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White Matter Integrity in Individuals At-Risk for PTSD Development: a Longitudinal Investigation

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WHITE MATTER INTEGRITY IN INDIVIDUALS AT-RISK FOR PTSD DEVELOPMENT: A LONGITUDINAL INVESTIGATION

by

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ABSTRACT

WHITE MATTER INTEGRITY IN INDIVIDUALS AT-RISK FOR PTSD DEVELOPMENT: A LONGITUDINAL INVESTIGATION

by

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Trauma exposure is prevalent and while most are resilient, some go on to develop post-traumatic stress disorder (PTSD)—an anxiety-related disorder that results from traumatic experience. The brain changes that result from traumatic experience and PTSD are not well understood. Further, little is known about what distinguishes those who are resilient after trauma from those at risk for developing PTSD. Previous work indicates white matter integrity may be a useful biomarker in predicting PTSD and researchers have found changes in the integrity of three white matter tracts—the cingulum bundle, corpus callosum (CC), and uncinate fasciculus (UF)—in the aftermath of trauma. However, few have examined the relationship between white matter integrity and PTSD symptoms longitudinally. Thus, the aims of the current study are 1) to investigate the predictive utility of white matter integrity in the acute stages of trauma to chronic PTSD symptoms and 2) to examine how white matter integrity varies with PTSD symptoms over time. Fifty-seven individuals being treated for traumatic injuries in the emergency department at Froedert Hospital (Milwaukee, WI) completed several self-report measures and underwent structural and diffusion-weighted magnetic resonance imaging at 2 weeks (T1) and 6 months (T2) post-trauma. At T1 greater UF integrity at T1 was related to greater T2 arousal symptoms. In addition, greater T1 anterior cingulum integrity was related to greater T2 re-experiencing symptoms. However, decreased anterior cingulum and CC integrity from T1 to T2 was related to

increased symptoms over time. Therefore, acute white matter integrity post-trauma may be a useful predictor of chronic PTSD symptoms, and changes in white matter integrity may track changes in symptoms over time. Together these results suggest white matter integrity may be a potential biomarker for clinicians to help identify those at risk for PTSD development.

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LIST OF ABBREVIATIONS

AFNI	Analysis of Functional NeuroImages
AUDIT	Alcohol Use Disorders Identification Test
CAPS	Clinician Administered PTSD Scale
CC	Corpus Callosum
DAST	Drug Abuse Screening Test
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Images
FA	Fractional Anisotropy
FSL	FMRIB Software Library
MD	Mean Diffusivity
MRI	Magnetic Resonance Imaging
PCL-5	PTSD Checklist for DSM-5
PTSD	Post-Traumatic Stress Disorder
T1	2-weeks post-trauma
T2	6-months post-trauma
UF	Uncinate Fasciculus

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Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a disorder which follows exposure to one or more traumatic events. The definition of a traumatic event is one in which an individual feels that their life and/or safety is threatened. Examples of such events include, but are not limited to, war and combat, assault, sexual violence, terrorism, natural or man-made disasters, motor vehicle crashes, other serious accidents and interpersonal violence. The individual may have experienced the event directly, witnessed it, or learned about it happening to someone close to them (American Psychiatric Association, 2013). Symptoms include re-experiencing the event through intrusive thoughts, nightmares, and flashbacks, avoiding trauma-related stimuli, hyperarousal, and experiencing negative thoughts or emotions that begin or worsen after the event. These symptoms must persist for more than one month, be distressing, and disrupt daily function (American Psychiatric Association, 2013).

The lifetime prevalence of PTSD, using DSM-5 criteria, is about 9.4% in the US (Kilpatrick et al. 2013). Despite some differences in criteria, lifetime prevalence estimates using the DSM-IV are similar, at about 8.7% (American Psychiatric Association, 2013). Women are affected more than men with lifetime prevalence estimated to be 12.8% and 5.7% respectively, due in part to the fact that women tend to be exposed to more sexual and interpersonal violence than men (Kilpatrick et al., 2013). Prevalence varies by geographic region as exposure to trauma varies (Benjet et al., 2016). The World Mental Health Surveys (WMHS) conducted by the World Health Organization (WHO) estimated the lifetime prevalence of PTSD for trauma exposed individuals from 24 countries to be 5.6% (Koenen et al., 2017). Rates of PTSD are highest in

combat veterans, rape survivors, and survivors of captivity, internment, and genocide (American Psychiatric Association, 2013). PTSD shows high comorbidity with other mental disorders including depression, bipolar, anxiety, and substance use disorders (American Psychiatric Association, 2013; Karam et al., 2014). All of these factors make the burden on public health due to PTSD substantial as these individuals require more mental health-related resources than other psychological disorders, such as major depressive disorder (Ivanova et al., 2011).

Trauma exposure is quite prevalent. The U.S. Department of Veterans Affairs estimates that about 60% of men and 50% of women will experience at least one trauma in their lives (Gradus, 2017). Another calculation of trauma exposure rates in the US estimates that nearly 90% of people will experience a trauma, including a 50% likelihood of experiencing direct interpersonal violence (Kilpatrick et al., 2013). Globally, the WMHS estimates the prevalence at 70% for any traumatic exposure and about 40% for direct interpersonal violence (Benjet et al., 2016). Data from these surveys also suggests that risk of PTSD development increases with the number of trauma exposures (Karam et al., 2014). Although trauma is extremely common, most individuals are resilient and do not go on to develop PTSD or other disorders following exposure (Thompson et al., 2018; Wolf et al., 2017; Lee et al., 2014; Wu et al., 2013; Bonanno, 2004). However, a substantial subset of trauma-exposed individuals do go on to develop chronic PTSD and related disorders (Karam et al., 2014; Powers et al., 2014; Bonanno, 2004; Foa & Riggs, 1995; Riggs, Rothbaum, & Foa, 1995).

Critically, at this point, clinicians do not have an accurate method of predicting who is at risk of developing PTSD after a traumatic event. This makes early intervention difficult to administer because clinicians are unable to identify those who need treatment and what pathophysiology is putting them at risk. If clinicians had sensitive and specific biological or

behavioral markers of risk for PTSD, they could provide more timely and precise interventions to help prevent symptom onset or progression. Ideally, markers evident soon after trauma exposure could be used to identify those at risk for chronic distress so that appropriate preventative interventions could be administered (Bryant, 2003). Researchers have been working to identify such biomarkers, and it seems structural integrity of the brain may be one of the more robust indicators and potential predictors of symptoms due to its reliable measurement and consistent results as documented in animal models of the disorder and human research (Pitman et al., 2012; Karl et al. 2006; Bremner, 2005).

Diffusion-Weighted Magnetic Resonance Imaging

White matter tracts are the myelinated axons of neurons that connect the cell bodies of neurons between brain regions. They conduct action potentials to coordinate the passage of information throughout the brain (Blumenfeld, 2010). Diffusion-weighted magnetic resonance imaging (MRI) is a relatively new imaging technique that can non-invasively characterize the integrity of these tracts in the brain by measuring the signal attenuation of water movement within brain tissue (Alexander, Eun Lee, Lazar & Field, 2007; Mori & Tournier, 2014; Soares, Marques, Alves, & Sousa, 2013). The most commonly used method of diffusion MRI is diffusion tensor imaging (DTI) (Alexander et al., 2007). In DTI, a diffusion tensor is estimated at every spatial location in the brain that defines the principal direction of water movement along brain tissue. This tensor estimation is quantified as fractional anisotropy (FA), or the degree of anisotropic water diffusion, which is an approximation of the coherence of tissue in that area (Alexander et al., 2007; Mori & Tournier, 2014). The higher the FA, the more anisotropic the water diffusion and the more parallel or spatially coherent the tissue is in that region (Mori & Tournier, 2014). Thus, FA provides an estimate of structural connectivity between brain regions

and allows for anatomically well-defined white matter tracts to be quantitatively compared across individuals (Alexander et al., 2007). In addition to FA, mean (MD), radial (RD), and axial diffusivity (AD) can also be measured, representing average diffusion rate, diffusion rate along the principal axis of diffusion, and the diffusion rate along the transverse axis, respectively (Soares et al., 2013; Mori & Tournier, 2014; Alexander et al., 2007). Greater cohesion of white matter fibers, due to myelination, fiber orientation leads to higher AD and lower MD and RD, as water movements are better constrained along the tissue in one principal direction. Thus, these various diffusion measures together can be used to assess the integrity of white matter tracts by quantifying the direction and rate of water diffusion. This makes DTI an informative method for understanding the microstructural architecture in a given brain area (Alexander et al., 2007).

To assess the integrity of particular pathways, white matter atlases can be used to extract DTI measures for only tracts of interest. Alternatively, whole brain voxel-wise analysis techniques, such as tract-based spatial statistics (TBSS), can also be used to assess white matter integrity without *a priori* spatial constraints (Soares et al., 2013; Smith et al., 2006). However, as a technique, DTI is limited by its inadequate account of crossing fibers, which invariably exist (Alexander et al., 2007). Since only one principal diffusion direction may be estimated at a time, it is important to consider DTI measures and their interpretations carefully. Nonetheless, diffusion MRI provides a noninvasive characterization of white matter tracts which can be used to identify aberrations in pathways relevant to psychological disorders including PTSD.

White Matter Changes in Chronic PTSD

The symptoms of PTSD and the cognitive and behavioral alterations that occur as a result vary by individual, but how and why these symptoms occur is not well understood. To identify symptom origin, it is important, if possible, to localize disruptions in the brain that underlie

maladaptive behaviors and cognitions so that targeted pharmacological or behavioral interventions can be implemented without disrupting unrelated and intact neural processes. Structural connectivity studies using diffusion MRI have yielded robust results suggesting the potential utility of white matter integrity as a biomarker of psychological disorders including PTSD (Alexander et al., 2007; Soares et al., 2013). More specifically, changes in FA and disruption of specific white matter tracts including the cingulum, corpus callosum, and uncinate fasciculus have consistently correlated with PTSD symptom severity adding to its potential utility as a predictive correlate of disorder presentation (Fani et al., 2015, Abe et al., 2006; Kennis et al., 2017; Bierer et al., 2015; Jackowski et al., 2008; Hu et al., 2016; Saar-Ashkenazy et al., 2016).

Cingulum integrity and PTSD. The cingulum is a white matter tract that projects from the cingulate gyrus to the hippocampus and medial temporal lobe cortices (Schmahmann et al., 2007). This fronto-limbic pathway plays an important role in emotion and emotion regulation, and has been hypothesized to contribute to the dysregulated emotions seen in PTSD (Sanjuan et al., 2013). In addition, given its connectivity with structures important for memory in medial temporal lobes, the cingulum may also play a role in re-experiencing symptoms (Kantarci et al., 2011). In a sample of African-American women with high trauma exposure, lower cingulum FA was associated with greater startle response and re-experiencing symptoms, but not avoidance or hyperarousal symptoms (Fani et al., 2015). The authors argue this disruption of connectivity may partially explain the exaggerated appraisal of threat in PTSD. Similarly, reduced FA, RD, and AD in the dorsal cingulum, indicative of reduced integrity, have been found in Afghanistan and Iraq veterans with PTSD (Sanjuan et al., 2013). Fani et al. (2012) also identified lower FA bilaterally in the posterior region of the cingulum, adjacent to the hippocampi, in a sample of

women with a history of trauma. In addition, a review of PTSD and childhood trauma revealed that the most consistent FA result is a decrease in integrity of the cingulum (Daniels et al., 2013). Some researchers have argued that repeated exposure to trauma results in the microstructural degradation of the cingulum (Li et al., 2016). Weaker structural connectivity in the cingulum has been posited to reflect insufficient top-down emotion appraisal and regulation as well as dysregulated memory retrieval evident in PTSD (Sanjuan et al., 2013).

While some researchers have noted lower cingulum FA in samples of trauma-exposed individuals, others have found *higher* FA. In a sample of individuals afflicted by an act of terrorism, those with PTSD showed higher FA in the left anterior cingulum which correlated with symptom severity (Abe et al., 2006). In a mixed-trauma sample of PTSD patients, Reuveni et al. (2016) found a positive correlation between cingulum integrity and PTSD symptom severity. Similarly, in samples of veterans with PTSD, greater cingulum integrity, characterized by higher FA, predicted avoidance symptoms at follow-up (Kennis et al., 2017), and correlated positively with overall PTSD symptom severity (Bierer et al., 2015). These changes in the cingulum are posited to reflect greater microstructural integrity due to the hippocampus coupling with the cingulate. This coupling is thought to lead to some of the intrusive traumatic memories seen in PTSD (Bierer et al., 2015).

Despite the inconsistencies in the literature, altered integrity of the cingulum has been repeatedly linked with PTSD. Meta-analytic work further cements cingulum integrity as a specific marker of PTSD. In particular, compared to healthy controls, individuals with PTSD, but not other disorders, show lower FA in the left cingulum (Jenkins et al., 2016). Overall the literature implicates compromised cingulum integrity in chronic PTSD.

Of interest to the current study, Hu et al. (2016) found that cingulum integrity may be a useful acute post-trauma marker of risk. When compared to trauma-exposed controls, motor vehicle crash (MVC) victims showed lower FA in the cingulum just 2 days after the incident. Further, integrity measures at baseline correlated with symptom severity at 6-month follow up such that decreased integrity, as evidenced by lower FA and higher RD, was related to greater symptom severity (Hu et al., 2016). Due to its relevance in emotion regulation and memory systems, in combination with the above findings, compromised cingulum integrity may be a potential predictor of PTSD symptom severity.

Corpus callosum integrity and PTSD. Another white matter tract that has been implicated in PTSD symptom presentation is the corpus callosum (CC). The CC is a large bundle of fibers that connects the cerebral hemispheres. It is often segmented into thirds called the genu, midbody, and splenium corresponding to the anterior, middle, and posterior portions respectively (Hofer & Frahm, 2006). The CC connects many prefrontal and parietal cortical regions important for various memory functions and the processing of emotions, both of which have been shown to be disrupted in PTSD (Akiki et al., 2017; Mahan & Ressler, 2012; Pitman et al., 2012; Jackowski et al., 2008). In a sample of earthquake survivors, Li et al. (2016) found that higher FA and lower RD and AD in the splenium of the left CC was associated with greater symptom severity. The authors argue greater integrity in this particular part of CC may relate to the presentation of flashbacks, due to its connectivity with visual areas involved with mental imagery.

However, like the cingulum, there have been contradictory results in the direction of integrity changes in the CC as a result of trauma. In a sample of children with a history of abuse who developed PTSD, the anterior and posterior midbody of the CC showed lower FA. This reduction also correlated with PTSD symptom severity (Jackowski et al., 2008). Saar-Ashkenazy

et al. (2016) found the same results in a sample of individuals with mixed trauma exposure. Among those who recently experienced a motor vehicle crash, Sun et al. (2015) found those who went on to develop PTSD showed lower FA in the genu of the CC in the commissural tracts connecting the bilateral superior middle frontal gyrus. In a similar sample, Hu et al. (2016) also found lower FA in the CC that predicted symptom severity at 6-month follow-up. Reduced or impaired connectivity in the CC may underlie altered emotion processing that lead to avoidance or hypervigilance symptoms (Sun et al., 2015). These findings of compromised CC integrity in the acute stages of trauma (Sun et al., 2015; Hu et al., 2016) suggests its potential utility as a biomarker of risk for PTSD development.

Uncinate fasciculus integrity and PTSD. Finally, the uncinate fasciculus (UF), a white matter tract which connects the temporal and frontal cortices through the limbic region, has also been implicated in PTSD (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Decreased UF integrity has been linked to impaired extinction learning as well as misevaluation of social-emotional stimuli that may result in avoidance behaviors seen in PTSD (Jovanovic & Ressler, 2010; Von Der Heide et al., 2013; Olson et al., 2015; Koch et al., 2017). A review of the development of the UF indicates that early life abuse or stress may be associated with decreased structural integrity due to the sensitivity of limbic regions to the negative effects of stress hormones (Olson et al., 2015). Accordingly, in children with a history of maltreatment, researchers have noted reduced UF integrity (Hanson, Knodt, Brigidi, & Hariri, 2015; Daniels et al., 2013). In addition, lower FA in the UF has been found to be predictive of psychological vulnerability to future stress or trauma (Hanson et al., 2015). In a sample of police officers, those with PTSD had decreased integrity of the UF, evidenced by higher MD, which correlated with measures of anxiety (Koch et al., 2017). In a community sample of individuals with PTSD,

Olson et al. (2017) found a significant reduction in FA in the UF. In a sample of acute trauma survivors, lower FA in the UF 1 month post-trauma was significantly related to PTSD symptoms at 6 months post-trauma (Fani et al., 2017). These results suggest compromised integrity of the UF may be a useful biomarker of PTSD symptoms.

The discrepancies in results within these various white matter tracts may be due to systematic differences in participant samples, such as age and time since trauma. Few studies have investigated changes in white matter integrity over time, though this may be the best method to help clarify the direction of white matter changes as a function of trauma and trauma-related symptoms. For instance, a longitudinal study reported increased rates of gross brain tissue atrophy in frontal and temporal regions for veterans with PTSD whose symptoms did not improve over time, and recovery of tissue volumes for those whose symptoms improved (Cardenas et al., 2011). Others have reported more specific structural changes over time. In a sample of veterans with PTSD, Zhang et al. (2012) reported increased FA in the posterior cingulate gyrus over time, a region adjacent to the posterior cingulum and splenium of the CC. Similarly, Kennis, van Rooij, Reijnen, & Geuze (2015) found that over the course of treatment, veterans with persistent PTSD showed an increase in FA of the dorsal cingulum. Those with persistent PTSD also had higher FA in this region than those with remitted PTSD at baseline and at 6-month follow up (Kennis et al., 2015). The authors posit that this increased connectivity may be related to hyperactivity of the cingulate, which may be associated with intrusive memories and thoughts. However, more evidence is needed to understand changes in these brain regions and how or if these changes relate to symptom development.

Longitudinal research has yielded some insights into the structural changes that accompany PTSD; however, fewer studies have investigated how structural changes may inform

PTSD development in acute trauma survivors. It is important to identify acute post-trauma predictors in chronic PTSD so that clinicians may target treatments that can directly offset the development of PTSD. If changes in structural connectivity could be plotted over time against symptom presentation, cognitive and behavioral treatments could be targeted to the cognitive processes affected by disruptions in localized brain regions.

Current Study

Therefore, the current study aims to a) assess whether acute post-trauma white matter integrity can predict chronic PTSD symptoms, and b) examine if changes in white matter integrity from the acute to chronic post-trauma periods correspond to changes in symptom severity over time. It is clear from previous research that particular white matter tracts including the cingulum (Fani et al. 2012; Hu et al. 2016; Abe et al., 2006; Zhang et al., 2012; Kennis et al., 2017), corpus callosum (Li et al. 2016; Jackowski et al., 2008; Sun et al. 2015; Hu et al. 2016; Saar-Ashkenazy et al., 2016), and uncinate fasciculus (Von Der Heide et al., 2013; Olson et al., 2015; Fani et al., 2017) are affected by traumatic experiences.

With respect to the first aim, I hypothesize that the structural integrity of the cingulum, CC, and UF in the acute aftermath of trauma will correlate with symptom severity at follow-up. While the findings on cingulum and CC integrity in PTSD are mixed, in keeping with the few studies of acute trauma survivors to date, I predict that decreased cingulum and CC integrity will predict greater subsequent risk for PTSD evidenced by greater overall symptom severity. Finally, for the UF, I hypothesize that decreased integrity at baseline will predict symptom severity at follow-up.

In addition to overall symptom severity, I will explore how tract integrity of the cingulum, CC, and UF might relate to specific symptom clusters of PTSD. Since the cingulum

and CC are both related to emotion regulation and memory processes, I predict their integrity will be related to negative cognitive or mood symptoms and intrusive PTSD symptoms at follow-up. Since the UF is related to extinction learning and social-emotional processes, I expect its integrity to be related to avoidance and negative cognitive or mood PTSD symptoms at follow-up.

With respect to the second aim, I hypothesize that changes in structural integrity of the cingulum, CC, and UF from acute to chronic post-trauma periods will correspond with changes in symptom severity from acute to chronic post-trauma periods. I predict changes in cingulum and CC integrity will correlate with changes in symptom severity, and for the UF, I hypothesize decreased integrity over time will correspond with changes in overall symptom severity. Like the first aim, I will explore how changes in integrity over time relate not only to overall PTSD symptom severity, but also to symptom clusters. I expect changes in cingulum and CC integrity to correspond with changes in negative cognitive or mood symptoms and intrusive symptoms. For the UF, I expect decreased integrity over time will relate to avoidance and negative cognitive or mood symptoms.

Method

Participants

Ninety-nine individuals who recently experienced a traumatic event and were treated for injuries at the Emergency Department (ED) at Froedtert Hospital in Milwaukee, WI were included in this study. Inclusion criteria include those who meet criterion A of PTSD diagnosis as defined by the DSM-IV. Criterion A states an individual must be exposed to actual or threat of death, serious injury, or sexual violence through direct experience, witnessing the event, learning about the event happening to someone close to them, or experiencing repeated or extreme

exposure to the details of the event (American Psychiatric Association, 2013). Individuals must also score a minimum of 3 on the Predicting PTSD Questionnaire, developed by Barbara Rothbaum, that assesses exposure to risk factors to chronic PTSD development including prior trauma, current trauma severity, dissociation during current trauma, childhood trauma exposure, and family history of psychopathology. A minimum score of 3 therefore indicates an individual has experienced at least 3 of these risk factors which considerably increases their risk of developing chronic PTSD. With these screening criteria, we are oversampling those at risk for PTSD development to ensure a sufficient range in PTSD symptom severity at follow-up. In addition, individuals must be aged 18-60, English speaking, and able to schedule their first research visit within 30 days of the trauma.

Exclusion criteria include head injury more severe than a mild TBI (score of 13 or higher on the Glasgow Coma Scale), spinal cord injury with neurological deficit or any condition affecting brain structure or function, self-inflicted traumatic injury, severe vision or hearing impairments, history of psychotic or manic symptoms, currently on antipsychotic medications, clear substance abuse, on police hold to be released to jail, and any contraindications for MRI scanning including metal objects or fragments in the body, claustrophobia, and pregnancy or planned pregnancy within the next 6 months.

Of the 99 participants only 64 had complete diffusion weighted imaging datasets; however, of the 64, 7 individuals were dropped due to excessive motion in the MRI scan leaving a final sample of 57 participants (27 male, 30 female; M_{age}=31.67, SD_{age}=9.80). Males and females did not significantly differ in age across the sample. Seventy-seven percent (23 male, 21 female) of the sample were traumatically injured in a motor vehicle crash, 12% (1 male, 6 female) were injured in an assault, 5% (3 male, 0 female) were struck as pedestrians, and 5% (0

male, 3 female) were injured in another way. At 6-months, 24% of participants (7 male, 7 female) met criteria for PTSD diagnosis according to the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) (Weathers et al., 2013).

Procedure

Participants were recruited directly from the ED at Froedtert Hospital (Milwaukee, WI) or by phone following discharge. After expressed interest in study participation the participant received a complete verbal overview of the study and were screened to ensure eligibility. Participants came to research visits at two time points, within 2-3 weeks (T1) and 6 months (T2) following the trauma that resulted in their ED admittance. At both visits, a large battery of behavioral, cognitive, self-report questionnaires, as well as structural and functional imaging data were collected. However, given the scope of the current study only select questionnaires (PCL-5, LEC, and abbreviated AUDIT and DAST; see Measures) and the structural and diffusion MRI data from the 2 visits were analyzed.

Measures

PTSD Symptoms. To assess PTSD symptoms, we used the PTSD Checklist for DSM-5 (PCL-5) (U.S. Department of Veterans Affairs, 2017; Blevins et al., 2015) was administered at T1 and T2. The PCL-5 is a 20-item self-report measure that assesses symptoms of PTSD according to the DSM-5 criteria. Scores from the PCL-5 can be summed to attain a total symptom severity measure and can also be summed according to the 4 symptom clusters of PTSD—re-experiencing symptoms, avoidance, negative cognitions or mood, and arousal.

Prior Trauma History. To assess prior trauma history, we used the Life Events Checklist (LEC) (Gray, Litz, Hsu, & Lombardo, 2004). The LEC has good internal (Kappa=0.61) and test-retest reliability (r=0.82) and assesses occurrence of 17 major life events

that a person may have experienced (e.g. natural disaster, assault, combat, life-threatening illness or injury). Summary scores of the LEC were calculated by summing the number of events one had experienced firsthand, witnessed, or heard about happening to someone close to them. The current sample experienced on average 17 major life events (M_{LEC}=17.28, SD_{LEC}=8.26).

Substance Use. Since substance use can have direct effects on brain structure and function, metrics of alcohol and drug use were included in statistical analyses as covariates of no interest. Alcohol use at both time points were evaluated using an abbreviated version of the Alcohol Use Disorder Identification Test (AUDIT) (Bush et al., 1998). Scores can range 0-12 with greater scores indicating greater alcohol quantity and frequency of use. This abbreviated version included the following three questions from the AUDIT: 1) How often have you had a drink of alcohol?, 2) How many standard drinks containing alcohol do you have on a typical day?, and 3) How often have you had six or more drinks on one occasion?

Similarly, drug use was assessed using summary scores from an abbreviated version of the Drug Abuse Screening Test (DAST) (Skinner, 1982). Scores can range from 0-10 with greater scores indicating more drug use. This abbreviated version included the following 10 yes or no questions from the DAST: 1) Have you used drugs other than those required for medical reasons?, 2) Have you abused more than one drug at a time?, 3) Were you always able to stop using drugs when you wanted to?, 4) Have you had "blackouts" or "flashbacks" as a result of drug use?, 5) Have you ever felt bad or guilty about your drug use?, 6) Has your spouse (or parents) complained about your involvement with drugs?, 7) Have you neglected your family because of your drug use?, 8) Have you engaged in illegal activities in order to obtain drugs?, 9) Have you had withdrawal symptoms when you stopped taking drugs?, and 10) Have you had medical problems as a result of your drug use?

For both of these measures, at T1 questions were asked with a reference period of the past 12 months, whereas at T2 the reference period was the time since the previous research visit the participant attended. In this way, we were able to obtain a metric for baseline drug and alcohol usage as well as the change in usage from T1 to T2 (Table 1).

Table 1 Average Drug and Alcohol Use

	T1	T2
	M (SD)	M (SD)
DAST	2.24 (1.89)	1.77 (1.41)
AUDIT	2.26 (1.87)	3.98 (2.51)

DAST, Drug and Alcohol Screening Test; AUDIT, Alcohol Use Disorder Identification Test; M, mean; SD, standard deviation; T1, 2-weeks post-trauma; T2, 6-months post-trauma.

MRI Acquisition

MRI was collected on a 3.0T short bore GE Signa Excite system. High resolution spoiled gradient recalled (SPGR) images were acquired in a sagittal orientation (TR=8.2 ms; TE=3.2 ms; FOV=24 cm; flip angle=12°; voxel size=1 x 0.9375 x 0.9375mm). Diffusion weighted images (DWI) were collected using an echoplanar pulse sequence with 70 contiguous 2mm thick axial slices and 38 non-collinear diffusion gradients (TR=10s; TE=77.99ms; b value=800 s/mm^2; FOV=25.6 cm; flip angle=90°; voxel size=2 x 2 x 2mm).

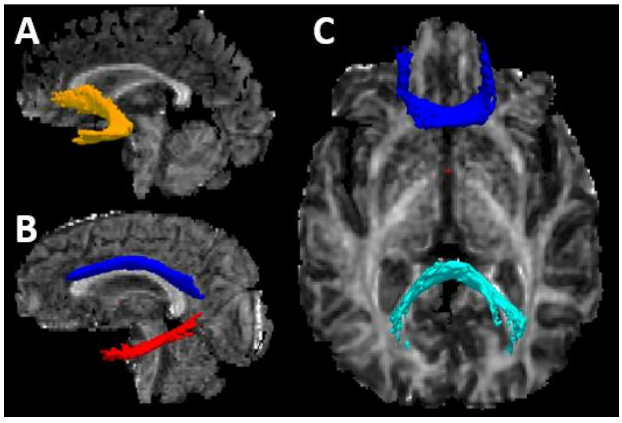

Figure 1. Tracts of interest as reconstructed in TRACULA for a representative participant. A) Uncinate fasciculus, B) anterior (blue) and posterior (red) cingulum bundle, C) forceps major (blue) and forceps minor (teal).

Outlying DTI measures were calculated for each tract in each hemisphere for each measure (FA and MD) as being +/- 2.5 standard deviations from the mean and were removed from the final analysis. No more than 3 participants' data were removed per tract per DTI measure using this outlier criterion. Note that participants were not excluded from analysis for any other outlying measures including head motion parameters, PCL-5, DAST, or AUDIT scores.

Whole-brain voxel-based analysis

In addition to the hypothesis driven tract-based analysis, to see if white matter changes occur outside of the tracts of interest, an exploratory whole-brain voxel-based analysis was completed using FSL (Smith et al., 2004) and AFNI (Cox, 1996). Fifty-two participant's original T1 and T2 DWI were first corrected for distortions by applying a reverse polarity scan using FSL's *topup* protocol (Andersson, Skare, & Ashburner, 2003). There were 8 participants who did not have reverse polarity DWI scans for at least one of the time points (5 at T1 and 3 at T2); however, they were still included to increase the sample size to 57 for Aim 1 analyses and to 55 for Aim 2. The DWI scans were then corrected for eddy current distortions using FSL's *eddy* (Andersson & Sotiropoulus, 2016). After these corrections, DWI were masked to include only voxels in the brain using a mask created from each individual's b0 T2-weighted image. Next, diffusion tensors were fit in FSL and the resultant FA and MD map images were then aligned to a standard MNI (MNI152_T1_2009c) template in AFNI.

For Aim 1 analysis, the normalized FA and MD maps from T1 for each participant were then masked to include only white matter voxels and entered into separate regressions using AFNI's *3dttest++* with PTSD symptoms from the PCL-5 to see how FA and MD at T1 relate to T2 total PTSD symptom severity. For Aim 2, the normalized integrity maps from T1 were

subtracted from the T2 maps for each individual resulting in whole brain change score integrity maps. These new maps were then entered into AFNI's *3dttest++* with change in total PCL-5 symptoms (T2-T1) to see how change in FA or MD over time related to changes in PTSD symptom severity. Given the exploratory nature of this analysis and for simplicity, the 4 PTSD symptom clusters from the PCL-5 were not evaluated, only total symptom severity scores were used. To correct for multiple comparisons, AFNI's *3dClustSim* was used to obtain voxel-wise ($p<.01$) and cluster thresholds ($p<.05$, $k=7$). All results were thresholded at these levels.

Results

Two sample t-tests of PCL-5 scores show a significant decrease in PCL-5 re-experiencing symptoms over time ($t(56) = 2.75$, $p=0.006$). No other subscales from the PCL-5 or total PTSD symptoms showed changes over time (Figure 2). However, this difference did not vary by gender. There were no gender differences in PTSD symptoms at T1 (Figure 3A), and at T2 the only gender difference was males showed greater cognitive symptoms than females ($t(56)=2.17$, $p=0.03$) (Figure 3B).

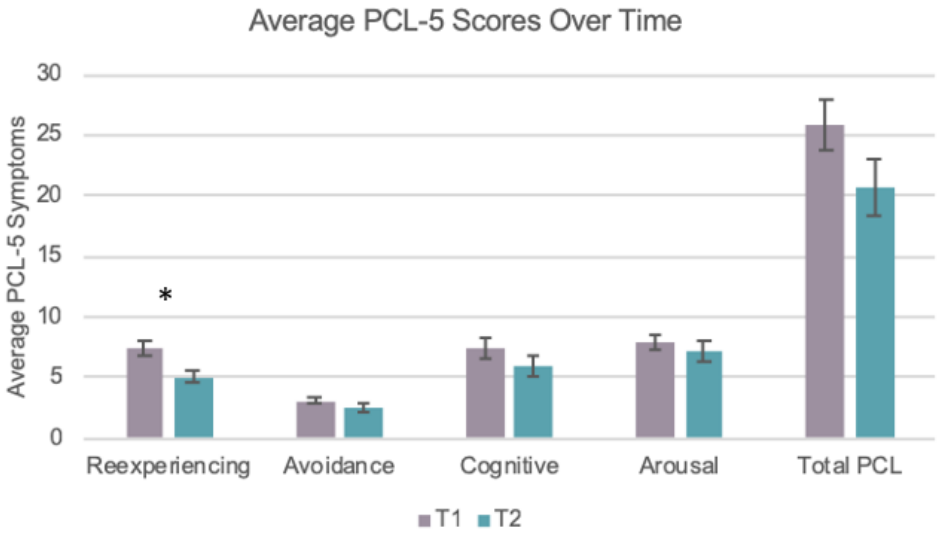

Figure 2. Re-experiencing symptoms decrease from T1 to T2. PCL-5, PTSD Checklist Civilian; T1, 2-weeks post-trauma; T2, 6-months post-trauma. *p<.05.

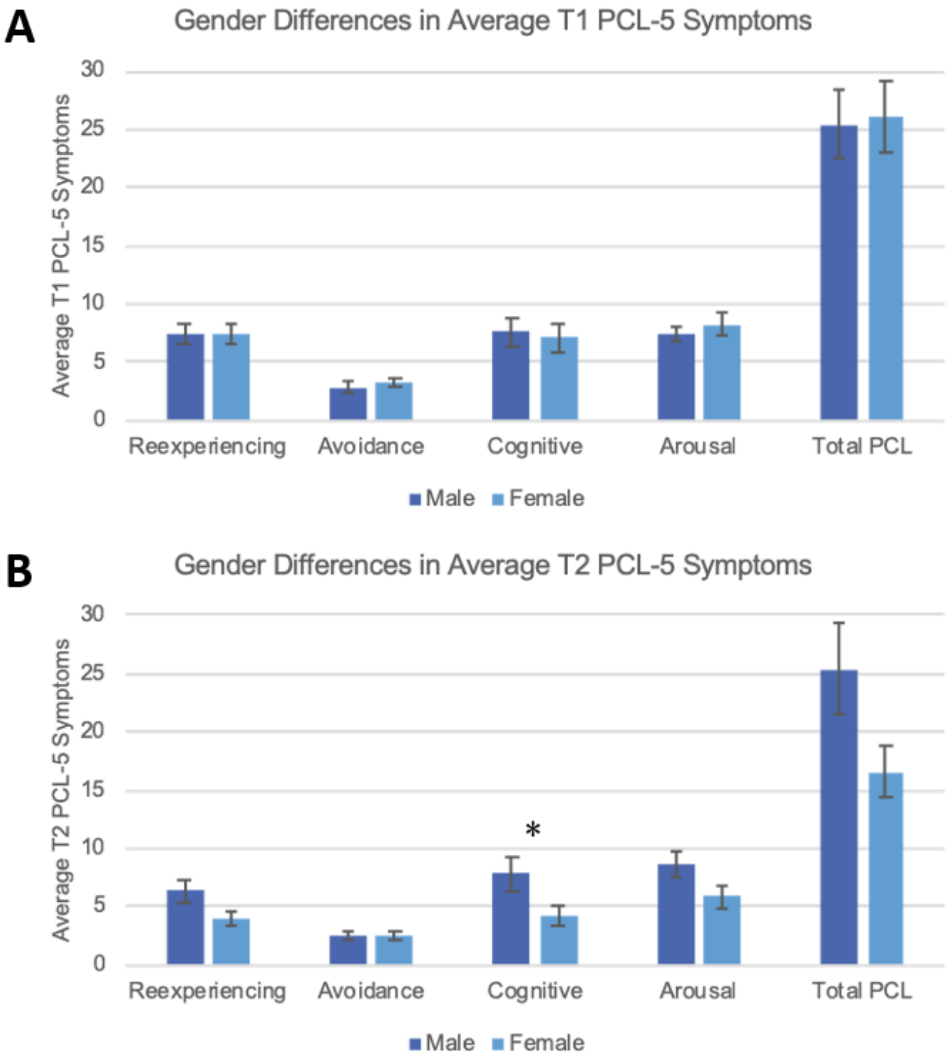

Figure 3. A) No gender differences in PCL-5 symptoms at T1. B) At T2, males show greater cognitive symptoms than females. PCL-5, PTSD Checklist Civilian; T1, 2-weeks post-trauma; T2, 6-months post-trauma. *p<.05.

Two-sample t-tests of DTI measures in each tract show a significant decrease in bilateral uncinate, posterior cingulum, and forceps minor FA from T1 to T2 (Figure 4A). In addition, there was a significant increase in left posterior cingulum MD (Figure 4B). Together these results suggest decreased white matter integrity of the uncinate, posterior cingulum, and forceps minor over time. This result is not driven by gender differences as males and females did not differ in FA or MD across time (all *p*'s >0.05).

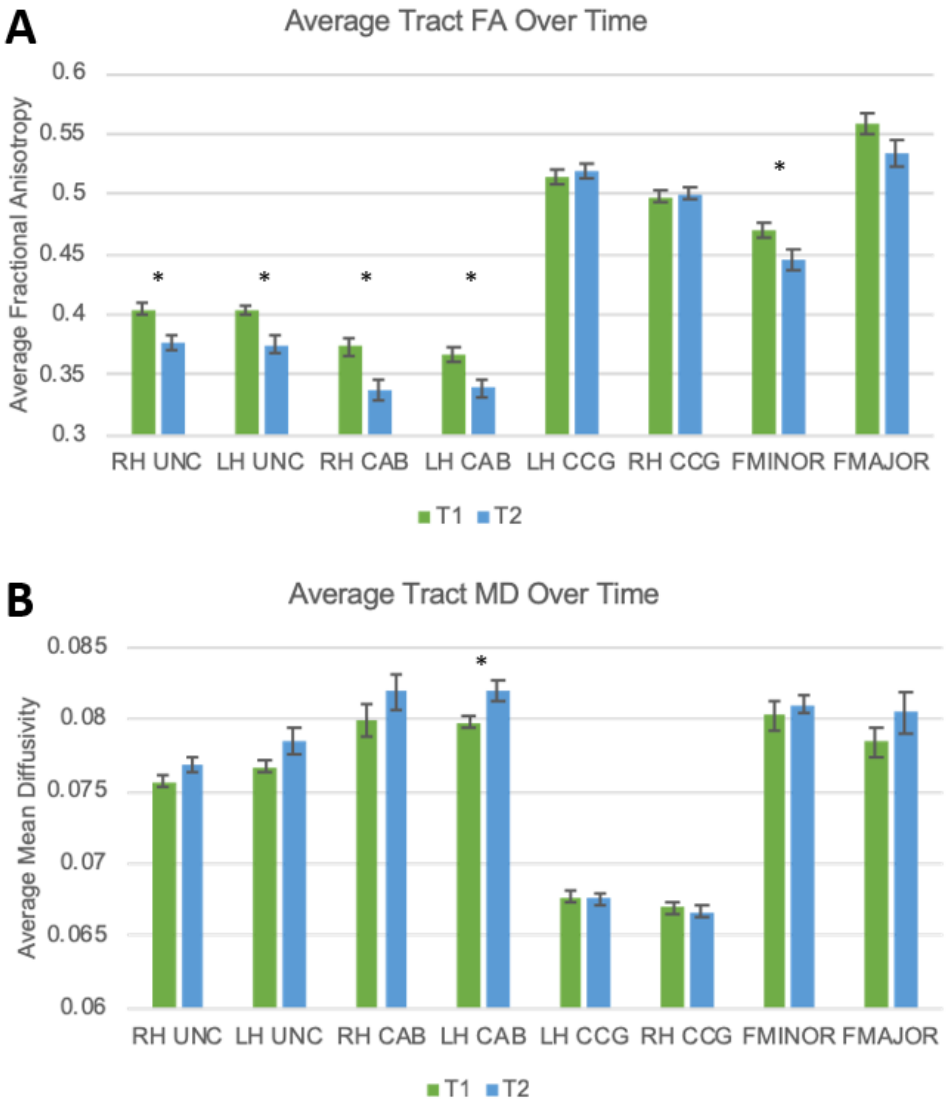

Figure 4. A) Bilateral uncinate, posterior cingulum, and forceps major decrease in integrity over time as evidence by decreases in FA from T1 to T2. B) The left posterior cingulum shows decreased integrity (increased MD) from T1 to T2. UNC, uncinate fasciculus; CAB, posterior cingulum; CCG, anterior cingulum; FMINOR, forceps minor of the CC; FMAJOR, forceps major of the CC; FA, Fractional Anisotropy; MD, Mean Diffusivity; PCL-5, PTSD Checklist Civilian; T1, 2-weeks post-trauma; T2, 6-months post-trauma. *p<.05.

Aim 1 Results: Does white matter integrity at T1 predict PTSD symptoms at T2?

In the tract-based analysis, linear regression was used to examine the utility of T1 white matter integrity in predicting T2 PTSD symptoms. For each regression, PTSD symptoms from the PCL-5 were the outcome variable and DTI measures (FA and MD) were the predictors. Since there were no *a priori* hypotheses regarding hemispheric differences nor were there hypotheses regarding specific differences in FA and MD separately, as well as to minimize the penalty for

multiple comparisons, both right and left hemisphere and both FA and MD measures for each tract were included together in each model, for example:

PCL-5 (T2) ~ RH_UF_FA (T1) + RH_UF_MD (T1) + LH_UF_FA (T1) + LH_UF_MD (T1)

Separate regression models were run for each combination of PCL-5 scores (i.e. total score, each of 4 subscales) and white matter tract for a total of 25 models (5 tracts x 5 symptom clusters).

While DTI measures and tracts across hemispheres tend to be highly correlated, multicollinearity among tract measures was evaluated to ensure they could be included in the same regression models. Variance inflation factors (VIF) were calculated for FA and MD from right and left hemispheres for each tract. Results of this analysis suggest there were no multicollinearity issues (all VIF<4.0)

To account for head motion in DWI, average T1 and T2 translation and rotation motion parameters were calculated by TRACULA. Spearman correlations were calculated to test for monotonicity among head motion and DTI measures. Average translation at T1 was related to T1 left uncinate FA (r= -0.32, p=0.02), forceps major FA (r=0.29, p=0.04) and MD (r= -0.45, p=0.00). Average rotation at T1 was related to T1 right anterior cingulum MD (r=0.32, p=0.02). Average Rotation at T2 was related to T2 left uncinate FA (r=-0.35, p=0.01) and MD (r= 0.42, p=0.00), left posterior cingulum FA (r=-0.37, p=0.00), left anterior cingulum FA (r=-0.29, p=0.03) and MD (r= 0.40, p=0.00), and right anterior cingulum MD (r=0.28, p=0.04).

Since head motion was correlated with several tract DTI measures at T1, the first set of general linear models included T1 head motion as the only covariate. Results of this analysis show that T1 right anterior cingulum FA was a significant predictor of T2 re-experiencing symptoms (t(54)=2.51, p=0.01; Figure 5), such that greater integrity was related to greater symptoms. In addition, T1 right uncinate fasciculus FA was a significant predictor of T2 arousal symptoms (t(52)=2.57, p=0.01; Figure 6), such that greater integrity was related to greater

symptoms. No other T1 tract integrity measures were significant predictors of T2 PTSD symptoms (total or subscales) (all *p's* > 0.05).

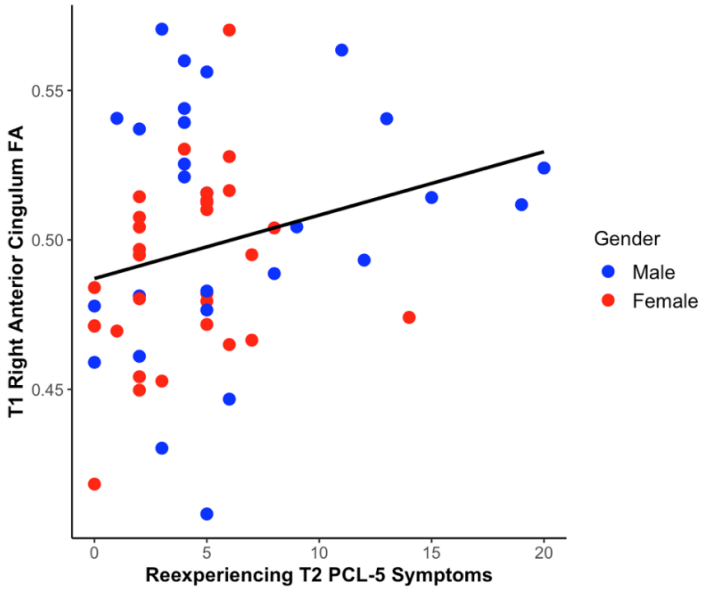

Figure 5. Greater right anterior cingulum integrity at T1 is predictive of greater T2 re-experiencing symptoms. FA, Fractional Anisotropy; PCL-5, PTSD Checklist Civilian; T1, 2-weeks post-trauma; T2, 6-months post-trauma.

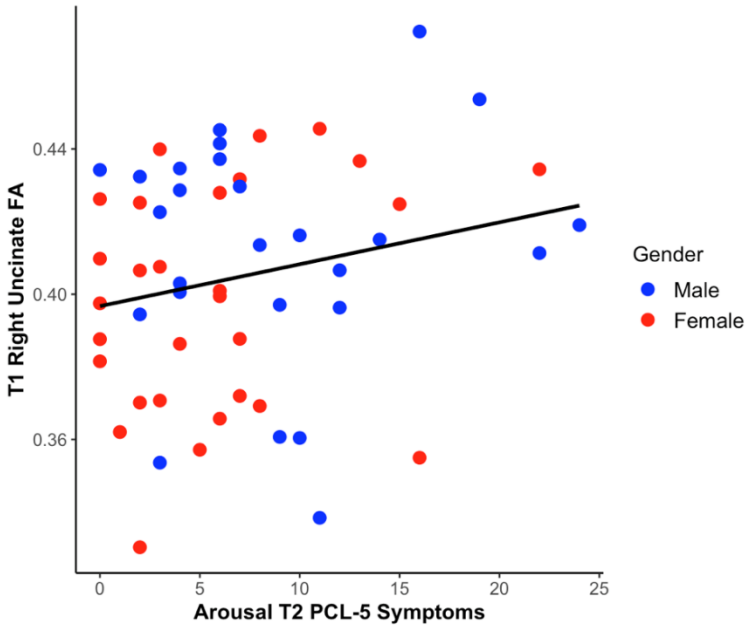

Figure 6. Greater right uncinate fasciculus integrity at T1 is predictive of greater T2 arousal symptoms. FA, Fractional Anisotropy; PCL-5, PTSD Checklist Civilian; T1, 2-weeks post-trauma; T2, 6-months post-trauma.

The second set of general linear models were run the same as the first, but in addition to T1 head motion, gender and age were included as covariates to account for potential gender (Montag et al., 2012; Kranz et al. 2014; Hsu et al., 2008; Menzler et al., 2011) and age differences (Lebel & Beaulieu, 2011; Hsu et al., 2008) that have been well documented in the tracts of interest. In addition, to control for baseline PTSD symptoms, T1 PCL-5 scores to control for baseline PTSD symptoms at the time of the DTI scan were also included. For the purposes of the current study, PCL-5 scores were used rather than LEC scores because the LEC reflects the number of instances of trauma a person has experienced rather than the symptoms that result from those traumatic experiences. For reference, correlations of LEC with tract DTI measures are reported in Table 2.

Table 2 Correlation Coefficients of DTI measures with PTSD symptoms and Trauma Exposure at T1 (n=57)

Tract	Hemisphere		PCL-5 Re-experiencing	PCL-5 Avoidance	PCL-5 Cognition	PCL-5 Arousal	PCL-5 Total	Total LEC
UNC	LH	FA	0.11	0.05	0.10	0.08	0.10	-0.16
		MD	-0.14	0.00	-0.02	0.14	0.00	-0.01
	RH	FA	0.19	0.13	0.20	0.22	0.22	0.06
		MD	0.03	0.06	0.09	0.09	0.10	-0.03
CCG	LH	FA	0.09	**0.33***	0.14	**0.28***	0.20	-0.25
		MD	-0.17	**-0.29***	-0.17	-0.17	-0.20	-0.05
	RH	FA	0.18	0.25	0.17	0.18	0.19	-0.05
		MD	-0.23	-0.24	-0.18	-0.20	-0.21	-0.08
CAB	LH	FA	0.14	0.11	0.02	0.17	0.11	-0.21
		MD	0.04	0.04	0.03	-0.06	0.02	-0.11
	RH	FA	0.00	0.07	0.02	0.16	0.08	-0.01
		MD	0.04	0.02	0.02	-0.13	-0.02	0.04
FMINOR		FA	-0.02	0.01	-0.03	-0.11	-0.04	**0.28***
		MD	-0.06	-0.12	0.03	-0.04	-0.02	-0.18
FMAJOR		FA	-0.18	-0.09	-0.18	-0.06	-0.12	0.14
		MD	-0.01	-0.02	-0.01	0.12	0.01	-0.07

***p<.05**

PCL-5, PTSD Checklist Civilian; LEC, Life Events Checklist; FA, fractional anisotropy; MD, mean diffusivity; UNC, uncinate fasciculus; CCG, cingulum cingulate gyrus; CAB, cingulum angular bundle; FMAJOR, forceps major; FMINOR, forceps minor.

Finally, to account for substance use, Spearman correlations were calculated for DAST and AUDIT scores and DTI measures and PTSD symptoms. T1 drug use was related to T1 left uncinate MD (r=0.29, p=0.03) and right anterior cingulate MD (r=0.27, p=0.04). T1 drug and alcohol use were not related to T1 PCL-5 symptoms. T2 alcohol use was related to T2 right uncinate FA (r=-0.39, p<0.05) and MD (r=0.43, p<0.05). T2 drug and alcohol use were not related to PCL-5 symptoms. Given the relationship of substance use to the integrity of some tracts of interest, T1 DAST and AUDIT scores were also included as covariates into the general linear models described above. No T1 tract integrity measures were significant predictors of T2 symptoms. However, there were several gender, baseline PTSD symptoms, and drug use effects in predicting symptoms. For complete results of this analysis, see Table 3. The effects of gender and baseline PTSD symptoms can be explained by the sample differences previously described. The effects of substance use on T2 symptoms are beyond the scope of the current study and therefore will not be discussed in detail.

Table 3

Aim 1 General Linear Models with all covariates (T1 DTI predicting T2 PCL-5 symptoms)

		Total	Re-experiencing	Avoid	Cognitive	Arousal
		t(p)	t(p)	t(p)	t(p)	t(p)
Uncinate Fasciculus						
Intercept		0.20 (0.83)	0.03 (0.97)	0.38 (0.70)	-0.90 (0.92)	0.56 (0.57)
RH	FA	0.57 (0.56)	0.28 (0.77)	-0.27 (0.78)	0.61 (0.54)	0.97 (0.33)
	MD	0.14 (0.88)	0.31 (0.75)	-0.43 (0.66)	-0.03 (0.97)	0.49 (0.62)
LH	FA	-1.80 (0.07)	-1.82 (0.07)	-0.99 (0.32)	-1.52 (0.13)	-1.75 (0.08)
	MD	0.72 (0.47)	0.93 (0.35)	0.96 (0.33)	1.05 (0.29)	-0.37 (0.70)
Age		-0.15 (0.87)	0.43 (0.66)	-0.33 (0.73)	0.51 (0.61)	-1.33 (0.19)
Gender		**-2.97 (0.00)***	**-3.15 (0.00)***	-1.17 (0.24)	**-3.07 (0.00)***	**-2.41 (0.02)***
T1 PCL Symptoms		**2.07 (0.00)***	**2.25 (0.02)***	1.93 (0.06)	**2.63 (0.01)***	**3.03 (0.00)***
T1 DAST		**-2.35 (0.02)***	**-2.67 (0.01)***	-1.52 (0.13)	**-2.67 (0.01)***	-1.36 (0.18)
T1 AUDIT		-0.89 (0.37)	-0.84 (0.40)	-1.02 (0.31)	-0.30 (0.76)	-1.14 (0.25)
T1 Rotation		0.60 (0.54)	-0.02 (0.98)	0.34 (0.73)	0.74 (0.46)	0.84 (0.40)
T1 Translation		-1.42 (0.16)	-0.39 (0.69)	-0.67 (0.50)	-1.42 (0.16)	-1.83 (0.07)
Posterior Cingulum						
Intercept		0.92 (0.36)	0.44 (0.65)	0.53 (0.59)	0.61 (0.54)	1.45 (0.15)
RH	FA	-0.07 (0.94)	0.26 (0.79)	-0.71 (0.47)	-0.25 (0.80)	-0.12 (0.89)
	MD	0.72 (0.47)	1.04 (0.30)	0.73 (0.46)	0.35 (0.72)	0.55 (0.57)
LH	FA	-0.51 (0.60)	-0.16 (0.87)	-0.03 (0.97)	-0.12 (0.89)	-1.24 (0.22)
	MD	-1.33 (0.18)	-1.18 (0.24)	-0.73 (0.46)	-0.79 (0.43)	-1.55 (0.12)
Age		0.12 (0.90)	0.56 (0.57)	-0.40 (0.68)	0.41 (0.67)	-0.76 (0.45)
Gender		**-3.09 (0.00)***	**-2.92 (0.02)***	-1.16 (0.25)	**-2.77 (0.00)***	**-3.18 (0.00)***
T1 PCL Symptoms		**3.53 (0.00)***	**2.13 (0.04)***	**2.50 (0.01)***	**2.81 (0.00)***	**4.34 (0.00)***
T1 DAST		**-2.14 (0.03)***	**-2.42 (0.02)***	-1.01 (0.31)	**-2.18 (0.03)***	**-1.71 (0.09)**
T1 AUDIT		-0.94 (0.35)	-0.92 (0.36)	-0.80 (0.42)	**-0.30 (0.76)**	**-1.47 (0.14)**
T1 Rotation		1.22 (0.22)	0.78 (0.43)	1.01 (0.31)	1.06 (0.29)	1.28 (0.20)
T1 Translation		-1.24 (0.22)	-0.38 (0.70)	-0.66 (0.50)	-1.03 (0.30)	-1.84 (0.07)
Anterior Cingulum						
Intercept		-0.40 (0.68)	-0.29 (0.77)	-0.88 (0.38)	-0.10 (0.92)	-0.20 (0.83)
RH	FA	0.92 (0.35)	1.09 (0.28)	0.95 (0.34)	0.44 (0.66)	1.01 (0.31)
	MD	1.25 (0.21)	1.10 (0.27)	-0.20 (0.84)	1.03 (0.30)	1.66 (0.10)
LH	FA	-0.37 (0.70)	-0.28 (0.77)	0.35 (0.72)	-0.36 (0.71)	-0.75 (0.45)
	MD	-0.99 (0.32)	-1.13 (0.26)	0.67 (0.50)	-0.88 (0.38)	-1.39 (0.17)
Age		-0.55 (0.58)	0.11 (0.90)	-0.51 (0.60)	0.03 (0.97)	-1.65 (0.10)
Gender		**-2.56 (0.01)***	**-2.47 (0.01)***	-0.96 (0.33)	**-2.53 (0.01)***	**-2.21 (0.03)***
T1 PCL Symptoms		**3.71 (0.00)***	**2.69 (0.01)***	**2.34 (0.02)***	**3.43 (0.00)***	**4.01 (0.00)***
T1 DAST		**-2.05 (0.04)***	**-2.17 (0.03)***	-0.76 (0.44)	**-2.26 (0.02)***	-1.46 (0.14)
T1 AUDIT		-0.94 (0.34)	-0.96 (0.34)	-0.83 (0.40)	-0.38 (0.70)	-1.20 (0.23)
T1 Rotation		0.73 (0.46)	0.85 (0.85)	0.17 (0.86)	0.80 (0.42)	1.01 (0.31)
T1 Translation		-0.61 (0.54)	0.74 (0.74)	0.26 (0.79)	-0.64 (0.52)	-1.44 (0.15)

Forceps Minor						
Intercept		0.59 (0.55)	0.17 (0.86)	-0.27 (0.78)	0.88 (0.38)	0.81 (0.41)
	FA	1.32 (0.19)	1.67 (0.10)	1.61 (0.11)	0.95 (0.34)	1.01 (0.31)
	MD	-0.91 (0.36)	-0.69 (0.49)	-0.05 (0.95)	-1.23 (0.22)	-0.84 (0.40)
Age		0.48 (0.63)	1.03 (0.30)	-0.04 (0.96)	1.01 (0.31)	-0.45 (0.64)
Gender		**-2.56 (0.01)***	**-2.54 (0.01)***	-0.73 (0.46)	**-2.68 (0.01)***	**-2.35 (0.02)***
T1 PCL Symptoms		**3.14 (0.00)***	**2.21 (0.03)***	1.74 (0.08)	**3.32 (0.00)***	**3.43 (0.00)***
T1 DAST		**-2.25 (0.02)***	**-2.75 (0.00)***	-1.55 (0.12)	**-2.42 (0.01)***	-1.37 (0.17)
T1 AUDIT		-0.56 (0.57)	-0.44 (0.65)	-0.60 (0.54)	-0.03 (0.97)	-1.06 (0.29)
T1 Rotation		0.97 (0.33)	0.45 (0.65)	0.77 (0.44)	1.00 (0.31)	1.02 (0.30)
T1 Translation		-1.11 (0.26)	-0.08 (0.93)	-0.59 (0.55)	-1.12 (0.26)	-1.66 (0.10)
Forceps Major						
Intercept		0.42 (0.67)	0.60 (0.55)	-1.22 (0.22)	0.91 (0.36)	0.62 (0.53)
	FA	0.54 (0.58)	0.45 (0.65)	1.76 (0.08)	-0.22 (0.82)	0.53 (0.59)
	MD	-0.40 (0.68)	-0.80 (0.42)	1.17 (0.24)	-0.80 (0.42)	-0.46 (0.64)
Age		-0.70 (0.48)	-0.21 (0.83)	-0.31 (0.75)	-0.31 (0.75)	-1.53 (0.13)
Gender		**-2.51 (0.01)***	**-2.44 (0.01)***	-0.49 (0.62)	**-2.79 (0.00)***	**-2.29 (0.02)***
T1 PCL Symptoms		**2.81 (0.00)***	2.00 (0.05)	**2.07 (0.04)***	**2.75 (0.00)***	**3.10 (0.00)***
T1 DAST		-1.26 (0.21)	-1.54 (0.12)	-0.97 (0.33)	-1.24 (0.21)	-0.81 (0.41)
T1 AUDIT		-1.09 (0.27)	-1.20 (0.23)	-0.77 (0.44)	-0.63 (0.52)	-1.32 (0.19)
T1 Rotation		0.82 (0.41)	0.31 (0.75)	0.87 (0.38)	0.87 (0.38)	0.76 (0.44)
T1 Translation		-1.08 (0.28)	-0.17 (0.85)	-0.36 (0.71)	-1.12 (0.26)	-1.56 (0.12)

PCL-5, PTSD Checklist Civilian; DAST, Drug Abuse Screening Test; AUDIT, Alcohol Use Disorders Identification Test; RH, right hemisphere; LH, left hemisphere; FA, fractional anisotropy; MD, mean diffusivity, *p<.05.

Aim 1 Whole Brain Analysis:

Results of the correlations of whole-brain FA maps with total T2 PTSD symptoms are depicted in Figure 8. Notable results include clusters where greater FA (greater integrity) at T1 is related to greater T2 PTSD symptoms in the cingulum, superior and inferior longitudinal fasciculi, genu and splenium of the corpus callosum, thalamic radiation, and in cortical association tracts. There are also several clusters where lesser T1 FA (lesser integrity) is related to greater T2 PTSD symptoms including the corticospinal tract, corpus callosum, and cortical association tracts.

Similarly, results of the correlations of whole-brain MD maps with total T2 PTSD symptoms are depicted in Figure 9. Some clusters where greater MD (lesser integrity) at T1 is related to greater T2 PTSD symptoms include cortical association tracts, and the corpus callosum. There are also several clusters where lesser T1 MD (greater integrity) is related to greater T2 PTSD symptoms including the corona radiata, internal capsule, and longitudinal fasciculi.

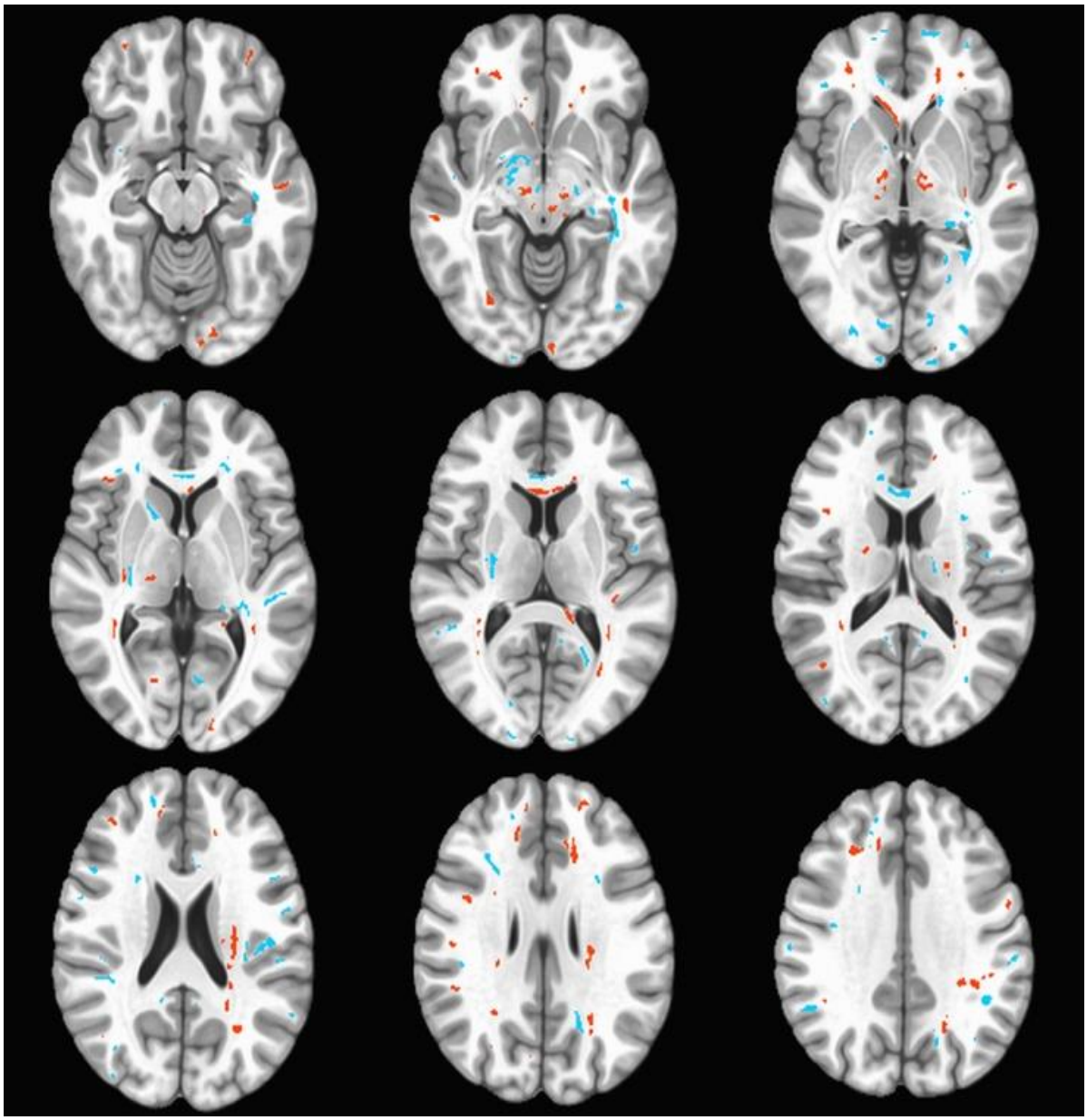

Figure 8. Axial slices of VBA results depicting changes in FA maps at T1 as they relate to T2 PCL-5 total symptom severity. Red clusters indicate areas where greater FA is related to greater symptom severity. Blue clusters indicate areas where greater FA is related to lesser symptom severity.

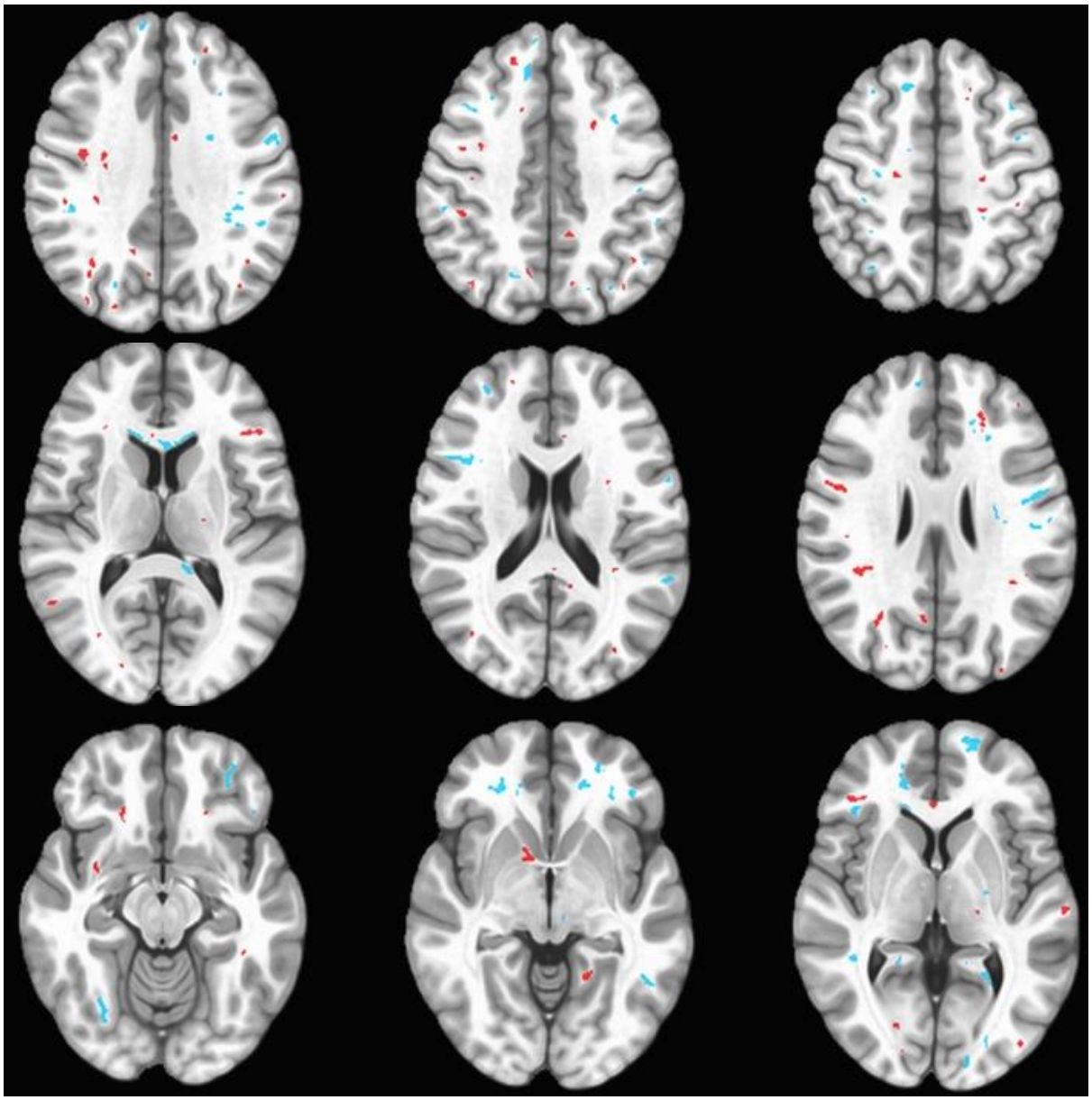

Figure 9. Axial slices of VBA results depicting changes in MD maps at T1 as they relate to T2 PCL-5 total symptom severity. Red clusters indicate areas where greater MD is related to greater symptom severity. Blue clusters indicate areas where greater MD is related to lesser symptom severity.

Aim 2 Results: Do T1 and T2 DTI measures vary with PTSD symptoms over time?

In the tract-based analysis, linear mixed effects (LME) models were used to examine the relationship of change in white matter integrity and PTSD symptoms over time. This statistical method was chosen due to the ability of LME modeling in handle unbalanced and missing data across time points or variables. It is also a superior method to repeated measures ANOVA for highly correlated longitudinal data as fixed effects are permitted to vary randomly for each individual (Bernal-Rusiel, et al., 2013). For each LME, PTSD symptoms from the PCL were the outcome variable and DTI measures (FA and MD) and time (T1 and T2) were the fixed effects, with subject as the random factor. Similar to the Aim 1 analysis, since there were no *a priori* hypotheses regarding hemispheric differences nor were there hypotheses regarding specific differences in FA and MD separately as well as to minimize the penalty for multiple comparisons both left and right hemispheres and both FA and MD measures for each tract were included together in each model:

$$PCL\text{-}5\ (T2) \sim Time * [RH\_UF\_FA\ (T1) + RH\_UF\_MD\ (T1) + LH\_UF\_FA\ (T1) + LH\_UF\_MD\ (T1)] \mid subject$$

Both main effects and interactions of DTI measures with time were investigated. Separate LME were run for each combination of PCL-5 scores (i.e. total score, each of 4 subscales) and white matter tract for a total of 25 LME models (5 tracts x 5 symptom clusters).

Like in Aim 1, the first set of LMEs only included head motion as covariates of no interest. Results of this analysis show a significant interaction of time and right anterior cingulum MD related to total ($F(1, 99)= 6.62$, $p=0.01$; Figure 10A), re-experiencing ($F(1, 99)=4.42$, $p=0.03$; Figure 10B), cognitive ($F(1,99)= 7.20$, $p=0.008$; Figure 10C), and arousal symptoms ($F(1,99)=6.43$ $p=0.01$; Figure 10D). Greater MD (less integrity) of the anterior cingulum over time was related to greater total, re-experiencing, and cognitive symptoms, and

lesser arousal symptoms over time. There was also a significant interaction of time and forceps major MD and arousal symptoms ($F(1,99)=3.99$, $p=0.04$; Figure 11) such that greater MD (less integrity) was related to increased arousal symptoms over time. Finally, there was a main effect of time such that re-experiencing symptoms reduced over time (all p's < 0.01). No other tracts were related to symptoms over time.

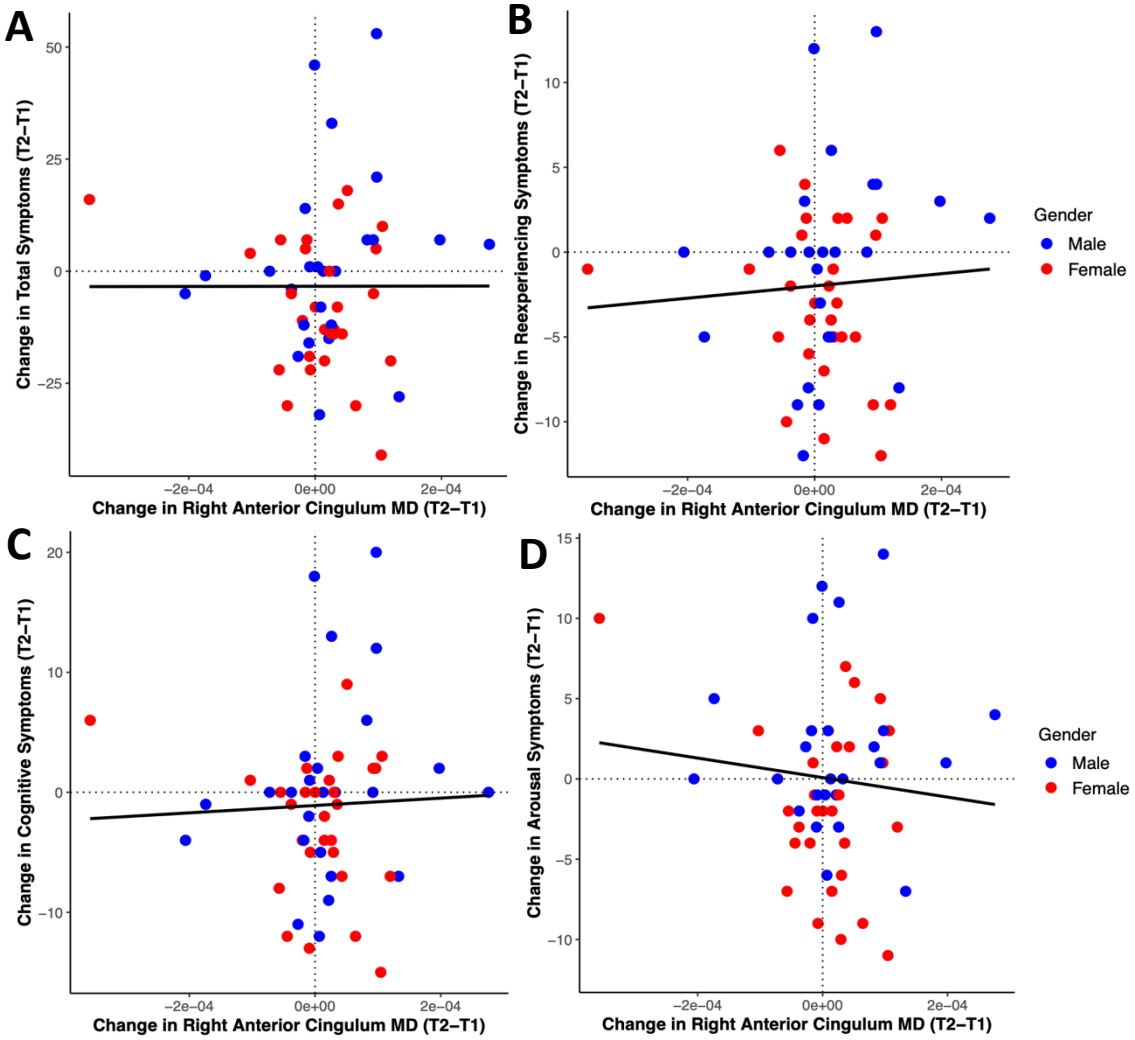

Figure 10. Changes in right anterior cingulum MD over time in relation to changes in A) total, B) re-experiencing, C) cognitive, and D) arousal symptoms over time. Change was calculated by subtracting T1 integrity measures and symptoms from T2 measures. Dotted lines indicate where there is no change in symptoms or integrity measures over time. Solid black lines show regression lines, though regression was not the statistical analysis performed on this data, these plots merely show the direction of integrity changes over time as they relate to changes in symptoms. Positive slopes here indicate that decreased integrity (increased MD) of the anterior cingulum over time is related to increased total, re-experiencing, and cognitive PTSD symptoms over time; whereas negative slopes indicate decreased integrity over time related to decreased arousal symptoms over time.

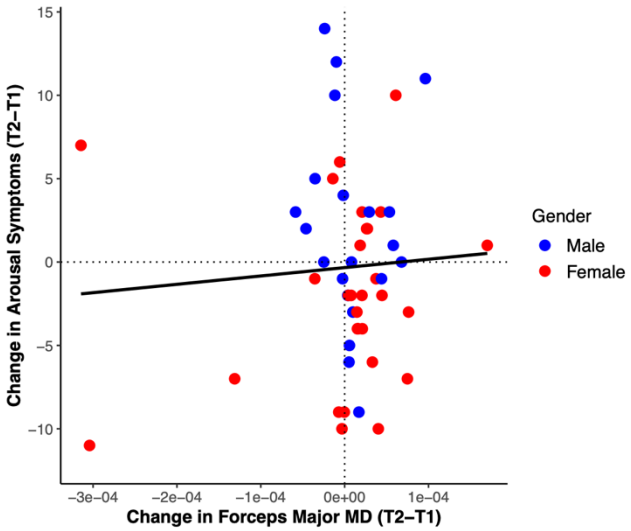

Figure 11. Changes in forceps major MD over time in relation to changes in arousal symptoms over time. Change was calculated by subtracting T1 integrity measures and symptoms from T2 measures. Dotted lines indicate where there is no change in symptoms or integrity measures over time. Solid black lines show regression lines, though regression was not the statistical analysis performed on this data, these plots merely show the direction of integrity changes over time as they relate to changes in symptoms. The positive slopes here indicates that decreased integrity (increased MD) of the forceps major over time is related to increased arousal PTSD symptoms over time.

The second set of LMEs added age, gender, and substance use as covariates of no interest. Results of this analysis show a significant interaction of time and right anterior cingulum MD related to Total ($F(1, 92)= 6.95$, $p=0.009$), re-experiencing ($F(1, 92)=4.77$, $p=0.03$), cognitive ($F(1,92)= 6.87$, $p=0.01$), and arousal symptoms ($F(1,92)=6.93$ $p=0.009$). There was also significant interactions of time and forceps major FA related to total ($F(1,88)= 4.01$, $p=0.04$; Figure 12A), and re-experiencing symptoms ($F(1,88)= 4.11$, $p=0.04$; Figure 12B). Increased FA (greater integrity) of the forceps major was related to decreased total symptoms and more specifically re-experiencing symptoms over time.

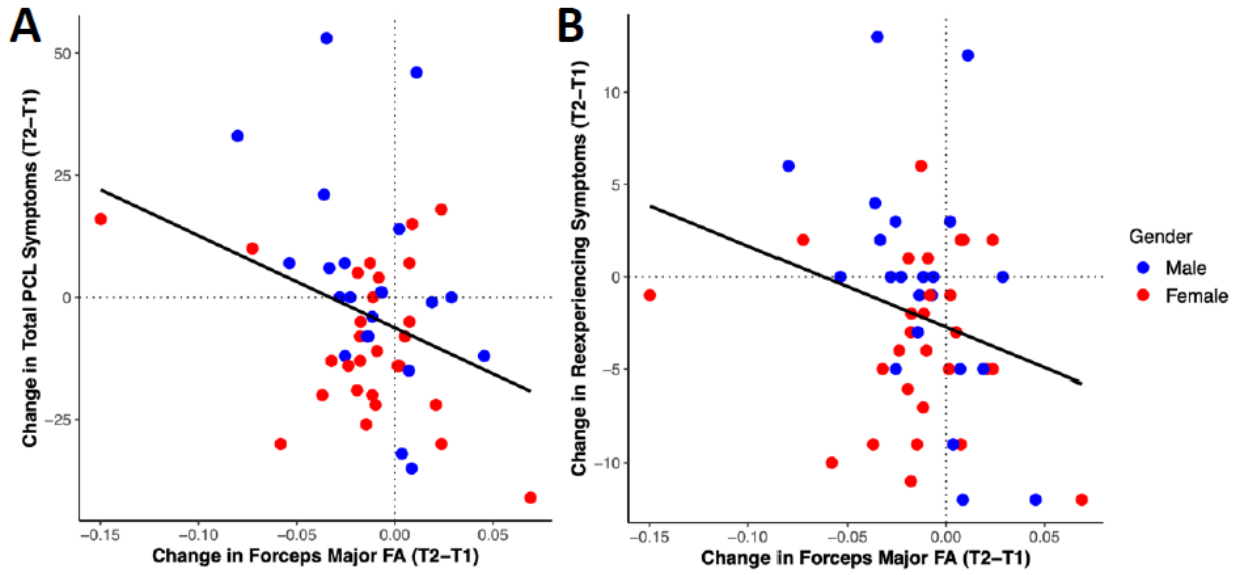

Figure 12. Changes in forceps major FA over time in relation to changes in A) total, and B) re-experiencing symptoms over time. Change was calculated by subtracting T1 integrity measures and symptoms from T2 measures. Dotted lines indicate where there is no change in symptoms or integrity measures over time. Solid black lines show regression lines, though regression was not the statistical analysis performed on this data, these plots merely show the direction of integrity changes over time as they relate to changes in symptoms. Negative slopes depicted here indicate that increased integrity (increased FA) of the forceps major over time is related to decreases in total and re-experiencing PTSD symptoms over time.

Aim 2 Whole Brain Analysis:

Results of the correlations of whole-brain change score maps with change in total T2 PTSD symptoms are depicted in Figure 13. Compared to Aim 1 analysis there are significantly fewer clusters that survive correction. Notable results include clusters where increased FA (increased integrity) is related to increased total PTSD symptoms over time in the forceps major, cingulum, superior and inferior longitudinal fasciculi, and thalamic radiation. There are also several clusters where decreased FA is related to decreased total PTSD symptoms including the inferior longitudinal fasciculus, forceps major, and corticospinal tract. Similarly, results of the correlations of whole-brain change score MD maps with change in total PTSD symptoms are depicted in Figure 14. Some clusters where increased MD (decreased integrity) is related to greater T2 PTSD symptoms over time include superior and inferior longitudinal fasciculus,

uncinate fasciculus, and cortical association tracts. There are also several clusters where decreased MD (increased integrity) is related to decreased total PTSD symptoms over time including the forceps major and superior longitudinal fasciculus.

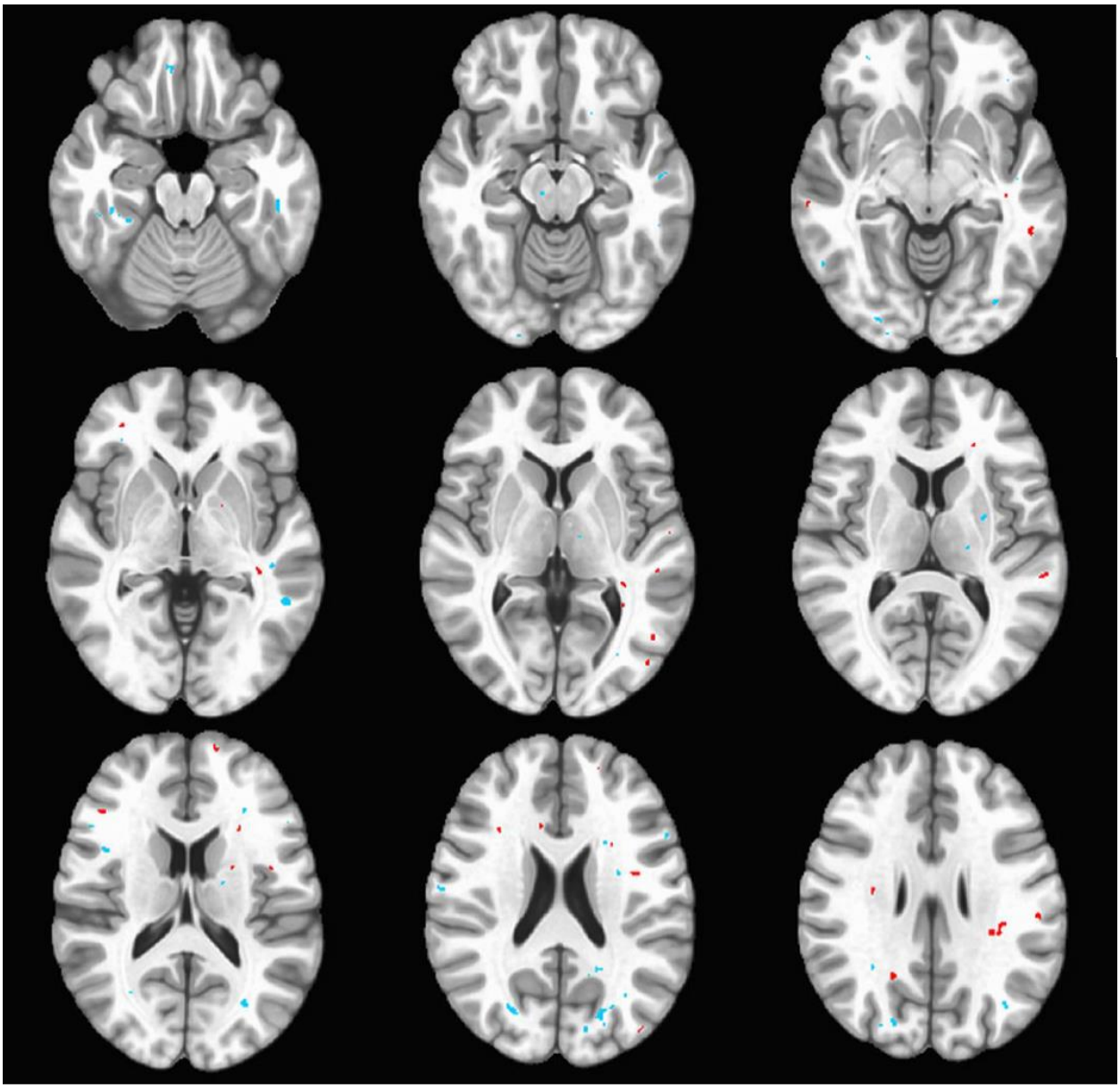

Figure 13. Axial slices of VBA results depicting changes in FA maps as they relate to change in T2 PCL-5 total symptom severity over time. Red clusters indicate areas where increased FA (increased integrity) over time is related to increased symptom severity over time. Blue clusters indicate areas where decreased FA (decreased integrity) over time is related to decreased symptom severity over time.

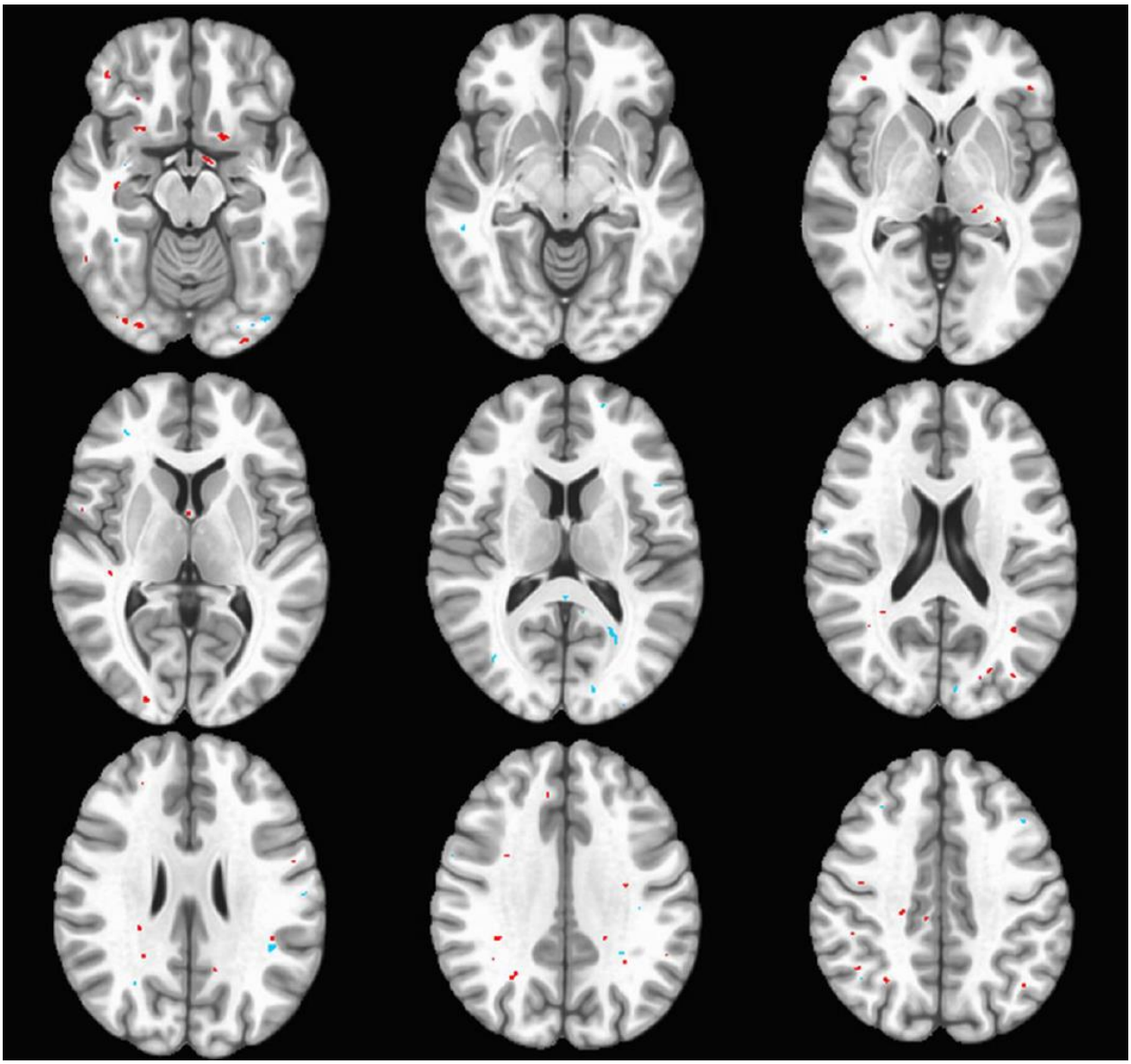

Figure 14. Axial slices of VBA results depicting changes in MD maps as they relate to change in T2 PCL-5 total symptom severity over time. Red clusters indicate areas where increased MD (decreased integrity) over time is related to increased symptom severity over time. Blue clusters indicate areas where decreased MD (increased integrity) over time is related to decreased symptom severity over time.

Discussion

The current study investigated structural connectivity of the brain in the aftermath of trauma to understand how structural changes may relate to PTSD development and symptoms over time. Based on previous literature, I expected decreased integrity of the cingulum and CC at T1 to be related to greater overall PTSD symptom severity and more specifically negative cognitive or mood symptoms and intrusive symptoms at T2. I also expected decreased UF integrity at T1 would be related to symptom severity at T2 and more specifically avoidance and negative cognitive or mood symptoms. I also predicted changes in these tracts over time would correspond to changes in symptom severity.

Tract-Based Analysis

The first main result of Aim 1 was that *increased* integrity of the right anterior cingulum at T1 was predictive of *greater* re-experiencing symptoms at T2. Given the limited amount of longitudinal research on this topic, I had hypothesized decreased integrity of the cingulum would be related to greater intrusive symptoms based on the results of Hu et al. (2016) who showed MVC survivors showed acute decreased integrity of the cingulum was related to greater symptom severity at a 6-month follow up. The results of the current study would suggest integrity of the cingulum is predictive of symptoms in the opposite direction. However, this result is supported by others, albeit not in a longitudinal framework, who have found increased cingulum integrity is related to PTSD symptom severity (Abe et al., 2006; Reuveni et al., 2016; Kennis et al., 2016; Bierer et al., 2015).

Interestingly, in Aim 2, *decreased* integrity of the right anterior cingulum over time was related to *increased* total, re-experiencing, and cognitive symptoms, and lesser arousal symptoms over time. This result is contrary to one of the few other longitudinal studies to date who found

veterans with PTSD showed increased integrity of this tract over time (Kennis et al., 2015). However, impaired integrity of the anterior cingulum over time is complementary to the results of Cardenas et al. (2011) who showed greater gross tissue atrophy over time in veterans with PTSD compared to those without. Similarly, O'Doherty et al. (2017) and Hu et al., (2016) also found impaired integrity of this region was related to greater PTSD symptoms in trauma survivors, though not in a longitudinal study design.

This change in the direction of the relationship of anterior cingulum integrity with symptoms is noteworthy. Acutely, *greater* integrity of this tract is related to *greater* chronic symptoms; however, over time it was *decreased* integrity that related to *increased* symptoms. This change may suggest that in the acute stages of trauma white matter integrity is adaptive in one direction, but over time becomes maladaptive. In other words, short term lesser integrity of the anterior cingulum acutely may confer less risk of chronic PTSD symptoms, whereas if this reduced integrity persists over time it may confer greater risk of symptoms.

The anterior cingulum is the portion of the cingulum that runs the length of the cingulate gyrus connecting medial prefrontal cortices (mPFC) with the posterior cingulate cortex (PCC). Animal tracer studies have shown the mPFC to have many inputs from limbic structures, particularly the hippocampus, which are important for memory retrieval and consolidation (Gabbott et al., 2005). Functional connectivity studies have also shown activity of the mPFC to be modulated by salience (Rushworth et al., 2011). Together this suggests the mPFC coordinates responsivity to salience in an adaptive way given previous experiences (Euston, Gruber, McNaughton, 2012). The PCC has been shown in functional and structural connectivity studies to play a role in integrating information and activity from cortical and subcortical structures (Hamilton et al., 2015). The PCC is also a critical structure in the default mode network where it

has been implicated in internally focused thought (Leech & Sharp, 2014). Therefore, greater structural connectivity between the mPFC and PCC in the acute aftermath of trauma may be indicative of unregulated and maladaptive activity of self-referential thoughts and memories that over time may result in re-experiencing or intrusive PTSD symptoms. However, degradation of this tract over time lead to a reduction in top-down control of the prefrontal cortices over the PCC. This may leave the PCC unregulated and free to engage in activity that ultimately may lead to more symptoms.

The other main result for Aim 1 was that *greater* right UF integrity at T1 was related to *greater* T2 arousal symptoms. However, this finding is not in line with my hypothesis, or most previous research, as most have found that reduced integrity of the UF is related to poorer outcomes post-trauma (Jovanovic & Ressler, 2010; Von Der Heide et al., 2013; Olson et al., 2015; Koch et al., 2017; Hanson et al., 2015; Olson et al., 2017; Fani et al., 2017). The UF connects the temporal and frontal cortices through limbic structures (i.e. hippocampus, amygdala). It has been shown to be important in associative learning and episodic memory paradigms as well as in social-emotional processing (Von Der Heide et al., 2013). Given the connectivity of this pathway, some have proposed the UF plays a role in modifying behavior with real time information about the value of a representation or situation (Von Der Heide et al., 2013). Greater integrity of this tract may therefore result in inappropriate evaluation of a given stimulus or context as dangerous or related to prior trauma that could result in greater arousal symptoms (Jovanovic & Ressler, 2010; Von Der Heide et al., 2013; Olson et al., 2015; Koch et al., 2017). Similarly, aberrant connectivity along the UF could result in unregulated top-down control of prefrontal cortices over limbic structures responsible for emotional and trauma-related

reactivity that over time may manifest as re-experiencing or intrusive symptoms (Koch et al. 2017).

The other main result of Aim 2 was that *decreased* integrity of the forceps major was related to *increased* total, re-experiencing, and arousal symptoms over time. Notably, these results held even after accounting for age, gender, head motion, and substance use. This result is in line with previous cross-sectional research that has also found reduced integrity of the forceps major related to greater PTSD symptoms (Olson et al., 2017; Hu et al., 2016; Saar-Ashkenazy et al., 2016). However, the direction of integrity as it relates to symptoms is still unclear, as others have found increased integrity of this tract in those with PTSD (Li et al., 2016). The forceps major connects the occipital lobes through the splenium of the CC and is largely implicated in the integration of visual processing systems (Knyazeva, 2013; Hofer & Frahm, 2006). Given this connectivity, impaired integrity of this tract may give rise to increased visual re-experiencing symptoms such as flashbacks. The CC has also been implicated in the processing of emotions, and thus reduced integrity of this tract may underlie altered emotion processing that leads to greater arousal symptoms (Sun et al., 2015).

While the results of the anterior cingulum and forceps major in Aim 2 held after adding covariates, the results of the anterior cingulum and UF in Aim 1 did not. This suggests the predictive utility of white matter integrity is not that strong given that tract integrity measures as the primary predictors of chronic PTSD symptoms were not significant. However, given the effects of gender, baseline PTSD symptoms, and substance use covariates (Table 3), these and other variables should be examined as predictors of PTSD symptoms in future studies. Nonetheless, the results of the current study suggest perhaps the better way to examine the relationship of white matter integrity and symptoms is to examine them concurrently over time.

Whole Brain Voxel Based Analysis

Results of the whole brain VBA are quite diffuse as there does not seem to be any clear or particular patterns of white matter integrity correlations with PTSD symptoms for both Aim 1 and 2. Significant clusters are widespread and indicate mixed relationships with symptoms. Despite this, it is clear that there are regions outside of the 3 primary tracts of interest to this study where acute integrity measures are predictive of chronic PTSD symptoms. Some of these regions include the superior and inferior longitudinal fasciculi, thalamic radiation, cortical association, and corticospinal tract. Previous work has implicated these tracts in PTSD, for example, Olson et al. (2017) found lesser integrity of the ILF in those with PTSD compared to trauma-exposed controls. The SLF, thalamic radiation integrity (Olson et al., 2017; Hu et al., 2016; Jenkins et al., 2016), and corticospinal integrity have also been linked to PTSD symptom severity and diagnosis (Hu et al., 2016).

The SLF is a long association fiber that links dorsal lateral and middle parietal regions with lateral frontal cortices and is thought to be related to attention and perception in PTSD (Thiebaut de Schotten et al., 2012; Daniels et al., 2013; Fani et al., 2012). The ILF is a long association fiber that roughly connects ventral occipital regions important for vision with ventral temporal cortices important for memory which may be related to the inability to suppress irrelevant sensory stimuli in PTSD (Schmahmann et al., 2007; Thiebaut de Schotten et al., 2012; Olson et al., 2017). Finally, the thalamic radiation links the internal capsule to the cortex and impaired integrity may be involved in the inability to downregulate fear circuitry common in PTSD (Olson et al., 2017; Sanjuan et al., 2013; Daniels et al., 2013).

While most previous research has found decreased integrity of these tracts is related to PTSD symptoms, there are still others who have reported increased integrity is related to

symptoms (Daniels et al., 2013). This and the results of the current study suggest more work needs to be done to clarify the relationship between whole brain white matter integrity and PTSD symptoms.

Limitations

The current study is not without limitations. The sample used in the current study is demographically quite heterogeneous. Similarly, mechanisms of traumatic injury varied across the sample which may confer different likelihoods of resilience or PTSD symptom development; however, the sample was underpowered to adequately assess for these differences. In addition, the sample had a substantial amount of previous trauma history as quantified by the LEC. This previous trauma may be a contributing factor in the PTSD symptoms and brain structural integrity assessed in the current study. It could be that the white matter changes reported here are the result of more chronic exposure to trauma rather than the single qualifying trauma that determined participant eligibility in the current study. Finally, there are a wide variety of other factors not included or discussed in the current study that may contribute to PTSD symptoms and brain changes over time (i.e. medical conditions, therapy, social support, genetics, etc.). Future research should continue to examine white matter as a predictor of PTSD symptoms in the aftermath of trauma in a larger sample where variability in sample characteristics can be more appropriately accounted for.

General Conclusions

The current study sought to understand the relationship between white matter integrity and PTSD symptoms in the aftermath of trauma. Results suggest acute white matter integrity of the anterior cingulum and UF may be potentially useful biomarkers in predicting chronic PTSD symptoms, though other variables may have more predictive utility. Similarly, changes in white

matter integrity over time, specifically in the anterior cingulum and forceps major, may track changes in symptoms over time. Thus, white matter integrity may be a useful biomarker in predicting and understanding PTSD symptoms post-trauma.

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