Smaller Regional Brain Volumes Predict Posttraumatic Stress Disorder at 3 Months after Mild Traumatic Brain Injury

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Abstract

BACKGROUND: Brain volumes in regions such as the hippocampus and amygdala have been associated with risk for development of PTSD. The objective of this study was to determine whether a set of regional brain volumes, measured by MRI at 2 weeks following mTBI (GCS 13–15), are predictive of PTSD at 3- and 6-months post-injury.

METHODS: This study uses data from TRACK-TBI, a prospective longitudinal study of patients with mTBI. We included patients (N = 421) assessed after evaluation in the Emergency Department, and at 2 weeks (including MRI), 3-, and 6-months post-injury. Probable PTSD diagnosis (PCL-5 score   33) was the outcome. The Freesurfer 6.0 processing pipeline was used to perform volumetric analysis of 3D T1-weighted MRI at 3 Tesla. Brain regions selected *a priori* for volumetric analyses were insula, hippocampus, amygdala, superior frontal cortex, rostral and caudal anterior cingulate, and lateral and medial orbitofrontal cortex.

RESULTS: 77 (18.3%) and 70 (16.6%) patients had probable PTSD at 3- and 6-months. A composite volume derived as the first principal component (PC1) incorporating 73.8% of the variance in insula, superior frontal cortex, and rostral and caudal cingulate contributed to prediction of 3-month (but not 6-month) PTSD in multivariable models incorporating other established risk factors.

CONCLUSIONS: Results, while in need of replication, provide support for a brain reserve hypothesis of PTSD and proof-of-principle for how prediction of at-risk individuals might be accomplished to enhance prognostic accuracy and to enrich clinical prevention trials for individuals at highest risk of PTSD following mTBI.

Keywords

posttraumatic stress disorder (PTSD); brain; Insula; cingulate; Amygdala; traumatic brain injury (TBI)

INTRODUCTION

Posttraumatic stress disorder (PTSD) is an important mental disorder caused by exposure to traumatic stress. Whereas the traumatic stress may be psychological in nature (e.g., threat of injury or death), it may also involve physical injury (e.g., fractures or gunshot wounds). Numerous, well-replicated risk factors for PTSD following trauma have been established (1). These include perceived likelihood of death at the time of trauma, presence of concomitant physical injury, female sex, low education, low IQ, and a history of childhood maltreatment. Genetic and epigenetic risk factors for PTSD are also being identified (2).

Brain morphometric measures have also been identified and replicated as risk factors for development or persistence of PTSD following exposure to traumatic stress. Brain structures of persons with and without PTSD, differ on average, (3) with the former having smaller hippocampal (4–6) and cortical (7) volumes, and reduced cortical thickness (8).

Traumatic brain injury (TBI) is an injury that is especially liable to result in PTSD, though the pathological bases for this co-occurrence are as yet incompletely understood (9–13). Given the findings of structural brain differences between patients with PTSD and healthy controls, there is particular interest in determining the prognostic utility of brain measurement for subsequent PTSD. Among patients with mild TBI (Glasgow Coma Scale [GCS] 13–15), risk factors for PTSD post-TBI include female sex, cause of injury (intentional harm vs. accidental), and history of pre-existing mental health disorder (14). However, these are imperfect predictors of PTSD symptoms; brain imaging represents a promising objective avenue for developing more accurate early biomarkers. Magnetic resonance imaging (MRI) is especially suited for this purpose because of its wide availability, safety, convenience, and excellent image quality.

Few studies have addressed the issue of brain morphometry in PTSD in relation to comorbid mTBI or with reference to outcomes. In a small (N=30) study of patients with PTSD, larger anterior cingulate volume at baseline was shown to be a predictor of recovery (15). In another small study, patients with mTBI with significant PTSD symptoms (n = 12) were found to have larger entorhinal cortex volumes than patient with mTBI without significant PTSD symptoms (n = 27) (16).

In the present study, we investigated MRI quantification of global and regional brain volumes as early biomarkers of PTSD, assessed with the PTSD Checklist for DSM-5 (PCL-5) (17). We limited analysis to the following structures based on pre-existing evidence for their involvement in PTSD: insula, hippocampus, amygdala, superior frontal gyrus, rostral and caudal ACC, medial and lateral orbitofrontal gyri (5–7, 18, 19). We explored whether early MRI volumetrics (obtained at 2 weeks after mTBI) are predictive of PTSD at 3- and 6-months post-injury using the 3 Tesla (3T) high-resolution brain MRI scans of patients with mTBI from the multicenter Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study.

MATERIALS AND METHODS

Participants

Patients were enrolled at 11 academic Level 1 trauma centers in the United States within 24 hours of injury, following evaluation in the Emergency Department (ED) for TBI as part of the prospective TRACK-TBI study (20); all received a computed tomography (CT) scan per order of the evaluating ED physician. Exclusion criteria included: significant polytrauma that would interfere with follow-up; penetrating TBI; prisoners or patients in custody; pregnancy; patients on psychiatric "hold"; being non-English or non-Spanish speaking; having a contraindication to MRI; major debilitating mental (e.g., schizophrenia or bipolar disorder) or neurological disorders (e.g., stroke, dementia) or any other disorder that would interfere with assessment and follow-up or provision of informed consent. Written consent was obtained from all subjects to participate in a protocol approved by the University of California, San Francisco Institutional Review Board (IRB) and by the IRBs at participating sites.

This paper analyzed a subset of the TRACK-TBI U01 cohort with the following criteria: adult (age   17), GCS ED arrival scores of 13–15, PCL-5 outcome measure collected at both 3 months and 6 months, with MR volumetric measures analyzed from a research-acquired 3D T1-weighted MRI at 2 weeks after injury. (Figure: CONSORT DIAGRAM). Subjects not included in the analysis due to missing PCL-5 outcomes (N=57) did not differ significantly from those who were included (N=421) on any sociodemographic, clinical, or injury-related parameter.

Measures

Within 24 hours of injury, demographic and clinical characteristics of the patients were collected, including age, sex, race, ethnicity, years of education, history of psychiatric conditions including substance abuse, prior history of TBI, and the cause of the recent injury, categorized as incidental falls, road traffic incidents, violence/assaults, and other causes. Glasgow Coma Scale scores (21) were acquired at the time of presentation to the ED. All patients in the analyses reported here had ED admission GCS score of 13–15.

PTSD Checklist for DSM-5 (PCL-5) was obtained to measure past-month posttraumatic stress disorder symptoms. The range of the scale is 0–80. Signal detection analyses against a clinical gold standard have shown that PCL-5 scores of 31 to 33 are optimally efficient for diagnosing PTSD (17). We used scores of   33 to indicate probable PTSD. PCL-5 subscales of reexperiencing, avoidance, negative cognitions and mood, and hyperarousal were also examined as continuous measures.

For the 3-month follow-up, the assessment was completed at mean = 3 months (IQR: 2.9–3.1, range 2.7–3.5) from the time of injury; for the 6-month follow-up the assessment was completed at mean = 6 months (IQR: 5.9–6.2, range 5.4–6.7) from the time of injury.

MR Image Acquisition

Patients underwent 3D T1-weighted imaging at approximately 2 weeks after injury using 3T MRI scanners. Harmonization across MRI platforms was achieved with the Alzheimer Disease Neuroimaging Initiative (ADNI) standard, including the ADNI phantom for monitoring any geometric distortions (22). Briefly, this acquisition consisted of a sagittal 3D Fast Spoiled Gradient Echo (FSPGR) T1-weighted sequence (General Electric) or a sagittal 3D Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) T1-weighted sequence (Philips and Siemens) using 8-channel (General Electric and Philips) or 12-channel (Siemens) head radiofrequency coils and at a spatial resolution of $1.0 \times 1.0 \times 1.2$ mm. The imaging protocol also included 3D T2-weighted fluid attenuated inversion recovery (FLAIR), 3D T2*-weighted gradient echo and 3D T2-weighted sequences for radiological interpretation of abnormal MRI findings.

MR Image Processing and Analysis

Cortical reconstruction and volumetric segmentation of the 3D T1-weighted images were performed with the FreeSurfer Version 6.0 processing framework (http://surfer.nmr.mgh.harvard.edu/). This process includes motion correction, removal of nonbrain tissue (23), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (24, 25), intensity normalization (26), tessellation of the gray matter - white matter boundary, automated topology correction, and surface deformation (27, 28) to produce representations of cortical thickness. Using the entire 3-dimensional MR volume in segmentation and deformation procedures, the representation of cortical thickness is calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex (29). The produced maps use spatial intensity gradients, are not restricted to the voxel resolution of the original data and can detect submillimeter group differences. Using an automated labeling system based on the Desikan-Killiany Atlas the cortex was divided into 33 gyral regions in each hemisphere (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation). In addition to the Freesurfer 6.0 automated Quality Control (QC) process, all segmented scans were visually inspected by an experienced operator and segmentations were manually corrected when necessary.

As noted above, we limited analysis to the following structures based on pre-existing evidence for their involvement in PTSD and computed estimated volumes according to standard FreeSurfer volume segmentation: insula, hippocampus, amygdala, superior frontal gyrus, rostral and caudal ACC, medial and lateral orbitofrontal gyri and total intracranial volume (ICV). None of the laterality indices for ROIs showed significant association with PTSD at 3 or 6-months post-injury in the bivariate analyses; therefore, for paired structures, the total volume as the sum of left and right hemispheres was used in all analyses.

The CT and MRI scans were interpreted by a board-certified neuroradiologist blinded to the patients' clinical information using the NIH Common Data Elements (CDEs) for TBI pathoanatomic classification (30). Patients with any acute abnormal CT or MRI findings related to the recent injury were categorized as "CT positive" or "MRI positive," respectively. Most CT findings were small contusions and small subarachnoid hemorrhages

whereas MRI findings largely consisted of microbleeds due to hemorrhagic axonal injury and small contusions; neither CT or MRI positivity were significantly associated with PTSD outcomes, and so they were not included in any of the analyses.

Statistical Analysis

Bivariate and multivariable (adjusting for sociodemographic characteristics and other known PTSD risk factors including sex, race, ethnicity, education, prior TBI, history of psychiatric illness, cause of injury, and early PTSD symptoms at 2 weeks) associations between individual standardized brain volume metrics and probable PTSD outcomes at 3- and 6-months post-injury were analyzed for each of the 8 preselected regions using logistic regression. Benjamini-Hochberg's method (31) was used to adjust for multiple testing. To avoid problems with multicollinearity when simultaneously including multiple regions in the models, principal components analysis (PCA) was conducted on four volumetric measures (Insula, Superior frontal, Rostral Anterior Cingulate, and Caudal Anterior Cingulate), chosen because they were associated with 3-month PTSD outcome at Benjamini-Hochberg FDR-adjusted p   0.20 in the multivariable analyses. Subsequent multivariable models evaluated the association between the first principal component (PC1) as a composite score – which explained the majority of the variance in those four regional volumes– and the PTSD outcomes, adjusting for known demographic and clinical risk factors.

The composite of these 4 regions (PC1) was also tested for association with sub-domains of PTSD symptoms, as measured by the PCL-5 subscales, at 3- and 6-months post-injury. The distribution of PCL-5 subscales were skewed with excessive zeros, so a zero-inflated negative binomial (ZINB) regression model was used to jointly assess the associations of brain volumes with presence or absence of PCL symptoms (OR component) and with severity of the symptoms (FC component). Statistical analyses were performed in R version 3.6.1 (http://www.r-project.org).

RESULTS

Demographic and clinical characteristics of the study participants are shown in Table 1. Approximately two-thirds of the sample was male, and mean age of the sample was 38.7 (SD 16.1) years. Consistent with our findings in a larger sample of TRACK-TBI patients (14), of whom the present sample is a subset who had MRIs (FIGURE: CONSORT DIAGRAM), characteristics most strongly associated with risk for PTSD at either the 3- or 6-month follow-up included pre-injury psychiatric history, prior TBI, and less education.

Bivariate and multivariable associations between volumes in each of the 8 regions of interest and probable PTSD status at 3-months post-injury are shown in Table 2. Smaller volumes of three regions (superior frontal, rostral and caudal ACC) were individually predictive of PTSD at 3 months in the fully adjusted analyses (Table 2B, **right panel**). Insula also showed a trend (raw p-value=0.084, BH-adjusted p-value=0.168) (Table 2, **right panel**) Using principal components analysis (PCA), we determined that a single principal component (PC1) that incorporated 73.8% of the variance in those 4 regional volumes predicted 3-month PTSD, even in multivariable models incorporating other established risk markers including early (2-week) PTSD symptom severity (Table 3a). When considering individual

symptom sub-domains at 3-months as measured by the PCL-5, severity and presence or absence (at a trend level) of hyperarousal symptoms was the only symptom sub-domain significantly predicted by PC1 (Table 3b).

The 4-region composite (PC1) was not predictive of PTSD at 6 months in the multivariable model (Supplemental Table S1). However, when considering individual symptom sub-domains at 6 months as measured by the PCL-5, only severity (but not presence or absence) of hyperarousal symptoms was significantly predicted by a model that included PC1 (Table 4).

DISCUSSION

In this analysis of a pre-specified cohort from the TRACK-TBI study, regional brain volumes on structural MRI at 2-weeks post-injury were analyzed in relation to PTSD outcomes at 3- and 6-months post-injury. Smaller insula, superior frontal cortex, and rostral and caudal anterior cingulate volumes at 2 weeks following mTBI each contributed to prediction of PTSD at 3 months (but not 6 months). TBI is known to be an important risk factor for PTSD development following injury (12, 14); the current study provides important data on the relationship between volumetric brain measures and PTSD in the context of acute mTBI.

Reduced gray matter volume and decreased cortical thickness in patients with PTSD have been consistently reported in the anterior cingulate (6, 7) prefrontal cortex (8), and hippocampus (5, 6). Reduced volumes of the hippocampus, ACC and prefrontal cortex are vulnerability factors for PTSD, as is increased connectivity of the salience network and the default mode network, as recently reviewed (32). We therefore limited our investigation of volumes to regions within these structures. We created a single principal component (PC1) that explained much (74%) of the variance in the regional volumes of the insula, superior frontal cortex, and rostral and caudal anterior cingulate to avoid multicollinearity issues. The observation that larger brain volumes indicate less likelihood of symptoms at 3 months lends support to the concept of brain reserve (33) as an important factor in resilience to PTSD (34–37).

There were no significant interactions of brain volume metrics with prior TBI for PTSD outcomes at either 3- or 6-months post injury. We found that PC1 predicted PTSD at 3 months and, importantly, that it had predictive value even in models where 2-week PTSD symptoms (measured with the PCL-5) were included. This finding suggests that biological variables such as regional brain volumes can contribute to PTSD risk prediction beyond the value of early symptom measurement alone. We wish to emphasize however, that this study provides proof-of-principle only; the actual magnitude of the increase in risk prediction provided by regional brain volume measurement – while statistically significant – was small in effect compared with the predictive value of early (e.g., 2-week post-injury) symptom measurement and would be, at most, of marginal prognostic benefit.

For reasons that are not presently understood, 2-week PTSD symptoms continued to predict 6-month PTSD outcomes, but brain volumes (including PC1) did not. It may be the case that

as time from the TBI advances, multiple biological and psychosocial factors intervene to lessen the importance of these factors. Interestingly, however, whereas overall PTSD symptoms were not predicted by regional brain volumes at 6-months post-injury, they continued to significantly predict severity of the PTSD subdomains, hyperarousal symptoms, as they had at 3-months post-injury. It may be the case that differences in regional brain volumes found in this study reflect a set of structures and their interrelationships that subserve elements of arousal that are dysfunctional in PTSD. This is a hypothesis that deserves testing with more direct focus on neuropsychological functions that parallel the trajectory of hyperarousal symptoms during the longitudinal course of PTSD after mTBI.

There is a robust literature documenting smaller hippocampal volumes in PTSD (5, 6), but we did not find hippocampal volume to be predictive of PTSD in this study. It is unclear why our results differ from many others in this regard, but it is possible that PTSD occurring in the context of mTBI has a different brain structural basis than PTSD acquired via other types of trauma. In addition, given the more acute time frame of the current study (within 6 months of trauma), it may be that hippocampal volumes reflect PTSD at much further time points from injury. Our findings, in particular, of smaller posterior cingulate volume being associated with PTSD at 3-month follow-up does suggest that the default mode network may be involved, particularly in the genesis of PTSD, a hypothesis that has been supported by multiple resting-state functional connectivity studies in PTSD (38–41).

Our study has several noteworthy strengths and limitations. There are 2 major advantages and disadvantages to using MRI volumetrics for investigating brain structure in relation to PTSD symptoms following injury. First, an advantage is that it should be relatively insensitive to the physical effects of milder head trauma at the early subacute stage of injury. A potential disadvantage, though, is that we cannot be certain that the brain volumes obtained here at 2 weeks post-TBI are reflective of the pre-injury state or are influenced by variously evolving inury-related changes. A second advantage is that MRI volumetrics can be performed reproducibly with high precision across different MRI scanners of different types when a standardized acquisition protocol is used, enabling the aggregation of large multicenter datasets. The major disadvantage is that volumetrics cannot probe brain microstructure, function, or connectivity, which can be much more sensitive to inter-individual variation in brain organization relevant to complex mental disorders such as PTSD. It must also be noted that even though the principal component containing information about the 4 regions was statistically significant in the predictions shown, not all of its individual components withstood correction for multiple testing. This speaks to the need for replication of these results in larger samples. Another important limitation of the study is the fact that the PCL-5 assessment of PTSD symptoms was administered agnostic to the index trauma, i.e., participants responded based on their worst lifetime trauma, which may not have been the injury that resulted in their index TBI. Whereas we adjusted our models for pre-existing psychiatric history – which was the only information collected that might indicate pre-injury PTSD – we cannot know for certain whether the symptoms reported on the PCL-5 reflect *de novo* PTSD from the injury, or persistence of worsening of pre-injury PTSD.

In summary, we found that MRI volumetrics of several brain regions (insula, anterior and posterior cingulate, superior frontal cortex) early after mild traumatic brain injury was associated with PTSD prediction at 3- but not 6-months post-injury. Whereas the incremental effect size of inclusion of these volumetric measures was small and unlikely to be of clinical significance in their current form, results provide proof-of-principle for how prediction of at-risk individuals might be accomplished to enhance prognostic accuracy and to enrich clinical prevention trials for individuals at highest risk of PTSD following mTBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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2697 TRACK-TBI U01 subjects

145 pediatric subjects (<16yo)
1793 TBI subjects without 2W Phase I MRI

759 adult TBI
with 2W Phase I MRI

74 GCS ≠ 13-15

685

207 did not have MR volumetric measures available on the 2W Phase I MRI

478

57 PTSD outcome not available at both 3 months and 6 months

421 adult TBI subjects,
- GCS 13-15
- 2W Phase I MRI scans with MR volumetric measures
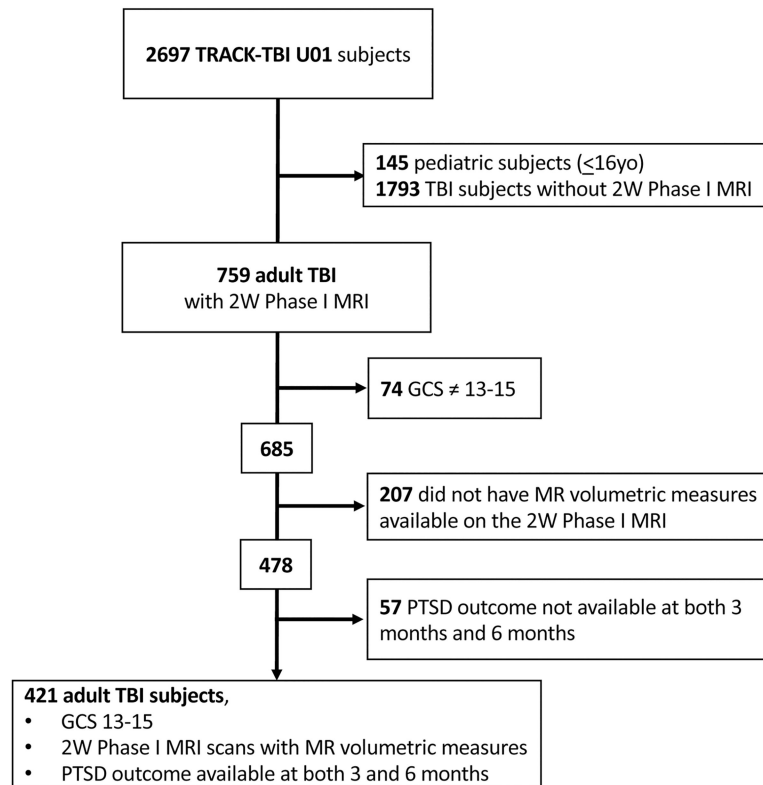- PTSD outcome available at both 3 and 6 months

Figure:
CONSORT DIAGRAM

Table 1.

Demographic and clinical characteristics.

	N	PTSD at 3-months post-injury			PTSD at 6-months post-injury		
		No (n=344)	Yes (n=77)	p-value	No (n=351)	Yes (n=70)	p-value
Age (Mean (SD))	421	38.9 (16.5)	37.8 (14.2)	.70	39.2 (16.5)	36.6 (13.5)	.32
Years of Education (Mean (SD))	417	14.3 (2.8)	13.2 (2.2)	<.001	14.4 (2.7)	12.8 (2.5)	<.001
Patient Type	421			.61			.89
ED Discharge	175	140 (40.7%)	35 (45.5%)		145 (41.3%)	30 (42.9%)	
Hospital admit no ICU	170	139 (40.4%)	31 (40.3%)		141 (40.2%)	29 (41.4%)	
Hospital admit with ICU	76	65 (18.9%)	11 (14.3%)		65 (18.5%)	11 (15.7%)	
Sex	421			.033			.039
Female	141	107 (31.1%)	34 (44.2%)		110 (31.3%)	31 (44.3%)	
Male	280	237 (68.9%)	43 (55.8%)		241 (68.7%)	39 (55.7%)	
Race	418			.054			<.001
White	309	255 (74.3%)	54 (72%)		264 (75.6%)	45 (65.2%)	
Black	76	57 (16.6%)	19 (25.3%)		53 (15.2%)	23 (33.3%)	
Other	33	31 (9.0%)	2 (2.7%)		32 (9.2%)	1 (1.5%)	
Hispanic	419			.73			.86
No	349	287 (83.7%)	62 (81.6%)		292 (83.4%)	57 (82.6%)	
Yes	70	56 (16.3%)	14 (18.4%)		58 (16.6%)	12 (17.4%)	
Injury Cause	421			.024			.020
Road traffic incident	267	216 (62.8%)	51 (66.2%)		219 (62.4%)	48 (68.6%)	
Incidental fall	91	82 (23.8%)	9 (11.7%)		83 (23.7%)	8 (11.4%)	
Violence/assault	23	15 (4.4%)	8 (10.4%)		15 (4.3%)	8 (11.4%)	
Other	40	31 (9.0%)	9 (11.7%)		34 (9.7%)	6 (8.6%)	
Psychiatric History	421			<.001			.002
No	347	295 (85.8%)	52 (67.5%)		299 (85.2%)	48 (68.6%)	
Yes	74	49 (14.2%)	25 (32.5%)		52 (14.8%)	22 (31.4%)	
Prior TBI	420			.003			.019
No	276	237 (69.1%)	39 (50.7%)		239 (68.3%)	37 (52.9%)	

		PTSD at 3-months post-injury			PTSD at 6-months post-injury		
	N	No (n=344)	Yes (n=77)	p-value	No (n=351)	Yes (n=70)	p-value
Yes	144	106 (30.9%)	38 (49.4%)		111 (31.7%)	33 (47.1%)	
CT	417			.26			.028
CT−	299	240 (70.4%)	59 (77.6%)		241 (69.5%)	58 (82.9%)	
CT+	118	101 (29.6%)	17 (22.4%)		106 (30.6%)	12 (17.1%)	
MRI	421			.80			.19
MRI−	234	190 (55.2%)	44 (57.1%)		190 (54.1%)	44 (62.9%)	
MRI+	187	154 (44.8%)	33 (42.9%)		161 (45.9%)	26 (37.1%)	

Table 2.

Bivariate model 1 * (left) and bivariate model 2 ** (right) association between each volumetric measure (standardized) and probable PTSD at 3-months post-injury.

	Bivariate Model 1			Bivariate Model 2			
	AOR	95% CI	p-value	AOR	95% CI	p-value	BH-adjusted p-value
Insula	.66	.47–.94	.020	.66	.41–1.06	.084	0.168
Hippocampus	1.16	.85–1.59	.36	1.09	.71–1.67	.70	0.70
Amygdala	1.12	.82–1.54	.47	0.82	.53–1.25	.35	0.40
Superior Frontal	.70	.51–.96	.026	.53	.34–.84	.007	0.036
Rostral Anterior Cingulate	.70	.50–.96	.028	.58	.37–.92	.019	0.051
Caudal Anterior Cingulate	.78	.57–1.05	.10	.57	.37–.87	.009	0.036
Medial Orbitofrontal	.87	.64–1.19	.38	.82	.54–1.24	.35	0.40
Lateral Orbitofrontal	.86	.64–1.16	.32	.78	.52–1.18	.24	0.39

AOR = Adjusted odds ratio; BH = Benjamini-Hochberg method to adjust for multiplicity controlling for the family discovery rate

*
Models include the specified ROI and are adjusted for intracranial volume

**
Models include the specified ROI and are adjusted for intrancranial volume, sex, race, ethnicity, years of education, history of psychiatric illness, prior traumatic brain injury, injury cause, and 2-week PTSD symptom score

Table 3a.

Multivariable logistic regression model assessing the association between risk factors, including early (2-week) PTSD symptom severity as assessed by the PCL-5, and PTSD at 3-months post- injury (n=405).

	OR	95% CI	Chi-sq	p-value
PC1	.65	0.49–0.87	8.75	.003
ICV (standardized)	2.03	1.19–3.48	6.67	.01
Male (ref: Female)	.72	0.31–1.68	.58	.45
Black (ref: White/Other)	1.05	0.42–2.63	.01	.92
Hispanic (ref: White/Other)	1.31	0.50–3.38	.30	.58
Years of Education	.96	0.84–1.10	.31	.58
Any psychiatric history (ref: None)	1.89	0.84–4.28	2.35	.13
Any prior TBI (ref: None)	1.63	0.81–3.28	1.90	.17
Violent injury cause (ref: Accidental)	1.40	0.39–5.10	.26	.61
PCL-5 Total Score at week 2	1.09	1.07–1.12	65.54	< .001

PC1: first principal component that explained 73.8% of the variance in the regional volumes of the insula, superior frontal cortex, and rostral and caudal anterior cingulate.

Table 3b.

Multivariable zero-inflated negative binomial regression model assessing the association between risk factors and PCL-5 Hyperarousal subscale at 3-months post-injury (n=405)

	FC	95% CI	p-value	OR	95% CI	p-value
PC1	.94	0.88–0.99	.031	1.27	0.99–1.64	.06
ICV (standardized)	1.13	1.00–1.27	.049	.79	0.49–1.26	.31
Male (ref: Female)	.99	0.82–1.19	.89	.96	0.44–2.11	.92
Black (ref:White/Other)	1.21	0.99–1.48	.063	1.48	0.63–3.44	.37
Hispanic (ref: non-Hispanic)	1.09	0.89–1.33	0.43	1.66	0.66–4.18	.28
Education (y)	.96	0.93–0.99	0.013	1.11	0.98–1.25	.09
Any psychiatric history (ref: None)	1.16	0.96–1.40	0.128	2.06	0.77–5.52	.15
Any prior TBI (ref: None)	1.17	0.997–1.37	0.055	1.35	0.68–2.67	.39
Violent injury cause [*] (ref: Accidental)	1.05	0.79–1.39	0.76	--	--	--
PCL-5 Hyperarousal at week 2	1.07	1.05–1.08	<0.001	1.35	1.20–1.50	<0.001

PC1: first principal component that explained 73.8% of the variance in the regional volumes of the insula, superior frontal cortex, and rostral and caudal anterior cingulate

FC: Estimated fold change with 95% confidence interval of the predictor variable associated with severity of hyperarousal symptoms when the symptoms are present.

OR: Estimated odds ratio with 95% confidence interval of the predictor variable associated with presence (non-zero scores) vs. absence (zero scores) of hyperarousal symptoms.

[*] Injury cause was not modeled in the zero-inflation part due to zero-count in one of the cells which would lead to an infinite confidence interval.

Table 4.

Multivariable zero-inflated negative binomial regression model assessing the association between risk factors and PCL-5 Hyperarousal subscale at 6-months post-injury (n=405).

	FC	95% CI	p-value	OR	95% CI	p-value
PC1	.89	.83–.95	.001	1.11	.83–1.49	.47
ICV (standardized)	1.16	1.02–1.32	.029	.88	.50–1.53	.65
Male (ref: Female)	1.07	.87–1.32	.52	.61	.23–1.64	.33
Black (ref: White/Other)	1.13	.91–1.41	.26	1.57	.57–4.30	.38
Hispanic (ref: non-Hispanic)	1.07	.86–1.34	.55	2.48	.72–8.49	.15
Years of Education	.97	.94–.997	.033	1.07	.94–1.22	.31
Any psychiatric history (ref: None)	1.13	.92–1.39	.24	2.16	.64–7.27	.21
Any prior TBI (ref: None)	1.13	.96–1.34	.15	.97	.47–1.99	.93
Violent injury cause (ref: Accidental)	1.40	1.05–1.88	.024	--	--	--
PCL-5 Hyperarousal at week 2	1.08	1.07–1.10	<.001	1.26	1.09–1.46	.002

PC1: first principal component that explained 73.8% of the variance in the regional volumes of the insula, superior frontal cortex, and rostral and caudal anterior cingulate.

FC: Estimated fold change with 95% confidence interval of the predictor variable associated with severity of hyperarousal symptoms when the symptoms are present.

OR: Estimated odds ratio with 95% confidence interval of the predictor variable associated with presence (non-zero scores) vs. absence (zero scores) of hyperarousal symptoms.

*
Injury cause was not modeled in the zero-inflation part due to zero-count in one of the cells which would lead to an infinite confidence interval.