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Altered White Matter Diffusivity of the Cingulum Angular Bundle in Posttraumatic Stress Disorder

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Keywords

Posttraumatic stress disorder · Cingulum · Cingulate · White matter tractography · Fractional anisotropy · TRActs Constrained by UnderLying Anatomy · Neuroimaging · Veteran · Diffusion magnetic resonance imaging · Diffusion tensor imaging

Abstract

Purpose of the Study: Prior studies showed posttraumatic stress disorder (PTSD)-related alterations in white matter integrity, but most of these studies have used region-based approaches. We address this limitation by investigating the relationship between PTSD severity and fractional anisotropy (FA) using a tract-based approach. **Procedures:** Structural and diffusion magnetic resonance imaging were acquired from 67 combat-exposed US Veterans and processed using FSL/FreeSurfer TRActs Constrained by UnderLying Anatomy. Partial correlations were conducted between PTSD severity

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E-Mail karger@karger.com www.karger.com/mnp and FA of the cingulum and uncinate fasciculi covarying for age, sex, and head motion. Results: Only FA of the left cingulum angular bundle (CAB) was positively correlated with PTSD symptom severity (r = 0.433, p = 0.001, df = 57) and remained significant after Bonferroni correction. Conclusions: This finding may imply greater organization of the CAB with increasing PTSD severity. The CAB connects directly to the cingulate cortex and the hippocampal subiculum, critical nodes of the default mode network, as well as being implicated in neurodegeneration pathology, decision-making, and executive functions, which may help explain previously shown alterations in this network in PTSD. Message of the Paper: Further study of white matter tract integrity in PTSD is warranted, particularly to investigate whether the CAB connections with both higher-order cognitive functioning and emotion processing regions contribute to the pathophysiology and comorbidity of PTSD.

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Introduction

Despite decades of psychiatric research, a comprehensive understanding of the network disruptions [1] predisposing and underlying posttraumatic stress disorder (PTSD) is still emerging [2, 3]. While the majority of neuroimaging investigations have focused on structural [4] and functional [5] aspects of PTSD, there is a growing body of literature regarding white matter integrity related to the disorder. Using diffusion-weighted magnetic resonance imaging (dMRI), researchers can use methods such as diffusion tensor imaging (DTI) and fiber tractography to estimate the density and directionality of neural and membrane integrity, using the proxy measures of fractional anisotropy (FA) and mean diffusivity [6–8].

Although other regions of interest (ROI) have been implicated, analyses using DTI and tractography have most consistently demonstrated microstructural alterations of the cingulum and the uncinate fasciculus (UNC) in PTSD [9-19]. However, there have been inconsistencies in the literature in the directionality and extent of alterations. These inconsistencies are highlighted by a meta-analysis of DTI studies in PTSD, which identified clusters of both increased and decreased FA in the bilateral cingulum [20]. Among other reasons, it is possible that these inconsistencies may be due to methodological differences and limitations. Prior literature has focused primarily on region-based, rather than tract-based, FA assessment. In this study, we attempted to address this potential gap in the literature by examining the relationship between PTSD severity and cingulum/UNC FA in combat-exposed US Veterans, using a tract-based approach termed TRActs Constrained by UnderLying Anatomy (TRACULA) [21].

The cingulum and UNC are fiber bundles of the fronto-limbic circuit. The cingulum hugs the corpus callosum and is predominantly comprised of short fibers that connect the cingulate cortex, and nearby regions of the frontal, parietal, occipital, and temporal lobes [22]. Of particular relevance to PTSD, the cingulum connects the cingulate cortex and the hippocampus [15], 2 regions implicated in the pathophysiology of PTSD [23-26], which, if impaired, may delay or prevent recovery after exposure to trauma due to their respective roles in learning, memory, and fear processing [27]. The UNC connects portions of the temporal lobe with the inferior frontal gyrus [18]. This connection facilitates communication between the amygdala and the medial prefrontal cortex, a relationship that is critical for appropriate fear expression and threat response [28].

To address the limitations of deterministic, local tractography, including seed and target selection, and to facilitate comparison of voxel-wise data across subjects and populations, Yendiki et al. [21] developed TRACULA, a probabilistic, global method to automate reconstruction of white matter pathways while incorporating information from anatomical priors. This method may yield more robust, clinically relevant biomarkers of PTSD severity because it is standardized, automated, and constrained by underlying anatomy [21]. Based on prior studies, we predicted that PTSD symptom severity would be correlated with FA of the cingulum and uncinate tracts. In addition, to inform future studies, we conducted a number of exploratory analyses investigating other white matter tracts, as well as differences in these tracts by group (i.e., PTSD vs. combat control [CC]).

Methods

Participants

Sixty-seven US Veterans consented into a study approved by the Institutional Review Boards of the Yale School of Medicine and the VA Connecticut Healthcare System. All 67 participants were combat-exposed, of which 33 PTSD subjects and 34 CCs were well matched in terms of age, sex, and IQ. This group of participants has been discussed in prior publications from our group, in which we reported on PTSD associations with: gray matter integrity [29, 30], volumetric alterations [31], and functional dysconnectivity [32]. In this manuscript, we present the first DTI results from this cohort. Eligibility was specific to the parent study, which excluded psychotic, bipolar, learning, attentional, and major neurological disorders; moderate or severe traumatic brain injury; MRI safety concerns; and use of benzodiazepines. To improve generalizability, comorbidities common to PTSD were permitted in the study, such as depression, anxiety, substance and alcohol disorders, and stable antidepressant use.

Clinical Measurement

The Clinician Administered PTSD Scale for the DSM-IV (CAPS) [33] was used to ascertain PTSD diagnosis and symptom severity, and psychiatric comorbidities were assessed using the Structured Clinical Interview for the DSM-IV [34]. The Combat Exposure Scale [35] and the Wechsler Test of Adult Reading [36] were used to estimate trauma exposure and premorbid IQ respectively.

Neuroimaging Acquisition and Processing

All subjects completed structural MRI (sMRI) and dMRI MRI, which were acquired in a Siemens TIM Trio 3 Tesla magnet with a 32-channel head coil. Structural MRI included 2 T1weighted MPRAGE scans (TR = 2,530 ms; TE = 2.71 ms; TI = 1,200 ms; Flip = 7°; Voxel = $1.0 \times 1.0 \times 1.0$ mm) and dMRI were acquired with diffusion weighting (b = 1,000 s/mm²) along 128 vectors (TR = 7,400 ms; TE = 115 ms; Flip = 90°; Voxel = $1.7 \times 1.7 \times$ 3.0 mm). The first image was acquired without diffusion weighting

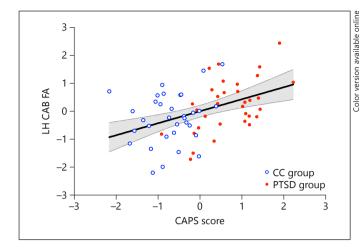


Fig. 1. PTSD Severity is Associated with Fractional Anisotropy (FA) in the Left Cingulum Angular Bundle (CAB). Plotted CAPS score and FA values are residuals after controlling for age, sex, antidepressant status, and motion.

(*b* = 0 s/mm²). Consistent with prior literature [21, 32, 37, 38], and described in greater detail in the online supplementary Materials (for all online suppl. material, see www.karger.com/doi/10.1159/000490464), DTI processing was conducted using FMRIB Software Library (FSL; https://fsl.fmrib.ox.ac.uk/fsl/fslwi-ki) [39], and TRACULA (FreeSurfer; https://surfer.nmr.mgh.harvard.edu) [40].

Statistical Analysis

Online supplementary Table S1 provides a summary of personal and clinical characteristics as well as dMRI head motion variables for comparison of PTSD and CC participants. CAPS score, age, sex, head motion, and all white matter data were evaluated for normality and were log-transformed if the variable was highly skewed or kurtosed. We conducted 2-tailed partial correlation analyses (1) to probe for associations between PTSD symptom severity and FA of the cingulum angular bundle (CAB), cingulum cingulate gyrus endings, and UNC; (2) to explore the other TRAC-ULA-defined fasciculi; and (3) to inform on possible methodological differences with tensor-based ROI similar to those used in past literature. Analyses are further described in the supplement.

Results

PTSD Severity and FA in Probabilistic Tracts (TRACULA)

FA of the left CAB was positively correlated with PTSD symptom severity for the full group (r = 0.433, p = 0.001, df = 57) and the PTSD group (r = 0.534, p = 0.005, df = 57; Fig. 1) but was not correlated with severity in the CC group (p = 0.492). Significant correlations remained after adjusting the alpha threshold for multiple comparison using Bonferroni (corrected alpha = 0.008; 6 com-

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parisons). There were no associations between PTSD severity and the right CAB, or with the cingulate gyrus endings or UNC in either hemisphere (Table 1). There was no significant association between PTSD severity and any other probabilistic white matter tract (Table 2). See online supplementary Table S2 for results of a multivariate GLM comparing FA in all tracts between PTSD and CC groups.

PTSD Severity and FA in Tensor-Based ROI

In this full-group analysis, FA in the left corticospinal tract was negatively correlated with PTSD symptom severity (r = -0.266, p = 0.040, df = 58). However, this correlation failed to retain significance after adjusting the alpha threshold for multiple comparison using Bonferroni (corrected alpha = 0.0008; 62 comparisons). There were no correlations between PTSD severity and any other ROI (see Table 3 for all correlations). Several trend-level associations were noted prior to Bonferroni correction: a negative trend with the splenium of the corpus callosum (r = -0.232, p = 0.074, df = 58), a negative trend with bilateral corticospinal tract (r = -0.239, p = 0.065, df = 58), a positive trend with the right IFO (r = 0.231, p = 0.076, df = 58), and a positive trend with the bilateral (L+R composite) IFO (r = 0.241, p = 0.063, df = 58).

Discussion

The results of this study partially confirmed our hypotheses. More specifically, we found that PTSD symptom severity was associated with integrity of the left CAB, although we did not find significant associations between PTSD symptoms and other cingulum tracts or the UNC. The CAB is connected with brain regions underlying both higher-order cognitive functioning and emotion processing and implicated in neurodegeneration pathology [41]. Moreover, associations have been reported between CAB integrity and functioning in episodic memory, decision-making, and executive control [42, 43]. The CAB has also been shown to directly connect the posterior cingulate cortex and the subiculum of the hippocampus [44], both of which are critical nodes in the default mode network shown to be altered in PTSD [1, 45]. The CAB connects the hippocampus and other regions of the medial temporal lobe with the posterior cingulate [43], an area that has been shown to exhibit alterations of gray matter integrity (thinning) in this group of participants [30]. Of similar relevance, we

Tract/FA	CAPS score (full group)			CAPS score (PTSD only)			CAPS score (combat controls)		
	r	р	df	r	р	df	r	P	df
CAB (LH)	0.433	0.001*	57	0.534	0.005*	24	0.141	0.492	24
CAB (RH)	-0.050	0.709	57	0.031	0.882	24	-0.067	0.744	24
CCG (LH)	-0.037	0.780	57	-0.190	0.352	24	-0.324	0.106	24
CCG (RH)	-0.061	0.648	57	-0.073	0.725	24	-0.194	0.343	24
UNC (LH)	0.002	0.986	57	-0.072	0.727	24	-0.048	0.817	24
UNC (RH)	-0.036	0.787	57	-0.287	0.155	24	-0.025	0.905	24

Table 1. Partial correlation of fractional anisotropy with PTSD severity: cingulum and uncinate tracts

* Indicates significance if $p \le 0.008$.

Bonferroni method was used to adjust alpha threshold for multiple comparison (0.05/6 = 0.008).

FA, fractional anisotropy; LH, left hemisphere; RH, right hemisphere; CAPS, Clinician Administered PTSD Scale for DSM-IV; r, partial correlation controlling for age; sex, head motion, and antidepressant use; CAB, cingulum angular bundle; CCG, cingulum cingulate gyrus endings; UNC, uncinate fasciculus.

Table 2. Partial correlation of PTSD severity with fractional anisotropy in other probabilistic white matter tracts

Tract	CAPS score x LH FA			CAPS score x RH FA			CAPS score x Bilateral FA		
	r	p	df	r	р	df	r	P	df
fmajor	_	_	_	_	_	_	-0.077	0.563	57
fminor	_	_	_	_	_	_	0.098	0.461	57
ATR	-0.037	0.778	57	-0.193	0.143	57	_	-	-
CST	0.047	0.722	57	0.061	0.646	57	-	-	_
ILF	0.097	0.465	57	0.001	0.996	57	_	-	_
SLFP	0.091	0.492	57	-0.028	0.834	57	_	-	_
SLFT	-0.092	0.490	57	0.075	0.571	57	_	_	_

FA, fractional anisotropy; LH, left hemisphere; RH, right hemisphere; CAPS, Clinician Administered PTSD Scale for DSM-IV; r, partial correlation controlling for age; sex, head motion, and antidepressant use; fmajor, corpus callosum forceps major; fminor, corpus callosum forceps minor; ATR, anterior thalamic radiations; CST, corticospinal tract; ILF, inferior longitudinal fasciculus; SLFP, superior longitudinal fasciculus parietal endings; SLFT, superior longitudinal fasciculus temporal endings. Bonferroni method was used to adjust alpha threshold for multiple comparison (0.05/12 = 0.004). No results were significant, before or after correction.

have previously reported various associations between PTSD symptom severity and the anterior hippocampus, including differences in morphometry [29], lower volume of the hippocampus-amygdala transition area [31], and both structural and anatomical dysconnectivity [32]. Given the purported associations with key regions of emotion, memory, and cognition, it is interesting to consider the implications of altered CAB integrity in the context of our earlier work with this cohort. While further study would be necessary to draw conclusions about a relationship between the current and past findings, the cumulative evidence from this cohort may provide further insight into the widespread neural alterations observed in PTSD and other stress-based disorders, and highlight the importance of continued study of the role of the cingulum in the pathophysiology of PTSD.

Surprisingly, we did not replicate prior results using region-based FA. It is possible that the failure to replicate past results is due to the nature of this cross-sectional study, which was optimized for a dimensional analysis of PTSD severity versus differences between diagnostic groups. Of note, Olson et al. [46] also failed to identify dimensional differences using TRACULA. Our control

ROI	CAPS sco x LH FA	CAPS score x LH FA			CAPS score x RH FA			CAPS score x single/bilateral FA		
	r	P	df	r	P	df	r	P	df	
CR	-0.052	0.692	58	-0.124	0.344	58	-0.093	0.481	58	
ACR	-0.087	0.510	58	-0.162	0.218	58	-0.132	0.313	58	
PCR	0.033	0.802	58	0.006	0.961	58	0.020	0.878	58	
SCR	-0.032	0.811	58	-0.090	0.495	58	-0.064	0.628	58	
IC	0.002	0.991	58	-0.030	0.821	58	-0.015	0.909	58	
ALIC	-0.119	0.363	58	-0.085	0.518	58	-0.108	0.413	58	
PLIC	0.051	0.697	58	0.047	0.723	58	0.051	0.701	58	
RLIC	0.052	0.691	58	-0.049	0.710	58	-0.005	0.967	58	
EC	-0.011	0.932	58	0.092	0.485	58	0.042	0.749	58	
CC	_	-	-	_	-	-	-0.159	0.224	58	
BCC	-	-	-	_	-	-	-0.166	0.206	58	
GCC	-	-	-	_	-	-	0.041	0.756	58	
SCC	-	-	-	-	-	-	-0.232	0.074	58	
CGC	-0.044	0.740	58	-0.042	0.750	58	-0.045	0.730	58	
CGH	0.055	0.676	58	-0.057	0.665	58	0.001	0.995	58	
CST	-0.266	0.040*	58	-0.150	0.252	58	-0.239	0.065	58	
FX	_	-	-	-	-	-	-0.215	0.099	58	
FXST	0.086	0.511	58	0.054	0.683	58	0.080	0.543	58	
IFO	0.174	0.185	58	0.231	0.076	58	0.241	0.063	58	
PTR	0.111	0.397	58	-0.131	0.320	58	-0.026	0.845	58	
SFO	-0.019	0.885	58	0.018	0.891	58	0.003	0.981	58	
SLF	0.186	0.155	58	0.109	0.409	58	0.157	0.232	58	
SS	0.031	0.815	58	-0.046	0.725	58	-0.011	0.935	58	
UNC	-0.132	0.314	58	-0.070	0.596	58	-0.104	0.428	58	

Table 3. Partial correlation of PTSD severity with fractional anisotropy in 24 DTI ROI

* $p \le 0.05$. No results reached significance at the level of $p \le 0.0008$.

ROI, region of interest; FA, fractional anisotropy; LH, left hemisphere; RH, right hemisphere; CAPS, Clinician Administered PTSD Scale for DSM-IV; r, partial correlation controlling for age, sex, head motion, and antidepressant use; CR, corona radiata; PCR, posterior corona radiata; ACR, anterior corona radiata; SCR, superior corona radiata; IC, internal capsule; ALIC, anterior limb of internal capsule; PLIC, posterior limb of internal capsule; RLIC, retrolenticular part of internal capsule; EC, external capsule; CC, corpus callosum; BCC, body of corpus callosum; GCC, genu of corpus collosum; SCC, splenium of corpus callosum; CGC, supra-genual cingulate bundles; CGH, cingulum of the hippocampal region; CST, corticospinal tract; FX, fornix; FXST, fornix/stria terminalis; IFO, inferior fronto-occipital fasciculus; PTR, Posterior thalamic radiation; SFO, superior frontooccipital fasciculus; SLF, superior longitudinal fasciculus; SS, sagittal stratum; UNC, uncinate fasciculus. Bonferroni method was used to adjust alpha threshold for multiple comparison (0.05/62 = 0.0008).

group was not fully asymptomatic, and this variance would have been lost if the data was reduced to make categorical inferences. Other reasons for the failure to replicate may be related to FA changes over the course of the illness. There is mounting evidence of increased FA early in the course of illness [9, 12, 17, 47], and reduced FA in chronic or complex PTSD (often featuring comorbid depression, brain injury, or alcohol use disorder) [10, 11, 15, 16, 19, 48]. Homogenous samples with early onset or highly chronic cohorts might be more successful at demonstrating a relationship between PTSD and FA.

Conclusion

Our findings provide important information regarding the potential importance of the CAB in PTSD. The study also underscores the lack of consistency in diffusivity alterations in PTSD. Investigations addressing some of the current study's limitations, in particular enrolling early course vs. chronic PTSD populations, will be valuable to further advance our understanding of alterations in white matter tracts in PTSD. Specifically, such study may elucidate the role the CAB, which has been implicated in both higher-order cognitive function and emotion processing. It will also be valuable to examine the potential role of alterations in the CAB relative to cognitive impairment in PTSD, perhaps especially so in older adults, as PTSD is associated with cognitive dysfunction and is a known risk factor for dementia [49, 50]. Future studies using high-density fiber tracking, "brain bank" data, and multi-modal imaging techniques may better elucidate the relationship between both gray and white matter integrity alterations in PTSD.

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Statement of Ethics

All participants provided informed consent, and all procedures undertaken were approved by the Human Studies Subcommittee (IRB) of the VA Connecticut Healthcare System.

Disclosure Statement

Dr. Chadi G. Abdallah has served as a consultant or on advisory boards for Genentech and Janssen. He also serves as editor for the journal *Chronic Stress* published by SAGE Publications, Inc. Dr. John H. Krystal is a consultant for AbbVie, Inc., Amgen, Astellas Pharma Global Development, Inc., AstraZeneca Pharmaceuticals, Biomedisyn Corporation, Bristol-Myers Squibb, Eli Lilly and Company, Euthymics Bioscience, Inc., Neurovance, Inc., FORUM Pharmaceuticals, Janssen Research and Development, Lundbeck Research USA, Novartis Pharma AG, Otsuka America Pharmaceutical, Inc., Sage Therapeutics, Inc., Sunovion Pharmaceuticals, Inc., and Takeda Industries; is on the Scientific Advisory Board for Lohocla Research Corporation, Mnemosyne Pharmaceuticals, Inc., Naurex, Inc., and Pfizer; is a stockholder in Biohaven Medical Sciences; holds stock options in Mnemosyne Pharmaceuticals, Inc.; holds patents for Dopamine and Noradrenergic Reuptake Inhibitors in Treatment of Schizophrenia, U.S. Patent No. 5,447,948 (issued September 5, 1995), and Glutamate Modulating Agents in the Treatment of Mental Disorders, U.S. Patent No. 8,778,979 (issued July 15, 2014); and filed a patent for Intranasal Administration of Ketamine to Treat Depression. US Application No. 14/197,767 (filed on March 5, 2014); US application or Patent Cooperation Treaty international application No. 14/306,382 (filed on June 17, 2014). All other authors report that there are no conflicts of interest to disclose.

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