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Reduced white matter integrity in the cingulum and anterior corona radiata in posttraumatic stress disorder in male combat veterans: A diffusion tensor imaging study

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Abstract

Posttraumatic stress (PTSD) and alcohol use (AUD) disorders are associated with abnormal anterior cingulate cortex/ventromedial prefrontal cortex, thalamus, and amygdala function, yet microstructural white matter (WM) differences in executive-limbic tracts are likely also involved. Investigating WM in limbic-thalamo-cortical tracts, this study hypothesized (1) fractional anisotropy (FA) in dorsal cingulum, parahippocampal cingulum, and anterior corona radiata (ACR) would be lower in individuals with comorbid PTSD/AUD compared to in individuals with AUD-only and (2) that FA would be related to both AUD and PTSD severity. 22 combat veterans with comorbid PTSD/AUD or AUD-only completed DTI scans. ANCOVAs indicated lower FA in right ($F(df=1,19)=9.091$, $P=0.0071$) and left ($F(df=1,19)=10.375$, $P=0.0045$) dorsal cingulum and right ACR ($F(df=1,19)=18.914$, $P=0.0003$) for individuals with comorbid PTSD/AUD vs. individuals with AUD-only, even controlling for alcohol use. Multiple linear regressions revealed that FA in the right ACR was inversely related to PTSD severity ($r=-0.683$, $P=0.004$). FA was not significantly related to alcohol severity. Reduced WM integrity in limbic-thalamo-cortical tracts is implicated in PTSD, even in the presence of comorbid AUD. These findings suggest that diminished WM integrity in tracts important for top-down control may be an important anomaly in PTSD and/or comorbid PTSD/AUD.

Keywords

Posttraumatic stress disorder; Alcohol; Diffusion tensor imaging; Anterior corona radiata; Cingulum; Magnetic resonance imaging

1. Introduction

Posttraumatic stress disorder (PTSD) is characterized by a constellation of symptoms including reexperiencing (e.g. flashbacks, nightmares), avoidance (e.g. of reminders), cognitive and mood disturbances (e.g. loss of interest, detachment), and hyperarousal (e.g. insomnia, hypervigilance) following a traumatic event (American Psychiatric Association, 2012, 2000). It has been conceptualized as a disturbance of emotion regulation (Etkin and Wager, 2007; Frewen and Lanius, 2006) and as a fear-conditioning disorder (Rauch et al., 2006; Shin and Handwerger, 2009). Neurobiologically, PTSD is associated with a pattern of physiological, structural, and functional brain abnormalities in the frontal lobe, primarily in the medial prefrontal cortex (mPFC)/anterior cingulate cortex (ACC) (Corbo et al., 2005; Etkin and Wager, 2007; Frewen and Lanius, 2006; Rauch et al., 2006, 2003; Shin et al., 2006, 2001; Yamasue et al., 2003), the thalamus (Lanius et al., 2003, 2001), and limbic brain regions (e.g. amygdala and hippocampus) (Shin et al., 2006, 2004; Villarreal et al., 2002). One theoretical model of PTSD proposes that susceptibility to PTSD involves insufficient top-down inhibition by the mPFC/ACC on the amygdala, consistent with data showing reduced functional integrity of the mPFC/ACC in PTSD (Etkin and Wager, 2007; Frewen and Lanius, 2006; Rauch et al., 2006; Shin and Handwerger, 2009; Shin and Liberzon, 2009).

An additional mechanism by which reduced control over amygdala by mPFC/ACC could occur is a disruption in the communication between these regions, as would be the case if the integrity of white matter (WM) tracts was impaired. Disturbances in WM pathways from the mPFC/ACC to the amygdala could result in reduced top-down control of the amygdala via reduced functional connectivity and poor signal transduction between frontal executive control mechanisms and amygdala. This would result in disruption to normal recovery processes following traumatic stress experiences. Previous research has demonstrated reduced WM volume in PTSD (Villarreal et al., 2002), which may indicate damage to the microstructure of WM tracts projecting to and from the mPFC/ACC.

Diffusion tensor imaging (DTI) is a method to investigate axonal integrity and organization through measurements of the diffusion of water molecules (Mori and Zhang, 2006). Fractional anisotropy (FA) is a value derived by DTI representing the relationship between axial and radial water diffusion and is sensitive to microstructural WM variations in integrity and organization. FA is defined on a scale ranging from mostly isotropic (FA value nearing 0) indicating poor integrity of the axons to mostly anisotropic (FA value nearing 1) indicating intact WM (Smith et al., 2006).

Most prior PTSD research using DTI has linked reduced FA in the cingulum and areas near the prefrontal cortex with PTSD (Kim et al., 2005, 2006; Schuff et al., 2011; Zhang et al., 2011), findings generally in agreement with a top-down communication insufficiency model. The cingulate sends projections via the cingulum bundle to the amygdala and prefrontal cortex (Pandya et al., 1981) and is thought to play a central part in emotional processing, including appraisal, cognitive reappraisal, negative emotional expression, emotional response generation (Etkin et al., 2011; Ochsner et al., 2009), and problem solving (Allman et al., 2001). The hippocampus, also consistently implicated in PTSD, is

hypothesized to play a role in PTSD-related impaired fear extinction (Bossini et al., 2008; Hedges and Woon, 2007; Karl et al., 2006; Milad et al., 2009; Shin and Handwerker, 2009). The cingulum bundle extends from prefrontal cortex to the entire medial-temporal limbic complex including parahippocampally (Wakana et al., 2004) and, as such, this WM tract may be central to PTSD development.

Limbic-thalamo-cortical circuitry plays a major role in emotional regulation (Drevets et al., 2008) and the fan-shaped anterior corona radiata (ACR) has been associated with functions of the executive attention network (Niogi et al., 2010; Yin et al., 2013). The ACR, although not previously identified in the few prior DTI studies on PTSD, is part of the limbic-thalamo-cortical circuitry and includes thalamic projections from the internal capsule (IC) to the cortex (Catani et al., 2002; Wakana et al., 2004) including those prefrontal cortex gray matter areas that have been associated with impaired top-down emotion regulation systems in PTSD. The internal capsule is in return a pathway to the thalamus, which has WM pathways with the amygdala (Makris et al., 1999; Zikopoulos and Barbas, 2012). WM abnormalities in the ACR could result in many of the cognitive and emotion regulation disturbances central to PTSD via the IC and the thalamus. Research suggests that the prefrontal cortex/ACR/IC/thalamus/amygdala pathway may play a greater role in PTSD than the theoretically more direct prefrontal cortex/uncinate fasciculus/amygdala pathway (Ayling et al., 2012; Lanius et al., 2003, 2001; Schuff et al., 2011; Von Der Heide et al., 2013).

The small number of DTI studies in PTSD necessarily limits the diversity of the samples examined to date. Schuff et al. (2011) is currently the only DTI study on combat PTSD. Moreover, previous DTI research on PTSD excluded participants with alcohol use disorder (AUD). This is despite high AUD prevalence among veterans returning from Iraq and Afghanistan (Hoge et al., 2004) and high AUD-PTSD comorbidity in the general population (Brady et al., 2004; Kessler et al., 2011, 1995). People with alcohol dependence show reduced FA in the corpus callosum compared to controls (Konrad et al., 2012; Müller-Oehring et al., 2009). Additionally, of particular relevance, people with current alcohol dependence have reduced FA in the right ACR compared to controls but not compared to those with remitted alcohol dependence (Monnig et al., 2013). Lower FA in the dorsal cingulum has also been linked to alcohol dependence (Pfefferbaum et al., 2009). The current study builds on this prior research by examining FA in a PTSD sample that represents the high level of AUD comorbidity in this population, while at the same time also examining associations between alcohol severity and WM integrity.

Specifically, this study investigated the hypotheses that (a) there would be group differences in WM integrity associated with three cortical regions of interest (dorsal cingulum, parahippocampal cingulum, and ACR) as measured by FA, in a sample of recent combat veterans with comorbid PTSD and AUD (PTSD/AUD) compared to controls with AUD but not PTSD (AUD-only), and that (b) WM integrity in these tracts would be associated with both AUD and PTSD severity.

2. Methods

2.1. Participants

Recruitment was confined to Afghanistan and Iraq combat veterans to reduce variability introduced from differing disease state chronicity (e.g. Vietnam veterans suffering PTSD for 40+ years compared to Iraq veterans with PTSD for 10 or less years), since chronic PTSD may involve a progressive deterioration of structure and function (Golier et al., 2006; Rauch et al., 2006). Veterans were recruited by flyers, radio advertisements, internet, presentations at veterans' organizations, and by word-of-mouth. Criteria for exclusion were: current neuroleptic or anti-convulsant use, history of traumatic brain injury, left-handedness, neurological disorders, severe medical illness, active suicidal or homicidal ideation, inability to give informed consent, and self-reported prior diagnosis of any DSM-IV Axis I disorder other than PTSD or substance use disorder. Additionally, participants were excluded if unable to comply with standard MRI safety protocols (e.g. had claustrophobia or metallic objects in the body).

This study was approved by the University of New Mexico institutional review board. All participants gave written informed consent after a detailed explanation of the study, an opportunity to ask questions, and after correctly answering questions identifying key issues in the consent document. All participants were equally compensated for participation.

Of the 56 individuals who contacted us for telephone screening, 27 did not meet inclusionary criteria. Of the remaining 29 participants 22 were male, had usable DTI data, and had a lifetime alcohol use disorder. Given the small number of females ($n = 2$ both in the no-PTSD group), reported sex differences in FA (Chou et al., 2011; Huster et al., 2009), and low power to compare across gender, the current study focuses on male participants. Twelve of these participants met criteria for PTSD and AUD (PTSD/AUD) and ten met criteria for the AUD-only control group.

The mean age of the participants was 29.7 ($SD=6.73$, range= 22–51). All were fluent in English; 32% were currently married; 41% were employed full time. Reported ethnicity was 59% Caucasian, 32% Latino, 27% Native American, 5% African–American, and 5% Asian. Some participants identified with more than one ethnic group. Ethnicities were equally distributed across PTSD groups. Among the participants, 36% gave their highest military rank as e4 (entry-level with little or no college), 50% as e5–e7 (mid-level rank with some college or bachelor's degrees), and 14% were o3–o6 (officers with bachelor's degrees or greater).

2.2. Procedures

2.2.1. Measures—All tests were administered by a licensed clinical psychologist or by trained research personnel closely supervised by a licensed clinical psychologist. PTSD diagnosis was determined using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995; Weathers, 2004). The 1/2 CAPS scoring rule was used to determine DSM-IV PTSD symptoms (Weathers, 2004). This is a common and validated scoring method where frequency scores of 1 (out of 4) and intensity scores of 2 (out of 4) are required to score a participant positive for a symptom (Weathers, 2004). PTSD severity scores were calculated

by summing intensity and frequency scores for all symptoms, and subscale scores were sums of intensity and frequency scores for symptoms in each DSM-IV criterion cluster (re-experiencing, avoidance, and hyperarousal) (American Psychiatric Association, 2000) as per the CAPS scoring manual (Weathers, 2004). IQ estimates were calculated using the Vocabulary and Matrix Reasoning subscales from the Wechsler Abbreviated Scale of Intelligence (WASI; Weschler, 1999). The presence of AUD was determined using the Structured Clinical Interview for DSM-IV Axis I Disorders Section E—Substance Use Disorder Module (SCID-E (First et al., 1997). Details regarding alcohol and other drug consumption for the past 90 days were collected using the Timeline Follow-back (Sobell et al., 1992). Depression severity was measured with the Beck Depression Inventory—Second Edition (BDI-II; Beck et al., 1996). Traumatic brain injury (TBI) was assessed with an unpublished detailed questionnaire developed for this purpose by the Mind Research Network, which queried about ever being knocked unconscious and then requested detailed information about duration of loss of consciousness (LOC) as well as associated symptoms (e.g. amnesia, headache, vomiting). Prospective participants who had an LOC of longer than 5 min as well as those who had ever experienced secondary symptoms or been diagnosed with a traumatic brain injury were excluded from the study. The majority of participants ($n = 14$) had no history of LOC, one had an LOC of 5 min and two had LOC of 2 min and the remaining five participants had LOC of less than 2 min. These were equally distributed across PTSD groups.

2.2.2. Diffusion tensor imaging—DTI data were collected along the anterior commissure/posterior commissure (AC/PC) line, throughout the whole brain, with field of view (FOV)= 256×256 mm, 128×128 matrix, 72 slices with a slice thickness of 2 mm (isotropic 2 mm resolution), number of excitations (NEX) =1, TE (echo time)=84 ms and TR (repetition time)=9000 ms. A multiple channel radio frequency coil was used, with generalized auto-calibrating partially parallel acquisition (GRAPPA) ($\times 2$), 30 gradient directions with a diffusion sensitivity, $b=800$ s/mm². The $b=0$ experiment was repeated five times (Jones et al., 1999), and equally inter-spread between the 30 gradient directions. The total imaging time was approximately 6 min. This experiment was repeated twice to increase the signal to noise ratio. The data from the two DTI experiments, each with a dimension of $128 \times 128 \times 72 \times 35$, were concatenated together to form one larger data set of dimensions $128 \times 128 \times 72 \times 70$. All $b=0$ images were registered to the first $b=0$ image with a 6 degrees-of-freedom transformation. This was followed by registering the $b=800$ s/mm² image to the $b=0$ image immediately before it by an affine 12 degrees-of-freedom transformation. The two transformations were multiplied and then one transformation applied to the $b=800$ s/mm² image to align it to the first $b=0$ image. This resulted in all images being registered to the first $b=0$ image. FLIRT (FMRIB's Linear Image Registration Tool) was used for all registration steps.

Analysis consisted of the following steps: (a) quality check: any gradient directions with signal dropouts caused by excessive motion were removed and not included in the analysis (if more than four gradient directions were removed then the subject was not included in the analysis); (b) motion and eddy current correction; (c) correction of gradient directions for any image rotation done during the previous motion correction step; (d) calculation of

diffusion tensor and scalar measures such as FA, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD); and (e) spatial normalization by FNIRT/FSL to MNI space. Mean values for FA, mean diffusivity (MD), AD, and RD were calculated for dorsal cingulum, parahippocampal cingulum, and ACR as defined by the JHU atlas (Wakana et al., 2004). See Fig. 1 for region definitions. There are a number of ways that representative FA values can be calculated from whole brain images. We have used an ROI approach. An alternative approach would have been the TBSS method of projecting FA values on a skeleton and then looking for voxel-by-voxel based differences on the skeleton (Smith et al., 2006). We have chosen the ROI approach in order to reduce multiple comparisons and improve the possibility of detecting small differences. The contribution of the gray matter voxels to the mean FA over an ROI was indirectly excluded. This was done based on the regions defined by the JHU atlas and by the additional condition that the mean FA across the subjects be greater than 0.2. In the spatially normalized space exactly the same volume was used across all subjects.

2.3. Data analysis

SPSS version 18 was used for all statistical analyses. Investigation of group differences for mean regional FA, AD, and RD values was accomplished using univariate ANCOVA. Age was included as a covariate because FA is known to decrease with age (Pfefferbaum et al., 2000). The analysis of AD and RD values were conducted to determine whether differences in FA correspond to differences in RD, AD, or both, as these relationships provide further information about underlying neurobiological abnormalities. Bonferroni corrections were applied to adjust for the six comparisons (right and left dorsal cingulate, parahippocampal cingulate, and ACR) for FA, AD, and RD each, so that alpha was set at 0.008. Relationships between FA and symptom severity were analyzed by calculating four linear multiple regressions, one for each hemisphere, first with PTSD severity and then with AUD severity as dependent variables and all with regional FA as independent variables controlling for age. Bonferroni corrections were applied to adjust for the four comparisons (right, left, PTSD, AUD).

3. Results

3.1. Participant characteristics

As displayed in Table 1, participants with PTSD/AUD had significantly higher PTSD severity scores on average than AUD-only controls ($P < 0.01$) and, notably, PTSD severity ranges did not overlap. The PTSD/AUD group also had significantly higher mean scores on the BDI-II than the AUD-only control group ($P < 0.05$), as expected. There were no group differences for age or estimated intelligence (however, as mentioned, age was still included as a covariate in the ANCOVA models). There were no differences between the PTSD/AUD and AUD-only groups in days since first combat, days since last combat, or number of combat tours.

3.2. Alcohol use

Lifetime alcohol severity (measured by DSM-IV symptom count), 90-day percent-drinking-days (PDD), and 90-day drinks-per-drinking-day (DPDD) did not differ between

PTSD/AUD and AUD-only groups. ANCOVA models were run both with and without alcohol variables as covariates in order to ensure that alcohol use did not account for PTSD group differences described below. None of the alcohol variables was significant in any of the models, nor did the addition of the alcohol variables change the pattern of the results for PTSD. Moreover, none of the alcohol variables correlated with FA in any of the ROIs. Therefore, the results that follow are reported for the ANCOVAs without the alcohol variables as covariates.

3.3. White matter integrity

FA values are presented in Table 2 for the PTSD/AUD group compared to the AUD-only control group. Participants with PTSD/AUD had significantly lower FA values in both right ($F(df=1,19) = 9.091, P=0.0071$) and left ($F(df=1,19) = 10.375, P=0.0045$) dorsal cingulum and right ACR ($F(df=1,19) = 18.914, P=0.0003$) than AUD-only controls even after controlling for age. See Fig. 2 for scatterplot representations of these data. We also ran a multivariate ANOVA separating the dorsal cingulum FA into anterior, posterior, and upper (i.e. the section between anterior and posterior) cingulate regions and found similar results for all sections.

Participants with PTSD/AUD had less axial diffusivity (AD) in the left dorsal cingulum than AUD-only controls (Table 3). Although there were some significant dorsal cingulum differences in the anticipated direction for right AD values and left or right radial diffusivity (RD) values between the two groups, these did not surpass our multiple correction threshold.

3.4. Symptom severity and DTI correlations

Linear multiple regressions were computed with regional FA values as predictors and age as a covariate. Initial linear regressions with all six regions included displayed a suppression effect due to high collinearity between FA values in the left and right hemispheres. Thus we conducted four regressions with FA values for each hemisphere calculated separately and with age as a covariate, both for PTSD severity and for AUD severity. Using a Bonferroni correction to control for Type I error across the four regressions, a P value of less than 0.0125 (0.05/4) was required for significance. The regression equation for the right hemisphere FA with PTSD severity was significant, $F(4,17)=5.80, P=0.004, R^2=0.577$. None of the other regression equations were significant (left hemisphere FA with PTSD severity or either hemisphere with AUD severity). See Table 4 for results of the linear regressions and Fig. 3 for scatter plots of the PTSD severity relationships.

Among the three regions examined in the right hemisphere FA with PTSD severity regression, only right ACR FA was significantly negatively associated with PTSD severity ($\beta = -0.585, P=0.004$). No other associations between FA and PTSD or AUD severity reached the corrected level of significance (Table 4). Post-hoc Pearson correlations showed that the relationship between the right ACR FA and PTSD severity was not driven by any one PTSD criteria domain and instead was similar for re-experiencing ($r = -0.477, P=0.025$), avoidance ($r = -0.679, P=0.001$), and arousal ($r = -0.612, P=0.002$) severity.

3.5. Post-hoc analyses

Calculation of Steiger's Z revealed that right ACR was significantly more correlated with PTSD severity than was left ACR ($z = -2.404$, $P = 0.0162$), suggesting that this effect is more pronounced in the right hemisphere.

These results indicate that reduced FA in cortico-thalamic-limbic tracts is associated with PTSD diagnosis as well as with PTSD severity.

4. Discussion

To our knowledge, this is the first DTI study examining WM integrity in combat veterans with comorbid PTSD/AUD and comprehensively reporting Axial (AD) and Radial (RD) diffusivity values. Moreover, this is the first study to report a relationship between ACR FA and PTSD severity. Overall, FA was lower in both the right and left dorsal cingulum and in the right ACR, and AD was also significantly lower in the left dorsal cingulum in the PTSD/AUD group compared to the AUD-only control group. FA in the right ACR was significantly correlated with PTSD severity. Although group differences in dorsal cingulum right AD and left and right RD did not reach statistical significance after correction, the pattern of these values was as expected. There were no findings in these regions for alcohol variables. This research compliments previous studies reporting gray matter functional and structural deficiencies in the ACC associated with PTSD (Bryant et al., 2008a, 2008b; Etkin and Wager, 2007; Felmingham et al., 2007; Liberzon and Martis, 2006; New et al., 2009; Shin et al., 2001; Whitford et al., 2008) as well as prior DTI studies showing that PTSD involves WM abnormalities (Kim et al., 2005, 2006; Schuff et al., 2011; Zhang et al., 2011).

Research using DTI to examine WM microstructure in PTSD has generally found reduced FA associated with PTSD. Examination of FA in survivors of a subway fire showed decreased FA in the left anterior cingulum bundle compared to controls and a negative correlation between FA and severity of reexperiencing and avoidance symptoms (Kim et al., 2006). PTSD was also associated with reduced FA in the medial frontal gyrus WM and left midbrain (Kim et al., 2005). Participants with PTSD from a mining accident compared to a sample with generalized anxiety disorder (GAD) had reduced FA near the right anterior cingulate gyrus and increased FA adjacent to the left superior frontal gyrus compared to controls (Zhang et al., 2011). Schuff et al. (2011), examining WM integrity in combat veterans, found PTSD associated with reduced FA near the ACC, prefrontal cortex, posterior internal capsule, and the posterior angular gyrus. Disruptions in WM integrity in the right ACR and dorsal cingulum likely contribute to alterations in prefrontal and limbic gray matter activity in the vmPFC, ACC, thalamus, and amygdala, associated with PTSD symptoms, as communications between these areas occur via adjacent WM. In a notable exception to this pattern of results, Abe et al. (2006) found *increased* FA in the left anterior cingulum subadjacent to ACC gray matter in participants with PTSD following the Tokyo sarin attack versus survivors without PTSD. This anomalous finding could be secondary to other variables such as sarin exposure, however, rendering their findings possibly less applicable to the present research.

As previously noted, prior findings of FA differences associated with PTSD are primarily located in the cingulum, consistent with the neurobiological model of PTSD. The cingulum sends projections to the amygdala and the prefrontal cortex (Pandya et al., 1981), and is considered to play a central part in emotional processing including the appraisal and expression of negative emotion and generation of emotional responses (Etkin et al., 2011). Communication between gray matter in the ACC and other areas of the brain occurs partly via the cingulum. The ACC has a role in cognitive reappraisal (Ochsner et al., 2009), focused problem solving, emotional self-control, emotion recognition, error recognition, and adaptive responses to changing conditions (Allman et al., 2001). Research on gray matter in PTSD has consistently found that hypoactivation of the ACC/mPFC region is specifically associated with PTSD versus other anxiety disorders (Etkin and Wager, 2007) especially during emotional response tasks (Liberzon and Martis, 2006). In addition, ACC activation predicts PTSD treatment response (Bryant et al., 2008a, 2008b) and ACC activation changes with treatment (Felmingham et al., 2007). Together this provides substantial evidence for the theory that insufficient top-down neurological functioning involving ACC/vmPFC to amygdala communication (such as would occur via the cingulum) is implicated in PTSD.

The anterior corona radiata (ACR) is another likely contributor to PTSD symptoms. The fan-shaped ACR includes thalamic projections from the internal capsule to the cortex (Catani et al., 2002; Wakana et al., 2004). The thalamus in turn has WM pathways with the amygdala (Makris et al., 1999; Zikopoulos and Barbas, 2012). Limbic-thalamo-cortical circuitry plays a major role in emotional regulation (Drevets et al., 2008). The ACR has also been associated with functions of the executive attention network involving the conflict components of attention mediating inhibitory control and the resolution of conflicting stimuli impacting decision making (Niogi et al., 2010; Yin et al., 2013). WM abnormalities in the ACR could result in many of the disturbances central to PTSD by impairing communication between areas required for emotion regulation, attention, decision-making, and cognitive reappraisal due to a breakdown in top-down cognitive control communications (American Psychiatric Association, 2000; Buckley et al., 2000; Etkin and Wager, 2007; Frewen and Lanius, 2006). Although the uncinate fasciculus is sometimes proposed as a critical pathway for anxiety (Kim and Whalen, 2009), our results suggest that other, more complex modulatory pathways contribute to PTSD, which is in line with other research implicating the limbic-thalamo-cortical pathway (Lanius et al., 2003, 2001; Schuff et al., 2011). The present data also showed that FA in the right ACR was strongly negatively correlated with PTSD severity, where individuals with higher PTSD severity had lower FA.

Although it is not clear why the data implicated impaired WM only in the right ACR and not the left, other research has found right vmPFC gray matter to be associated with social, decision making, and emotional functions (Tranel et al., 2002), abilities also found to be impaired in PTSD. Theoretically, it is possible that poor ACR microstructure could result in a right hemisphere emotional disconnection syndrome in which prefrontal control of the components of a right hemisphere emotion circuit was weakened. This could result in relative disinhibition of component networks and increased emotional dysregulation, which could in turn lead to a reduced ability to recover from traumatic events. Future studies examining the relationship between WM microstructure and functional responses during emotional regulation may provide key evidence regarding this hypothesis.

Because of alcohol's toxic effects on the brain, prior DTI studies on PTSD have excluded individuals with AUDs, although AUDs are very common among veterans and civilians with PTSD (Hoge et al., 2004; Kessler et al., 2011, 1995). This study built on prior research by studying participants who were all recent combat veterans with a lifetime alcohol use disorder diagnosis. Yet, although studies have found reduced FA to be associated with AUD in the ROIs we examined (Monnig et al., 2013; Pfefferbaum et al., 2009), we did not find any association between lifetime AUD severity and FA. It may be the case that WM integrity varies more between those with AUD and those who have never had an AUD, as studied in most prior research, than it does between levels of AUD severity among individuals with AUDs.

However, lower FA in the dorsal cingulum continues to be related to PTSD in this previously unrepresented comorbid PTSD/AUD population, providing further support for the theory that WM disturbance in this region is associated with PTSD. The association of PTSD severity in the ACR is a new finding and may be specific to PTSD comorbid with AUD; for example, individuals who develop AUD while “self-medicating” PTSD symptoms may be more likely to have abnormal ACR WM integrity than individuals with PTSD alone.

Combat exposure differs from single traumatic events in that the exposure to trauma is chronic and of long duration (deployment). Recurring exposure to trauma is a risk for more chronic PTSD development and maintenance (Johnson and Thompson, 2008). Additionally, increasing changes in brain structure occur over time as a result of PTSD (Felmingham et al., 2009). This study controlled for PTSD duration by only recruiting veterans from the recent conflicts in Iraq and Afghanistan versus including veterans from prior conflicts (e.g. Vietnam, Korea, Gulf). There were no differences between groups for PTSD duration or cumulative dose of trauma (i.e. number of tours). The results reported here are in agreement with past DTI PTSD studies not controlling for PTSD duration or that examined single-event traumas. This suggests that WM abnormalities associated with PTSD are not limited to one type of trauma nor caused by damage accumulated over time from stress, but instead likely have either a more acute trauma-related source or predate the trauma entirely.

4.1. Limitations

Similar to many imaging studies (Anderson et al., 2012), the current study was limited by small sample size. Prior DTI studies with PTSD patients have included 25 to 45 participants, with PTSD sample sizes ranging from 9 to 21. In order to compensate for this we restricted comparisons to the right and left dorsal cingulum, ACR, and parahippocampal cingulum, where we expected to find larger effects. These regions were selected based on work from research groups examining WM microstructure as well as activation of gray matter in PTSD. However, although we feel we chose the most appropriate regions, there may be other WM abnormalities associated with PTSD or with AUD that lie outside the six well-defined regions we examined. Additionally, the cross-sectional nature of this study is a limitation making it impossible to determine the direction of causality. We sought to reduce the chance that these differences were the result of chronic PTSD, by limiting our participants to only those from recent combat. Similarly, although we screened for traumatic brain injury (TBI), mild TBI can be difficult to detect, is highly comorbid with PTSD, and shares many

symptoms with PTSD. As such, we may have missed some cases of mild TBI in participants who did not experience concussions or who did not accurately report TBI events. Still, our questionnaire should have screened out most mild and virtually all moderate cases of TBI. One of the major strengths of this study is our control group, carefully chosen to correspond to the PTSD group by duration of trauma exposure, type of trauma exposure, and time since trauma exposure. Although these trauma characteristics are typically controlled for in PTSD research, many prior imaging studies have not controlled for these factors. This is especially important since some of these factors could play a role in white matter integrity. We feel the careful selection of our PTSD and control samples, unique among PTSD studies utilizing DTI, makes a valuable contribution despite the limitations.

4.2. Conclusion

Decreased FA in the left and right dorsal cingulum and right ACR suggest that altered fiber integrity, myelin abnormalities, reduced axonal thickness, or altered crossing patterns in WM pathways connecting frontal cortical regions with the thalamus and amygdala are associated with PTSD. Moreover, altered WM microstructure in the right ACR is correlated with PTSD severity, further implicating this anomaly as specifically related to PTSD. No WM differences were attributable to AUD severity. This supports the theory that neuronal alterations in PTSD exist not only in the gray matter, but also in WM regions connecting critical regions such as the vmPFC, ACC, thalamus, and amygdala. Inadequate emotion regulation and executive function seen in PTSD patients may not be due solely to reduced frontal cortex neuronal activity and increased amygdala activity, but also to poor communication between those areas.

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Fig. 1. Regions of interest (ROIs) selected for analysis: dorsal cingulum (red and dark blue), anterior corona radiata (green and light blue), and parahippocampal cingulum (yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2. Scatterplot showing individual fractional anisotropy values for combat veterans with PTSD compared to those without PTSD for (a) right dorsal cingulum, (b) left dorsal cingulum, and (c) right anterior corona radiata.

Fig. 3. Scatterplots with regression lines showing the relationship of PTSD severity as measured by the CAPS with FA values for the six regions.

Table 1

Participant characteristics by PTSD group.

	AUD (n=10)			PTSD/AUD (n=12)			t	P
	Mean	SD	Range	Mean	SD	Range		
PTSD Severity*	23.60	13.083	7-43	68.50	18.033	45-98	6.556	0.00
BDI*	11.6	8.62	3-26	52.0	23.58	2-52	2.444	0.02
Age	28.10	5.363	22-41	31.08	7.657	22-51	1.036	0.31
IQ estimate**	110.90	13.337	94-132	101.55	11.961	79-116	1.695	0.11
AUD severity	3.60	1.578	1-6	5.50	2.84	2-10	1.978	0.06
DPDD	2.97	2.955	0-10	5.48	6.026	0-21	1.199	0.25
PDD	20.78	27.121	0-94	17.31	15.823	0-48	0.374	0.71
Days since 1st combat	1624	576.5	673-2747	2014	1514.3	861-6628	-0.766	0.45
Days since last combat	1210	604.9	226-2147	1190	498.7	426-2129	0.082	0.94
Number of tours	1.6	0.69	1-3	1.42	0.51	1-2	0.708	0.48

PTSD severity=severity score from the Clinician Administered PTSD Scale, BDI=beck depression inventory II, IQ estimate=intelligence quotient estimated using the Wechsler Abbreviated Scale of intelligence (WASI), AUD severity=structured clinical interview for DSM-IV axis I disorders alcohol symptom count-scale ranges from 0 to 11, DPDD=drinks per drinking day for the past 90 days, PDD=percent drinking days over the past 90 days (DPDD and PDD measured using the Timeline Followback). PTSD=posttraumatic stress disorder. AUD=alcohol use disorder. SD=standard deviation.

* $P < 0.05$,

** Computed with 19 df because of unreliable data for one participant.

Table 2

Fractional anisotropy by PTSD group controlling for age.

PTSD/AUD		AUD		F	P
Mean	SD	Mean	SD		
Dorsal cingulum					
Left	0.500	0.0201	0.522	0.0186	10.395 0.0045*
Right	0.453	0.0172	0.474	0.0203	9.091 0.0071*
Anterior corona radiata					
Left	0.419	0.0169	0.428	0.0170	1.457 0.2422
Right	0.423	0.0114	0.451	0.0168	18.914 0.0003*
Parahippocampal cingulum					
Left	0.403	0.0319	0.405	0.0249	0.306 0.5865
Right	0.390	0.0188	0.375	0.0211	2.984 0.1003

F and P values are for ANCOVAs controlling for age, but Means and SD values are raw values.

PTSD=posttraumatic stress disorder. AUD=alcohol use disorder. SD=standard deviation.

* P < 0.008 still significant with Bonferroni corrections for six comparisons.

Table 3

Radial and axial diffusion by PTSD group controlling for age.

PTSD/AUD		AUD		F	P
Mean	SD	Mean	SD		
Dorsal cingulum axial diffusion					
Left	0.00121	0.000033	0.00125	0.000030	9.954 0.0052*
Right	0.00119	0.000034	0.00122	0.000037	4.489 0.0475
Dorsal cingulum radial diffusion					
Left	0.00052	0.000022	0.00050	0.000021	5.160 0.0349
Right	0.00057	0.000022	0.00055	0.000015	4.933 0.0387
Anterior corona radiata axial diffusion					
Left	0.00120	0.000018	0.00120	0.000032	0.160 0.6932
Right	0.00117	0.000037	0.00120	0.000045	2.653 0.1198
Anterior corona radiata radial diffusion					
Left	0.00062	0.000023	0.00061	0.000028	0.955 0.3406
Right	0.00060	0.000025	0.00058	0.000027	3.854 0.0644
Parahippocampal cingulum axial diffusion					
Left	0.00114	0.000067	0.00117	0.000056	1.194 0.2882
Right	0.00121	0.000062	0.00122	0.000040	0.102 0.7534
Parahippocampal cingulum radial diffusion					
Left	0.00063	0.000037	0.00063	0.000028	0.000 1.0000
Right	0.00066	0.000038	0.00068	0.000034	1.490 0.2372

F and P values are for ANCOVAs controlling for age, but Means and SD values are raw values.

PTSD=posttraumatic stress disorder. AUD=alcohol use disorder. SD=standard deviation.

* P < 0.008 still significant with Bonferroni corrections for six comparisons for each set of analyses (AD and RD).

Table 4

Betas for regional FA by hemisphere for PTSD and AUD severity controlling for age.

<i>Region</i>	Dependent variable, <i>n</i>=22			
	PTSD severity		AUD severity	
	Beta	Model	Beta	Model
Right		<i>F</i> =5.800*		<i>F</i> =1.252
<i>Anterior corona radiata</i>	−0.585*		−0.221	
<i>Dorsal cingulum</i>	−0.197		−0.013	
<i>Parahippocampal cingulum</i>	0.239		0.340	
Left		<i>F</i> =3.089		<i>F</i> =0.848
<i>Anterior corona radiata</i>	−0.091		−0.016	
<i>Dorsal cingulum</i>	−0.401		−0.244	
<i>Parahippocampal cingulum</i>	−0.427		0.234	

PTSD severity was calculated using the CAPS severity scoring guidelines (sum of intensity and severity for each symptom). AUD severity was calculated as the symptom count of DSM-IV AUD symptoms measured by the SCID.

* Significant after Bonferroni correction for 4 comparisons at $P < 0.0125$.