Title

Traumatic Brain Injury and Post-Traumatic Stress Disorder Symptoms in OEF/OIF Veterans : : A Combined Diffusion Tensor Imaging and Cortical Thickness Study

Author

Sorg, Scott Francis

Publication Date

2013

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Traumatic Brain Injury and Post-Traumatic Stress Disorder Symptoms in OEF/OIF Veterans: A Combined Diffusion Tensor Imaging and Cortical Thickness Study

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Clinical Psychology

by

Scott Francis Sorg

Committee in Charge:

University of California, San Diego

Professor Mark W. Bondi, Chair
Professor Lisa Delano-Wood
Professor Dean C. Delis
Professor Michael J. Taylor

San Diego State University

Professor Paul Gilbert
Professor Georg Matt

2013

The Dissertation of Scott Francis Sorg is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

San Diego State University

2013

DEDICATION

To my Grandfather,

James E. Sorg

May 1924 – April 2013

World War II Combat Veteran

Bronze Star Recipient

Artist

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to first thank my mentors, Drs. Mark Bondi and Lisa Delano-Wood, for their invaluable assistance throughout each stage of this project, for always supporting me to explore my research interests, and for their valued mentorship. I would also like to thank Dr. Michael J. Taylor, for his continued support through the various phases of my graduate study. I also thank the other members of my dissertation committee, Drs. Dean Delis, Paul Gilbert and Georg Matt for their assistance with this project. Also, I thank other members of the research lab including Drs. Dawn Schiehser and M.J. Meloy for their collaborative support, and Norman Luc and Elisa Lanni for their tireless efforts at subject recruitment, data collection and MRI scanning and processing. I extend a special appreciation to the Veterans who participated in this project for their initial self-sacrifice of serving in the US military and for their willingness to sacrifice their own time and energies toward furthering our understanding of TBI and PTSD. Finally, and most importantly, I thank my wife Joann. From traveling for those initial interviews to comprehensive examinations, from internship applications to dissertations, her unwavering love, support and sacrifice throughout each phase and milestone of my graduate studies has made this possible. With her love, and with our two sons, Jack and Charlie, I confidently look forward toward the next milestone.

The Introduction, Methods, Results and Discussion chapters were coauthored, in part, by Mark Bondi and Lisa Delano-Wood and are together being prepared for publication. Scott Sorg is the principal author of this material.

VITA

2005	Bachelor of Science, Northeastern University
2005-2007	Research Assistant, Massachusetts General Hospital
2007-2013	Graduate Research Assistant, University of California, San Diego
2010	Master of Science, San Diego State University
2013	Doctor of Philosophy, San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology

ABSTRACT OF THE DISSERTATION

Mild Traumatic Brain Injury and Post-Traumatic Stress Disorder Symptoms in OEF/OIF Veterans: A Combined Diffusion Tensor Imaging and Cortical Thickness Study

by

Scott Francis Sorg

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2013

San Diego State University, 2013

Professor Mark W. Bondi, Chair

Mild to moderate traumatic brain injury (TBI) is associated with increased risk of Post-Traumatic Stress Disorder (PTSD) in returning veterans of the Iraq and Afghanistan wars. Evidence from neuroimaging and neuropsychological studies suggests that PTSD and TBI may share a common neural network, and that disruption of this network may increase the risk of developing PTSD symptoms. The purpose of this study was to investigate the overlapping neuropsychological and neuroanatomical substrates of PTSD and TBI within a sample of veterans. We predicted that both TBI and increasing PTSD symptom severity would be associated with poorer neuropsychological performance,

lower integrity of white matter fiber bundles, and thinning of the frontal and temporal cortical regions.

A final sample of 38 veterans [ages 21-50; mild: *n*=33; moderate: *n*=5)] approximately four years removed from their TBI event(s) were compared to 17 veterans without a history of TBI. Assessments included neuroimaging, cognitive testing, a detailed TBI interview, and the Post-traumatic Stress Disorder Check List-Military Version (PCL-M). Cortical thickness measures were derived from structural MR imaging, and measures of white matter integrity were derived from diffusion tensor imaging.

Compared to control participants the TBI group had higher PCL-M scores ($p<.01$), lower white matter integrity in the cingulum bundle ($p<.01$) and the genu ($p<.05$), poorer memory performance and slower processing speed (p's$<.05$). Slower processing speed was associated with lower white matter integrity across many white matter pathways (p-values ranged from <.001–.05). Higher PCL-M scores were associated with cortical thinning of the left orbitofrontal cortex ($p<.05$) and unexpectedly with lower diffusion in the fornix ($p<.05$).

The results found little evidence for a disrupted "common network" between TBI and PTSD. Instead, they support unique and non-overlapping effects of TBI and PTSD symptom severity such that TBI is associated with deficits in memory and processing speed, and disrupted frontal white matter myelin integrity, whereas PTSD was associated with thinning of a cortical region associated with emotional regulation. Results suggest that persisting neurocognitive deficits may be associated with TBI-related disrupted myelin integrity to a greater degree than comorbid psychiatric illness.

INTRODUCTION

TBI and PTSD Rates in OEF/OIF Veterans

Both traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are considered hallmark injuries of the military conflicts in Iraq and Afghanistan. The increase in recorded TBI cases has been attributed to the greater survivability of previously fatal injuries, improved armor, and enhanced sensitivity to TBI diagnosis (Warden et al., 2005). Self-reported symptoms consistent with a diagnosis of TBI have been found in 15% of OEF/OIF veterans surveyed (Hoge et al., 2008), and clinician-certified TBI was recently reported in roughly 23% of soldiers in an Army brigade deployment to Iraq (Terrio et al., 2009). Rates of TBI greatly increase within populations of active duty military who sustained blast force injuries, the most common mechanism of injury sustained in current combat theaters (Owens, Kragh, Macaitis, Svoboda, & Wenke, 2007). Indeed, 59% of veterans treated for blast-related injuries were diagnosed with TBI in one study (Okie, 2005), and a recent survey found that approximately 79% of OEF/OIF veterans who sustained injury with a loss of consciousness reported blast or explosion as the primary injury source (Hoge et al., 2008).

Mild TBI (mTBI) is the most commonly diagnosed severity of TBI in these populations (Warden, 2006). Similarly, PTSD is the most commonly diagnosed mental illness in this population and has been reported in roughly 12-20% of returning service men and women (Hoge et al., 2004; Seal, Bertenthal, Miner, Sen, & Marmar, 2007). Comorbid mTBI and PTSD has recently been a topic of much discussion, and PTSD has been reported to occur more often in military personnel with TBI than in those with non-TBI injuries (Gaylord et al., 2008; Hoge et al., 2008). For example, in one study 44% of

those who reported having a loss of consciousness also screened positive for PTSD (Hoge et al., 2008). Moreover, rates of PTSD were significantly higher in OEF/OIF veterans who sustained blast injuries, itself a risk for mTBI, relative to those with non-blast injuries (Sayer et al., 2008). Unfortunately, although the clinical co-occurrence of these conditions is a frequent phenomenon, the relationship between mTBI and PTSD is not fully understood (Hoge et al., 2008; Schneiderman, Braver, & Kang, 2008).

PTSD in the Context of TBI

The differential diagnosis between PTSD and mTBI presents a significant challenge due in large part to the high degree of overlap between these two conditions (Bryant, 2001; Stein & McAllister, 2009). While parsing the etiology of the symptoms observed is considerably difficult, a body of research is emerging that has examined the onset of PTSD following TBI. For example, research performed on civilian populations suggests that the degree of posttraumatic amnesia and loss of consciousness associated with more severe forms of TBI may be protective factors that perhaps attenuate the development of PTSD—as the amnesia prevents the encoding of a memory of the traumatic event (Glaesser, Neuner, Lutgehetmann, Schmidt, & Elbert, 2004; Klein, Caspi, & Gil, 2003). Thus, these findings suggests that, although PTSD can occur in both mTBI and more severe TBI (Bryant & Harvey, 1995; Bryant & Harvey, 1999; Harvey & Bryant, 1998; Harvey & Bryant, 2000; Ohry, Rattok, & Solomon, 1996), persons with mTBI may have a greater risk for developing PTSD relative to those who sustain severe brain injuries and longer periods of unconsciousness (Klein et al., 2003).

It has recently been suggested that neuropathology secondary to TBI may contribute to the development of PTSD (Vasterling, Verfaellie, & Sullivan, 2009), and a causation model has been proposed to determine if psychiatric conditions following TBI are the result of disrupted biological processes secondary to injury (Hill, 1965; van Reekum, Streiner, & Conn, 2001). Rogers and Read (2007) and van Reekum et al. (2001) have posited that the following pieces of evidence are needed in order to associate psychiatric syndromes to underlying neurobiological pathology: 1) a strong association between the hypothesized contributing agent (e.g., TBI) and outcome (e.g., PTSD); 2) the presence of a biological gradient wherein greater severity produces poorer outcome; 3) consistent evidence supporting the association, 4) the establishment of a temporal sequence; 5) the relationships observed are consistent with a biological rationale, 6) supporting experimental evidence; and 7) analogous evidence. Some support for the biological link between TBI and PTSD has been found, but, to date, the data are very limited. In support of the first criterion, the incidence of PTSD in context of TBI is significantly higher than in the general population and is strongly associated with the occurrence of mTBI in OEF/OIF veterans, as previously discussed (Hoge et al., 2008; Rogers & Read, 2007). Establishing a temporal sequence of PTSD following mTBI in the warzone is difficult given that personnel may experience traumatic events prior to and after blast exposure. Tentative support for the presence of a biological gradient linking TBI severity to PTSD symptoms has been reported (Sojka, Stalnacke, Bjornstig, & Karlsson, 2006), although there is currently no convergent neuroimaging evidence linking TBI severity to PTSD symptom severity. Establishing such convergent linkages via imaging and neuropsychological methods is one of the primary aims of this study.

TBI in the Warzone

Blast injury refers to a range of injuries sustained from an explosive device (e.g., improvised explosive device [IED], grenade, or landmine). *Primary* blast injuries result from barotrauma—the rapid change in pressure relative to atmospheric levels caused by a blast wave (DePalma, Burris, Champion, & Hodgson, 2005) and commonly affects air-filled organs (e.g., lungs, ears) and air-fluid interfaces (e.g., bowels), though the direct contribution of blast waves to TBI remains unclear. *Secondary* blast injuries are blunt or penetrating injuries caused by projectiles or debris set into motion by the blast. *Tertiary* damage results from the victim being physically thrown into a hard surface as a result of the blast wave. Lastly, *quaternary* blast injuries cover a gamut of explosion related injuries including the victim being crushed by collapsed building debris, burns, and inhaling toxic gas (Dennis & Kochanek, 2007; DePalma et al., 2005).

Although the pathophysiology of TBI as a result of secondary, tertiary, and quaternary blast injury likely resembles that seen in non-military settings (e.g., motor vehicle accidents, falls; Dennis & Kochanek, 2007; D. Warden, 2006), the neurotraumatic effects of the primary blast wave is controversial and remains unresolved. This issue is particularly important when one considers that Kevlar helmets may protect soldiers from blunt force trauma, but may not adequately shield them from the effects of the blast wave. For instance, in a simulation study, the standard Kevlar helmet provided no additional protection from a blast wave than the skull alone (Nyein et al., 2010). Thus, to the extent that blast waves do have a deleterious effect on the brain, the absences of outward signs of trauma may mask the presence of brain injury (Okie, 2005).

Various mechanisms have been proposed by which primary blast force can cause TBI. For instance, barotrauma may produce arterial air emboli that cause damage when they reach the cerebral vasculature (Dennis & Kochanek, 2007). In animal studies, blast waves have been shown to lead to TBI even if the head is not directly affected by the blast (Cernak, Wang, Jiang, Bian, & Savic, 2001). The authors suggested that blast waves may oscillate through the torso and into the brain via large blood vessels, causing a surge in arterial or venous pressure that results in injury. Another hypothesis proposes that the high-pressure phase of the blast wave accelerates the skull, forcing the brain into the rigid skull surface. This impact is mirrored in a coup and contre-coup fashion as the lower pressure blast phase pulls the head in the opposite direction (Dennis & Kochanek, 2007). Clearly, blast TBI is complex, involving multiple mechanisms for injury as well as varying levels of severity. While it remains to be determined whether blast injury represents a distinct pathology from that observed in more typical blunt force mechanisms of injury, most evidence to date suggests that neural damage from blast induced TBI is similar to that of non-blast, closed head injuries (Cernak et al., 2001).

Neuronal Damage Following mTBI

Brain white matter is particularly vulnerable to all forms of TBI, including even very mild forms of neurotrauma (Bigler, 2001). Damage following TBI is thought to result from the tearing and shearing of nerve fibers from rapid acceleration and deceleration forces at the initial time of the injury (Park, Bell, & Baker, 2008) as well as from a delayed, secondary injury process which may account for the majority of damage following TBI (Park et al., 2008; Buki & Povlishock, 2006). This secondary injury process results from a cascade of cellular events set into motion by the rapid influx of

calcium following increased cell membrane permeability and disruption of sodium ion channels following the initial impact (Park et al., 2008; Buki & Povlishock, 2006). It is thought that both gray matter and white matter structures are affected by this dynamic process, resulting in axonal disconnection and cell death (Park et al., 2008).

Diffusion Tensor Imaging

In the absence of large lesions indicative of severe TBI, traditional MRI techniques are not thought to be sensitive to the presence of TAI, due to the relative homogeneity of the T1 signal within white matter. Recently, researchers have turned to diffusion tensor imaging (DTI) to investigate TAI *in vivo*. DTI is an MRI method that is sensitive to the movement of water molecules within brain structures. The pattern of water movement in a voxel can be isotropic, meaning that it moves equally in all directions, or may be anisotropic, meaning that the movement favors a particular orientation. In highly organized tissue, such as neural white matter, these patterns of molecular water movement can be used to describe the neuronal integrity of the tissue, a common index of which is *fractional anisotropy* (FA; Pierpaoli & Basser, 1996). FA values range from zero in voxels where the diffusion is equal in all directions, to one, in regions with a high degree of directional uniformity. Thus, higher FA values are indicative of healthy tissue with uniform structure, while relatively lower values suggest a disruption of this structure and tissue damage (Pierpaoli & Basser, 1996). DTI studies have consistently found evidence for disrupted white matter integrity consistent with TAI in frontal and limbic white matter regions in both mild and severe TBI populations (Arfanakis et al., 2002; Bendlin et al., 2008; Huisman et al., 2004; Kraus et al., 2007; Levin et al., 2008; Lipton et al., 2008; Sidaros et al., 2008; Wilde et al., 2006; Yuan et al.,

2007). Reductions in FA may result from a decrease in axial diffusivity (AD) (diffusion along the principal diffusion direction [along the axon]), an increase in radial diffusivity (diffusion perpendicular to the primary diffusion direction), or an additive or synergistic effect of the two. Although there is some debate as to the specific meaning of the component diffusion measures (Madler et al., 2008; Wheeler-Kingshott & Cercignani, 2009), AD has most commonly been interpreted as describing axonal integrity, and RD has been described as a proxy for myelin integrity (Song et al., 2003).

Gray Matter Atrophy and Cortical Thickness in TBI

Numerous neuroimaging studies have established that gross and local cortical gray matter volume loss is a common consequence following TBI (Bigler, 2001; Ding et al., 2008; Gale, Baxter, Roundy, & Johnson, 2005; Levine et al., 2008; Sidaros et al., 2009). While global atrophy is common, the greatest atrophy across individuals is found in the frontal and the anterior/mesial temporal lobes (Kim et al., 2008; Levine et al., 2008). Such findings are consistent with the observation that proximity to bony protrusions within the lower surfaces of the cranial vault makes these brain regions especially vulnerable to TBI (Hayes, Povlishock, & Singha, 1992). Most such studies focused on moderate to severe TBI, although this pattern of frontotemporal sensitivity was also demonstrated within a subgroup of mTBI patients who showed reduced volume in these regions compared to healthy age-matched controls (Levine et al., 2008). The majority of such studies used strictly volumetric analyses, though other measures may be sensitive to mTBI-induced atrophy.

Cortical thickness analysis has been shown to be a reliable measure of regional cortical atrophy (Rosas et al., 2002), and cortical thinning has been associated with

conditions known to affect cortical gray matter such Alzheimer's disease (Dickerson et al., 2009). Despite the sensitivity of cortical thickness measures to brain atrophy, only one group appears to have employed cortical thickness analysis in TBI. The studies published from this group focus on moderate to severe pediatric TBI and have reported diffuse reductions in cortical thickness along with correlations to cognitive measures (Bigler et al., 2010; Hanten et al., 2011; Merkley et al., 2008). No study to date has investigated cortical thickness measures in veterans with mTBI.

Brain Abnormalities in PTSD

Numerous neuroimaging studies have reported abnormal brain structure and function in persons with PTSD. PTSD has been associated with abnormal activation of cortical and subcortical regions involved in modulating emotional regulation, including frontal regions such as the anterior cingulate cortex (ACC; Shin et al., 2001), amygdala (Bremner, 2004; Protopopescu et al., 2005; Shin et al., 2005), medial prefrontal cortex (Liberzon & Sripada, 2008), and temporal lobe regions (Lindauer et al., 2008). Additionally, volumetric studies have shown an association between PTSD vulnerability and decreased hippocampal volume (Gilbertson et al., 2002), and decreased ACC volume (Rauch et al., 2003). Few studies have investigated cortical thickness in PTSD. In one study using Dutch veterans with PTSD, prefrontal lobe thickness was found to be thinner in the PTSD group compared to combat control participants without PTSD (Geuze et al., 2008). In another study, which included both Vietnam and Gulf War veterans, thinner cortex was found in the PTSD group in the cingulate, frontal, and temporal regions (Woodward, Schaer, Kaloupek, Cediel, & Eliez, 2009). Together, these findings suggest that disrupted circuitry in neural pathways that mediate emotional regulation may

underlie the manifestation of PTSD symptoms. Consistent with this view, significantly decreased white matter integrity in the anterior cingulum bundle of persons with PTSD relative to controls has been reported (Kim, Lyoo, Kim, Sim, Kim, Choi, Jeong, Covell, & Renshaw, 2005). This finding suggests that damage to the cingulum bundle may result in reduced inhibitory control of the ACC over the potentially over-responsive amygdala in PTSD (Kim et al., 2005).

Neuropsychological Functioning in mTBI and PTSD

Mild TBI.

As stated above, the majority of TBI cases are classified as mild (Cassidy et al., 2004), which is typically defined by minimal to no losses of consciousness, mild to negligible periods of posttraumatic amnesia, and Glasgow Coma Scale scores (if available) ranging from 13-15 (Bigler, 2008). Chronic neuropsychological impairment following mild traumatic brain injury (mTBI) is controversial and is often debated due in large part to the equivocal findings across mTBI studies. Although deficits in processing speed, attention, working memory, memory, and executive functions are often demonstrated in the acute phase following injury (Landre, Poppe, Davis, Schmaus, & Hobbs, 2006; McAllister & Arciniegas, 2002), the prevalence and severity of cognitive deficits in the post-acute phase are less clear. Meta-analytic and case-control studies have found support for chronic, albeit mild, deficits following mTBI in memory, working memory, and executive functions (Binder, Rohling, & Larrabee, 1997; Vanderploeg, Curtiss, & Belanger, 2005), although other studies have not found such associations (Dikmen et al., 2009; Ettenhofer & Abeles, 2009; Frencham, Fox, & Maybery, 2005). Despite these conflicting findings, it has been estimated that many mTBI victims, from

14-24%, continue to struggle with long-term difficulties in the post-acute phase such as difficulty with employment (Binder, 1997) or persistent post-concussive symptoms that have been associated with neurocognitive functioning (Ponsford et al., 2000; Sterr, Herron, Hayward, & Montaldi, 2006). Several factors have been linked with the occurrence of persistent post-acute difficulties including degree of injury as well as confounding psychiatric conditions such as depression and anxiety (Bigler, 2008; Dikmen, Machamer, & Temkin, 1993; Ponsford et al., 2000).

PTSD

Several studies have found an association between neuropsychological functioning and PTSD symptom severity. Deficits in sustained and focused attention (Jenkins, Langlais, Delis, & Cohen, 2000), response inhibition, executive functioning (Leskin & White, 2007; Stein, Kennedy, & Twamley, 2002), and memory (Brewin, Kleiner, Vasterling, & Field, 2007; Verfaellie & Vasterling, 2009) have been associated with PTSD diagnosis and/or symptom severity. However, the degree to which TBI-related cognitive impairments are associated with PTSD symptomatology remains unclear. One group of researchers has suggested that increases in intellectual functioning may lead to an increase in coping skills potential that may then attenuate PTSD vulnerability (McNally & Shin, 1995). This theory posits that deficits or depleted reserves in these areas secondary to mTBI may be associated with differential vulnerabilities to PTSD symptomatology. There have been few studies that have examined the combined effect of TBI and PTSD within military or veteran populations, although results of the few studies that have investigated both conditions have been largely inconsistent. For example, executive functioning performance was found to be

lower in an OEF/OIF PTSD+TBI group, relative to groups with either PTSD or TBI alone (Campbell et al., 2009). However, another recent study failed to show any group differences in memory or executive functioning performance between those with TBI and those with TBI and PTSD (Gordon, Fitzpatrick, & Hilsabeck, 2011). Given its frequent co-occurrence among our veterans, further research on the neuropsychological consequences of comorbid PTSD and TBI is needed to resolve this disparity.

Summary and Model

Recent research on both civilian and military populations, including OEF/OIF veterans, has found that mTBI is associated with an increased risk for developing PTSD (Hoge et al., 2008). A key component of PTSD is thought to be diminished frontal inhibition of limbic structures (Kim et al., 2005). Corresponding morphometric and functional imaging abnormalities in frontal lobe regions (e.g., volume reductions and cortical thinning in the ACC and the medial prefrontal gyrus) have been reported in persons with PTSD, as well as reduced white matter integrity within frototemporal limbic pathways (Geuze et al., 2008; Kim et al., 2005; Woodward et al., 2009). These same regions (i.e., the prefrontal cortex and temporal lobes) are consistently shown to be vulnerable to TBI (Kim et al., 2008; Levine et al., 2008). Thus, structural disruptions from the effects of mTBI looks to affect those regions also implicated in PTSD. Neuropsychological studies have also shown some convergence between these conditions, as deficits in working memory, executive functions, and memory have been reported in both PTSD and mTBI (Vasterling et al., 2009). Overall, the evidence suggests that the presentation of PTSD and symptoms following mTBI may share a common

neural network, and that disruption of this network (e.g., via mTBI) may increase the risk of developing PTSD symptoms following traumatic experiences.

The purpose of this study was to investigate the overlapping neuropsychological and neuroanatomical substrates of PTSD and mild to moderate TBI within a sample of OEF/OIF veterans. Furthermore, in an effort to explore a potential biological gradient between TBI and PTSD, a major goal of the current study was to determine the degree to which white matter injury and cortical thickness in returning OEF/OIF veterans with mTBI relates to PTSD symptom severity. We specifically hypothesized a weakening of the connection between, and reduced cortical thickness among, structures involved in emotional regulation as a consequence of brain injury. Additionally, whether and how neuropsychological impairment relates to PTSD was also investigated. It was expected that the TBI characteristics would be associated with brain and neuropsychological measures such that poorer cognitive functioning and compromised neurostructure would be associated with the presence and/or magnitude of TBI. Lastly, the interrelationships among white matter microstructure, cortical thickness, and cognition were investigated in an exploratory manner to better elucidate how these important variables may be associated with post-TBI psychiatric presentations.

Aims and Hypotheses

Aim 1. To investigate the degree to which white matter integrity relates to both PTSD symptomatology and mTBI status in OEF/OIF veterans, and to determine if similar regions are implicated in both conditions within this sample.

Hypothesis 1a. Measures of white matter integrity within frontal regions will be associated with greater PTSD symptom severity (PCL-M).

Hypothesis 1b. Measures of white matter integrity in frontal regions will differ between those with TBI and those without a history of TBI.

Hypothesis 1c. Measures of white matter integrity in frontal regions will be associated with TBI injury characteristics such as number of events, number of blast exposures, and presence of loss of consciousness.

Hypothesis 1d. The same regions that show a significant relationship between PTSD severity and white matter integrity will also show a relationship between mTBI characteristics and white matter integrity.

Aim 2. To examine the degree to which cortical thickness relates to both PTSD symptomatology and mTBI status in OEF/OIF veterans, and to determine if similar regions are implicated in both conditions within this sample.

Hypothesis 2a. Reduced cortical thickness in frontal regions implicated in TBI and PTSD (e.g., anterior cingulate cortex and orbitofrontal cortex) will be associated with greater PTSD symptom severity.

Hypothesis 2b. Reduced cortical thickness in frontal regions implicated in TBI and PTSD (e.g., anterior cingulate cortex and orbitofrontal cortex) differ between those with TBI and those without a history of TBI.

Hypothesis 2c. Reduced cortical thickness in frontal regions implicated in TBI and PTSD (e.g., anterior cingulate cortex and orbitofrontal cortex) will be associated with TBI injury characteristics such as number of events, number of blast exposures, and presence of loss of consciousness.

Hypothesis 2d. The same regions that show a significant relationship between PTSD severity and cortical thickness will also show a relationship between mTBI characteristics and cortical thickness.

Aim 3. To investigate the degree to which neuropsychological performance is related to both PTSD symptomatology and mTBI status in OEF/OIF veterans, and to determine if similar domains are implicated in both conditions within this sample.

Hypothesis 3a. Poorer performance on neuropsychological measures sensitive to mTBI (e.g., attention/working memory, executive functioning, and processing speed) will be associated with greater PTSD symptom severity.

Hypothesis 3b. Neuropsychological testing performance will be lower in the TBI group than the control group.

Hypothesis 3c: Neuropsychological testing performance in those domains associated with PTSD severity will be associated with TBI injury characteristics described above.

Hypothesis 3d. The same domains that show a significant relationship between PTSD severity and testing performance will also show a relationship between mTBI characteristics and testing performance.

The Introduction, Methods, Results and Discussion chapters were coauthored, in part, by Mark Bondi and Lisa Delano-Wood and are together being prepared for publication. Scott Sorg is the principal author of this material.

METHODS

Participants

Data for this project was gathered from ongoing studies of mTBI in returning OEF/OIF veterans being conducted by Drs. Lisa Delano-Wood and Dawn Schiehser. Forty-nine veterans with TBI histories were originally screened for participation in this study. Following application of exclusionary criteria, including exclusion of those with effort test results below published cutpoints, a final sample of 38 veterans with TBI participated. Another age-matched control group of OEF/OIF veterans with no reported history of TBI (n = 17) was also recruited for participation. Of note, the targeted sample size for the TBI group was 40, and was 20 for the control group. TBI participants were recruited from consecutive admissions for outpatient treatment of TBI or orthopedic injuries at the SDVAHS, and were identified as having TBI related to either blast or mechanical force. As part of their enrollment in the study, all patients meeting criteria for TBI completed detailed cognitive, neurologic, genetic, and psychosocial/clinical evaluations.

TBI group inclusion/exclusion criteria. OEF/OIF veterans diagnosed with a mild or moderate closed head TBI (n = 38) from either blast exposure (e.g., secondary to IED, land mine, or rocket grenade) or mechanical force (e.g., motor vehicle accident, or other closed head injury [blunt trauma]) were included in the study. The criteria delineated by Vanderploeg, Curtiss, & Belanger (2005) was used for classifying injury severity in TBI. Specifically, *mild TBI* (n = 33) was defined as: alteration or loss of consciousness (LOC) ≤ 30 minutes, if available an initial *Glasgow Coma Scale* (GCS; Teasdale & Jennett, 1974) score between 13-15, a post-traumatic amnesia (PTA) ≤ 24

hours, and no visible lesions on MRI or CT scan. *Moderate TBI* (n = 5) was defined as: LOC ≤ 6 hours, an initial GCS score between 9-12, a PTA ≤ 7 days, and either the presence or absence of focal lesions on MRI. Additionally, many participants may not report an overt loss of consciousness, but nonetheless report being dazed or disoriented for a period of time following a blast wave or a blow to the head. Such participants were included in the TBI group, consistent with previous publications (Hoge et al., 2008). No participants included in this study showed focal lesions on MRI.

Exclusion criteria included severe head injury (GCS ≤ 8); a prior history of other neurological disorder (e.g., multiple sclerosis, tumor, seizure disorder); developmental learning disability; current (within past 30 days) substance or alcohol abuse according to DSM-IV criteria; pre-injury metabolic or other diseases known to affect CNS functions; or contraindication to scanning (e.g., claustrophobia, shrapnel). In addition, participants with poor performance on effort testing, described in more detail below, were excluded from analyses.

Control group inclusion/exclusion criteria. OEF/OIF veterans who do not meet criteria for TBI as described above comprised the control group. Exclusion criteria included a history of concussion or other neurological disorder; developmental learning disability; current substance or alcohol abuse according to DSM-IV criteria; presence of a psychotic disorder or bipolar disorder as defined by DSM-IV criteria, or metabolic or other diseases known to affect CNS functions. Due to the high rate of psychiatric disorders in returning veterans, the presence of an Axis I psychiatric disorders according to DSM-IV criteria did not represent an exclusionary criterion.

Measures

All participants completed a comprehensive evaluation of neuropsychological functioning, emotional and behavioral functioning. Neuropsychological testing was performed by trained technicians within the Neuropsychology Unit of the VA San Diego Healthcare System or by trained research assistants employed by Drs. Delano-Wood and Schiehser. Administration time for the proposed neuropsychological battery was estimated at approximately 3 hours and administration time for the mood and functional measures took approximately 15 minutes.

Neuropsychological testing. A battery of tests designed to sensitive to the abilities most frequently affected by TBI was administered. These include measures of:

Premorbid functioning: The Wide Range Achievement Test-4th Edition, Reading subtest, (Wilkinson & Robertson, 2006) was used as an estimate of premorbid verbal intellectual skills. Single-word reading ability has been found to be one of the most resilient skills to brain dysfunction in general (Wechsler, 2001).

Memory: The California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) was used to assess verbal memory. Variables included trials 1-5 total correct, long delay free recall total, and recognition discriminability index. Visual memory was evaluated using the Rey-Osterrieth Complex Figure Test recall total score (Spreen & Strauss, 1998).

Executive Functions: Wisconsin Card Sorting Test-64 total errors (Heaton, 1981); D-KEFS Verbal Fluency Switching total number of responses, and Trail Making Test letter number switching total time (Delis, Kaplan, & Kramer, 2001).

Processing Speed: The Wechsler Adult Intelligence Scale-III (WAIS-III, Wechsler, 1997) and Wechsler Adult Intelligence Scale-IV (WAIS-IV, Wechsler, 2008a) Digit Symbol subtest were used to derive a processing speed variable. Due to changes in the VA Neuropsychological Assessment Clinic, some participants received the WAIS-III version (n = 9) and most others completed the WAIS-IV version (n = 42). The basis for combining these measures lies in these two tests being almost identical in terms of task demands, and boasts a .85 correlation with the previous version and there were no significant differences in mean age-corrected performance between the two measures (Wechsler, 2008b). Means z-scores were calculated within each test version and were then combined into one measure as a z-score with a mean of zero and a standard deviation of one.

Attention/working memory: Similar to the process speed measures, some participants received the WAIS-III (Wechsler, 1997) Digit Span subtest (n = 24) and others completed the WAIS-IV (Wechsler, 2008a) Digit Span subtest (n = 31). These two measures also demonstrated a strong correlation with each other (r = .74) and age-corrected scores did not differ in the WAIS standardization sample (Wechsler, 2008b). However, the raw scores from this measure were not directly comparable since the WAIS-IV version added another whole component (sequencing), and added two more 2-digit trials to the backward condition. Aside from modest changes in the numbers used for each item, the measures were otherwise identical. The WAIS-IV score was modified in an effort to form some equivalency between the two. First the sequencing condition was dropped from the total score. Next, each backward condition was checked to ensure that the participants completed all 4 of the 2-digit trials, and then 2 points were deducted

to place measure on the same scale as the WAIS-III version. The two measures were then combined into one variable and a z-score was generated about the grand mean.

Validity of Measures: The Test of Memory Malingering (TOMM; Tombaugh, 1996) and the Forced-Choice Recognition Trial of the CVLT-II were used to assess effort. Cut-off scores for identifying inadequate effort (TOMM second trail <45 and CVLT-II Forced-Choice Recognition Trial <15) were taken from Tombaugh (1996) and Moore & Donders (2004) respectively.

Psychological/Psychosocial Assessment.

The PTSD Checklist—Military Version (PCL-M; Weathers, Litz, Herman, Huska, & Keane, 1993) was used to rate the frequency and intensity of PTSD-related symptoms. The PCL-M provides point-to-point correspondence between individual items and the DSM-IV diagnostic symptom criteria for PTSD, it correlates strongly with other measures of PTSD symptomatology and has been validated as an instrument sensitive to PTSD in returning OEF/OIF veterans (Bliese et al., 2008; Ruggiero, Del Ben, Scotti, & Rabalais, 2003). Levels of self-report depressive symptoms were assessed using the Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 1996). Participants were also administered the Neurobehavioral Symptom Inventory (Cicerone &Kalmar, 1995) and the Alcohol Use Disorders Identification Test (AUDIT, Babor, de la Fuente, Saunders, & Grant, 1992) and a subsample completed the Combat Exposure Scale (n = 18, Keane et al., 1989).

TBI Interview

Each participant was asked detailed questions regarding the characteristics of their mTBI including the number of TBIs they sustained, the number of blasts to which they

were exposed, and whether or not they lost consciousness. Estimated duration of the loss of consciousness, and duration of post-traumatic amnesia, were not included in the present analyses due to the paucity of reported duration of either phenomenon.

Imaging Procedures

All participants underwent structural MRI and DTI on 3T General Electric (GE) MRI scanners housed within the UCSD Functional Magnetic Resonance Imaging (FMRI) Center on the UCSD La Jolla campus. Forty-three participants were scanned on with the scanner equipped with the Excite HDx platform and, following the FMRI Center's scanner upgrade, data on 12 subjects were acquired with the scanner running the MR750 platform.

Structural scanning: A sagittally-acquired high-resolution 3D T1-weighted anatomical MRI was collected with the following parameters: FOV 24 cm, 256 x 256 x 192 matrix, 0.94 x 0.94 x 1 mm voxels, 176 slices, TR=20 ms, TE=4.8 ms; flip angle 12˚, scan time was roughly 7 minutes.

Diffusion Tensor Imaging: DTI images were collected with a dual spin echo EPI acquisition (Reese et al., 2003) with the following parameters: FOV = 240 mm, slice thickness = 3 mm, matrix size 128 X 128, in-plane resolution = 1.875 x 1.875, TR = 10900 ms, TE = 93 ms. The ten scans from the MR750 platform used identical scanning parameters though TR was shortened to 8000 ms to reduce scan time without affecting image quality. Across scanners, thirty-four slices were acquired with 61 diffusion directions distributed on the surface of a sphere according to the electrostatic repulsion model (Jones et al., 1999) and a b-value of 1500 s/mm^2, as well as one T2 image with no diffusion weighting (b = 0). Two field maps with the same spatial parameters as those of

the DTI scan were collected in order to correct for distortions due to magnetic field inhomogeneities. Total DTI acquisition time with field mapping was roughly 12-16 minutes.

Image Processing

Diffusion Tensor Imaging Data

The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Package (FSL, Smith et al., 2004) was used for all processing of DTI data. The two field maps were used to unwarp the DTI acquisitions. Additionally, a linear alignment tool to reduce the effects of gradient coil eddy currents and a six-degree of freedom affine motion correction for head motion was completed. Each image was visually inspected for quality and the FSL program *bet* was used to remove non-brain voxels from the analysis. The FSL program *dtifit* was used on the corrected data to fit a diffusion tensor model at each voxel. This program yields eigenvalues, eigenvectors and measures of white matter integrity (i.e., fractional anisotropy [FA]) on a voxel-by-voxel basis. Axial diffusivity was defined as the amount of diffusion corresponding to the principal diffusion direction ($AD = \lambda_1$). Radial diffusivity was defined as the average of the two eigenvalues orthogonal to the principal diffusion direction ($RD = [\lambda_2 + \lambda_3]/2$).

Quantitative Fiber Tracking

Quantitative fiber tracking has been successfully implemented in other studies of white matter integrity following TBI (Levin et al., 2008; Wilde et al., 2006). Fiber tracts were generated in TrackVis (MGH) following the FACT method (Mori, Crain, Chacko, & van Zijl, 1999). To produce the fiber tracts, regions of interest (ROIs) were drawn in each tract and used as "seed points" for tractography. They were placed bilaterally (as

necessary) within white matter tracts known to be affected in mTBI and in tracts associated with emotional processing. These include the anterior and posterior limbs of the internal capsule (IC), sub-regions of the corpus callosum (CC, i.e., the genu, body and splenium), the fornix, and the cingulum bundle. One rater (SS), blind to each image's group status, drew seed ROIs individually in each subject's color-map image in FSL. The color-map, seen by loading the principle eigenvector image in FSL, uses a color-coded scheme to display the main orientation of diffusion within each voxel. Using this information in combination with the non-diffusion weighted b = 0 map, a rater can delineate seed points (ROIs) for fiber tracking using intra-subject diffusion weighted and anatomical reference images. The seed points drawn on the color-maps were loaded into TrackVis for fiber tracking. To help reduce partial voluming effects of encroaching gray matter, tracking was restricted to include only those voxels with an FA value greater than .20 (Mori & van Zijl, 2002). Additionally, to restrict aberrant tracking an angle threshold of 41.4 degrees was used (Mori & van Zijl, 2002). This restriction limited contiguous tracking to only those voxels wherein the difference in the angle of the principal eigenvectors is less than 41.4 degrees. FA, RD and AD values from each of the tracts produced was then extracted for each subject and imported into STATA for regression analysis. Depictions of the tracts are shown in Figure 1.

Corpus Callosum: The whole of the corpus callosum (CC) was tracked by placing an ROI along the length of the CC, in red-colored voxels, in the midsagittal slice corresponding to known CC anatomy (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). CC sub-divisions were identified using an adapted classification method based on cortical connectivity derived from DTI fiber tracking (Hofer & Frahm, 2006).

Genu: The posterior border of the genu was defined by a perpendicular line coursing through the anterior most point of the inner convexity. CC voxels anterior to this line (including the rostrum and the anterior sixth of the length of the CC) represented the seed ROI for fiber tracking.

Splenium: The splenium was defined as the posterior fourth of the whole CC. The whole length of the CC was defined as the distance from the anterior end to the posterior end.

Body: The body of the CC consisted of the middle portion bordered by the genu and the splenium as described above.

Internal Capsule: ROIs were placed in the internal capsule following DTI derived segmentation as follows(Wakana et al., 2004).

Anterior: An ROI was placed in the anterior internal capsule within green colored voxels (voxels running anterior posterior). The ROI was placed on the color-map image in the axial plane in green-colored voxels between the putamen and the caudate.

Posterior: An ROI was placed in the axial plane in blue-colored voxels medial to the lenticular nucleus (putamen and pallidum) and lateral to the thalamus.

Cingulum: This tract was easily distinguished in the coronal plane as green voxels inferior to the cingulum gyrus and superior to the corpus callosum. Separate ROIs were placed in the anterior portion, the middle, and the posterior portion following the description of Concha, Gross, & Beaulieu (2005).

Fornix: To produce fiber tracks of the fornix, the method described by (Concha et al., 2005) was used. ROIs were placed in three regions in the fornix (the body, the crus and the column) on the color-map while using the b = 0 map for anatomical reference.

T1 Structural Processing and Cortical Thickness Estimation.

Each subject's T1 structural scan was processed through the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) to produce cortical reconstructions, volumetric segmentations and cortical thickness estimates

Cortical Thickness Measurement. The FreeSurfer program utilizes a series of automated imaging algorithms to produce a mesh of the pial surface and the white matter surface to calculate cortical thickness (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl & Dale, 2000; Fischl et al., 2004). Briefly, the procedure involves Talairach transformation, skull-stripping, intensity normalization, gray and white matter segmentation, gray/white matter border tessellation, topology correction and surface deformation to optimize the placement of the gray/white and gray/CSF borders. Cortical thickness is calculated as the closest distance from the gray/white matter boundary to the gray matter/cerebral spinal fluid boundary at each vertex on the cortical surface (Fischl & Dale, 2000). Importantly, the resultant data is not constrained to the resolution of the original images, allowing for the quantification of submillimeter group differences. The validity of cortical thickness measurement procedures as described above has been verified using both manual measurements (Kuperberg et al., 2003; Salat et al., 2004) and histological analysis (Rosas et al., 2002). One rater (SS), blind to participant characteristics, followed the recommended automated reconstruction procedures detailed within the FreeSurfer online documentation (http://surfer.nmr.mgh.harvard.edu/fswiki/RecommendedReconstruction) and identified and corrected errors made during the cortical reconstruction. This procedure involves verification of the Talairach transformation and of the automated skull-stripping, as well

as a slice-by-slice (in the coronal plane) inspection of the gray/white and gray/CSF surfaces. Modifications to the surfaces were made as necessary to correct for obvious tissue misclassifications (e.g., residual dura matter classified as cortex). Following inspection, an automated parcellation technique within FreeSurfer divided the cortex of each hemisphere into 32 independent regions (Desikan et al., 2006; Fischl et al., 2004), include 13 frontal regions, and 9 temporal regions. Cortical thickness estimates for parcellation regions was extracted for subsequent statistical analysis. Of primary interest were six regions in the frontal and temporal lobes that, due to their vulnerability in TBI and associations with emotional functioning, may best correlate with neurotrauma and PTSD symptom severity. These regions are shown in Figure 2 and included the middle frontal gyrus, the inferior frontal gyrus, the orbitofrontal cortex, the anterior cingulate cortex, the medial temporal cortex and the lateral temporal cortex (Desikan et al., 2006).

Statistical Analyses

Prior to conducting the statistical analyses, data were examined for violations of normality and heteroskedasticity. Violations were found in only 8 of the 48 variables and those variables did not have bearing on the final results (e.g., no significant effects), even after making adjustments to the data or models (e.g., Robust regression) to account for such effects.

The hypotheses defined within the specific aims were analyzed following the procedures detailed below. For many analyses, multivariate multiple regression (MMR) was used. This method enables multiple outcome measures to be included in the models and allows for statistical comparison of regression coefficients between the different outcome variables. That is, this approach enables one to test whether the association

between frontal cortical thickness and PTSD severity differs from the association between frontal cortical thickness and mTBI. Such comparisons are necessary to test the model that disruption of a common neural network underlies the presentation of symptoms in both PTSD and mTBI. MMR also allows one to test whether the effects of PTSD or mTBI differ across models. For example, it is possible to statistically test whether the effect of mTBI differs across all white matter regions with respect for FA, RD and AD. This such analysis could show whether some brain regions, or cognitive domains, are more sensitivity to the effects of PTSD or TBI than others. MMR still allowed for more multiple regression analyses (i.e., we can directly test the hypothesis that PTSD symptom severity is related to DTI indices, independent of the effects of mTBI, depression, and age). These analyses were done in STATA via the *mvreg* command. For other analyses (e.g., correlations among neuropsychological test scores and DTI), the partial correlation function was used to factor in the effect of age. For all analyses beyond the MMR models, SPSS 18 was used. Alpha was set at .05 for significance.

Aim 1: DTI

DTI indices were extracted from the tracts as described in the DTI analysis section. Multivariate multiple regression (MMR) was used to determine the extent to which DTI metrics are associated with PTSD symptom severity and mTBI. To this end, regional DTI measures (i.e., either FA, RD or AD) from the tracts represented the multiple outcome variables (i.e., the dependent variables) and PTSD symptom severity and mTBI status comprised the predictor variables (i.e., the independent variables). A separate MMR was conducted for each DTI index (i.e., FA, RD and AD). Since

depressive symptoms are commonly associated with both TBI and PTSD, BDI-II scores were included in the regression. Also, since age is often associated with FA values, participant age was included in the regression. In addition, since years of education differed between controls and TBI participants, years of education was also entered into the model. Tests for hypothesis 1c were done by replacing mTBI status in the model above by an injury severity variable (e.g., number of TBIs) and were conducted within the mTBI group alone. Post-tests (i.e., Wald tests) in STATA were used to test for differences in the magnitude any significant associations between regional DTI indices and the two predictor variables.

Aim 2: Cortical Thickness

Mean cortical thickness was extracted from the ROIs as described in the cortical thickness analysis section. MMR was used to determine the extent to which cortical thickness is associated with PTSD symptom severity and mTBI. To this end, mean cortical thickness from the frontal and temporal ROIs now represented the multiple outcome variables (i.e., the dependent variable), in place of the DTI indices in the previous model, and PTSD symptom severity and mTBI status again comprised the predictor variables (i.e., the independent variables). BDI-II scores, age and years of education were also entered into the model. Tests for hypothesis 2c were done by replacing mTBI status in the model above by an injury severity variable (e.g., number of TBIs) and were run within the mTBI group alone. Post-tests in STATA were used to test for differences in the magnitude any significant associations between regional cortical thickness and the two predictor variables.

Aim 3: Neuropsychological Testing

All scores were converted into z-scores based on the grand mean. Composite score were calculated executive functions and memory by averaging the z-scores within those domains. MMR was used to determine the extent to which neuropsychological performance in different domains is associated with PTSD symptom severity and mTBI status. Domain z-scores (or composites) were the outcome variables and PTSD symptom severity and mTBI status were the predictor variables (i.e., the independent variables). BDI-II scores, age and years of education were also entered into the model. Tests for hypothesis 3c were conducted by replacing mTBI status in the model above with an injury severity variable (e.g., number of TBIs). Post-tests in STATA were used to test for differences in the magnitude of the association between domain z-scores and the two predictor variables.

The Introduction, Methods, Results and Discussion chapters were coauthored, in part, by Mark Bondi and Lisa Delano-Wood and are together being prepared for publication. Scott Sorg is the principal author of this material.

RESULTS

Sample Characteristics

As shown in Table 1, TBI and control participants did not significantly differ in most demographic characteristics except for years of education, where the control sample had, on average, completed one more year of education. However, the groups did not differ in WRAT-4 Reading, suggesting that the difference in education was not related to differences in premorbid intellectual functioning. Groups also did not significantly differ in alcohol use, as indicated by the AUDIT. However, the TBI sample reported significantly higher levels of psychiatric distress including higher ratings on depression and PTSD symptom severity scales as well as higher ratings on a measure of post-concussive symptoms (NSI). Only a portion of the sample completed a measure on combat experiences, and, while limited in sample, it indicated that the TBI group reported more combat exposure than the control group. TBI injury characteristics are shown in Table 2. In the TBI sample, most reported experiencing more than one mTBI, half reported sustaining a head injury that was combat related, and half reported being exposed to blast waves, and most reported LOC associated with any one TBI.

Primary Analyses

Tables 4-8 show the results of the main regression analyses as hierarchical regression models, with age, education and BDI (and ICV) scores entered in the first model, PCL scores entered in the second model, and TBI grouping entered in the third model. The third models are identical to those entered into the MMR modeling, and are presented in this way to the highlight additive effect of TBI beyond the effects of PTSD in the neuropsychological testing and DTI analyses.

Neuropsychological Testing

As described, raw test scores were converted to z-scores about the grand mean and domain scores were created for executive functions (EF) and memory, and single-test scores were used as measures of attention/working memory (Digit Span), and processing speed (Digit Symbol Coding). Z-scores for the four domains by group are depicted in Figure 3, and the individual tests are presented in Table 3.

The Multivariate Multiple Regression (MMR) was run in order to compare the PTSD symptom severity and the TBI grouping coefficients within each NP outcome variable, and to test for an overall effect of PTSD or TBI across all outcome variables. The results are presented in hierarchical regression in Table 4. The following variables were simultaneously included in the model as predictors: age, years of education, BDI score, PCL score and group [mTBI (n = 38) vs. Military Controls (n = 17)]. Because of instances of missing neuropsychological test data, the number of complete observations was reduced to 49 (i.e., 6 missing cases). All the missing cases were within the mTBI sample and included 4 missing the EF composite, 1 missing memory composite, 1 missing digit span, and 4 missing digit symbol coding tests. . When the missing data is replaced by the grand mean, effects of TBI are found that are consistent with the results of running individual models.

A Wald test for the overall effect of PCL score across all domains was significant [$F(4,49) = 4.03$, $p = .007$], and a Wald test of whether an effect of PTSD differed across domains was significant [$F(3,49) = 5.01$, $p = .004$]. However, in no individual models did the association between PCL scores and domain scores reach significance at $p < .05$. Trends toward significance were observed in both the memory model ($p = .06$) and in the

coding model (p = .07), in the direction that higher PCL scores tended to be associated with higher performance scores on testing. This would suggest that some aspects of cognition may be more sensitive to the effects of PTSD than others, though the lack of any significant associations between PCL scores and individual domains somewhat lessens the meaningfulness of this result.

A Wald test for the effect of TBI was also significant [$F(4,49) = 2.53$, p = .05]. TBI was significantly associated with poorer performances in both memory (p = .02) and coding (p = .03), controlling for age, years of education, and BDI and PCL scores. However, and a Wald test of whether the effect of TBI was differed across domains did not reach significance [$F(3,49) = 1.48$, p = .23], suggesting that while there may be effects of TBI on memory and processing speed, these effects, while significant, are not greater than those observed in auditory attention or executive functions. Significant follow-up Wald tests were found that compared the effect of PCL scores to the effect of TBI on memory [$F(1,49) = 5.37$, p = .02] and coding [$F(1,49) = 5.01$, p = .03], suggesting that the variance in these domains accounted for by TBI exceeds that of PCL scores. There were no significant PCL by TBI interactions (all p-values >.10).

Associations Among TBI Injury Characteristics and Neuropsychological Domains

There were no significant associations between number of TBIs or number of blasts with any of the neuropsychological domain scores (all p-values > .10). There was a trend toward slower processing speed in the LOC group (n = 24) compared to the AOC group (n = 13, p = .06).

DTI Tractography Results

There were a total of 10 regions of interest identified and tracked by one rater, blind to TBI status. Intra rater reliabilities calculated via intraclass correlation coefficient for FA ranged from .70 - .99, with 9 of the 10 regions above .85, and 7 above .90. The lowest ICC value (.70) was for the left anterior internal capsule. Overall, the analysis indicated strong reliability.

The Multivariate Multiple Regression (MMR) was run in order to compare the PTSD symptom and the TBI grouping coefficients within each tract, and to test for an overall effect of PTSD or TBI across all tracts. Due to the large number of regions (10), the results below describe only those with significant ($p < .05$) findings. Age, years of education and BDI total score were included as covariates in the each model.

FA Regression Models. The significant results of the FA analysis are presented in hierarchical regression in Table 5. Group comparisons across the tracts are shown in Figure 4 (the fornix is not included due to greatly different scaling in this region). The Wald test for the overall effect of PTSD across all tracts was not significant [$F(10,49) = 1.03$, $p = .43$]. A test of whether an effect of PTSD differed across regions was likewise not significant [$F(9,49) = 1.13$, $p = .36$]. In terms of individual regression equations, PCL total score was not a significant predictor in any model (p's > .23).

A Wald test for the overall effect of TBI was significant [$F(10,49) = 2.65$, $p = .013$], and there were significant differences with respect to the effect of TBI across the white matter tracks [$F(9,49) = 2.74$, $p = .01$]. TBI was a significant predictor of FA values in both the genu of the corpus callosum ($p = .03$) and in the left cingulum bundle ($p = .01$). A trend toward significance was observed in the right cingulum bundle ($p = .08$), while no other regions approached significance (all p's > .10). Follow-up Wald tests

found that the effect of TBI was significantly greater than the effect of PCL total score in both the genu [F(1,49) = 5.04, p = .03] and in the left cingulum bundle [F(1,49) = 7.35, p = .01]. Significant PCL by TBI status interactions were found in three regions: the body of the CC ($\hat{\beta}$ = -.021, p = .04), the fornix ($\hat{\beta}$ = -.028, p = .01), and in the splenium ($\hat{\beta}$ = -.020, p = .03), such that, in these three regions, the effect of PCL scores on FA values is greater in the controls compared to the TBI participants.

RD Regression Models. The significant results of the RD analysis are presented in hierarchical regression in Table 6 and RD group comparisons are shown in Figure 5. Wald tests were significant for both the overall effect of PTSD across all tracts [F(10,49) = 2.50, p = .02], and for the overall effect of TBI [F(10,49) = 2.38, p = .02]. In addition, the effect of PTSD significantly differed across white matter tracts [F(9,49) = 2.62, p = .01] and the effect of TBI also significantly differed across white matter tracts [F(9,49) = 2.20, p = .04]. In the individual regression models, TBI was found to be a significant predictor of higher RD in the left cingulum bundle (p = .01), right cingulum bundle (p = .04), and the genu (p = .01). Higher PCL scores were associated with lower RD only in the fornix (p = .03). That is, greater self-reported PTSD symptom severity was associated with *lower* RD in the fornix. Wald test comparing the effect of TBI to the effect of PCL were significant for the left cingulum [F(1,49) = 7.86, p < .01], right cingulum [F(1,49) = 4.77, p = .03] and the genu [F(1,49) = 7.25, p < .01], while the fornix only trended toward significance [F(1,49) = 3.45, p = .07]. There were no significant PCL by TBI interactions (all p's >.10).

AD Regression Models. The significant results of the AD analysis are presented in hierarchical regression in Table 7. A Wald test for the overall effect of PCL scores

across all models was not significant [F(10,49) = 1.27, p = .28], nor was the test for the effect of TBI [F(10,49) = 1.29, p = .26]. Similarly, a Wald test of the effect of PTSD did not significantly differ across white matter tracts [F(9,49) = 1.41, p = .21], nor did the effect of TBI [F(9,49) = 1.12, p = .36]. In individual regression models, TBI was associated with greater AD in the fornix (p = .01), and lower PCL scores were also associated with higher AD in the fornix (p = .02). A Wald test comparing the effect of TBI to the effect of PCL on the fornix AD was significant [F(1,49) = 6.72, p = .01] and, based on a comparison of the $\hat{\beta}$ coefficients, seems to suggest that the effect of TBI in the fornix AD is greater than that of PCL-M. A significant PCL by TBI interaction was found in the right cingulum ($\hat{\beta}$ = -3.35 x 10-5, p = .03) such that effect of PCL scores on AD values is greater in the controls compared to the TBI participants.

Associations Among TBI Injury Characteristics and Regional DTI Values

Number of blasts reported and whether or not the participant ever experienced LOC in a TBI event were not significantly associated with regional FA, RD or AD values. Number of TBIs reported was significantly negatively associated with FA in the left AIC ($\hat{\beta}$ = -.0027, t = -2.13, p = .04), and right AIC ($\hat{\beta}$ = -.0025, t = -2.08, p = .05).

Cortical Thickness Analyses

Mean cortical thicknesses from the six identified cortical regions of interest (middle frontal gyrus, inferior frontal gyrus, orbitofrontal gyrus, medial temporal gyrus, lateral temporal gyrus, and anterior cingulate cortex) were entered in to a MMR model to test whether PCL scores and/or the presence of TBI are associated with cortical thickness. Separate models were run for each hemisphere. One TBI subject was excluded from this analysis due to poor quality of the cortical reconstruction assessed via visual inspection.

In addition to age, years of education, and BDI, the estimated total intra-cranial volume was included as a covariate to account for cortical thickness variance attributed to head size.

Left Hemisphere Results

A Wald test for the overall effect of PCL total score across all regions trended toward significance [$F(6,47) = 2.18$, $p = .06$], while a test of whether the effect of PCL total score differed by regions was significant [$F(5,47) = 2.60$, $p = .04$]. PCL score, however, was associated with decreased cortical thickness in the left orbitofrontal cortex ($p = .047$). The Wald test for the overall effect of TBI did not approach significance [$F(6,47) = .48$, $p = .82$], nor did the test of the regional difference of any effect of TBI [$F(5,47) = 0.32$, $p = .90$]. TBI was not significantly associated with cortical thickness in any region (all p's > .19). A comparison of the magnitude of the effect on orbitofrontal thickness between PCL total score and TBI was not significant [$F(1,47) = 2.11$, $p = .15$]. There were no significant PCL by TBI interactions (all p's >.10).

Right Hemisphere Results

A Wald test for the overall effect of PCL scores across all models was not significant [$F(6,47) = 1.12$, $p = .36$], nor was the test of whether the effect of PCL total score differed by regions [$F(5,47) = 1.26$, $p = .30$]. A test for the effect of TBI across models was not significant [$F(6,47) = 0.55$, $p = .77$], and a test of whether the effect of TBI differed by region was not significant [$F(5,47) = 0.46$, $p = .46$]. Additionally, in no models were the effect of PCL total score or TBI significant predictors of right hemisphere regional cortical thickness (all p's > .05). There were no significant PCL by TBI interactions (all p's >.10).

Subcortical Volume

As an exploratory analysis, the effect of TBI and/or PTSD on volume of subcortical structures was investigated. There were no significant associations found between hippocampus or amygdala and the PCL total score or the presence of TBI (all *p*'s > .10). There were no significant PCL by TBI interactions (all *p*'s >.10).

Associations Among TBI Injury Characteristics and Regional Cortical Thicknesses

No significant associations were found between regional cortical thicknesses and any of the TBI injury characteristics (all *p*'s > .05).

Correlations with PCL Scores within the TBI Group

Partial correlations, adjusting for age, were conducted between regional DTI values and PCL total score. There were no significant correlations with FA. RD significantly negatively correlated with PCL scores in the fornix (r = -.49, *p* = .002) and genu (r = -.35, *p* = .04). AD also significantly negatively correlated with PCL scores in the fornix (r = -.48, *p* = .003) and in the genu (r = -.33, *p* = .05). Neuropsychological domain scores and cortical thicknesses (also adjusting for ICV) did not significantly correlate with PCL scores.

TBI Severity and Time Since Injury

Only five participants self-reported a LOC duration consistent with a moderate TBI classification, while the vast majority of TBI participants (n = 33) were classified as mild. Due to the self-report nature of the interview, it is not possible to verify the true duration of LOC, though those five participants each endorsed LOC of greater than 30 min. The above analyses were conducted again with the exclusion of those 5 potentially moderate TBI participants, and the results were not changed. Correlation analysis failed

to find significant associations between months since injury and either neuropsychological domain scores or imaging variables.

Correlations Among Dependent Variables

Neuropsychological Domain Scores and Imaging Variables

Significant partial correlations between neuropsychological domain scores and regional DTI variables are presented in Table 9. There were no significant partial correlations between regional cortical thicknesses and neuropsychological domain scores, controlling for age and ICV.

Cortical Thickness and Regional DTI Values

Significant partial correlations between regional cortical thicknesses and DTI values are presented in Table 10. All significant correlations were positive, such that greater FA values were consistent with thicker cortices, and, in two areas, greater RD values corresponded with increased thickness. Twelve correlations were significant for the right hemisphere to eight on the right.

The Introduction, Methods, Results and Discussion chapters were coauthored, in part, by Mark Bondi and Lisa Delano-Wood and are together being prepared for publication. Scott Sorg is the principal author of this material.

DISCUSSION

The overarching goal of this project was to investigate the relative contributions of PTSD symptom severity and mild to moderate TBI across neuropsychological test performance, white matter integrity and cortical thickness to find evidence supporting that mild to moderate TBI and PTSD share a common neural network. Evidence in support of a detrimental effect of TBI was found in both the neuropsychological and DTI findings, whereas evidence in support of a detrimental association with PTSD symptom severity was equivocal. This discrepant relationship was further supported when the effects of TBI and PTSD were directly tested against each other. When examining the neurocognitive domains and white matter pathways associated with TBI, the effects of TBI were found to be significantly greater than any associations with PTSD symptoms. In addition, TBI was not associated with the one region where greater PTSD symptoms were significantly associated with lower values on brain measure (i.e., orbitofrontal cortical thickness). This study is not alone in failing to find support for such an association between brain regions affected in TBI and PTSD symptoms. In another recent study of veterans where widespread effects of TBI upon white matter integrity were reported, there was no association with PTSD symptoms (Morey et al., 2012).

This of course does not suggest that no association between PTSD and mTBI exists. The shared symptom presentation (Stein & McAllister, 2009), the higher incidence of PTSD within veterans who sustained mild head injuries (Hoge et al., 2008), and the previously described overlap of implicated neuronal systems strongly argue for this possibility. In fact, another recent report found PTSD severity was associated with higher, non-specific white matter diffusivity in a sample of veterans that also indicated

lower overall white matter FA with blast exposure (Bazarian et al., 2012). However, the current work did not find evidence in support of a "biological gradient" wherein the possible neurotrauma associated with mTBI itself contributes toward, or exacerbates, PTSD symptoms as measured by the PCL-M. Thus, additional research is needed in this area to more completely understand whether brain trauma presents a biological risk factor moderating the symptom presentation of PTSD. Nonetheless, the findings do add insights into the factors associated with complicated recovery from mTBI, namely, that persisting symptoms and difficulties following multiple mTBIs have a biological basis independent of comorbid psychiatric illness.

Traumatic Brain Injury

TBI was associated with both poorer performance on memory testing as well as slower processing speed, even after including accounting for the effects of psychiatric distress (i.e., depression and PTSD symptom ratings). Indeed, previous reports on mild TBI have found no effect of TBI after accounting for comorbid psychiatric distress (Hoge et al., 2008; Vasterling et al, 2012). However, in this study, the observed neuropsychological effects of mild TBI appears to be independent of comorbid psychiatric distress, suggesting that those factors alone do not explain the presence of persisting symptoms. In fact, there was no evidence of a detrimental effect of PTSD symptom severity on neuropsychological functions in this sample.

Both slowed processing speed and poorer memory performance are often demonstrated in the acute phase of injury following mTBI, in addition to deficits in attention, working memory and executive functions (Landre et al., 2006; McAllister & Arciniegas, 2002), although most meta-analytic studies, especially those using unselected

and prospective samples (i.e., non-clinical samples), report that these deficits are temporary and that most participants return to the normal range by three months (Binder et al., 1997, Frencham et al., 2005, Rohling et al., 2011, Schretlen & Shapiro, 2003). When studies include clinical samples (i.e., self-referred and/or with persisting cognitive complaints), such as the present work, medium to large effect sizes have been found in multiple cognitive domains in the post-acute phase (Belanger et al., 2005, Zakzanis et al., 1999) including processing speed and delayed memory. Problems associated with comorbid psychiatric distress (Bigler, 2008; Dikmen et al., 1993; Ettenhofer & Abeles, 2009, Ponsford et al., 2000), and effort and litigation (Belanger et al., 2005, Larrabee, 2007) have also been implicated as possible contributing factors to sustained impairment in clinical samples. However, in the present work, participants with insufficient effort were excluded, and, as described above, comorbid psychiatric symptoms do not appear to be driving the observed neuropsychological deficits. With a mean time since injury of 4 years, the findings suggest that the acute effects of mTBI, in this sample, have persisted long after any spontaneous recovery would have occurred.

The DTI findings provide some indications to what may be contributing to this prolonged recovery. In the regression models TBI was associated with lower white matter integrity in the cingulum bundles and in the genu of the corpus callosum. Lowered white matter integrity in these regions is consistent with what has been reported in previous mild and moderate TBI studies (Bendlin et al., 2008; Huang et al., 2009; Inglese et al., 2005; Kraus et al., 2007; Kumar et al., 2009; Niogi et al., 2008). A recent study reported a wide distribution of major white matter pathways associated with chronic mild TBI in military veterans (Morey et al., 2012). As was the case with the

neuropsychological findings, the reductions in white matter integrity associated with TBI were independent of psychiatric comorbidity effects. Additionally, there was some limited evidence in support of a dose effect of mTBI, such that increasing numbers of mTBIs reported was associated with reduced bilateral anterior internal capsule FA, however it is noted that this relationship did not extend to other regions. These three regions comprise the most anterior tracts sampled in this analysis, with segments of the genu, the cingulum bundles and the anterior internal capsules each coursing within the anterior frontal white matter. In comparison, other tracts sampled, including the body and splenium of the corpus callosum, the posterior internal capsule and the fornix, have none or limited projections to and from the frontal lobes and showed no association with mTBI. This frontal localized susceptibility aligns with results of other studies implicating a specific frontal vulnerability to TBI (Kim et al., 2008; Levine et al., 2008).

The DTI findings are also informative in terms of the form of physiological damage incurred upon the white matter. As previously described, the axial diffusivity (AD) is a proxy measure of axonal integrity, whereas radial diffusivity (RD) is thought to increase following alterations to membrane permeability or myelin compromise (Song et al., 2003). The reduction in FA values observed in the cingulum bundle and in the genu coincides with *increases* in RD, without significant changes in AD, which is suggestive of myelin compromise. When one considers that one role of myelin is to quicken the propagation of neuronal signaling, degradations in myelin integrity would be expected to be accompanied by reductions in processing speed, which is precisely what this study found. This association is more directly supported by the robust associations found between processing speed and white matter integrity, with 9 of the 10 tracts showing

strong correlations between slower processing speed and increased RD, including those regions found to be associated with mTBI, the genu of the corpus callosum and the right and left cingulum bundles.

The lack of an association between TBI and cortical thickness measures suggests that cortical gray matter may not be directly affected in mild TBI or, at this stage, the observed changes in white matter integrity have not translated into cerebral atrophy within the frontal and temporal lobes (Park et al., 2008). This lack of association between white matter integrity and cortical gray matter is reflected, in part, in the inconsistent results of the correlation analyses between the regional DTI indices and cortical thickness. Broadly, there were only two significant associations between RD and cortical thickness, as shown in Table 10, and these were in the direction of *increased* RD corresponding to thicker cortex values. On the other hand, increases in AD, which are considered to be reflective of axonal health, were associated with thicker cortex in 5 cortical regions. Thus, the attenuation of RD seen in the TBI sample may not translate to cortical thinning for the reason that cortical thickness appears to be relatively insensitive to myelin integrity and is instead more likely to be associated with axonal integrity (Park et al., 2008).

White Matter Disconnection?

That subcortical white matter damage would persist in mTBI is consistent with the conclusions of a recent review that found white matter to be the brain structure most vulnerable in mTBI (Bigler & Maxwell, 2012). They summarize that axonal disconnection or secondary axotomy may fragment neural networks and lead to a functional disconnection among cortical and subcortical gray matter. The present

findings are largely consistent with this model and indicate that white matter damage associated with one or multiple TBIs may persist beyond the acute recovery phase of three months. In fact, the processing speed measure used in this study (Digit-Symbol Coding) is well suited to demonstrate such a disconnection. Digit-Symbol coding depends on the fluid and speeded integration of many cognitive processes for optimal performance including visual scanning and attention, working memory, response speed, incidental learning and visuomotor coordination (Lezak et al. 2004). As such it relies on the synchronized output of many cortical and subcortical regions and any disconnection among those gray matter centers, such as that shown in the current study (i.e., genu), is likely to lead to poorer performance.

Neuropathology of Mild to Moderate TBI

Any imaging analysis, even one that is incrementally more sensitive to the effects of mTBI, such as DTI, can only grossly indicate that neuropathology may be present and does not directly inform, at a cellular level, what neuropathological processes may be present. Recent work by Goldstein and colleagues (2012) on postmortem brains from U.S. military veterans with blast exposure and/or concussive injury found tau-immunoreactive neurofibrillary tangles (NFTs) within cortical gray matter and evidence for disrupted subcortical white matter subjacent to cortical tau pathology along with other indications for persistent chronic traumatic encephalopathy (CTE). Importantly, in their analysis, the cause of death was not related to the head trauma, and there were no neuropathological distinctions found between those with blast injury and those with sports-related concussion only. In addition, they found similar CTE neuropathology in rodent models of blast injury including functional deficits in the form of slowed axonal

conduction, and impaired learning and memory, two functions that are also implicated in the current work. Omalu and colleagues (2011) reported similar evidence of CTE in a tragic case of a 27-year-old US Marine Corps veteran of the Iraq war who committed suicide following multiple head traumas including blast injury. Despite few neuropsychological impairments limited to source memory errors on word list recall and poor planning on copy and impaired incidental memory of a complex figure, NFTs were found in the cortical and subcortical gray matter, concentrated within the frontal lobes, along with CTE-related pathology within the subcortical white matter. The complex case histories shown in these studies mirrors, in some ways, the cases included in the TBI group in this study with high levels of psychiatric comorbidity along with multiple instances of head trauma in the majority of cases.

PTSD

The elevated psychiatric symptom ratings (i.e., PTSD-related or depressive symptom ratings) in the mTBI group relative to control participants are consistent with other studies that have showed that reported neurotrauma, in general, and psychiatric distress are highly co-morbid among OEF/OIF veterans (Hoge et al., 2008, Levin et al., 2010, Schneiderman et al., 2008). In contrast to the observed effects of mTBI, the evidence in support of an effect of PTSD symptomotology, as measured by the PCL-M, was limited and was often not consistent with expectations. For example, while the MMR for the neuropsychological test data returned an overall significant effect for the PCL-M, there were no significant predictors in the individual models, and, when trends were observed, those tentative associations when against expectations with greater symptom severity (i.e., higher PCL-M scores) corresponding to *better* testing

performance. Some previous studies have not reported a positive association between post-traumatic distress and neurocognition (Leskin & White, 2007; Stein, Kennedy, & Twamley, 2002; Brewin, Kleiner, Vasterling, & Field, 2007; Verfaellie & Vasterling, 2009), although the findings of the effect of PTSD on neuropsychological functioning in veterans with TBI have not been consistent (Campbell et al., 2009; Gordon, Fitzpatrick, & Hilsabeck, 2011).

The imaging findings show some associations between limbic brain structures and PTSD symptom severity. However, the data supporting a relationship between PTSD symptom severity and white matter integrity was equivocal. PCL-M scores were significantly associated with RD in the multivariate analysis, but the results again were contrary to expectations. For example, *lower* fornix RD was associated with greater symptom severity. Again, other published studies that do report a relationship between PTSD and DTI values tend to show an opposite pattern, with decreased FA (and increased diffusivity) corresponding to increased post-traumatic distress (e.g., Bazarian et al., 2012; Kim et al., 2005). On the other hand, lower fornix AD, a possible measure of neuronal integrity, was associated with greater symptom severity. It is important to note here that the theorized relationship between diffusivity indices and myelin and axonal integrity is less straightforward within the fornix since this structure lies close to the lateral ventricles, making it highly susceptible to encroaching cerebral spinal fluid that could increase diffusivity generally and lower FA values. Thus, while the DTI indices suggest a relationship between the fornix and PTSD symptomotology in this sample, the form of that relationship is not clear, and may suggest that more intact fornix white matter (i.e., lower diffusivity) is associated with greater symptom severity. Such a

relationship is not entirely implausible. Since the fornix is a crucial structure related to memory and emotions, it is possible that disruptions of fornix integrity may in effect reduce the number or quality of intrusive trauma-related episodic memories, a hallmark feature of PTSD.

The left orbitofrontal cortex (OFC) was the only other brain structure associated to PTSD symptom severity in the full regression models. The finding for reduced left OFC thickness being associated with higher PCL-M ratings is consistent with other reports showing reduced frontal cortical thickness being associated with significant post-traumatic distress (Geuze et al., 2008; Woodward et al., 2009). Investigations into fear conditioning have found that thinner OFC is associated with poorer extinction retention (Milad et al., 2005; Hartley, Pischl & Phelps, 2011), and others have posited that the ventral medial prefrontal cortex, including the OFC, is responsible for top-down regulation of amygdala hyper-reactivity to conditioned stimuli in PTSD (Rauch et al., 2006) and would thus be crucial toward inhibiting fear expression. While the OFC appears to be related to the presentation of PTSD symptoms in this sample, it was not associated with TBI, suggesting that this independent association may represent a premorbid vulnerability or could be related to another process.

Strengths and Limitations

One of the strengths of this study is the exclusion of 11 participants with sub-threshold scores on effort testing. Other DTI studies that have failed to show significant effects of TBI in combat veterans (e.g., Levin et al., 2010) have not formally employed effort inclusion criteria, which may have attenuated possible group differences on biological markers. The exclusion of participants with low effort in the current study

mitigates this issue and adds credibility to the neuropsychological findings associated with TBI. Additionally, the integration of the many modalities of study including neuropsychological test performance, DTI and cortical thickness represents a step toward a more nuanced analysis of the components that may be affected in mTBI and PTSD, as suggested in a recent review on this topic (Dolan et al., 2012).

However, there are some limitations that warrant discussion. First, our data are cross-sectional, and it is possible that the observed differences in FA and neuropsychological performance may reflect premorbid differences that are perhaps unrelated to the mTBI. Vasterling and colleagues (2012) found that, when pre-deployment test data is available, there are no persisting neurocognitive effects attributed to mTBI. However, the neuropsychological test battery used for that study relied heavily on computerized testing and did not include measures found to be affected by TBI in the present study, including verbal list learning and written digit-symbol coding. Second, the generalizability of our findings to single-event mTBIs is limited as most of our mTBI participants endorsed having sustained more than one TBI. Another limitation, as previously discussed, is the use of clinical data, and the integration of two test forms (e.g., WAIS-III and WAIS-IV coding), though it is notable that significant effects for TBI are found even with the exclusion of those 9 participants with the WAIS-III coding data. The use of a self-report measure to gauge the current degree of PTSD symptom severity (i.e., the PCL-M) presents another limitation in that there may be inconsistencies among the participants' subjective ratings of being "bothered" by certain symptoms. However, the PCL-M is generally reliable (Wilkins, Lang & Norman, 2011).

There were no overt corrections made for the multiple comparisons conducted. The threshold for reporting significance was set to $p < .05$, and the reporting of trends was used sparingly and only when the tentative findings would have added to the discussion. It is clear that, given the number of comparisons, a Bonferroni-like correction would have significantly limited the number of findings. However, while individual regression findings may not survive a strict correction, the multivariate findings (i.e., significant overall effect of TBI on neuropsychological test scores, FA and RD) would remain significant within their respective models and speak to the main aims of this study.

Finally, the tensor model of diffusion-weighting is limited in regions with more complex architecture (e.g., where crossing fibers exist within a single voxel), and thus the measured FA may be attenuated in some regions (Madler et al., 2008). The relationship between RD and myelin integrity or, membrane permeability, is indirect and is susceptible to further uncertainty within highly complex white matter bundles within a voxel (Wheeler-Kingshott & Cercignani, 2009). Although this possibility may have altered the FA measures to some degree, this effect is assumed to be consistent across the groups such that differences in diffusivity measures, while imprecise, continue to signify altered white matter integrity.

Future Directions

Numerous epidemiological studies have identified TBI as a risk factor for developing Alzheimer's disease (AD) later in life (Johnson, Stewart & Smith, 2010; Shively, 2012). Other reports have found that TBI may interact with genetic risk factors for AD (i.e., apolipoprotein ε4) to contribute to even greater risk (Mayeux, Ottman &

Maestre, 1995). These associations between TBI and AD are further supported by the presence of amyloid-β (Aβ) plaques, a neuropathological indication of AD, that are found in brain of persons with TBI at ages prior to developing AD (Johnson, Stewart & Smith, 2010), though the role of these plaques in mTBI is unclear. The recent emphasis on the study of mTBI provides an opportunity to further explore this association in longitudinal designs.

Another promising direction is to integrate functional MRI into this multi-modal imaging approach. Some research has found greater spread of activation in persons with mTBI compared to healthy controls on tasks of working memory (McAllister et al, 2006). It has been proposed that such compensatory recruitment of additional cortical regions may be driven, in part, by disrupted signaling within white matter microstructure (McAllister et al., 2006). However, this hypothesis has yet to be confirmed in mTBI samples. Given the current findings, as well as others (Morey et al., 2012), that found reduced white matter integrity in chronic mTBI, along with poorer neurocognitive performance, it is possible that abnormal fMRI activity may also be present. Future studies would do well to integrate functional MRI into the current framework.

Summary and Conclusions

This study sought to evaluate the individual effects of mTBI and PTSD symptom severity on neuropsychological performance, white matter integrity, and cortical thickness in a sample of OEF/OIF veterans, and to investigate any overlap in potential behavioral and biological makers. The results found little evidence for a disrupted "common network" between mTBI and PTSD. Instead, they support unique and non-overlapping effects of mTBI and PTSD symptom severity such that mTBI is associated with deficits in memory and processing speed as well as disrupted frontal white matter myelin integrity, whereas PTSD was associated with thinning of a cortical area associated with emotional regulation. The possibility of a biological link between mTBI and PTSD remains but was not convincingly supported by the current findings. On the other hand, persisting neurocognitive deficits, especially in the form of slowed processing speed, was associated with disrupted myelin integrity that was also related to a history of mTBI.

The Introduction, Methods, Results and Discussion chapters were coauthored, in part, by Mark Bondi and Lisa Delano-Wood and are together being prepared for publication. Scott Sorg is the principal author of this material.

FIGURES AND TABLES

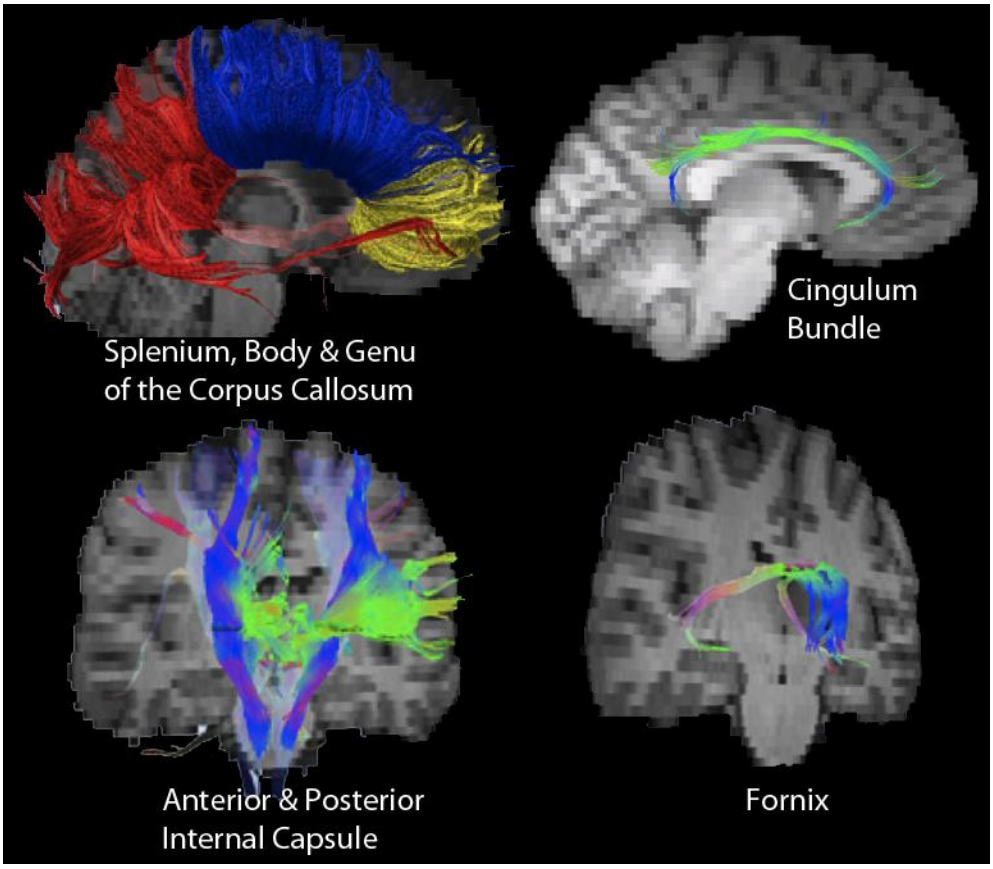

Figure 1. Diffusion Tensor Imaging Tracts.

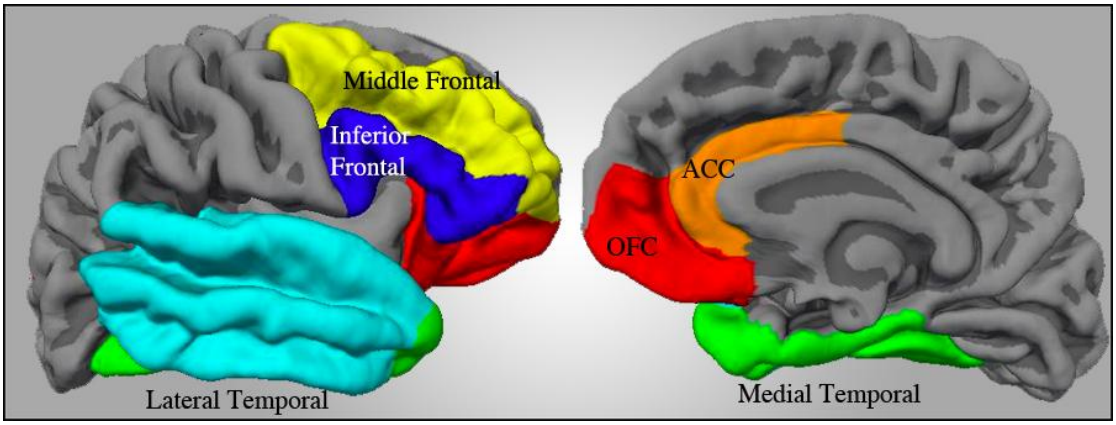

Figure 2. Cortical Regions of Interest. Note: OFC = Orbitofrontal Cortex; ACC = Anterior cingulated cortex.

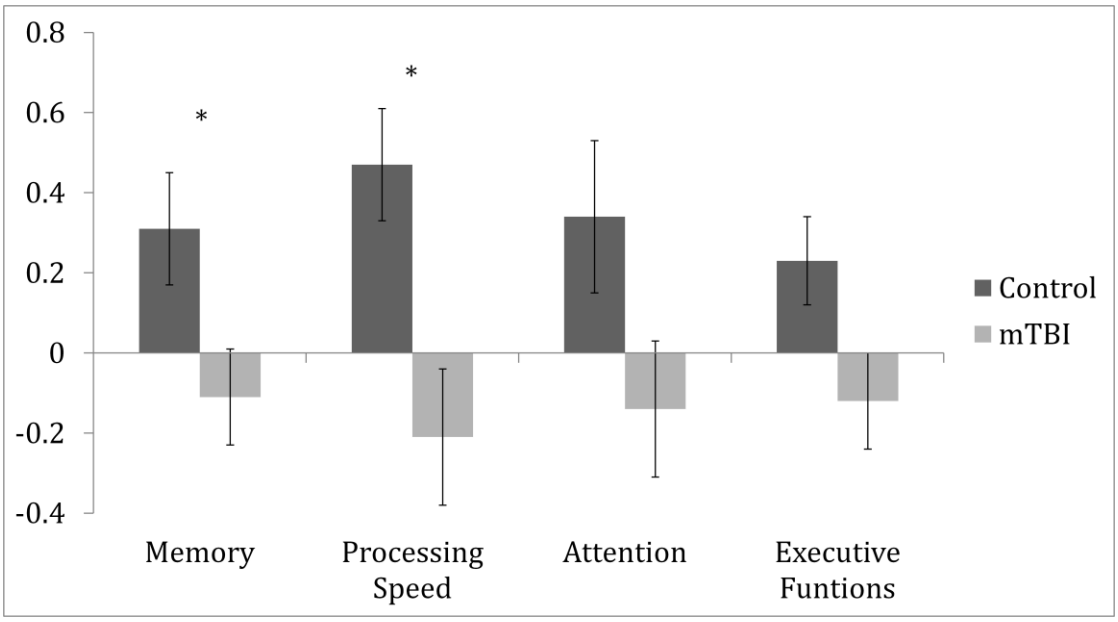

Figure 3. Neuropsychological Domain Z-Scores by Group. Note: Error bars represent standard error. *Domains significantly differed in the full regression models.

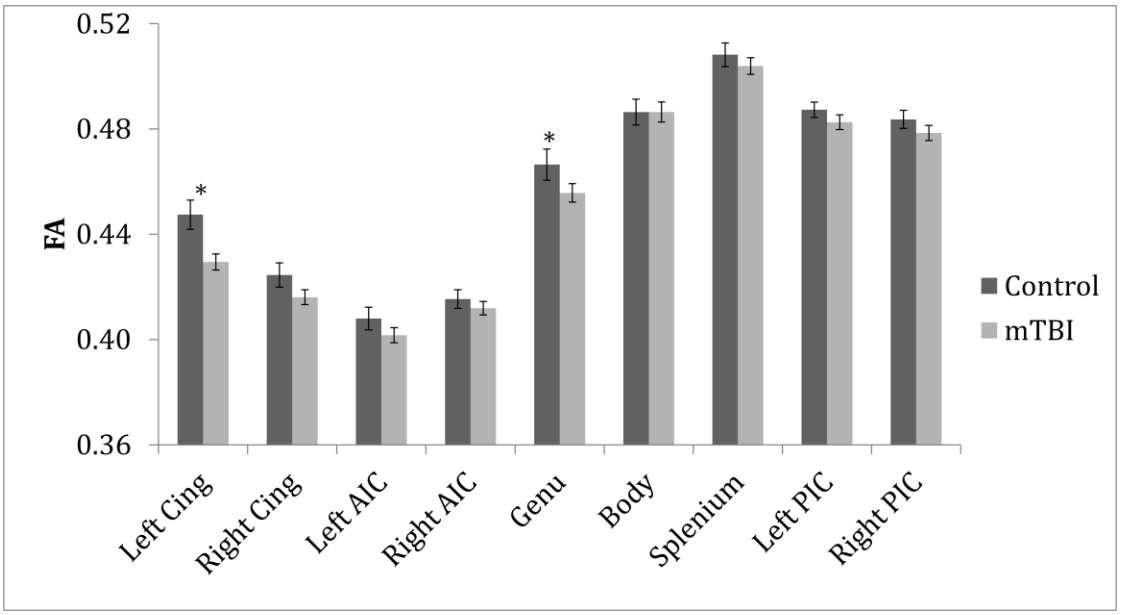

Figure 4. Regional FA Values by Group. Note: Cing = Cingulum, AIC = Anterior Internal Capsule, PIC = Posterior Internal Capsule, Fornix not shown due to scaling; error bars represent standard error. *Domains significantly differed in the full regression models.

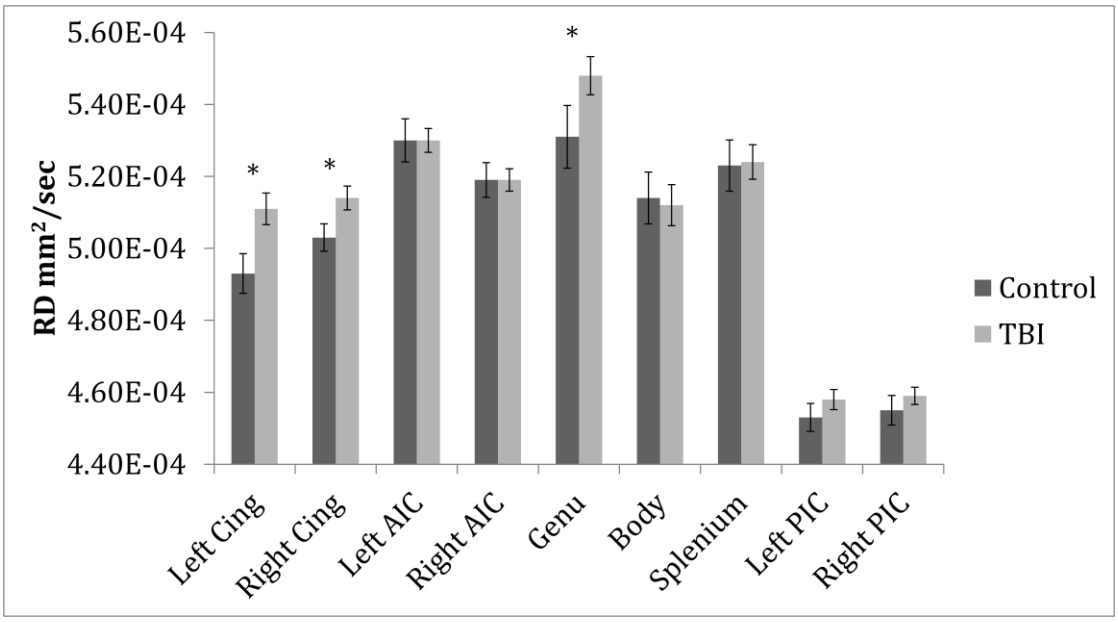

Figure 5. Regional Radial Diffusivity Values by Group. Note: Cing = Cingulum, AIC = Anterior Internal Capsule, PIC = Posterior Internal Capsule, Fornix not shown due to scaling inconsistency; error bars represent standard error. *Significantly different in full regression model.

Table 1. Sample Characteristics of the Control and mTBI Groups

	Control	mTBI	*p*
n	17	38	-
Age (years)	33.7 (8.7)	31.2 (9.1)	.37
BMI	27.1 (5.5)	27.0 (3.4)	.93
WRAT-4 Reading (SS)	105.8 (9.1)	105.6 (12.2)	.95
Years of Education	14.7 (2.0)	13.4 (1.4)	.01
% Male	77%	90%	.21
% Caucasian	77%	55%	.14
African American	1	6	
Hispanic/Latino	1	9	
Asian/Pacific Islander	0	2	
Other	2	0	
Military Branch			.22
Marines	3	16	
Navy	2	12	
Army	1	8	
Air Force	1	0	
Exposed to Combat	3/9 Reporting	29/36 Reporting	.005
Combat Exposure Scale	7.6 (8.6) (8 Reporting)	18.5 (12.1) (10 Reporting)	.05
AUDIT	4.1 (3.8)	5.6 (5.8)	.36
AUDIT > 7	18% (3/17)	28% (10/36)	.42
NSI	4.9 (4.1)	35.2 (13.7)	<.001
BDI-II *	5.1 (8.4)	17.8 (12.5)	<.001
PCL-M *	22.4 (10.9)	43.0 (17.5)	<.001
PCL Reexperiencing	5.7 (2.2)	12.1 (5.6)	<.001
PCL Avoidance/Numbing	9.2 (4.9)	17.3 (8.1)	<.001
PCL Arousal	7.8 (4.0)	14.4 (5.1)	<.001
PCL > 50 (Possible PTSD)	6% (1/17)	37% (14/38)	.02
PTSD via Chart or Report	0	55% (21/38)	<.001

Notes. mTBI = mild traumatic brain injury; SS = scaled score; LOC = loss of consciousness; WRAT-4 = Wide Range Achievement Test, Fourth Edition; AUDIT = Alcohol Use Disorders Identification Test; NSI = Neurobehavioral Symptom Inventory; BDI-II = Beck Depression Inventory-2; PCL-M = Post-traumatic Stress Disorder Check List- Military Version.

Table 2. TBI Group Injury Characteristics

Months Since mTBI	48.3 (31.8)
Mean Number of mTBIs	2.7 (2.2)
% > 1 mTBI	68%
% Combat mTBI	50%
% Reporting Any LOC at TBI	63%
% Reporting Blast Related mTBI	54%
No. of Blasts Exposed	6.9 (23.7)
No. of Times Dazed from Blasts	2.2 (2.9)

Table 3. Neuropsychological Domain and Individual Test Z-Scores by Group

	Control	TBI	*p*
Memory	.31 (.59)	-.11 (.72)	.04
CVLT-II 1-5 Total	.45 (1.03)	-.21 (.93)	.02
CVLT-II Long Delay Free Recall	.38 (.83)	-.17 (1.03)	.06
CVLT-II Discriminability	.14 (1.14)	-.06 (.94)	.49
Rey- Osterrieth Delay	.09 (.53)	-.04 (1.16)	.66
Processing Speed	.47 (.57)	-.24 (1.07)	.01
WAIS-IV Coding	.54 (.53)	-.33 (1.08)	.01
WAIS-III Coding	-.53 (x)	.07 (1.05)	.61
Executive Functions	.24 (.44)	-.13 (.77)	.07
WCST Total Errors	.03 (.71)	-.01 (1.11)	.89
D-KEFS Verbal Switching	.50 (.81)	-.24 (1.00)	.01
D-KEFS Trails Switching	.21 (.65)	-.10 (1.12)	.30
Attention	.34 (.77)	-.15 (1.07)	.10
WAIS-IV Digit Span	.56 (.50)	-.16 (1.06)	.09
WAIS-III Digit Span	.18 (.90)	-.13 (1.08)	.48

Note: Values represent mean (SD); CVLT-II = California Verbal Learning Test, Second Edition; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test; D-KEFS = Delis-Kaplan Executive Functioning System; *p*-values reflect ANOVAs not adjusted for psychiatric factors (depression and PTSD), or demographic variables (years of education) that differed between groups.

Table 4. Summary of Individual Hierarchical Regression Analyses Predicting Neuropsychological Performance for Each Domain

			Model 1			Model 2			Model 3	
Domain	Variable	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2
Executive	Age	-0.023*	0.01	0.09	-0.024	0.01	0.10	-0.024	0.01	0.10
Functions	Years of Education	0.156**	0.055	0.12	0.148	0.056	0.11	0.139	0.057	0.10
	BDI	-0.003	0.007	0.00	0.006	0.013	0.31	0.006	0.013	0.00
	PCL-M				-0.007	0.01	0.01	-0.005	0.01	0.00
	TBI							0.218	0.215	0.02
	R^2		0.21			0.01			0.02	
	F for change in R^2		4.42**			0.6			1.03	
Memory	Age	0.009	0.011	0.01	0.011	0.011	0.02	0.01	0.011	0.02
	Years of Education	-0.013	0.063	0.00	0.003	0.064	0.00	-0.019	0.062	0.00
	BDI	-0.006	0.008	0.01	-0.024	0.015	0.05	-0.023	0.015	0.04
	PCL-M				0.015	0.011	0.04	0.021	0.011	0.07
	TBI							0.559*	0.234	0.10
	R^2		0.03			0.04			0.1	
	F for change in R^2		0.43			1.9			5.72*	
Auditory	Age	-0.036*	0.015	0.10	-0.039**	0.014	0.12	-0.039**	0.015	0.12
Attention	Years of Education	0.048	0.083	0.01	0.024	0.083	0.00	0.015	0.084	0.00
	BDI	-0.021	0.011	0.06	0.007	0.02	0.00	0.007	0.02	0.00
	PCL-M				-0.023	0.014	0.04	-0.021	0.015	0.03
	TBI							0.213	0.32	0.01
	R^2		0.17			0.04			0.01	
	F for change in R^2		3.40*			2.7			0.45	
Processing	Age	-0.016	0.015	0.02	-0.014	0.015	0.02	-0.014	0.014	0.02
Speed	Years of Education	0.116	0.083	0.03	0.135	0.084	0.05	0.107	0.081	0.03
	BDI	-0.012	0.011	0.02	-0.033	0.02	0.05	-0.033	0.019	0.05
	PCL-M				0.018	0.014	0.03	0.026	0.014	0.05
	TBI							0.712*	0.309	0.09
	R^2		0.1			0.03			0.09	
	F for change in R^2		1.78			1.6			0.532*	

*p < .05. **p < .01.

BDI = Beck Depression Inventory-II; PCL-M = PTSD Check List-Military Version

Table 5. Summary of Significant Individual Hierarchical Regression Analyses Predicting Fractional Anisotropy

			Model 1			Model 2			Model 3	
Region	Variable	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2
Genu	Age	-4.2 x 10-4	3.6 x 10-4	0.03	-4.1 x 10-4	3.69 x 10-4	0.02	-4.15 x 10-4	3.55 x 10-4	0.02
	Years of Education	1.66 x 10-3	2.06 x 10-3	0.01	1.76 x 10-3	2.11 x 10-3	0.01	1.06 x 10-3	2.05 x 10-3	0.00
	BDI	1.9 x 10-4	2.7 x 10-4	0.01	8.1x10-5	5.04 x 10-4	0.00	9.92 x 10-5	4.85 x 10-4	0.00
	PCL-M				9.0x10-5	3.59 x 10-4	0.00	2.86 x 10-4	3.56 x 10-4	0.01
	TBI							1.76 x 10-2*	7.79 x 10-3	0.09
	R^2		0.04			0.001			0.09	
	F for change in R^2		0.68			0.062			5.12*	
Left	Age	1.04 x 10-4	3.38 x 10-4	0.00	8.94 x 10-5	3.43 x 10-4	0.00	8.41 x 10-5	3.24 x 10-4	0.00
Cingulum	Years of Education	3.24 x 10-3	1.92 x 10-3	0.05	3.12 x 10-3	1.97 x 10-3	0.05	2.36 x 10-3	1.87 x 10-3	0.03
	BDI	1.96 x 10-5	2.48 x 10-4	0.00	1.56 x 10-4	4.69 x 10-4	0.00	1.76 x 10-4	4.42 x 10-4	0.00
	PCL-M				-1.15 x 10-4	3.34 x 10-4	0.00	9.84 x 10-5	3.25 x 10-4	0.00
	TBI							1.92 x 10-2**	7.10 x 10-3	0.12
	R^2		0.07			0.002			0.12	
	F for change in R^2		1.24			0.12			7.28**	
Right	Age	-2.85 x 10-4	2.84 x 10-4	0.02	-2.90 x 10-4	2.89 x 10-4	0.02	-2.93 x 10-4	2.82 x 10-4	0.02
Cingulum	Years of Education	2.35 x 10-3	1.61 x 10-3	0.04	2.31 x 10-3	1.65 x 10-3	0.04	1.86 x 10-3	1.64 x 10-3	0.02
	BDI	1.49 x 10-4	2.09 x 10-4	0.01	1.92 x 10-4	3.95 x 10-4	0.00	2.04 x 10-4	3.86 x 10-4	0.01
	PCL-M				-3.59 x 10-5	2.81 x 10-4	0.00	8.95 x 10-5	2.84 x 10-4	0.00
	TBI							1.12 x 10-2^t	6.20 x 10-3	0.06
	R^2		0.05			0			0.06	
	F for change in R^2		0.92			0.02			3.29^t	

*p < .05, **p < .01

^{t}p < .10

BDI = Beck Depression Inventory-II; PCL-M = PTSD Check List-Military Version

Table 6. Summary of Significant Individual Hierarchical Regression Analyses Predicting Radial Diffusivity

			Model 1			Model 2			Model 3	
Region	Variable	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2
Genu	Age	8.08 x 10-8	5.43 x 10-7	0.00	6.89 x 10-8	5.53 x 10-7	0.00	7.75 x 10-8	5.21 x 10-7	0.00
	Years of Education	-3.26 x 10-6	3.08 x 10-6	0.02	-3.36 x 10-6	3.17 x 10-6	0.02	-2.14 x 10-6	3.02 x 10-6	0.01
	BDI	-6.26 x 10-7	4.00 x 10-7	0.05	-5.17 x 10-7	7.56 x 10-7	0.01	-5.49 x 10-7	7.12 x 10-7	0.01
	PCL-M				-9.22 x 10-8	5.38 x 10-7	0.00	-4.37 x 10-7	5.23 x 10-7	0.01
	TBI							-3.09 x 10-5**	1.14 x 10-5	0.12
	R^2		0.05			0.001			0.12	
	F for change in R^2		0.92			0.03			7.29**	
Left	Age	-3.98 x 10-7	4.14 x 10-7	0.02	-3.78 x 10-7	4.21 x 10-7	0.01	-3.72 x 10-7	3.95 x 10-7	0.01
Cingulum	Years of Education	-4.48 x 10-6	2.35 x 10-6	0.06	-4.31 x 10-6	2.41 x 10-6	0.06	-3.35 x 10-6	2.29 x 10-6	0.03
	BDI	-4.51 x 10-7	3.05 x 10-7	0.04	-6.37 x 10-7	5.75 x 10-7	0.02	-6.62 x 10-7	5.40 x 10-7	0.02
	PCL-M				1.57 x 10-7	4.10 x 10-7	0.00	-1.12 x 10-7	3.97 x 10-7	0.00
	TBI							-2.41 x 10-5**	8.67 x 10-6	0.12
	R^2		0.11			0.003			0.12	
	F for change in R^2		1.99			0.15			7.73**	
Right	Age	-1.45 x 10-7	2.88 x 10-7	0.00	-1.26 x 10-7	2.92 x 10-7	0.00	-1.22 x 10-7	2.82 x 10-7	0.00
Cingulum	Years of Education	-4.66 x 10-6	1.63 x 10-6	0.13	-4.50 x 10-6	1.67 x 10-6	0.12	-3.97 x 10-6	1.63 x 10-6	0.09
	BDI	-4.14 x 10-7	2.11 x 10-7	0.06	-5.96 x 10-7	3.99 x 10-7	0.04	-6.10 x 10-7	3.85 x 10-7	0.04
	PCL-M				1.53 x 10-7	2.84 x 10-7	0.00	4.63 x 10-9	2.83 x 10-7	0.00
	TBI							-1.33 x 10-5*	6.19 x 10-6	0.07
	R^2		0.17			0.01			0.07	
	F for change in R^2		3.39			0.29			4.64*	
Fornix	Age	1.63 x 10-6	1.49 x 10-6	0.02	1.30 x 10-6	1.47 x 10-6	0.01	1.32 x 10-6	1.43 x 10-6	0.01
	Years of Education	6.98 x 10-6	8.46 x 10-6	0.01	4.26 x 10-6	8.43 x 10-6	0.00	6.68 x 10-6	8.30 x 10-6	0.01
	BDI	-1.32 x 10-6	1.10 x 10-6	0.03	1.67 x 10-6	2.01 x 10-6	0.01	1.61 x 10-6	1.96 x 10-6	0.01
	PCL-M				-2.52 x 10-6	1.43 x 10-6	0.05	-3.20 x 10-6*	1.44 x 10-6	0.08
	TBI							1.32 x 10-6	1.43 x 10-6	0.06
	R^2		0.1			0.05			0.06	
	F for change in R^2		1.83			3.1			3.77	
*p < .05. **p < .01.										
BDI = Beck Depression Inventory-II; PCL-M = PTSD Check List-Military Version										

Table 7. Summary of Hierarchical Regression Analyses Predicting Fornix Axial Diffusivity

			Model 1			Model 2			Model 3	
Region	Variable	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2
Fornix	Age	1.61 x 10-6	2.20 x 10-6	0.01	1.15 x 10-6	2.18 x 10-6	0.00	1.18 x 10-6	2.06 x 10-6	0.00
	Years of Education	1.74 x 10-5	1.25 x 10-5	0.03	1.35 x 10-5	1.25 x 10-5	0.02	1.83 x 10-5	1.19 x 10-5	0.04
	BDI	-1.72 x 10-6	1.62 x 10-6	0.02	2.57 x 10-6	2.98 x 10-6	0.01	2.44 x 10-6	2.81 x 10-6	0.01
	PCL-M				-3.61 x 10-6	2.13 x 10-6	0.05	-4.96 x 10-6*	2.07 x 10-6	0.09
	TBI							-1.21 x 10-4*	4.52 x 10-5	0.11
	R^2		0.11			0.05			0.11	
	F for change in R^2		2.09			2.88			7.18**	
*p < .05. **p < .01.										
BDI = Beck Depression Inventory-II; PCL-M = PTSD Check List-Military Version										

Table 8. S Summary of Hierarchical Regression Analyses Predicting Left Orbitofrontal Cortex Cortical Thickness

			Model 1			Model 2			Model 3	
Region	Variable	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2	β-hat	SE(β-hat)	sr^2
Left OFC	Age	-3.40 x 10-3	2.83 x 10-3	0.03	-4.02 x 10-3	2.71 x 10-3	0.04	-4.09 x 10-3	2.69 x 10-3	0.04
	Years of Education	5.7 x 10-4	1.60 x 10-2	0.00	-7.03 x 10-3	1.56 x 10-2	0.00	-1.01 x 10-2	1.56 x 10-2	0.01
	BDI	-9.23 x 10-5	2.16 x 10-3	0.00	8.84 x 10-3*	4.19 x 10-3	0.40	8.56 x 10-3*	4.17 x 10-3	0.37
	ICV	1.6 x 10-7	1.6 x 10-7	0.02	7.1 x 10-8	1.6 x 10-7	0.00	7.1 x 10-8	1.6 x 10-7	0.00
	PCL-M				-7.19 x 10-3*	2.94 x 10-3	0.58	-6.11 x 10-3*	3.03 x 10-3	0.42
	TBI							7.72 x 10-2	5.86 x 10-2	0.04
	R^2		0.05			0.11			0.03	
	F for change in R^2		0.71			5.98*			1.74	
*p < .05. **p < .01.										
BDI = Beck Depression Inventory-II; PCL-M = PTSD Check List-Military Version; ICV = Intracranial Volume										

Table 9. Significant Partial Correlations between Neuropsychological Domain Scores and DTI

		Executive Functions	Processing Speed
FA	AIC Right	.27*	ns
	Cingulum Left	.38**	.38**
	Cingulum Right	.27*	.33**
	Genu	ns	.44**
	Body	.37**	.43**
	Splenium	.36**	.31*
	PIC Left	.51***	.50***
	PIC Right	.49***	.27*
RD	AIC Left	ns	-.27*
	Cingulum Left	ns	-.40**
	Cingulum Right	ns	-.37**
	Genu	ns	-.45**
	Body	-0.30*	-.48***
	Splenium	ns	-.36**
	Fornix	ns	-.39**
	PIC Left	-0.30*	-.48***
	PIC Right	-0.27*	-.28*
AD	Body	ns	-.29*
	Fornix	ns	-.40**
	PIC Right	.32*	ns

Results of partial correlation controlling for age
*p<.05, **p<.01, ***p<.001

Table 10. Significant Partial Correlations between Cortical Thickness and DTI

		L. Middle Frontal	L. Orbito-frontal	L. Medial Temporal	L. Lateral Temporal		R. Lateral Temp	R. Inf. Frontal	R. Orbito-frontal	R. Medial Temporal
FA	Cingulum Left	.31*	.38**						.34*	.29*
	Splenium							.41**		.37**
	PIC Left		.33*							
RD	Body				.32*					
	Fornix								.33*	
AD	Cingulum Left		.30*	.31*					.34*	
	Cingulum Right			.35**						
	Genu			.28*						
	Body				.32*		.38**			
	Splenium				.28*					
	Fornix								.28*	
	PIC L			.35**						
	PIC Right			.31*						
Results of partial correlation controlling for age and ICV										
*p<.05, **p<.01, ***p<.001										

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