent unique subjects.

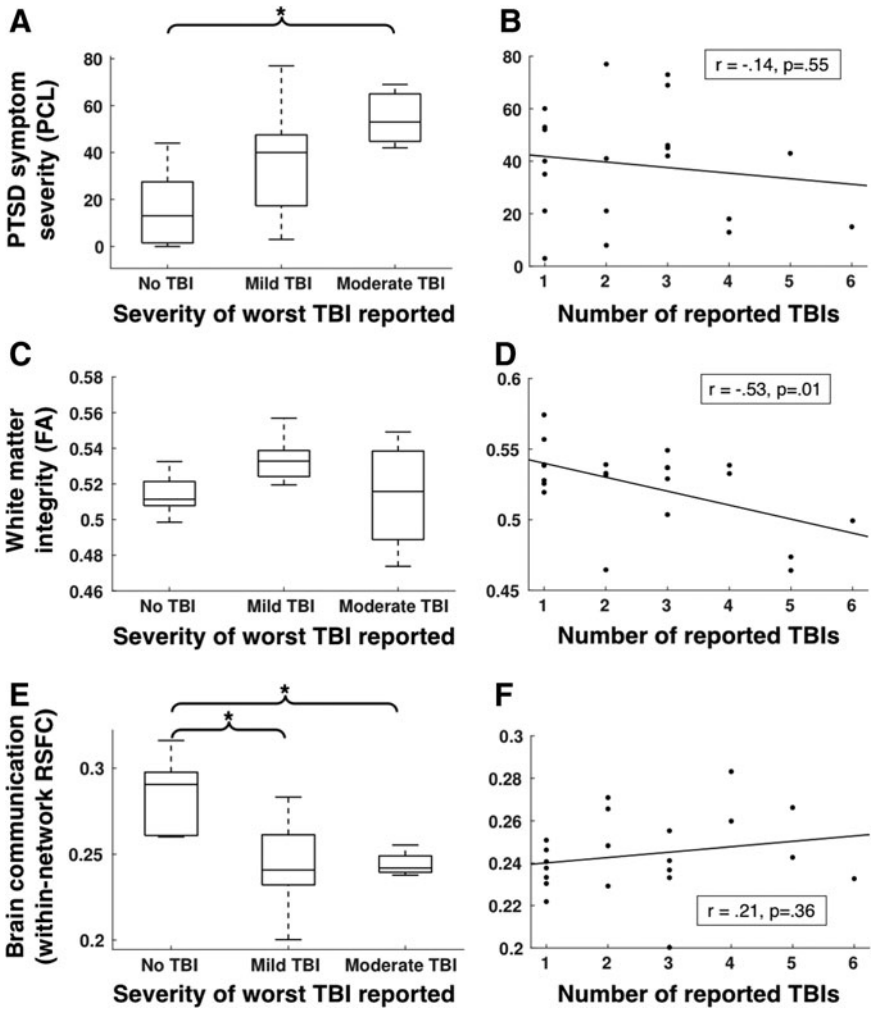


**FIG. 4.** Relationships among traumatic brain injury (TBI) status/number and Post-Traumatic Stress Disorder (PTSD) Check List for *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (PCL-5), fractional anisotropy (FA), and resting-state functional connectivity (RSFC). **(A,C,E)** Analyses of variance (ANOVAs) tested whether PCL-5 scores **(A)**, whole-brain FA **(C)**, or whole-brain RSFC **(E)** differed among groups who had sustained no TBIs, at least one mild TBI, or at least one moderate TBI. *Indicates significant ($p < 0.05$) post-hoc pairwise differences identified after observing a significant main effect of TBI status. **(B,D,F)** Correlations tested whether the total number of TBIs sustained (in individuals with at least one TBI) was associated with PCL-5 scores **(B)**, whole-brain FA **(D)**, or whole-brain RSFC **(F)**.

$p = 0.002$; No TBI vs. Moderate TBI: $t[7] = 3.19$, $p = 0.02$). However, RSFC strength did not differ between individuals with a mild TBI history and those with a moderate TBI history ($t[19] = 0.01$, $p = 0.99$), indicating that RSFC is decreased in individuals with any history of TBI, regardless of severity.

By contrast, TBI number was not related to RSFC strength either alone ($r[20] = 0.21$, $p = 0.36$; Fig. 4F), or when controlling for TBI status (partial $r[19] = 0.18$, $p = 0.39$).

White matter integrity is not related to RSFC strength. We tested whether average FA values across all white matter tracts were related to RSFC strength within networks. We found no significant association between these measures ($r[25] = -0.22$, $p = 0.27$).

Reduced RSFC strength is associated with increased PTSD symptom severity. We examined whether RSFC strength within networks was related to PCL-5 scores. We found that weaker RSFC connections were associated with increased PCL-5 scores ($r[24] = -0.47$, $p = 0.02$; Fig. 5B). This effect remained significant at trend level when excluding one participant who had the lowest RSFC strength and the highest PCL-5 score ($r[23] = -0.35$, $p = 0.09$).

RSFC strength mediates relationships between TBI status and PTSD. We examined whether the strength of within-network RSFC connections mediates the relationship between TBI status and PCL-5 scores. We found that including RSFC strength as a covariate reduced the TBI status–PCL relationship to nonsignificance ($F[2,21] = 1.45$, $p = 0.25$), indicating that within-network RSFC mediates the effect of TBI status on PTSD symptoms.

Reduced white matter integrity is related to increased PTSD symptom severity in combination with RSFC strength. We tested whether average FA values within white matter tracts were associated with total PCL-5 score. We found that FA values did not significantly correlate with PCL-5 scores ($r[24] = -0.21$, $p = 0.29$; Fig. 5A). However, when FA values and within-network RSFC strength were both entered as factors of interest explaining PCL-5 scores, we found that both were significant (FA: $F[1,22] = 4.13$, partial $r[23] = -0.40$, $p = 0.05$, Fig. 5C; RSFC: $F[1,22] = 9.47$, partial $r[23] = -0.55$, $p = 0.005$, Fig. 5D), together explaining 41% of the total variance in PCL-5 scores. This indicates that white matter integrity is related to PTSD symptom severity only after controlling for differences in functional connectivity.

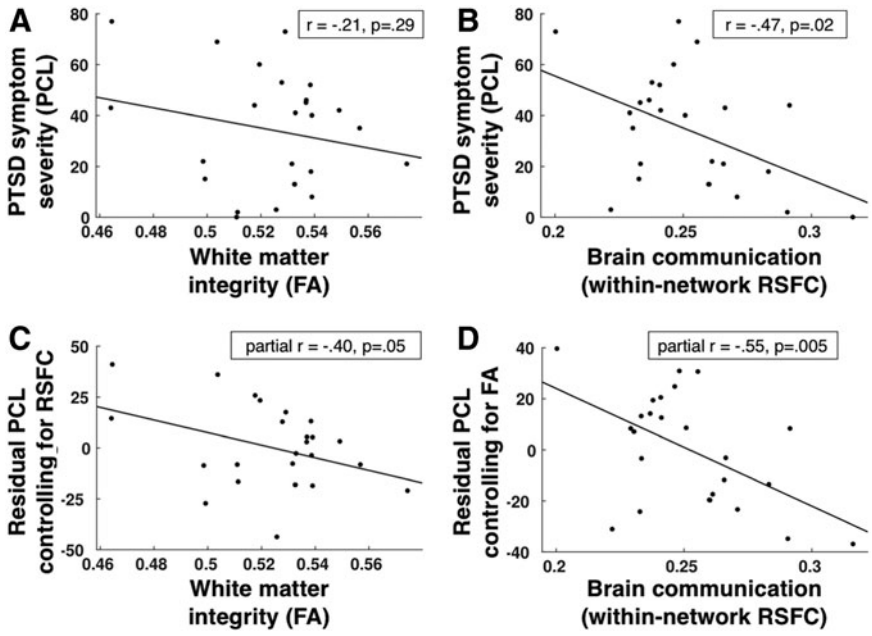


**FIG. 5.** Relationships between fractional anisotropy (FA)/resting-state functional connectivity (RSFC) and Post-Traumatic Stress Disorder (PTSD) Check List for *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (PCL-5) scores**. (A)** Relationship between whole-brain FA and PCL-5 score. **(B)** Relationship between whole-brain RSFC and PCL-5 score. **(C)** Relationship between whole-brain FA and PCL-5 score after controlling for RSFC. **(D)** Relationship between whole-brain RSFC and PCL-5 score after controlling for FA.

### *Observation of relationships among TBI, white matter integrity, functional connectivity, and PTSD symptoms requires large amounts of data*

We examined whether observation of relationships among TBI, brain connectivity, and PTSD severity requires collection of large quantities of data. All RSFC measures were recalculated using only the first 10 min of fMRI data collected, and all FA measures were recalculated using only the first DTI scanning session. These quantities represent the typical amounts of data that are collected in the literature. We then tested whether the relationships among TBI status/number, within-network RSFC, FA, and PTSD symptom severity could still be observed when employing these quantities of data.

We found that when we used these less-reliable measures, within-network RSFC strength no longer differed by TBI status ($F[2,25] = 2.29, p = 0.12$) or correlated with PCL scores ($r[24] = -0.22$, $p = 0.28$). FA values still correlated with the number of TBI events sustained ($r[20] = -0.51$, $p = 0.02$), but FA values were no longer associated with PCL scores in combination with RSFC strength ($F[1,22] = 1.40$, $p = 0.25$).

### *Relationships among TBI, whole-brain white matter integrity, whole-brain functional connectivity, and PTSD severity are not driven by the integrity of the amygdala–vmPFC link*

The integrity of the link between the vmPFC and the amygdala nucleus is thought to be a key factor in the risk for developing PTSD. In post-hoc tests, we examined whether the relationships observed above between whole-brain FA/whole-brain RSFC were driven by FA within the uncinate fasciculus and/or RSFC between the amygdala and the vmPFC. We found no significant relationship between mean FA in the bilateral uncinate fasciculus and PCL-5 scores ($r[24] = -0.05$, $p = 0.81$). We also found no relationship between bilateral amygdala to bilateral vmPFC RSFC and PCL-5 scores ($r[24] = -0.23$, $p = 0.27$), and no significant relationships when both uncinate FA and amygdala–vmPFC RSFC were entered into the same model explaining PCL-5 scores ($ps > 0.25$). Further, we found that whole-brain FC still significantly explained variance in PCL-5 ($p = 0.008$), and that whole-brain FA still explained PCL-5 at trend level ($p = 0.065$), after controlling for unincate FA and amygdala–vmPFC FC (which did not explain PCL-5 variance in this model, $ps > 0.35$). This indicates that the observed relationships among whole-brain FA, RSFC, and PCL-5 scores were not driven by the link between the vmPFC and the amygdala.

Notably, the lack of observed association between PCL-5 scores and amygdala–vmPFC connectivity may be influenced by signal loss in these specific regions, which could result in reduced reliability of these FA and RSFC measures relative to the rest of the brain (as shown in the study by Noble and colleagues[66]). A post-hoc reliability analysis (Fig. S6) examined the stability of these connection-specific measures in the same fashion as the whole-brain analysis shown in Figure S5 (see online supplementary material at http://www.liebertpub.com). This analysis suggested that reliability of uncinate fasciculus FA (expected $\Delta FA \sim = 0.01$) was moderately worse than the reliability of whole-brain FA (expected $\Delta FA \sim = 0.005$). However, the reliability of the amygdala–vmPFC RSFC measure (expected $\Delta RSFC \sim = 0.07$) was substantially worse than the reliability of the whole-brain within-network RSFC measure (expected $\Delta RSFC \sim = 0.015$), even with large amounts of data. Therefore, the lack of association observed here should not be treated as a definitive negative result.

## Discussion

Although there is a clear relationship between TBI and PTSD, exploration of mechanisms by which TBI affects PTSD symptomology is in its early stages.[22] TBI seems to increase the likelihood of developing PTSD,[48,49] even when controlling for mechanism of

injury.[90] This suggests that the brain alterations induced by TBI can act as a permissive ''gateway'' that induces a biological vulnerability to the development of PTSD (and other neuropsychiatric syndromes).[91,92] The neural mechanism behind this ''gateway'' effect has been hypothesized to be related to damage sustained in neural connections that enable the control or suppression of intrusive emotions and memories,[22,51] but such a mechanism has not clearly been demonstrated. Here, we demonstrate potential mechanistic links among TBI, brain connectivity, and PTSD severity (see Fig. 6 for graphical summary).

We identified these links among TBI, brain connectivity, and PTSD in a sample with very large amounts of per-individual MRI data, allowing elucidation of relationships that, as we demonstrate, could not be observed with more typical per-individual data quantities. Although our relatively small sample size can be considered a weakness of the study, the dramatic increase in reliability of the RSFC data gained by collecting large amounts of data (Fig 3B) is a considerable strength, and makes the data set unique. Previous work has argued that results obtained using small quantities of per-subject fMRI data (5–20 min) cannot precisely characterize brain function and organization.[63–66] Here, we demonstrate that this principle also holds in a TBI population. As RSFC reliability depends critically on the amount of data collected, the RSFC estimates obtained here are more accurate than those obtained in any previous work examining RSFC in TBI or PTSD, which permitted observation of effects that could not be seen if tested with low-data versions of this measure. Notably, although estimates of FA did not require multiple DTI scanning sessions to obtain high reliability (Fig. 3A), such estimates did not explain PTSD symptom severity, unless controlling for the (highly reliable) measures of RSFC strength. This work therefore illustrates the need for precise characterization of individual patients using high-data fMRI scanning in order to accurately elucidate relationships between TBI/PTSD and brain function.

We found not one but two dissociable pathways by which brain alterations mediated TBI effects on PTSD severity. First, we observed that the presence of TBI is associated with increased PTSD symptom severity, and that this effect was mediated by decreases in whole-brain RSFC. Although RSFC is known to be reduced

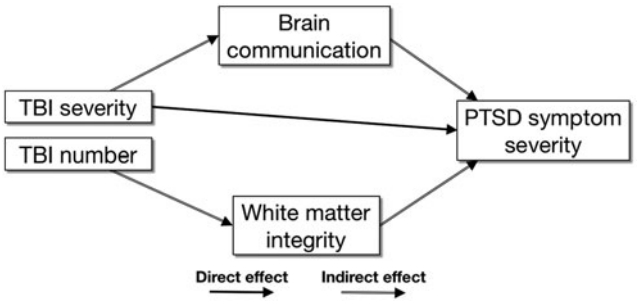


**FIG. 6.** Observed effects for how traumatic brain injury (TBI) increases risk for post-traumatic stress disorder (PTSD) symptoms by altering brain structure and function. We observed two separate pathways by which separable aspects of TBI influence PTSD severity. A direct effect (solid line) of TBI on PTSD severity was observed for TBI status but not number. This effect was mediated by an indirect effect of TBI on brain communication (resting-state functional connectivity [RSFC]). A separate indirect effect of TBI number was observed on white matter integrity (FA), which was independently related to PTSD severity after controlling for brain communication.

across many network connections in individuals with a history of TBI[26,29,33,35,36,39] and is known to be associated with PTSD symptom severity,[93–97] the present findings represent the first explicit linkage of these two effects. Interestingly, the locations of specific functional connections disrupted in TBI or contributing to PTSD severity have been inconsistent across these previous studies, ranging from the amygdala[93,94,96] to the hippocampus[96,97] to somatomotor regions[36] to regions of the default network (medial prefrontal and parietal cortex, and angular gyrus)[33,35,93,95–97] to widespread disruption across many cortical networks.[26,29,39] The present findings support the idea that TBI-related disruptions in RSFC are indeed widespread, and that such whole-brain disruptions contribute to PTSD symptoms.

Second, we observed that the number of TBIs sustained was unrelated to PTSD severity, but that it was associated with reduced whole-brain white matter integrity, which in turn was associated with PTSD severity after controlling for RSFC. Although it is well established that TBIs reduce white matter tract integrity,[21,22] explicit links between these TBI-induced white matter alterations and PTSD severity have been difficult to demonstrate.[98–100] The present results suggest a possible explanation for this difficulty: we observed that TBI-induced FA reductions were associated with PTSD symptom severity only after controlling for reductions in RSFC strength, which has not been attempted in previous work.

Our *a priori* model (Fig. 1) predicted that TBI would be associated with FA decreases, which would result in reduced RSFC, which in turn would increase PTSD severity. This model rested on the idea that disruptions in white matter integrity would impair functional connectivity. Surprisingly, we found no positive relationship between FA and RSFC. Although it is possible that these measures truly are linked, and that our failure to observe the relationship was the result of inaccurate measurement, we think that this explanation is unlikely, for several reasons. First, our high-data protocol resulted in highly reliable measures of both FA and RSFC (Fig. 3). Second, these measures were both associated with (separate) metrics of TBI, and were both behaviorally relevant, explaining independent variance in PTSD symptom severity. Third, although the existence of an FA–RSFC relationship is generally assumed, results of previous work that has actually examined this relationship have been inconsistent. Although studies by Andrews-Hanna and colleagues and van den Heuval and colleagues[101,102] demonstrated the expected positive relationships between FA and RSFC in specific default network tracts, Fjell and colleagues[103] demonstrated negative relationships between FA and RSFC in hippocampal-related connections, and both Tsang and colleagues[104] and Hirsiger and colleagues[105] failed to demonstrate significant FA–RSFC associations.

The present results suggest not only that reliable FA and RSFC estimates are uncorrelated at the whole brain level, but that they reflect partially separable biological factors that explain independent variance in PTSD severity and, importantly, are associated with different aspects of TBI. Reductions in FA were correlated with the number of TBIs sustained by participants, whereas reductions in RSFC were associated with the presence of any TBI history. Although the biological mechanisms behind this distinction are not yet clear, one potential explanation is that RSFC strength may be primarily indexing the integrity of local interneuron connections within the cortex (as the fMRI BOLD signal is known to correspond primarily to local processing rather than pyramidal spiking activity[106,107]), which may be sensitive to single insults. The tract-restricted FA calculated here, by contrast, reflects the integrity of robust white matter tracts in the center of the brain, which may be more continually

degraded by multiple insults. Further research is needed to investigate this speculation.

It is notable that PTSD severity was associated with whole-brain FA and RSFC, but not correlated with uncinate FA or amygdala–vmPFC RSFC. In the absence of TBI, alterations in structural[108] and functional[109,110] connectivity between the amygdala and the mPFC have been previously associated with PTSD, and are posited to reflect impairments in the top-down regulation of amygdala responses. It is possible that the presence of TBI my alter this relationship, potentially because of post-traumatic amnesia following the injury preventing the encoding of fearful aspects of the trauma into memory in the first place.[51] However, it is also plausible that these relationships could be not observed because, unlike the whole-brain measures, the specific reliability of the uncinate FA and (especially) the amygdala–vmPFC RSFC measures were relatively poor (Fig. S6) and may have been insufficient to obtain truly accurate individual estimates. This finding follows recent work suggesting that subcortical RSFC measures may be particularly unreliable.[66] Cortical RSFC measures may be more promising for examination of patient-specific effects related to PTSD.

### *Limitations*

As noted, this work employs measures of brain structure and especially function that are almost certainly more reliable than those used in any previous work. Although the precision of these measurements can help mitigate the problems with the small sample size employed here, they cannot eliminate it entirely. In particular, the No TBI and Moderate TBI groups had very small samples. As such, these findings must be considered preliminary, requiring replication and expansion using similar high-data protocols for reliable characterization of individuals.

It should also be noted that the technical quality of these scans, although relatively standard in the field, was not at the cutting edge. In particular, the quality of the diffusion imaging could be improved with higher spatial and angular resolution imaging, whereas the quality of the functional imaging could potentially be improved with the use of multi-band imaging allowing higher spatial and temporal resolution, resulting in greater specificity of effects. However, such improvements in resolution usually come at the cost of reduced signal to noise ratio (e.g., in the study by Todd and colleagues[111]), which would potentially reduce the reliability of individual-specific FA or RSFC measures. Further work should be done to determine scanning parameters that may result in an optimal combination of effect specificity and measure reliability at the individual level. Additional improvements in FA measures could also be gained by the correction of vibration artifacts using a phase-reversed image,[112] which should be incorporated in future work exploring these effects.

The T1 scans obtained here were visually inspected for the presence of abnormality and potential neuropathology relating to TBI. However, a more sensitive check for such pathology could be conducted using susceptibility weighted imaging (SWI) or fluid attenuation inversion recovery (FLAIR) images. Although such images are not strictly diagnostic of TBI, and in particular often fail to detect mild TBI,[113] identification of neuropathology using these modalities in individual patients has the potential to interface very well with the highly reliable, patient-specific DTI and fMRI measures obtained using this approach. Future work will test whether the presence of such pathology may predict impairments in structural or functional connectivity above and beyond a history of TBI, as well as whether it may combine with the connectivity measures to predict particularly severe PTSD symptoms or behavioral outcomes.

Notably, recent work has suggested that exposure to a blast may particularly alter measures of white matter integrity[59,62,98] and functional connectivity[31,114,115] above and beyond impact-related TBI, although it is not clear that blast exposure results in differential symptoms or outcomes.[116] Although our sample size precluded the ability to test for blast-specific effects in this work, future work should focus on examining how blast exposure may influence relationships among TBI, brain connectivity, and PTSD severity.

This work focuses on biological factors resulting from TBI that influence PTSD symptom severity. However, psychological factors stemming from traumatic experiences also influence PTSD.[117,118] Here, level of combat exposure (commonly including traumatic events) did not differ statistically between TBI groups (although numeric differences were apparent; Table 1). Although we do not think that different levels of trauma exposure among groups explain the complex TBI-connectivity-PTSD effects observed here, trauma exposure does likely influence brain function independently of TBI-induced damage, by driving activity/plasticity in emotion regulation circuits[119–121] A full examination of potential interactions among TBI injury severity, exposure to psychological trauma, measures of brain function, and PTSD symptoms is needed in future studies.

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## Author Disclosure Statement

No competing financial interests exist.

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