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## Mild traumatic brain injury impacts associations between limbic system microstructure and post-traumatic stress disorder symptomatology

Valerie J. Sydnor<sup>a</sup>, Sylvain Bouix<sup>a</sup>, Ofer Pasternak<sup>a</sup>, Elisabeth Hartl<sup>a,b</sup>, Laura Levin-Gleba<sup>a,c</sup>, Benjamin Reid<sup>a</sup>, Yorghos Tripodis<sup>d</sup>, Jeffrey P. Guenette<sup>a,e</sup>, David Kaufmann<sup>a,f</sup>, Nikos Makris<sup>a,g</sup>, Catherine Fortier<sup>c,h</sup>, David H. Salat<sup>c,i</sup>, Yogesh Rathia<sup>a</sup>, William P. Milberg<sup>c,h,j</sup>, Regina E. McGlinchey<sup>c,h,j</sup>, Martha E. Shenton<sup>a,e,k,l</sup>, Inga K. Koerte<sup>a,f,l,\*</sup>

<sup>a</sup> Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

<sup>b</sup> Department of Neurology, University Hospital, LMU Munich, Munich, Germany

<sup>c</sup> Translational Research Center for TBI and Stress Disorders (TRACTS), VA Boston Healthcare System, Boston, MA, United States

<sup>d</sup> Boston University School of Public Health, Boston University, Boston, MA, United States

<sup>e</sup> Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

<sup>f</sup> Department of Child and Adolescent Psychiatry, Psychosomatic, and Psychotherapy, Ludwig-Maximilian University, Munich, Germany

<sup>g</sup> Center for Morphometric Analysis, Departments of Psychiatry and Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

<sup>h</sup> Department of Psychiatry, Harvard Medical School, Boston, MA, United States

<sup>i</sup> Neuroimaging Research for Veterans (NeRVe) Center, VA Boston Healthcare System, Boston, MA, United States

<sup>j</sup> Geriatric Research, Education and Clinical Center (GRECC), VA Boston Healthcare System, Boston, MA, United States

<sup>k</sup> VA Boston Healthcare System, Brockton Division, Brockton, MA, United States

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### ABSTRACT

**Background:** Post-traumatic stress disorder (PTSD) is a psychiatric disorder that afflicts many individuals, yet the neuropathological mechanisms that contribute to this disorder remain to be fully determined. Moreover, it is unclear how exposure to mild traumatic brain injury (mTBI), a condition that is often comorbid with PTSD, particularly among military personnel, affects the clinical and neurological presentation of PTSD. To address these issues, the present study explores relationships between PTSD symptom severity and the microstructure of limbic and paralimbic gray matter brain regions, as well as the impact of mTBI comorbidity on these relationships.

**Methods:** Structural and diffusion MRI data were acquired from 102 male veterans who were diagnosed with current PTSD. Diffusion data were analyzed with free-water imaging to quantify average CSF-corrected fractional anisotropy (FA) and mean diffusivity (MD) in 18 limbic and paralimbic gray matter regions. Associations between PTSD symptom severity and regional average dMRI measures were examined with repeated measures linear mixed models. Associations were studied separately in veterans with PTSD only, and in veterans with PTSD and a history of military mTBI.

**Results:** Analyses revealed that in the PTSD only cohort, more severe symptoms were associated with higher FA in the right amygdala-hippocampus complex, lower FA in the right cingulate cortex, and lower MD in the left medial orbitofrontal cortex. In the PTSD and mTBI cohort, more severe PTSD symptoms were associated with higher FA bilaterally in the amygdala-hippocampus complex, with higher FA bilaterally in the nucleus

**Abbreviations:** ANTS, Advanced Normalization Tools; BAT-L, Boston Assessment of TBI-Lifetime; CAPS-CSS, CAPS-DX Current Symptom Severity; CAPS-DX, Clinician-Administered PTSD Scale-Diagnostic Version for DSM-IV; CSF, cerebrospinal fluid; DASS21, Depression Anxiety Stress Scales; dMRI, diffusion magnetic resonance imaging; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DTI, diffusion tensor imaging; FA, fractional anisotropy; FDR, false discovery rate; FLIRT, FMRIB's Linear Image Registration Tool; LDH, Lifetime Drinking History; LMM, linear mixed model; MD, mean diffusivity; MRI, magnetic resonance imaging; mTBI, mild traumatic brain injury; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OND, Operation New Dawn; PTSD, post-traumatic stress disorder; RDoC, Research Domain Criteria; REML, restricted maximum likelihood; ROI, region of interest; SCID, Structured Clinical Interview for DSM-IV-TR Axis I Disorders; TBI, traumatic brain injury; TMS, transcranial magnetic stimulation; TRACTS, Translational Research Center for TBI and Stress Disorders; VA, Veterans Affairs

\* Corresponding author at: Psychiatry Neuroimaging Laboratory, 1249 Boylston St. Boston, MA 02215.

E-mail address: [ikoerte@bwh.harvard.edu](mailto:ikoerte@bwh.harvard.edu) (I.K. Koerte).

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accumbens, with lower FA bilaterally in the cingulate cortex, and with higher MD in the right amygdala-hippocampus complex.

**Conclusions:** These findings suggest that the microstructure of limbic and paralimbic brain regions may influence PTSD symptomatology. Further, given the additional associations observed between microstructure and symptom severity in veterans with head trauma, we speculate that mTBI may exacerbate the impact of brain microstructure on PTSD symptoms, especially within regions of the brain known to be vulnerable to chronic stress. A heightened sensitivity to the microstructural environment of the brain could partially explain why individuals with PTSD and mTBI comorbidity experience more severe symptoms and poorer illness prognoses than those without a history of brain injury. The relevance of these microstructural findings to the conceptualization of PTSD as being a disorder of stress-induced neuronal connectivity loss is discussed.

## 1. Introduction

Approximately 23% (Fulton et al., 2015) of military service members deployed to Iraq (Operation Iraqi Freedom, OIF; Operation New Dawn, OND) and Afghanistan (Operation Enduring Freedom, OEF) experience deployment-related physical or emotional trauma and are subsequently diagnosed with post-traumatic stress disorder (PTSD), a psychiatric disorder associated with hyperarousal, avoidance behaviors, trauma re-experiencing, and alterations in cognition and mood. Despite this high prevalence, the pathogenesis of PTSD remains largely unknown, hindering prevention and treatment efforts. Further, although populations at high risk for PTSD (e.g., military populations) have a high incidence of exposure to traumatic brain injury (TBI), additional work is needed to fully characterize the ways in which TBI can affect the clinical and neurological presentation of PTSD (Spadoni et al., 2018; Tanev et al., 2014; Vasterling et al., 2009).

MRI studies of PTSD have reported changes in the macrostructure (i.e., volume, thickness, density) of limbic and paralimbic brain structures (Chao et al., 2013; O'Doherty et al., 2015; Bremner, 2007; Meng et al., 2014, 2016). These structures are thought to contribute to PTSD symptomatology due to their involvement in relevant affective and cognitive processes such as emotion regulation, self-referential processing, motivation, memory, and attention. Indeed, PTSD symptom load appears to influence the magnitude of limbic/paralimbic macrostructural brain alterations (Bing et al., 2013; Lindemer et al., 2013; Meng et al., 2016; O'Doherty et al., 2017; Rogers et al., 2009; Wrocklage et al., 2017), with greater symptom severity correlating with, for example, reduced hippocampal volumes (Nelson and Tumpap, 2017; O'Doherty et al., 2017) and reduced thickness of the cingulate cortex (Bing et al., 2013; Wrocklage et al., 2017). In addition, increased PTSD severity is associated with greater decrements in psychosocial functioning (Crowson et al., 1998; MacDonald et al., 1999), increased physical health concerns (Hoge et al., 2007; Pacella et al., 2013), and more severe neurocognitive deficits (Cohen et al., 2013; Twamley et al., 2009). Taken together, these findings suggest that PTSD symptoms and corresponding psychosocial, cognitive, and neurological changes occur along a continuum, further suggesting that PTSD may best be characterized and studied as a dimensional mental illness (Palm et al., 2009). This notion is supported by taxometric analyses that reveal a dimensional latent structure of PTSD (i.e., a continual rather than a taxonic structure) (Broman-Fulks et al., 2006; Forbes et al., 2005; Ruscio et al., 2002). This notion also fits well with the general Research Domain Criteria (RDoC) framework, which emphasizes the importance of studying clinical and biological variables along a spectrum (Insel et al., 2010). Adopting a dimensional approach to study PTSD may thus prove important for identifying neurological features that contribute to PTSD severity.

Exposure to mild TBI (mTBI), the “signature wound” of the Iraq and Afghanistan wars (Snell and Halter, 2010), may also impact PTSD severity. Not only is TBI often comorbid with, and potentially a risk factor for PTSD (Chemtob et al., 1998; Hoge et al., 2008; Lippa et al., 2015; Schneiderman et al., 2008; Yurgil et al., 2014), but individuals with PTSD and a history of mTBI often exhibit more severe PTSD symptoms

(Chemtob et al., 1998; Vanderploeg et al., 2009), poorer neurocognitive functioning, worse long term recovery (Vanderploeg et al., 2009), and more severe neurological changes (Lindemer et al., 2013; Spielberg et al., 2015) than those who have not sustained a mTBI. In OEF/OIF/OND populations, where approximately 12–35% of service members have sustained a TBI (the vast majority being mild) (Fortier et al., 2014; Lindquist et al., 2017; O'Neil et al., 2013; Schneiderman et al., 2008), it becomes critical to consider mTBI history when trying to obtain a comprehensive and accurate picture of neurological changes that contribute to PTSD symptomatology.

While structural MRI studies have provided evidence of macrostructural brain alterations in PTSD, such studies cannot provide information about microstructural processes that can impact symptom severity. Diffusion MRI (dMRI), on the other hand, can be used to examine brain microstructure (Alexander et al., 2017; McNab et al., 2013; Pasternak et al., 2018). For example, when applied to gray matter (e.g., Bouix et al., 2013; Bozzali et al., 2002; McKinstry et al., 2002; Rath et al., 2014; Seitz et al., 2018; Weston et al., 2015), dMRI can provide insight into changes in tissue composition (e.g. atrophy (Laitinen et al., 2015) and glial changes (Budde et al., 2011; Seehaus et al., 2015; Sizonenko et al., 2007)) and morphological complexity (e.g. alterations in dendritic arborization (Bock et al., 2010; Dean et al., 2013; Leigland et al., 2013)), thereby offering information that is complimentary to structural MRI. Yet only a few studies (Lei et al., 2015; Waltzman et al., 2017; Xie et al., 2015) have utilized dMRI to probe gray matter abnormalities in PTSD. The present study employs dMRI in veterans diagnosed with PTSD to investigate how PTSD symptom severity relates to microstructural properties of limbic and paralimbic gray matter structures. Importantly, this study differs from previous related dMRI investigations (Lei et al., 2015; Waltzman et al., 2017; Xie et al., 2015) in a number of ways. First, our study takes a dimensional approach to investigating PTSD symptoms, rather than utilizing a typical case-control design. We chose this approach because case-control studies may be less suitable for the study of veterans with PTSD, as some trauma-exposed individuals in the control group may still exhibit sub-diagnostic threshold PTSD symptoms (Grubaugh et al., 2005; Palm et al., 2009; Schützwohl and Maercker, 1999; Stein et al., 1997), which are associated with intermediate levels of neurological changes (Herringa et al., 2012; Lobo et al., 2015; Wrocklage et al., 2017). This can thereby decrease the power of case-control studies to detect PTSD-associated abnormalities. Second, we examine relationships between PTSD symptoms and brain microstructure in individuals who did and did not sustain a mTBI during military deployment, thus evaluating the impact of brain injury on the clinical and neurological presentation of PTSD. Third, the present analysis examines a large number of limbic/paralimbic regions of the brain given *a priori* hypotheses of their involvement in the neurocircuitry of PTSD. This differs from past studies that employed either whole-brain approaches (Lei et al., 2015; Xie et al., 2015), or that limited analyses to the caudate and the hippocampus (Waltzman et al., 2017). Fourth, and finally, we analyze dMRI data with free-water imaging, a dual compartment diffusion modeling approach that offers enhanced biological specificity compared to conventional diffusion

tensor imaging (DTI) (Pasternak et al., 2009). The main goals of this study are to (1) elucidate the extent to which limbic/paralimbic gray matter microstructural features contribute to PTSD symptom severity, and to (2) examine whether or not brain-symptom relationships are altered by mTBI.

2. Materials and methods

2.1. Participants

Participants were 102 male OEF/OIF/OND veterans diagnosed with current PTSD (mean age = 31.6 ± 7.4 years) assessed at the Translational Research Center for TBI and Stress Disorders (TRACTS) at the VA Boston Healthcare System Jamaica Plain Campus. The TRACTS sample is a convenience sample recruited from the Boston area (see details in McGlinchey et al., 2017). The TRACTS sample has been shown to be representative of OEF/OIF/OND veterans who use the VA Healthcare System with regards to age, sex, and branch of military service (McGlinchey et al., 2017). The 102 participants included in this study were obtained from the first 384 consecutively recruited participants assessed as part of the larger TRACTS sample. All participants gave written informed consent. Study procedures were approved by the VA Boston Healthcare System Institutional Review Board.

Initial inclusion criteria for this study included availability of complete imaging data (T1-weighted and diffusion imaging data) (N = 300 of 384 participants available) and consent to share data with investigators who are not core TRACTS faculty (N = 278 of 300 participants with imaging data). Exclusion criteria applied to the 278 eligible cases included a history of seizures or neurological illness unrelated to traumatic brain injury (1 excluded), a current DSM-IV diagnosis of a cognitive disorder, bipolar disorder, or a psychotic disorder (1 excluded), a history of moderate or severe traumatic brain injury (9 excluded), a history of anoxia (21 excluded), a history of meningitis or encephalitis (2 excluded), a history of brain surgery (2 excluded), exposure to neurotoxic chemicals (9 excluded), pre-deployment status (i.e., not yet deployed; 13 excluded), missing clinical data (10 excluded), MRI data that failed quality control procedures due to excessive motion or image artifacts (26 excluded), and female sex (5 excluded). Females were excluded given that the number of females was too small to provide meaningful data for comparisons with males, and neuroimaging studies have provided evidence of sex differences in the brain's response to trauma (Helpman et al., 2017; Panchal et al., 2018; Sollmann et al., 2018). These inclusion and exclusion criteria resulted in a sample of 179 eligible participants. Of these 179 participants, 102 had a current diagnosis of PTSD and were included in this study (see also Table 1 for a list of inclusion/exclusion criteria).

2.2. Demographic and clinical measures

Demographic and deployment information was obtained using self-report questionnaires. Depression and anxiety symptoms were assessed using the 21-item Depression Anxiety Stress Scales (DASS21) (Lovibond and Lovibond, 1996). A doctoral-level psychologist administered the Clinician-Administered PTSD Scale-Diagnostic Version for DSM-IV (CAPS-DX) (Blake et al., 1995), the Boston Assessment of TBI-Lifetime (BAT-L) (Fortier et al., 2014), and the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (SCID) (First et al., 2002), and reviewed the Lifetime Drinking History (LDH) semi-structured interview (Skinner and Sheu, 1982).

All 102 participants received a diagnosis of current PTSD via the CAPS-DX using DSM-IV criteria for PTSD+ (Weathers et al., 1999). Additionally, the CAPS-DX was used to assess the current frequency (scaled from 0–4) and intensity (scaled from 0–4) of 17 PTSD symptoms: intrusive recollections, distressing dreams, re-experiencing, trauma reminder-induced distress, trauma reminder-induced physical reaction, avoidance of trauma-associated thoughts or feelings,

avoidance of trauma-associated activities or situations, inability to recall the trauma, diminished interest in activities, detachment, restricted affect, sense of a foreshortened future, difficulty sleeping, difficulty concentrating, irritability, hypervigilance, and exaggerated startle response. Frequency and intensity scores for all 17 symptoms were summed to calculate a CAPS-DX Current Symptom Severity Score (CAPS-CSS score), which ranges from 0–136, thus capturing the spectrum of PTSD severity. The CAPS-DX has robust convergent validity with DSM-IV PTSD diagnoses (Foa and Tolin, 2000) and high internal consistency for the 17 item severity scores (Blake et al., 1995).

The BAT-L was administered to determine blast exposure history, lifetime history of mild, moderate, and severe TBI, and the number of mild TBIs sustained during deployment or military service (military mTBIs). A mild TBI was defined as a blow (or blast) to the head resulting in an altered mental state for <24 h, a loss of consciousness for <30 min, and/or post-trauma amnesia for <24 h. Diagnosis of a current mood, anxiety, or substance use disorder was made via the SCID. Information about alcohol consumption over one's lifetime was collected with the LDH, and a weight-corrected lifetime drinking score was calculated for each participant.

2.3. MRI acquisition

Structural and diffusion data were acquired on a Siemens 3T TIM Trio scanner at the VA Boston Jamaica Plain Campus between July 2010 and June 2014. Acquisition parameters for the T1-weighted (T1w) MPRAGE scan included: 256 slices, TI = 1000 ms, TR = 2530 ms, TE = 3.32 ms, voxel size = 1 mm<sup>3</sup>, flip angle = 7°, FOV = 256 × 256 mm<sup>2</sup>. Diffusion scans were acquired using a single shot echo planar sequence with a twice-refocused spin echo pulse. Sixty gradient directions with b = 700 s/mm<sup>2</sup> and 10 additional scans with b = 0 were acquired. Additional parameters included: 64 slices, TR/TE = 10000 ms/103 ms, flip angle = 90°, voxel size = 2 mm<sup>3</sup>, FOV = 256 × 256 mm<sup>2</sup>.

2.4. MR image processing

Imaging data for all participants passed rigorous quality control procedures. Diffusion images were corrected for motion and eddy current distortions by registering all gradient volumes to an undistorted b = 0 volume with an affine registration (FLIRT) (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) (Greve and Fischl, 2009; Jenkinson et al., 2002); gradient directions were correspondingly modified. In scanner head motion was quantified during this step. The dMRI data were then analyzed with free-water imaging (Pasternak et al., 2009) using in-house software. Free-water imaging is a two-compartment diffusion model that estimates an isotropic free water compartment and a tissue

**Table 1**  
**Study Inclusion and Exclusion Criteria.** Criteria applied to all available TRACTS data to generate the current study sample.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"><li>• T1-weighted and diffusion imaging data available.</li><li>• A current diagnosis of PTSD.</li><li>• Consent to share data.</li></ul>	<ul style="list-style-type: none"><li>• A current diagnosis of bipolar disorder, schizophrenia, or any psychotic disorder.</li><li>• A cognitive disorder.</li><li>• History of seizures or neurological illness.</li><li>• History of moderate or severe TBI.</li><li>• History of anoxia.</li><li>• History of meningitis or encephalitis.</li><li>• History of brain surgery.</li><li>• Exposure to neurotoxic chemicals.</li><li>• Pre-deployment status.</li><li>• MRI data that failed quality control procedures.</li><li>• Missing clinical data of interest.</li><li>• Female sex.</li></ul>



compartment in each voxel; the tissue compartment is modeled by a single diffusion tensor. The two compartment model parameters are estimated using a regularized non-linear minimization process. Free-water imaging was applied to remove signal arising from CSF (i.e., the free water compartment) and to generate CSF-eliminated fractional anisotropy (FA) maps and mean diffusivity (MD) maps. This dual compartment approach was employed to minimize partial volume effects at the gray matter-CSF boundary.

T1w images were anatomically parcellated with FreeSurfer 5.1 (<https://surfer.nmr.mgh.harvard.edu/>) and parcellations were visually inspected. When necessary, edits were made by a trained research assistant to the gray matter-white matter boundary and the gray matter-pial surface boundary, and the parcellation procedure was rerun. Parcellations were used to delineate 18 limbic/paralimbic regions of interest (ROIs, 9 per hemisphere): amygdala-hippocampus complex, cingulate gyrus, entorhinal cortex, insula, lateral orbitofrontal cortex, medial orbitofrontal cortex, nucleus accumbens, parahippocampal gyrus, and temporal pole (Fig. 1). The amygdala and hippocampus were analyzed as a single complex given prior research demonstrating that the complex represents a more accurate, methodologically rigorous FreeSurfer segmentation (Guenette et al., 2018). FreeSurfer parcellations were mapped onto FA and MD maps by non-linearly registering T1w images to a diffusion  $b = 0$  scan using Advanced Normalization Tools (ANTs) and applying the transformations to parcellations. The average FA and MD in each of the 18 ROIs was then calculated.

## 2.5. Statistical analysis

Statistics were performed with IBM-SPSS Statistics (Version 24). The sample ( $N = 102$ ) was subdivided into a cohort with a current diagnosis of PTSD and no history of military mTBI (PTSD only;  $N = 54$ ) and a cohort with a current diagnosis of PTSD and a positive history of military mTBI (PTSD + TBI;  $N = 48$ ). To estimate the effect of CAPS-CSS score on FA in the 18 limbic/paralimbic ROIs, a linear mixed model (LMM) with repeated measures (ROI FA) was conducted. CAPS-CSS score, age, and number of close range ( $<10$  meter) blast exposures were included in the model as fixed effects. The number of close range blasts was included given that non-concussive blast exposure is prevalent in the military (McGlinchey et al., 2017), and it can affect brain structure and function (Robinson et al., 2015; Trotter et al., 2015). The LMM was fit using the restricted maximum likelihood (REML) approach with an unstructured covariance matrix and applied separately to data from the PTSD only cohort and the PTSD + TBI cohort, in order to examine associations between PTSD symptoms and microstructure in veterans who did and did not sustain at least one military mTBI. As LMMs are linear regression-based models, they produce a t-statistic and a corresponding p-value to describe the association between CAPS-CSS score and FA for each of the 18 regions. To control for multiple comparisons within each model across the 18 regions, the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was used for false discovery rate (FDR) correction, and statistical significance was set at  $p < 0.05$ . The Satterthwaite approximation (Satterthwaite, 1946) was used to estimate degrees of freedom, and partial R values were calculated from t-values and degrees of freedom. LMMs controlled for age and blast exposure were additionally conducted independently in the PTSD only cohort and in the PTSD + TBI cohort to examine associations between CAPS-CSS scores and MD in the 18 ROIs. FDR correction was performed.

Because PTSD severity was significantly greater in the PTSD + TBI cohort, we performed a secondary analysis with a subset of the PTSD only cohort (CAPS-CSS scores  $>40$ ) so that the PTSD only cohort (now  $N = 48$ ) did not differ from the PTSD + TBI cohort in CAPS-CSS score or sample size. An FDR-corrected repeated measures LMM controlled for age and number of close range blasts was conducted (as detailed above) with the symptom-equilibrated PTSD only subgroup of 48 individuals, to examine CAPS-CSS score-FA associations across the 18 ROIs. The

goal of this secondary analysis was to differentiate between the effects of greater PTSD symptom severity versus the effects of mTBI on brain microstructure-symptom severity relationships.

Because this study did not exclude participants diagnosed with a current mood, anxiety, or substance use disorder, secondary analyses were additionally conducted to examine whether depression severity, anxiety severity, or lifetime alcohol use had significant effects on FA in the 18 ROIs. Three independent LMMs with repeated measures controlled for age were conducted using the entire sample to examine the association between ROI FA and DASS21 Anxiety Total scores, DASS21 Depression Total scores, and weight-corrected LDH scores. (Two individuals did not have data for the LDH and were not included in this model). The 3 LMMs were again fit with the REML approach using an unstructured covariance matrix, and FDR-corrected. The goal here was to better ascertain whether the CAPS-CSS findings were specific to PTSD symptoms or influenced by overall affective symptom load or lifetime alcohol use.

Of note, we were not able to examine potential effects of mTBI history only on ROI FA. An analysis of a “TBI only” cohort was not included because, of the 179 participants eligible for this study, only 16 had a history of military mTBI but no PTSD diagnosis, thus the sample size was not sufficient.

## 3. Results

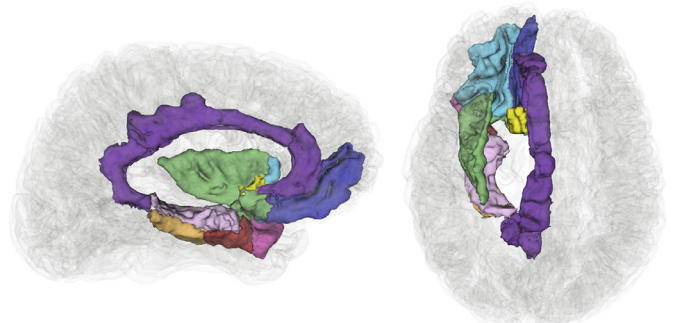
### 3.1. Sample characteristics

Demographic, military branch, and clinical characteristics of the PTSD only and PTSD + TBI cohorts are shown in Table 2. The PTSD + TBI cohort had significantly greater CAPS-CSS scores ( $t_{98.9} = -2.777, p = 0.007$ ) and more military mTBIs ( $t_{47.0} = -5.531, p < 0.001$ ) than the PTSD only cohort. The two cohorts did not significantly differ on any other demographic, deployment, or clinical variables (see Table 2). Age and CAPS-CSS scores were not significantly correlated.

Within the PTSD + TBI cohort, the average time since last TBI was  $4.9 (\pm 3.3)$  years. This timeframe is more consistent with chronic injury, rather than the acute phase of TBI. An FDR-corrected LMM controlled for age did not identify any significant associations between time since last TBI and FA for any of the 18 ROIs. Additionally, time since last TBI did not correlate with CAPS-CSS scores.

### 3.2. Associations between dMRI FA and CAPS-CSS scores

Across the entire study sample, head motion in the scanner did not correlate with FA in any of the 18 ROIs. The average FA across the



**Fig. 1. Limbic and Paralimbic Gray Matter Structures.** 3D model of the FreeSurfer-delineated limbic and paralimbic structures, shown from medial (left) and superior (right) views. Yellow: accumbens area, light pink: amygdala-hippocampus complex, purple: cingulate, red: entorhinal cortex, green: insula, light blue: lateral orbitofrontal cortex, dark blue: medial orbitofrontal cortex, orange: parahippocampal gyrus, pink: temporal pole.

**Table 2**

**Cohort Characteristics.** Demographic, deployment, and clinical characteristics of the PTSD only and PTSD + TBI cohorts. \*indicates significance; ^Independent samples *t*-test; + Fisher's exact test.

	PTSD Only	PTSD + TBI	<i>p</i> -value
Age	32.7 ( ± 7.5)	30.4 ( ± 7.1)	0.123^
Years of Education	13.6 ( ± 1.9)	13.7 ( ± 1.8)	0.925^
Race (Caucasian)	77.8%	83.3%	0.619+
Branch of Service (Army)	53.7%	54.2%	1.000+
Branch of Service (Marines)	31.5%	37.5%	0.539+
CAPS-DX Current Symptom Severity Score	60.2 ( ± 18.8)	69.6 ( ± 15.0)	0.007^*
Current Mood Disorder	27.8%	29.6%	0.216+
Current Anxiety Disorder	16.7%	18.8%	0.801+
Current Substance Use Disorder	14.8%	22.9%	0.320+
DASS21 Anxiety Symptoms Total Score	6.6 ( ± 7.2)	9.5 ( ± 7.6)	0.054^
DASS21 Depression Symptoms Total Score	9.9 ( ± 9.2)	13.0 ( ± 8.8)	0.081^
LDH Weight-Corrected Lifetime Drinking Score	2109.6 ( ± 2391.4)	1917.4 ( ± 1829.3)	0.651^
Number of Military Mild TBIs	0.0 ( ± 0.0)	1.9 ( ± 2.3)	<0.001^*
Number of Close Range Blasts (<10 m)	1.8 ( ± 7.6)	12.3 ( ± 59.8)	0.232^

entire study sample is listed in Table 3 for each of the ROIs. Regional mean FA did not differ significantly between the PTSD only cohort and the PTSD + TBI cohort in any of the 18 ROIs. We examined the association between CAPS-CSS scores and FA for the 18 limbic/paralimbic ROIs (9 per hemisphere) independently in the PTSD only and PTSD + TBI cohorts using repeated measures LMMs (Fig. 2).

### 3.2.1. PTSD only cohort

In the PTSD only cohort, there was a significant positive association between CAPS-CSS scores and FA for the right amygdala-hippocampus complex ( $t_{44.4} = 3.134$ ,  $p = 0.027$ , estimate = 0.00048), i.e., higher symptom severity scores were associated with higher FA. There was also a significant negative association between CAPS-CSS scores and right cingulate FA ( $t_{41.7} = -3.179$ ,  $p = 0.027$ , estimate = -0.00031), i.e., higher symptom scores were associated with lower FA (Fig. 2, Table 4).

### 3.2.2. PTSD + TBI cohort

In the PTSD + TBI cohort, there was a significant positive association between higher CAPS-CSS score and higher FA for the amygdala-hippocampus complex, bilaterally (left:  $t_{38.2} = 5.972$ ,  $p < 0.0001$ , estimate = 0.00093; right:  $t_{39.3} = 5.375$ ,  $p < 0.0001$ , estimate = 0.00092) and for the accumbens, bilaterally (left:  $t_{49.2} = 3.488$ ,  $p = 0.006$ , estimate = 0.00069; right:  $t_{49.3} = 3.335$ ,  $p = 0.007$ , estimate = 0.00071). A significant negative association was observed between higher CAPS-CSS score and lower FA, bilaterally, for the cingulate cortex (left:  $t_{45.3} = -2.890$ ,  $p = 0.018$ , estimate = -0.00026; right:  $t_{57.5} = -2.890$ ,  $p = 0.018$ , estimate = -0.00029) (Fig. 2, Table 5). Note that an estimate of, e.g., 0.00093 for the left amygdala-hippocampus complex indicates that a 1 point CAPS-CSS score increase corresponds to a predicted 0.00093 increase in FA in this region, on average. Hence, a 30 point CAPS-CSS score increase corresponds to a predicted 0.028 increase in right amygdala-hippocampal FA. When compared to the cohort mean FA of 0.358 in this region, a 0.028 increase in FA represents a 7.8% increase.

### 3.2.3. Associations between dMRI FA and CAPS-CSS scores in cohorts matched on symptom severity

Given that the PTSD + TBI cohort had significantly higher CAPS-CSS scores than the PTSD only cohort, it is difficult to know whether the findings reported in the main LMMs are due to the effects of increased

PTSD symptom severity in the PTSD + TBI cohort, or to the effects of mTBI history in the PTSD + TBI cohort. To distinguish between the two, a secondary analysis was conducted with 48 (out of the original 54) individuals in the PTSD only cohort who had the highest CAPS-CSS scores (>40). Importantly, there was no significant difference in CAPS-CSS scores between this PTSD only subgroup (now  $N = 48$ ) and the PTSD + TBI cohort ( $N = 48$ ).

This secondary analysis examined CAPS-CSS score-FA associations across the 18 ROIs in the PTSD only subgroup. After correcting for multiple comparisons, a negative association was observed between CAPS-CSS scores and FA for the right cingulate cortex, at trend level ( $t_{37.7} = -3.044$ ,  $p = 0.076$ , estimate = -0.00034). In this smaller PTSD only sample (sample size reduced by >10%), the association observed between right amygdala-hippocampus complex FA and CAPS-CSS score was no longer statistically significant. Importantly, this analysis strongly supports that the additional associations observed in the PTSD + TBI cohort between regional FA and CAPS-CSS score do not arise due to overall differences in symptom severity between the two cohorts.

### 3.3. Associations between dMRI FA and DASS21 and LDH scores

There were no statistically significant associations between DASS21 Depression Total scores and FA, DASS21 Anxiety Total scores and FA, or LDH weight-corrected lifetime drinking scores and FA, for any of the 18 ROIs.

### 3.4. Associations between dMRI MD and CAPS-CSS scores

We additionally examined associations between CAPS-CSS scores and MD in the 18 ROIs (Fig. 2). In the PTSD only cohort, there was a significant negative association between CAPS-CSS scores and MD for the left medial orbitofrontal cortex ( $t_{51.8} = -3.366$ ,  $p = 0.026$ , estimate = -0.00028). In the PTSD + TBI cohort, there was a significant positive association between CAPS-CSS scores and MD for the right amygdala-hippocampus complex ( $t_{57.2} = 3.180$ ,  $p = 0.043$ , estimate = 0.00020).

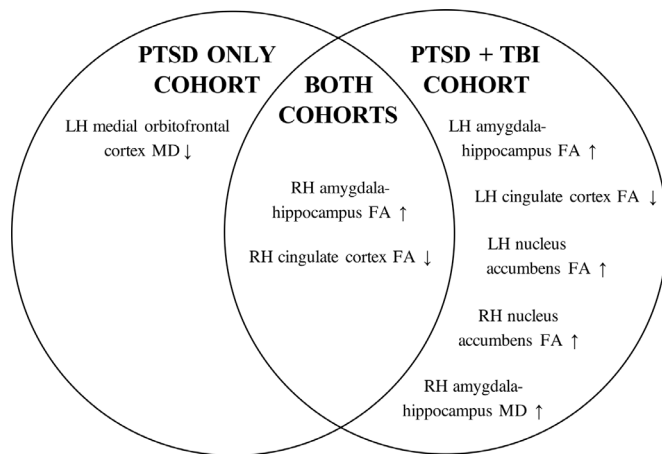
## 4. Discussion

In this study of veterans with current PTSD, PTSD symptom severity was shown to be associated with the microstructure of limbic and paralimbic gray matter brain regions, as evinced by dMRI. Specifically, in the PTSD only cohort, more severe PTSD symptoms were associated

**Table 3**

**Regional FA.** Average fractional anisotropy in the 18 limbic and paralimbic brain regions.

Brain Region	FA
Right amygdala-hippocampus complex	0.36 ( ± 0.02)
Left amygdala-hippocampus complex	0.36 ( ± 0.02)
Right cingulate cortex	0.26 ( ± 0.01)
Left cingulate cortex	0.25 ( ± 0.01)
Right entorhinal cortex	0.31 ( ± 0.03)
Left entorhinal cortex	0.31 ( ± 0.03)
Right insula	0.28 ( ± 0.01)
Left insula	0.28 ( ± 0.01)
Right lateral orbitofrontal cortex	0.28 ( ± 0.02)
Left lateral orbitofrontal cortex	0.28 ( ± 0.02)
Right medial orbitofrontal cortex	0.25 ( ± 0.02)
Left medial orbitofrontal cortex	0.27 ( ± 0.02)
Right nucleus accumbens	0.34 ( ± 0.03)
Left nucleus accumbens	0.33 ( ± 0.03)
Right parahippocampal gyrus	0.28 ( ± 0.03)
Left parahippocampal gyrus	0.29 ( ± 0.03)
Right temporal pole	0.29 ( ± 0.02)
Left temporal pole	0.28 ( ± 0.02)



**Fig. 2. Associations Between PTSD Symptom Severity and Microstructural dMRI Measures.** A Venn diagram showing the brain regions wherein associations between gray matter microstructural measures and symptom severity were observed, in the PTSD only and PTSD + TBI cohorts. Upward arrow ↑ indicates that greater PTSD symptom severity was associated with higher fractional anisotropy or higher mean diffusivity in the indicated region. Downward arrow ↓ indicates that greater PTSD symptom severity was associated with lower fractional anisotropy or lower mean diffusivity in the indicated region. FA: fractional anisotropy; LH: left hemisphere; MD: mean diffusivity; RH: right hemisphere.

**Table 4**

**Associations Between Brain Region FA and PTSD Symptom Severity: PTSD Only Cohort.** Regions showing a significant effect of CAPS-CSS score on fractional anisotropy in the repeated measures linear mixed model applied to data from the PTSD only cohort. False Discovery Rate (FDR)-corrected *p*-values and corresponding partial R values are reported.

PTSD ONLY COHORT		
Brain Region	Partial R	FDR-corrected <i>p</i> -value
Right amygdala-hippocampus complex	0.426	0.027
Right cingulate cortex	−0.442	0.027

**Table 5**

**Associations Between Brain Region FA and PTSD Symptom Severity: PTSD + TBI Cohort.** Regions showing a significant effect of CAPS-CSS score on fractional anisotropy in the repeated measures linear mixed model applied to data from the PTSD + TBI cohort. False Discovery Rate (FDR)-corrected *p*-values and corresponding partial R values are reported.

PTSD + TBI COHORT		
Brain Region	Partial R	FDR-corrected <i>p</i> -value
Right amygdala-hippocampus complex	0.651	< 0.0001
Left amygdala-hippocampus complex	0.695	< 0.0001
Right cingulate cortex	−0.356	0.018
Left cingulate cortex	−0.394	0.018
Right nucleus accumbens	0.429	0.007
Left nucleus accumbens	0.445	0.006

with higher right amygdala-hippocampal FA, lower right cingulate cortex FA, and lower left medial orbitofrontal MD. In the PTSD and military mTBI cohort, more severe PTSD symptoms were associated with microstructural measures in more widespread regions of the brain, specifically with higher bilateral amygdala-hippocampus complex and nucleus accumbens FA, with lower bilateral cingulate cortex FA, and with higher right amygdala-hippocampal MD. These findings provide preliminary evidence that mTBI may exacerbate the effects of limbic/paralimbic system microstructure on PTSD symptoms. This increased sensitivity to the microstructural environment of the brain may partially explain why mTBI comorbidity in PTSD is associated with

increased symptom severity and a poorer illness prognosis (Chemtob et al., 1998; Vanderploeg et al., 2009). Importantly, the aforementioned findings could not be solely attributed to greater PTSD symptom severity in the TBI comorbidity group, further supporting the notion that mTBI history *per se* may impact associations between tissue structure and symptomatology. We speculate below that these associations could arise due to heightened dendritic atrophy, reduced cell density, and an overall loss of neuronal connectivity in those with greater PTSD symptoms.

#### 4.1. Microstructural underpinnings of dMRI-symptom associations

Although dMRI is a technique that is highly sensitive to differences in the microstructural tissue environment, the precise microstructural underpinnings of the present findings are difficult to establish, given that FA and MD are not specific measures of any single cell type or neuropathology (Alexander et al., 2017; Pasternak et al., 2018). FA differences in gray matter, for example, can reflect differences in: (1) dendrites (Bock et al., 2010; Dean et al., 2013; Leigland et al., 2013; Leigland and Kroenke, 2011; Leuze et al., 2014); (2) cell density (Jonkman et al., 2016); (3) glia cells (Budde et al., 2011; Seehaus et al., 2015; Sizonenko et al., 2007; Stolp et al., 2018); and/or (4) axonal processes that connect to gray matter (Edwards et al., 2018; Leuze et al., 2014; McNab et al., 2013). Nonetheless, the direction of each association (i.e., positive versus negative) provides some insight into the nature of structural changes. Thus, although the resolution of dMRI does not allow us to differentiate experimentally between the aforementioned microstructural features, below we offer hypotheses, based on the literature, as to what structural features may underlie the associations observed in the current study with PTSD symptom severity.

##### 4.1.1. Amygdala-hippocampus complex

Greater PTSD symptom severity correlated with higher amygdala-hippocampus complex FA, unilaterally (right hemisphere) in the PTSD only cohort, and bilaterally in the PTSD + TBI cohort. Given that core PTSD symptoms include memory disturbances and hypervigilance, it is not surprising that the microstructure of the hippocampus and amygdala, regions involved in memory retrieval (Eldridge et al., 2000; Wiltgen et al., 2010) and threat detection (Öhman, 2005), respectively, contribute to PTSD symptomatology. Based on diverse studies demonstrating that reduced dendritic morphological complexity (i.e., decreased dendritic branch number or length) is associated with higher gray matter FA (Bock et al., 2010; Dean et al., 2013; Leigland et al., 2013; Leigland and Kroenke, 2011; Molet et al., 2016; Yu et al., 2016), this positive symptom severity-FA association may indicate that those with more PTSD symptoms exhibit reduced amygdala-hippocampal dendritic arborization. This interpretation is supported by the following converging lines of evidence from human and animal model studies of PTSD: (1) exposure to stressful events or environments in animals results in hippocampal dendritic atrophy (Han et al., 2013; Magariños and McEwen, 1995; McKittrick et al., 2000; Molet et al., 2016; Watanabe et al., 1992; Woolley et al., 1990); (2) smaller volume of the hippocampus (Hull, 2002; Karl et al., 2006; Kitayama et al., 2005; Kühn and Gallinat, 2013; Logue et al., 2018; Smith, 2005; Wang et al., 2010; Woon et al., 2010) and the amygdala (Karl et al., 2006; Logue et al., 2018; Morey et al., 2012; O'Doherty et al., 2017; O'Doherty et al., 2015) are consistently found in human neuroimaging studies of PTSD; and (3) as recently demonstrated by Molet et al. (2016), rodents exposed to chronic stress exhibit a coupling of these neural features—decreased hippocampal volume, reductions in hippocampal dendritic length, and, critically, higher hippocampal FA (note, the amygdala was not examined by Molet et al.). The finding of higher MD in the right amygdala-hippocampus complex in those with more severe symptoms corroborates this interpretation, as substantial dendritic arborization reductions should co-occur with increases in water diffusivity in the surrounding extracellular space (i.e., with



increases in MD).

#### 4.1.2. Cingulate cortex

Contrary to findings in the amygdala-hippocampus complex, greater PTSD symptomatology was associated with lower FA in the cingulate cortex (lower right cingulate FA in those with PTSD only, lower bilateral cingulate FA in those with PTSD and mTBI), suggesting that the neuropathological mechanisms that contribute to PTSD may be different in these two brain regions. The cingulate, a cortical region involved in emotion regulation, attention, and cognition (Bush et al., 2000; Etkin et al., 2011; Leech and Sharp, 2014), has consistently been shown to have lower volume, thickness, and density in structural MRI studies of PTSD (Chen et al., 2012; Kühn and Gallinat, 2013; Meng et al., 2014; Nardo et al., 2010; O'Doherty et al., 2015; Wrocklage et al., 2017). Magnetic resonance spectroscopy has additionally revealed that the concentration of N-acetylaspartate, a putative marker of neuronal cell density, is decreased in this region in individuals with PTSD symptoms (Quadrelli et al., 2018). Considering evidence that FA is higher in gray matter regions with higher cell density (Jonkman et al., 2016), it is quite possible that lower cingulate cell density in veterans with more PTSD symptoms underlies the negative FA-symptom severity association identified here. We point out, however, that no significant relationships were identified between CAPS-CSS scores and cingulate cortex MD—a diffusion measure that is believed to be affected by gray matter cell density. Hence, differences in other components of tissue microstructure may be accounting for the observed associations.

More specifically, changes in glia cells or axons that occur in PTSD could contribute to our findings. Animals exposed to stress exhibit decreased glial integrity and astrocyte loss (Averill et al., 2017; Sanacora and Banasr, 2013), microstructural alterations that will decrease regional FA (Budde et al., 2011; Stolp et al., 2018). The finding that veterans with more symptoms have lower cingulate FA may thus offer a dMRI correlate of cortical glial loss in PTSD. There is, furthermore, evidence of cingulum bundle abnormalities in PTSD (Fani et al., 2016, 2012; Kim et al., 2006; Sanjuan et al., 2013), and *in* and *ex vivo* studies of the human brain have established that axons contribute significantly to anisotropic diffusion in the cortex (Edwards et al., 2018; Gulban et al., 2018; Leuze et al., 2014). Accordingly, reductions in the packing density, myelination, or organizational coherence of axons with connections in the cingulate gyrus (i.e., structural changes that decrease FA) may be more severe in those who are more symptomatic. We note that while these explanations constitute viable hypotheses, additional neuroimaging and post-mortem studies are required to validate or refute them.

#### 4.1.3. Nucleus accumbens

In the PTSD+TBI cohort, greater symptom severity correlated with higher bilateral accumbens FA. Given that this association was observed in only those with a history of mTBI, this finding raises the possibility that the nucleus accumbens is a brain region particularly vulnerable to the interaction of TBI and PTSD-related pathologies.

Indeed, research has shown that the accumbens is susceptible to damage induced by both physical injury and psychological stress. Following brain injury, reductions in the volume of the accumbens have been observed (Hellström et al., 2017; Shah et al., 2012), as have changes in the release and reuptake of dopamine in this region (Chen et al., 2017). One consequence of these alterations is affect-related symptomatology, including diminished reward responsiveness and reduced motivation—symptoms that can contribute directly to overall PTSD severity, or that can decrease resilience (Taubitz et al., 2015) and thus one's ability to cope with PTSD. Independent of brain injury, PTSD is additionally associated with functional changes in the nucleus accumbens, primarily with diminished activity in response to positive and rewarding stimuli (Elman et al., 2009; Felmingham et al., 2014; Sailer et al., 2008). In light of this prior research, we hypothesize

that brain injury-related alterations in the nucleus accumbens may compound those that are already occurring in PTSD in a manner that strengthens the relationship between regional microstructure and symptom severity. However, this cannot be definitively concluded from this study and future studies are needed for clarification.

The microstructural features that contribute to these nucleus accumbens findings are difficult to define. There is some evidence that in rodents, chronic stress can induce dendritic hypertrophy in the nucleus accumbens (Bessa et al., 2013), a stress-induced change that would decrease, rather than increase, regional FA. Yet the pattern of dendritic changes observed in animal models is hard to reconcile with findings from human studies, which have consistently shown reductions in nucleus accumbens activity in stress-related disorders. Additional studies examining accumbens microstructure in animal models and patient post-mortem tissue are therefore needed to better inform a structural interpretation of this result.

#### 4.1.4. Additional considerations

The microstructural hypotheses discussed here—dendritic atrophy in the amygdala-hippocampus complex, reduced neuronal/glial density and axonal connectivity in the cingulate cortex, a change in the structural composition of the nucleus accumbens—align well with recent conceptualizations of PTSD as being a disorder of stress-induced synaptic connectivity loss (Averill et al., 2017; Krystal et al., 2017). Not all regions of the brain are equally vulnerable to the damaging effects of stress, however; the amygdala, hippocampus, striatum, and prefrontal cortex indeed typically exhibit the most stress-related neuropathology (Krystal et al., 2017). Although an association between left medial orbitofrontal MD and symptom severity was found in the PTSD only cohort, it is perhaps surprising that, given this prefrontal vulnerability to stress, additional associations between PTSD symptom severity and tissue microstructure were not found within e.g. the orbitofrontal cortex and insula. One possible source of this lack of statistically significant findings may be that multifaceted microstructural changes are occurring in these regions in PTSD (in a manner that scales with symptom severity), yet the effects of these changes on the diffusion signal are in opposition. For example, dendritic retraction and glia loss, both of which occur in the prefrontal cortex following chronic stress (Averill et al., 2017; Krystal et al., 2017), will increase and decrease gray matter FA, respectively. Alternatively, it is feasible that the diffusion acquisition and modeling approaches utilized here were not sensitive to some microstructural features that contribute to symptomatology, and that acquisitions with higher b-values, or the application of other multi-compartment or signal-based dMRI methods, may provide additional insight in the future (Pasternak et al., 2018).

#### 4.2. The role of mTBI comorbidity

In addition to providing evidence of microstructural correlates of symptom severity in PTSD, the present analysis suggests that mTBI can intensify PTSD symptomatology and affect relationships between brain microstructure and PTSD symptom severity. Brain injury may influence brain-symptom relationships in PTSD in a number of ways. It is possible, for example, that the sequelae of mild physical injuries and psychological injuries converge in stress-vulnerable brain regions (i.e., limbic/paralimbic regions), thereby increasing sensitivity to neurological changes in these regions. In other words, brain injury may produce a state of heightened neurological vulnerability, one that manifests itself clinically in more severe symptomatology. Additionally, mild TBI may decrease cognitive reserve, making individuals more susceptible to the effects of PTSD-related neuropathology (Stein and McAllister, 2009). Finally, brain injury may increase an individual's overall symptom load (including non-PTSD symptoms) in a manner that affects psychological stress, stress-related brain changes, and their association.

Although our results suggest that mTBI may impact both symptoms



and their neurological correlates in PTSD, we emphasize that these findings should be considered preliminary, rather than conclusive. Additional studies with larger sample sizes, as well as those with healthy control and “TBI only” cohorts, are needed to validate these early data, and to assess the generalizability of these findings.

#### 4.3. Predisposing factors or disorder sequelae?

The present study cannot discriminate between whether the identified neuroimaging correlates of more severe PTSD symptoms are sequelae of the disorder or, rather, predisposing risk factors for PTSD development. Support for the former comes from prospective, longitudinal, and twin studies showing that PTSD is associated with acquired brain alterations (Admon et al., 2013a; Carrion et al., 2007; Kasai et al., 2008; Metzger et al., 2008; Sekiguchi et al., 2013). It is possible, however, that variation in tissue microstructure existed prior to trauma exposure and influenced PTSD development, especially in light of studies linking brain structure to PTSD risk (Admon et al., 2013b; Gilbertson et al., 2002). It is therefore of interest for future longitudinal studies to ascertain whether limbic and paralimbic region FA and MD are altered following trauma, or whether these measures could be informative of PTSD risk.

#### 4.4. Clinical implications

The treatment of PTSD is often difficult, and it can be complicated by low engagement and treatment-resistance. Identifying the treatment most likely to be helpful for a given individual, and increasing treatment adherence, is therefore critical. Findings from this study offer a few insights relevant to the effective treatment of PTSD.

First, this study demonstrates the importance of obtaining an accurate head trauma history from individuals presenting clinically with symptoms of PTSD, as having a history of mTBI may, as demonstrated here, impact clinical presentation and underlying disorder pathomechanisms. Integrating strategies typically employed following a TBI, such as cognitive rehabilitation or psychostimulant pharmacotherapy, into treatment plans may thus prove to be constructive for decreasing PTSD symptoms in those with mTBI comorbidity. By improving cognitive abilities, for example, TBI-focused treatments may help individuals better engage with and benefit from cognitive-based PTSD therapies such as exposure therapy, cognitive processing therapy, or mindfulness-based therapies. More generally, future clinical studies may consider investigating whether the efficacy of PTSD treatments differs between individuals with and without mTBI history.

Our findings of associations between the microstructure of specific brain regions and PTSD severity additionally suggest that treatments that modulate these regions could be valuable in PTSD. Transcranial magnetic stimulation (TMS), for example, is able to affect activity in particular regions of interest in the brain (based on TMS coil placement), and it has been shown to be beneficial for some PTSD patients (Boggio et al., 2010; Cohen et al., 2004; Watts et al., 2012). Findings from the current study support that TMS protocols that alter activity in the amygdala, the hippocampus, the nucleus accumbens, and/or the cingulate may be particularly effective for diminishing PTSD symptoms. Although these brain regions cannot be directly modulated by TMS (given their subcortical and medial locations), there is promising evidence that downstream functional changes can be elicited in subcortical regions through neuromodulation of cortical regions they are strongly functionally connected to (Oathes et al., 2018).

Finally, this study provides neuroimaging metrics that could be used to monitor the neurological impact of PTSD treatments, especially treatments that alter regional microstructure. Ketamine and other glutamate-targeting treatments (Krystal et al., 2017), for example, are promising fast-acting therapeutics for PTSD (Averill et al., 2017; Feder et al., 2014) that are understood to change local microstructure via increasing spine formation, dendritic arborization, and synaptic

connectivity (Krystal et al., 2017; Li et al., 2011, 2010). These microstructural changes seem to be accompanied by concomitant changes in the macrostructure of the hippocampus and the nucleus accumbens in humans (Abdallah et al., 2017). Examining gray matter microstructural dMRI measures before and after the administration of glutamatergic psychotropics (e.g., ketamine) could thus provide an improved understanding as to whether they exert beneficial effects in PTSD by eliciting microstructural remodeling in stress vulnerable brain regions.

#### 4.5. Limitations

We note several study limitations. (1) mTBI history was determined based on self-recall of head injuries. As military record verification of head injury history was not available, the determination of mTBI history could be susceptible to self-report inaccuracies. (2) Previous research indicates that close range, non-concussive blasts can affect brain structure and function (Robinson et al., 2017; Robinson et al., 2015; Taber et al., 2015). We attempted to mitigate the potential effects of blast on brain region FA by controlling for this variable in the LMMs. However, the interplay between the neurological effects of blast exposure, mTBI, and PTSD may be quite complex, potentially necessitating more than just a statistical control. Unfortunately, an analysis excluding individuals with close range blast exposure was not feasible with the available sample. (3) The interaction between PTSD and mTBI on brain microstructure was not tested in one overarching model in this work. Hence, future studies prospectively designed to delineate and to test the direct interaction between PTSD and mTBI on neuroimaging metrics of brain structure and function are needed. These will be critical in substantiating the current hypothesis that mTBI may exacerbate PTSD. (4) Accurately identifying the boundaries of the cortex in dMRI images is difficult. We addressed this methodological limitation by using structural MRI data to delineate the cortex, warping the cortical parcellation to artifact-corrected diffusion images, and employing a diffusion model that minimizes partial volume effects. (5) This study was diagnostically inclusive as we did not exclude individuals with a current mood, anxiety, or substance use disorder diagnosis. Consequently, neurological changes associated with these disorders could, in theory, influence associations between CAPS-CSS scores and FA. However, we did not find any significant associations between DASS21 Anxiety Total scores, DASS21 Depression Total scores, or LDH weight-corrected lifetime drinking scores and FA, suggesting that the present findings are likely not attributable to overall affective symptom load or lifetime alcohol use. We chose not to exclude individuals with mood, anxiety, and substance use disorders as this would greatly diminish generalizability to typical veteran populations, where psychiatric comorbidity is high.

#### 5. Conclusions

This study of a representative OEF/OIF/OND veteran population provides insight into the pathomechanisms of PTSD, implicating microstructural differences in the amygdala-hippocampus complex, the cingulate, the prefrontal cortex, and the nucleus accumbens in disorder severity. Importantly, this study also suggests that mTBI may affect relationships between the brain and the severity of symptoms that are experienced by patients with PTSD. Further research on PTSD and mTBI comorbidity is needed to help elucidate how mTBI impacts the neuropsychosocial consequences of PTSD, and to determine how to approach treatment for individuals who both do and do not have a history of brain injury. The present findings additionally warrant studies investigating the use of dMRI measures as neuroimaging biomarkers of neuropathology or neurodegeneration in PTSD, especially given the potential of such biomarkers to provide insight into treatment mechanisms, and to improve long-term monitoring of patient health.

## CRediT authorship contribution statement

**Valerie J. Sydnor:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Sylvain Bouix:** Software, Supervision, Writing - review & editing. **Ofer Pasternak:** Funding acquisition, Methodology, Software, Writing - review & editing. **Elisabeth Hartl:** Methodology, Validation. **Laura Levin-Gleba:** Data curation, Software. **Benjamin Reid:** Data curation, Validation. **Yorghos Tripodis:** Formal analysis, Methodology. **Jeffrey P. Guenette:** Conceptualization, Methodology. **David Kaufmann:** Methodology. **Nikos Makris:** Methodology. **Catherine Fortier:** Investigation, Supervision. **David H. Salat:** Resources, Supervision. **Yogesh Rathi:** Software. **William P. Milberg:** Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing - review & editing. **Regina E. McGlinchey:** Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing - review & editing. **Martha E. Shenton:** Conceptualization, Funding acquisition, Supervision, Writing - original draft, Writing - review & editing. **Inga K. Koerte:** Conceptualization, Methodology, Supervision, Writing - original draft, Writing - review & editing.

## Declaration of Competing Interest

None.

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