Behavioral and neural correlates of chronic blast-related mild traumatic brain injury

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BEHAVIORAL AND NEURAL CORRELATES OF CHRONIC BLAST-RELATED MILD TRAUMATIC BRAIN INJURY

by

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ABSTRACT

Blast-related mild traumatic brain injury (mTBI) is a common injury among Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans due to the frequent use of improvised explosive devices (IEDs). A significant minority of veterans with blast-related mTBI complain of postconcussion symptoms (PCS) and cognitive difficulties, even years after the injury. Studies have suggested that these behavioral sequelae are primarily linked to mental health disorders such as posttraumatic stress disorder (PTSD). However, mTBI is associated with neural changes and the impact of these changes on behavioral sequelae is unclear. As such, this dissertation had three goals. First, this dissertation assessed whether the severity of PCS in blast-exposed individuals is associated with the extent of mTBI-related neural injury. Results revealed that individuals with mTBI with loss of consciousness (LOC) had significantly more white matter abnormalities than no-TBI controls and that these white matter abnormalities were spatially variable across individuals. Importantly, the extent of white matter abnormality was associated with physical PCS severity and mediated the relationship between mTBI with LOC and physical PCS. Second, this dissertation examined whether these white matter abnormalities were also associated with overall
cognitive impairment. In light of the observed variability in white matter injury, a measure of overall cognitive status that takes into account heterogeneity of cognitive impairment was used. Results showed that the extent of white matter abnormality was associated with cognitive status and mediated the relationship between mTBI with LOC and cognitive impairment. Third, this dissertation examined performance and brain function in the context of an experimental measure of cognitive control known to be sensitive to residual effects of mTBI. Results revealed that although behavioral performance was similar across groups, the mTBI group had enhanced functional connectivity between brain networks important for task performance, suggesting a potential compensatory mechanism in mTBI. Together, the findings of this dissertation suggest that mTBI is associated with structural and functional connectivity alterations years after the injury. Further, this dissertation suggests that whereas structural connectivity changes may have negative behavioral consequences, changes in functional connectivity may serve as a compensatory mechanism for successful performance.
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LIST OF ABBREVIATIONS

ACC ...................................................................................................... anterior cingulate cortex
ACRM ................................................................................................ American Congress of Rehabilitation Medicine
AD ................................................................................................................................. axial diffusivity
ADHD .................................................................................................................. attention deficit hyperactivity disorder
ANCOVA ........................................................................................................... analysis of covariance
AUDIT .................................................................................................................... Alcohol Use Disorder Identification Test
BET ........................................................................................................................... Brain Extraction Tool
BOLD ..................................................................................................................... blood oxygen level dependent
BVMT .................................................................................................................... Brief Visuospatial Memory Test
CAPS ...................................................................................................................... Clinician-Administered PTSD Scale
CEN ......................................................................................................................... central executive network
CSF ............................................................................................................................. cerebral spinal fluid
CT .................................................................................................................................. computed tomography
CTE ............................................................................................................................ chronic traumatic encephalopathy
CVLT ......................................................................................................................... California Verbal Learning Test
dACC ....................................................................................................................... dorsal anterior cingulate cortex
DLPFC ...................................................................................................................... dorsolateral prefrontal cortex
DMN ............................................................................................................................. default mode network
dMPFC ..................................................................................................................... dorsomedial prefrontal cortex
DSM-IV ............................................. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DTI ............................................................................................................................. diffusion tensor imaging
FA .............................................................. fractional anisotropy
FEAT .................................................................. fMRI Expert Analysis Tool
FLAME ................................................. FMRIB’s Local Analysis of Mixed Effects
FLIRT .......................................................... FMRIB’s Linear Image Registration Tool
fMRI ............................................................... functional magnetic resonance imaging
FMRIB ..................................................... Functional Magnetic Resonance Imaging of the Brain
FNIRT .......................................................... FMRIB’s Nonlinear Image Registration Tool
FSL ................................................................... FMRIB Software Library
FWHM .................................................................. full-width/half-max
GCS ...................................................................... Glasgow Coma Scale
ICA .............................................................. independent component analysis
ICA-AROMA ................................... ICA-based strategy for Automatic Removal of Motion Artifact
IED ................................................................. improvised explosive device
ImPACT ............................................. Immediate Post-Concussion Assessment and Cognitive Testing
LOC ..................................................................... loss of consciousness
MD .................................................................. mean diffusivity
MRI ............................................................... magnetic resonance imaging
MTBI ............................................................... mild traumatic brain injury
OEF/OIF .............................................. Operation Enduring Freedom/Operation Iraqi Freedom
PCC .................................................................. posterior cingulate cortex
PCL-M .......................................................... PTSD Checklist-Military Version
PCS .................................................................... postconcussion symptoms
PPI.......................................................... psychophysiological interactions
PTA.......................................................... posttraumatic amnesia
PTSD.......................................................... posttraumatic stress disorder
RD............................................................. radial diffusivity
ROI........................................................... region of interest
RPQ.................................................. Rivermead Postconcussion Questionnaire
RT .......................................................... reaction time
SE............................................................ standard error
SN .......................................................... salience network
SWI .................................................. susceptibility weighted imaging
TBI .......................................................... traumatic brain injury
TBSS ................................................ Tract-Based Spatial Statistics
TOMM ................................................ Test of Memory Malingering
VBA .................................................. voxel-based analysis
vMPFC ........................................... ventromedial prefrontal cortex
WTAR ................................................ Wechsler Test of Adult Reading
CHAPTER ONE: General Introduction

A traumatic brain injury (TBI) occurs when an external force causes a disruption in normal brain function. TBI is a major public health concern and is one of the leading causes of injury-related emergency room visits in the United States (Faul, Xu, Wald, & Coronado, 2010). In this section, I describe the core features of mild traumatic brain injury (mTBI), which is the least severe form and most common type of TBI. First, I briefly describe classification of TBI then outline the prevalence and significance of TBI in the United States. Next, I describe the neuropathology of mTBI, including civilian and blast-related etiologies. I then discuss the neuroimaging techniques used in mTBI, followed by a detailed description of the behavioral and cognitive sequelae commonly associated with mTBI. Finally, I conclude this section with a description of specific aims this dissertation sought to address.

TBI Severity and Classification

One of the most recognized systems to scale the severity of TBI is the Glasgow Coma Scale (GCS), which describes TBI severity using a single score ranging between 3 and 15. This score is based on neurologic function in three core areas including motor function, verbal responding, and the ability to open the eyes voluntarily or in response to external stimuli. According to this scale, severe TBI ranges from 3 to 9, moderate TBI ranges from 8 to 12, and mTBI ranges from 13 to 15 (Jennett & Teasdale, 1981). In severe TBI, the individual is grossly impaired in the three core neurologic areas of motor, verbal, and cognitive functions, which can last for hours to months after injury. In moderate TBI, there is neurologic impairment but to a lesser degree than severe TBI.
However, because the GCS largely describes states of severe neurologic dysfunction, it has limited application when used to assess mTBI. The majority of mTBI patients have subtle to very little impairments in motor function, verbal responding, and eye opening thereby resulting in a score of 15 for most patients (McCrea, 2008). This presents a challenge in diagnosing mTBI, as a score of 15 can also be interpreted as a completely normal neurologic status. Thus, accurate mTBI diagnosis must rely on other acute defining characteristics such as alterations in consciousness.

There are several diagnostic systems that are better suited for classifying mTBI than a single GCS score. One of the most commonly used systems to define mTBI comes from the American Congress of Rehabilitation Medicine (ACRM). According to the ACRM (1993), a mTBI must include at least one of the following: loss of consciousness (LOC) not exceeding 30 minutes, presence of posttraumatic amnesia (PTA) not exceeding 24 hours, any alterations in mental state (e.g., feeling dazed or confused), and/or a focal neurological deficit(s). LOC lasting longer than 30 minutes and PTA exceeding 24 hours would indicate a moderate or severe TBI.

Interestingly, the ACRM does not differentiate between mTBI associated with visible neural abnormalities and mTBI without visible neural abnormalities. However, general consensus is that when there is an abnormal finding on a brain scan, the classification changes to “complicated mTBI” as opposed to “uncomplicated mTBI”. Most brain scans reveal uncomplicated mTBI, with only an estimated 3-10% of mTBIs revealing an abnormality and less than 1% requiring neurosurgical intervention (Jagoda et al., 2002). For those who are diagnosed with complicated mTBI, outcome is generally
more consistent with moderate TBI (Williams, Levin, & Eisenberg, 1990). Complicated mTBI is associated with lower GCS scores, greater frequency of LOC, and higher incidence of skull fracture than uncomplicated mTBI (Iverson, Lovell, Smith, & Franzen, 2000).

Deployment-related mTBI has proven more difficult to diagnose than civilian mTBI. This is because medical records are rarely available in the warzone. Additionally, medics may not see the individual until hours after the injury, limiting the ability to diagnose immediate signs and symptoms. Thus, classification of deployment-related mTBI more often relies on retrospective self-report, which is subject to misremembering or reporting bias. Within the context of this limitation, deployment-related mTBI assessment is conducted with an in-depth structured interview that probes individuals about symptoms experienced after injury, which is currently the gold standard of diagnosis (Corrigan & Bogner, 2007).

Although deployment-related mTBI is one of the most common injuries of the recent wars in Iraq and Afghanistan, not much is known about the associated behavioral sequelae. This leaves unanswered questions about the neural and behavioral correlates of deployment-related mTBI. Therefore, for the purposes of this dissertation, I will focus on deployment-related mTBI and use the definition put forth by the ACRM.

**Epidemiology**

TBI is a major public health concern. Each year an estimated 1.7 million people sustain a TBI in the United States, with about 75% of these injuries categorized as mild (Cassidy et al., 2004). However, the incidence of TBI is likely severely underestimated,
as this number does not include individuals who do not seek treatment or who seek care in outpatient settings. In fact, it is estimated that 25% of all individuals with head injuries have no contact with a medical setting at any level, with the majority of these undocumented cases likely falling into the mild category (Sosin, Sniezek, & Thurman, 1996).

While the true incidence of TBI remains unknown, it is clear that TBI has become a substantial financial burden. In 2000, estimates suggested that TBI accounted for a total of $60 billion annually in the United States, of which mTBI accounted for 44% of these costs (McCrea, 2008; Thurman, 2001). Less is known about the cost of lost productivity in those individuals who did not seek medical care, particularly for those with mTBI.

Over the last decade, the United States’ involvement in the Iraq and Afghanistan wars has added to the financial and societal burden of brain injury, with more soldiers returning from these wars with mTBI. The frequency of these injuries has led to mTBI being called the signature injury of the wars, with estimates suggesting that as high as 19% of service members have experienced a mTBI (Tanielian & Jaycox, 2008). Due to the frequent use of improvised explosive devices (IEDs) and other blast emitting devices (e.g., mortars, landmines, grenades), the majority of these mTBIs experienced by Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) service members are blast-related.

**Neuropathology**

MTBI is associated with white matter injury in the brain otherwise known as traumatic axonal injury. Historically, these pathological white matter changes were
thought to be the result of diffuse shear strains that are the direct consequence of mechanical forces experienced at the time of injury (Adams, Graham, Murray, & Scott, 1982; Gennarelli et al., 1982; Holbourn, 1943, 1945). However, more recently it has become clear that although shearing of axons on impact may occur (Bigler, 2004; Oppenheimer, 1968), it is not the main cause of traumatic axonal injury in mTBI.

Rather, in the majority of cases of mTBI, there are a variety of pathophysiological changes that occur as a result of the injury that are capable of producing pathological white matter changes. This secondary cascade, referred to as the metabolic cascade, can occur after impact in mTBI in the absence of shear strain, and can functionally impair and ultimately injure an axon. In the metabolic cascade, ion imbalance contributes to the persistent dysfunction of otherwise intact axons (Johnson, Stewart, & Smith, 2013). As a result of the acceleration forces on the brain during injury, there is an abrupt release of neurotransmitters and an ionic shift, with an efflux of potassium and influx of calcium. The brain works to restore the neuronal membrane to its normal ionic potential, thereby creating an energy crisis within the brain. Eventually, after the initial state of hypermetabolism, the brain goes into a state of depressed metabolism with elevated calcium levels. This calcium flux can disrupt and impair mitochondria, neurofilaments, and microtubules, contributing to the dysfunction of axons after injury (Buki, Farkas, Doczi, & Povlishock, 2003; Maxwell, Kosanlavit, McCreath, Reid, & Graham, 1999).

The extent of injury and axonal dysfunction may be directly related to the severity of the TBI. One theory by Ommaya and Gennarelli (1974) posits that brain injury occurs in a centripetal manor. According to this view, less severe injuries that are associated
with alterations in consciousness (e.g., PTA, feeling dazed or confused) only involve changes to cortical regions. However, when the brain injury is more severe and involves traumatic unconsciousness, the extent of injury in the brain occurs in deeper structures such as the brainstem in addition to cortical and subcortical areas. Because the mesencephalon is less vulnerable than the temporal lobes and limbic system, PTA can occur without LOC, but the reverse can never occur. Therefore, a brain injury involving LOC is always associated with a period of PTA and will likely involve deeper and more diffuse axonal injury. Moreover, the duration of coma is influenced by the extent of traumatic axonal injury, with more widespread white matter injury present in TBI with longer periods of unconsciousness (Gennarelli et al., 1982).

While initial studies of the neuropathology of mTBI focused on civilian head injury (e.g., falls, motor vehicle accidents, sports), a multitude of research has surfaced suggesting that a blast also induces traumatic axonal injury (Budde, Janes, Gold, Turtzo, & Frank, 2011; Goldstein et al., 2012; Kwon et al., 2011). However, the biomechanics of blast are quite different from traditional head injury, leading to potentially different mechanisms for the resultant axonal injury. In civilian-related mTBI, the primary mechanism of injury is impact to the head. However, in blast-related mTBI, blast forces also significantly contribute to the injury and interact with both the head and body.

In an explosion, a blast wave emits both positive and negative air pressure and moves rapidly at high velocity as a sphere of compressed and expanding gases. Upon striking the individual, the blast wave can have direct interaction with the brain through the skull, creating acceleration forces on the head as well as loading pressure directly
onto the brain, or transfer kinetic energy through blood vessels in the abdomen and chest, generating waves that travel to the brain (Cernak et al., 2011; Cernak & Noble-Haeusslein, 2010; Sundaramurthy et al., 2012). However, a recent report investigating a mouse model of blast neurotrauma by Goldstein and colleagues (2012) suggests that neither thoracic mechanisms nor vascular effects significantly contribute to injury during blast exposure but rather a blast’s direct interaction with the brain is the primary biomechanical mechanism for injury.

In addition to the primary effects of the blast wave, additional forces from the explosion may also have impact on an individual. The blast wind travels at high speeds immediately following the initial blast wave and can displace an individual or object, further contributing to injury and creating coup-countercoup effects that are common in civilian head injury. Moreover, a blast wave can interact with the environment and reflect off walls or the ground to generate complex waves that can create more severe injuries (Cernak & Noble-Haeusslein, 2010).

As a result of these blast mechanisms, explosions may cause four types of injury: (1) primary blast injury occurs when the injury is the result from the blast wave without a direct blow to the head; (2) secondary injury occurs as a result of fragments or debris propelled by the explosion; (3) tertiary injury is the result of the acceleration of the body by the blast wind (e.g., individual is thrown against the ground); and (4) quaternary injury is the result of the heat of the explosion and includes flash burns (Cernak & Noble-Haeusslein, 2010). Although there have been some reports of the effects of primary blast injury (Hayes, Morey, & Tupler, 2011; Taber et al., 2015; Warden et al., 2009), primary
blast mTBI can be exceedingly difficult to isolate. Service members are likely to experience a combination of primary, secondary, and tertiary forces in an explosion that can result in mTBI.

**Neuroimaging**

Neuroimaging procedures provide a means to assess the neuropathology of mTBI in vivo. However, on clinical scans (e.g., computed tomography [CT], T1-weighted, T2-FLAIR), there is minimal evidence for neuropathology in mTBI, with the occasional finding consisting of macroscopic structural abnormalities such as cerebral contusions, subdural hematomas, epidural hematomas, edema, and white matter hyperintensities (Niogi & Mukherjee, 2010). This led to the popular notion that there were no brain changes associated with mTBI. Recently, newer, more sensitive techniques have made it possible to visualize brain pathology in mTBI.

**DTI**

One technique that has shown to be especially sensitive to the neuropathology of mTBI is diffusion tensor imaging (DTI). DTI is an in vivo magnetic resonance imaging (MRI) technique that measures water diffusion in neural tissue and thus provides information about the microstructure of the underlying tissue. Motion of water molecules in the brain is largely determined by brain tissue properties and type (i.e., gray matter, white matter, and cerebral spinal fluid [CSF]). For example, in CSF, water is unrestricted and moves randomly and freely (i.e., isotropic). However, in white matter, diffusion is restricted by axonal membranes, myelin sheaths, microtubules, and neurofilaments and diffuses more rapidly in one particular direction (i.e., anisotropic).
The two most common indices used to quantify diffusion are fractional anisotropy (FA) and mean diffusivity (MD). FA describes the directionality of water movement and ranges from 0 to 1, with 0 indicating diffusion that is completely isotropic, or free to move about unhindered, and 1 indicating diffusion that is entirely anisotropic, or moves along a single axis. Therefore, when diffusion is more isotropic, as in CSF and gray matter, FA is closer to 0. In contrast, when diffusion is more anisotropic, as in healthy white matter, FA is closer to 1. Thus, reduced FA in white matter is thought to indicate white matter integrity loss that may reflect damage to the axon membrane or myelin sheath.

MD is the rate of diffusion averaged along three principal diffusion directions, which includes a main direction and two perpendicular directions. The main diffusion direction is the largest magnitude of diffusion and is referred to as the axial direction. This measure can be used independently as axial diffusivity (AD) and is thought to represent the integrity of the axonal membrane. The other two directions are referred to as the radial axes and are perpendicular to the main diffusion direction. Measured alone, radial diffusivity (RD) is believed to reflect the integrity of the myelin sheath of the axon. MD is inversely related to FA so that in healthy white matter FA is high and MD is low.

Reduced FA and increased MD typically suggest microstructural damage. However, this may vary depending on the stage of injury. Several studies have shown that when measured acutely, FA is elevated and MD is reduced (Bazarian et al., 2007; Chu et al., 2010; Wilde et al., 2008; Wu et al., 2010 but see Lipton et al., 2009). Explanations for this altered pattern of diffusion metrics focus on the acute pathology of
mTBI (Niogi & Mukherjee, 2010). In the acute stage of mTBI, there is temporary axonal swelling, which restricts overall diffusion and therefore decreases MD. Additionally, these swollen axons restrict water movement in the extracellular space causing an increase in anisotropic diffusion and FA.

In the chronic stage of injury, there is evidence for reduced FA and increased MD in both civilian- and blast-related mTBI (Davenport et al., 2011; Jorge et al., 2012; Kraus et al., 2007; Little et al., 2010; Lo, Shifteh, Gold, Bello, & Lipton, 2009). This shift to decreased FA and increased MD with chronicity may be the result of the transition from cytotoxic toward vasogenic edema in chronic mTBI (Kou et al., 2010). Animal studies have provided evidence for vasogenic edema in chronic mTBI, suggesting that although initially axonal swelling may be the cause of axonal dysfunction, the breakdown of the blood brain barrier contributes to chronic dysfunction (Chen, Mao, Yang, Abel, & Meaney, 2014; Goldstein et al., 2012). Moreover, decreased FA and increased MD may also be the result of other white matter pathology that occurs as the injury progresses into the chronic stage, such as demyelination, prolonged axonal degeneration, and impaired axonal transport (Budde et al., 2011; Song et al., 2003).

There is much debate as to the best method to analyze diffusion metrics in mTBI research. Across the literature, there are five general approaches that are used. These include region of interest (ROI) analysis, tractography, voxel-based analysis (VBA), white matter load, and a voxel cluster-based method. The most common of these methods is ROI analysis, in which diffusion properties of specific white matter pathways are analyzed. Using this technique, results in civilian mTBI suggest that long white
matter frontal association pathways such as the anterior corona radiata, uncinate fasciculus, superior longitudinal fasciculus, and corpus callosum are the most commonly damaged tracts in chronic mTBI (Geary, Kraus, Pliskin, & Little, 2010; Kraus et al., 2007; Little et al., 2010; Lo et al., 2009; Niogi et al., 2008), although other white matter tracts have been reported in the literature (Kraus et al., 2007; Little et al., 2010). In blast-related mTBI, the findings have been mixed, with some studies finding white matter alterations in particular ROIs (Mac Donald et al., 2011; Mac Donald et al., 2013) whereas others do not (Davenport et al., 2011; Levin et al., 2010; Sorg, et al. 2013). A recent study by our lab may shed some light on this discrepancy in the blast literature. We found that in blast-related mTBI with LOC, FA was reduced in ROIs only as a function of repetitive blasts (Hayes, Miller, Lafleche, Salat, & Verfaellie, 2015).

Tractography is another commonly used diffusion method in mTBI studies. Tractography is an automatic reconstruction of white matter pathways from diffusion images. It can also be used to generate a specific white matter pathway between two a priori ROIs. Civilian mTBI studies using this method have found reductions in FA (Rutgers, Fillard, et al., 2008; Rutgers, Toulgoat, et al., 2008; Singh, Jeong, Hwang, Sungkarat, & Gruen, 2010). However, in the only study to examine white matter using tractography in blast-related mTBI, Levin and colleagues (2010) did not find any between group differences in FA.

VBA is a whole brain approach in which diffusion properties of the same voxel are compared across groups. Unlike the previous two methods, VBA is not limited to whole white matter pathways but instead can simultaneously examine white matter
voxels of the entire brain. Additionally, it is fully data-driven and can be used for exploratory analyses. However, this approach also has its difficulties. VBA focuses on the presence of white matter pathology in the same white matter voxel across individuals. Thus, similar to the methods mentioned previously, VBA is limited to pathology that is spatially consistent across subjects. This limitation may contribute to the inconsistent findings using this technique in the literature. In civilian chronic mTBI, studies using this method report significant differences in FA and MD between mTBI and controls (Lipton et al., 2008; Salmond et al., 2006). However, in chronic blast-related mTBI studies, the findings have been mixed, with some suggesting that this method is sensitive enough to detect differences between individuals with mTBI and controls (Matthews, Spadoni, Lohr, Strigo, & Simmons, 2012; Morey et al., 2012) and others not (Jorge et al., 2012; Taber et al., 2015).

White matter load studies have increased in popularity because this method can better account for spatially non-overlapping white matter abnormalities that are more consistent with the neuropathology of mTBI. In this method, the number of ROIs with abnormal white matter, rather than the integrity of particular ROIs, is examined. Using this technique, studies have found that individuals with mTBI have a significantly higher number of ROIs that are abnormal than controls in both civilian mTBI (Kraus et al., 2007) and blast-related mTBI (Hayes et al., 2015), although one study did not find any significant differences in blast-related mTBI using this method (Davenport et al., 2011).

Finally, the voxel cluster-based method is the newest form of analysis and may be the most sensitive for identifying mTBI neuropathology. This technique employs a whole
brain approach by examining the number of clusters of white matter voxels with altered diffusion metrics. In this way, researchers can measure injury that is not uniformly distributed across an entire fiber tract. Moreover, unlike VBA, the voxel cluster-based method can measure spatially heterogeneous white matter abnormalities by accounting for the number of abnormalities rather than the specific area of pathology. This technique may be particularly sensitive to blast-related mTBI, as studies using this technique have been more consistent in their findings, suggesting that individuals with mTBI have more abnormal white matter voxels than controls (Davenport et al., 2011; Jorge et al., 2012; Taber et al., 2015). The sensitivity of this technique is not limited to blast-related mTBI, as Lipton and colleagues (2012) reported similar findings using this technique in civilian mTBI. Together, these studies suggest that mTBI pathology, and in particular blast-related mTBI pathology, is diffuse and spatially heterogeneous and methods that are able to capture this heterogeneity may be best suited for investigating white matter integrity in mTBI.

**Behavioral Outcome**

Acute behavioral complaints are common after mTBI. These behavioral complaints are referred to as postconcussion symptoms (PCS) and include physical (e.g., dizziness, headaches), cognitive (e.g., slowed thinking, difficulties with concentration), and emotional (e.g., irritability, anxiety) complaints. Some of the most frequently reported symptoms after mTBI include headache, dizziness, sensitivity to light, mental fogginess, poor concentration, and memory difficulties (McCrea, 2008). PCS are typically transient with rapid or gradual resolution within days to weeks after injury.
(Carroll et al., 2004). McCrea and colleagues (2003) found that symptoms are most severe immediately following injury, with the initial stages of recovery beginning two hours after injury and continuing over the course of days to weeks. The trajectory of symptom recovery is often variable, with sports-related injuries resolving much quicker than other civilian-related injuries (McCrea et al., 2003). Nonetheless, the overwhelming majority of individuals experience full recovery by three months post-injury regardless of mTBI mechanism (McCrea, 2008).

While the majority of individuals with mTBI recover to pre-injury functioning, a minority suffer from persistent PCS (Carroll et al., 2004). Whereas PCS in the acute phase reflect the transient effects of mTBI, psychological and motivational factors play an important role in the persistence of these symptoms (McCrea, 2008). PCS are non-specific and are also associated with chronic pain and a variety of mental health disorders (Bigler, 2008; Donnell, Kim, Silva, & Vanderploeg, 2012; Smith-Seemiller, Fow, Kant, & Franzen, 2003), thus complicating efforts to disentangle the direct contribution of mTBI vs. comorbid factors to chronic PCS.

The non-specificity of PCS poses particular diagnostic difficulty in veterans who sustained mTBI during deployment, given the high rate of co-morbid psychiatric conditions in this population (Fear et al., 2009; Hoge et al., 2008). Despite evidence that some symptoms in the chronic stage may be associated with mTBI-related neuropathology (Bigler & Maxwell, 2012), recent behavioral studies of veterans with self-reported mTBI suggest that PCS symptoms are linked primarily to mental health symptoms (Belanger, Kretzmer, Vanderploeg, & French, 2010; Hoge et al., 2008; Lippa,
Pastorek, Benge, & Thornton, 2010; Schneiderman, Braver, & Kang, 2008; Verfaellie, Lafleche, Spiro, Tun, & Bousquet, 2013).

**Neuropsychological Sequelae**

Cognitive performance after mTBI has a similar trajectory to PCS. Acutely, individuals with mTBI are impaired on a variety of cognitive domains. In a meta-analysis, Belanger, Curtiss, Demery, Levowitz, and Vanderploeg (2005) found that individuals with mTBI were impaired in the cognitive domains of attention, executive function, memory acquisition, and visuospatial function with large deficits in fluency and delayed memory recall. Other studies have also found acute impairments across cognitive domains such as delayed memory, processing speed, and executive function (Belanger & Vanderploeg, 2005; Bleiberg et al., 2004; Collins et al., 1999; Landre, Poppe, Davis, Schmaus, & Hobbs, 2006). However, for the majority of individuals these impairments tend to resolve within days to months after injury depending on the nature of the mTBI.

In sports-related injuries, computerized testing suggests that by seven days after injury, athletes who experienced mTBI perform similarly to controls (McCrea et al., 2003). Likewise, performance on standardized neuropsychological testing typically resolves by seven days post-injury for most athletes (Belanger & Vanderploeg, 2005). In other civilian injuries, recovery from acute neuropsychological impairment is slower, with the majority of cases resolved by three months (Belanger et al., 2005; Dikmen, Machamer, Winn, & Temkin, 1995; Frencham, Fox, & Maybery, 2005; Schretlen & Shapiro, 2003). However, other research has pointed to subtle neuropsychological deficits in chronic mTBI, particularly in executive function (Binder, Rohling, &
Larrabee, 1997). Still others have suggested that only at the more severe end of the mTBI spectrum (i.e., abnormalities on structural imaging and longer durations of PTA or LOC) are neuropsychological deficits apparent in the chronic stage (Dikmen, Machamer, & Temkin, 2001).

There is evidence for residual cognitive impairment in blast-related mTBI (Hayes et al., 2011; Kontos et al., 2013; Verfaellie, Lafleche, Spiro, & Bousquet, 2014). However, neuropsychological performance is also impacted by psychiatric conditions such as posttraumatic stress disorder (PTSD), which has been associated with lower attention, executive function, verbal memory, and visuospatial memory (Leskin & White, 2007; Vasterling, Brailey, Constans, & Sutker, 1998; Vasterling et al., 2002). This poses particular challenges in blast-related mTBI, where the incidence of comorbid psychiatric conditions is high (Fear et al., 2009; Hoge et al., 2008). In a recent study that examined the contribution of PTSD symptom severity to cognitive performance in a group of OEF/OIF veterans, Verfaellie and colleagues (2014) found that there was no association between mTBI and neuropsychological functioning once PTSD symptom severity was taken into account, suggesting that cognitive performance differences in blast-related mTBI are attributable to PTSD.

Still, some studies have found residual cognitive impairments even after accounting for PTSD. In a meta-analysis focusing on chronic blast-related mTBI, Karr, Areshenkoff, Duggan, and Garcia-Barrera (2014) found that mTBI was associated with impairment in executive function, and in particular set-shifting, with a trend toward differences in processing speed and verbal delayed memory. However, PTSD was not
associated with performance in any cognitive domain. In another blast-related TBI study, Levin and colleagues (2010) found that individuals with chronic TBI performed worse than controls in verbal memory, while performance was not significantly associated with PTSD. These studies suggest that factors other than co-morbid psychiatric conditions may also impact cognition in individuals with blast-related mTBI.

One potential factor that may play a role in chronic cognitive impairment in blast-related mTBI is exposure to multiple blasts. In the civilian sports literature, there is evidence to suggest that repeated concussive or sub-concussive blows to the head impact cognitive performance (Collins et al., 1999; Downs & Abwender, 2002; Drew, Templer, Schuyler, Newell, & Cannon, 1986). In a meta-analysis, Belanger and colleagues (2010) found that a history of multiple self-reported concussions was associated with a reduction in executive function and delayed memory. Moreover, recent evidence suggests that repetitive blast exposures may lead to more extensive white matter injury than a single blast exposure (Bazarian et al., 2012; Davenport et al., 2011). Repetitive blows to the head have also been linked to a neurodegenerative disease years after injury that impacts cognition called chronic traumatic encephalopathy (CTE), although this has mainly been reported in athletes (McKee et al., 2009; Omalu et al., 2006; Omalu et al., 2005). However, two recent studies have found CTE in young OEF/OIF veterans with multiple blast exposures, suggesting that in some individuals, repetitive blast exposures may also begin an accelerated neurodegenerative process similar to that seen in sports-related injuries (Goldstein et al., 2012; Omalu et al., 2011).
Another potential factor is litigation. In a meta-analysis investigating moderating factors on neuropsychological performance, Belanger and colleagues (2005) found that litigation accounted for prolonged cognitive impairment in individuals with mTBI. However, this may not be as much of a concern in a research setting where goals are unrelated to diagnostic concerns and financial incentives (Nelson et al., 2010).

Despite some evidence that mTBI diagnosis is associated with residual cognitive impairment, the overwhelming majority of research suggests that it is primarily attributed to psychiatric comorbidities (Campbell et al., 2009; Nelson, Yoash-Gantz, Pickett, & Campbell, 2009; Nelson et al., 2012; Storzbach et al., 2015; Vasterling et al., 2012). However, a more sensitive means to assess cognitive difficulties in blast-related mTBI may be to examine the association with injury-induced neural changes. Studies that have examined the link between neural changes and cognition have found associations between cognitive impairment and mTBI-related white matter abnormalities (Hayes et al., 2015; Jorge et al., 2012; Levin et al., 2010; Taber et al., 2015).

**Specific Aims**

As demonstrated in this review, there is clear evidence of persistent neural dysfunction in mTBI. However, the extent to which this dysfunction plays a role in behavioral outcome and cognitive performance is less clear. As a result, I seek to address three specific aims in this dissertation.

First, I aim to assess whether behavioral outcome in blast-related mTBI is associated with the neuropathology of mTBI. Studies investigating this have suggested that behavioral outcome may be largely the result of comorbid factors such as PTSD.
(Belanger, Kretzmer, et al., 2010; Hoge et al., 2008; Lippa et al., 2010; Schneiderman et al., 2008; Verfaellie et al., 2013). However, this question has yet to be explored in depth using a more proximal measure of brain injury such as white matter integrity. As such, in Chapter 2 (Study 1), I use DTI to measure white matter integrity in a large cohort of OEF/OIF veterans and hypothesize that white matter abnormalities may be associated with PCS severity independently from PTSD in blast-related mTBI.

Second, I aim to address whether the extent of mTBI-related white matter abnormalities is associated with cognitive impairment and whether white matter abnormalities provide a mechanism by which mTBI influences cognitive function. Although the majority of research examining the contribution of blast-related mTBI to chronic cognitive outcome suggests that any residual impairment is linked primarily to PTSD (Campbell et al., 2009; Nelson, Yoash-Gantz, Pickett, & Campbell, 2009; Nelson et al., 2012; Verfaellie et al., 2014), there is evidence for an association between cognitive impairment and mTBI-related neuropathology. However, as will be discussed further in Chapter 3 (Study 2), findings are inconsistent as to which domains of cognition are affected by TBI-related white matter abnormalities. Recent evidence that white matter abnormalities associated with blast-related mTBI are spatially variable raises the possibility that the associated cognitive impairment is also heterogeneous. Thus, in Chapter 3 (Study 2), I hypothesize that the extent of mTBI-related white matter abnormalities is associated with a measure of overall cognitive status that takes into account heterogeneity of cognitive sequelae across individuals.
Finally, I aim to assess whether individuals with blast-related mTBI exhibit chronic cognitive impairment in cognitive control and whether this is reflected in brain function using functional MRI (fMRI). Although specific deficits in standard neuropsychological tests in chronic blast-related mTBI are subtle at best, it is possible that experimental tasks may be more sensitive. As I describe in Chapter 4 (Study 3), the civilian literature has documented residual deficits in cognitive control, but less is known about blast-related mTBI. As such, Chapter 4 (Study 3) examines performance on a cognitive control task and associated brain function in a cohort of OEF/OIF blast-exposed veterans with and without mTBI.
CHAPTER TWO: White Matter Abnormalities are Associated with Chronic
Postconcussion Symptoms in Blast-Related mTBI

Introduction

Previous behavioral studies investigating chronic PCS in blast-related mTBI have found that chronic symptoms are linked primarily to mental health symptoms (Belanger et al., 2010; Hoge et al., 2008; Lippa et al., 2010; Schneiderman et al., 2008; Verfaellie et al., 2013). However, in vivo characterization of traumatic axonal injury as is possible with DTI may be more sensitive to assess whether chronic PCS relate to neuropathology associated with mTBI. Consistent with this notion that chronic PCS may be linked to mTBI-related traumatic axonal injury, recent studies of civilian mTBI have found that DTI metrics (e.g., FA) in both white (Bartnik-Olson et al., 2014; Messe et al., 2012) and gray (Bouix et al., 2013) matter are associated with PCS in the chronic stage of injury, and that reductions in white matter abnormalities over time are associated with reductions in PCS severity (Ling et al., 2012). However, these findings may not generalize to war-exposed veteran samples, which are likely to include individuals with higher rates of trauma exposure and mental health disorders than civilians.

In a recent study that examined the contribution of microstructural white matter abnormalities to chronic PCS in OEF/OIF veterans with blast-related mTBI, Petrie et al. (2014) found no association between white matter integrity and PCS. However, two other studies examining PCS in OEF/OIF veterans did find a significant association with white

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matter (Levin et al., 2010; Yeh et al., 2014), although Levin and colleagues’ (2010) findings varied depending on the method of imaging analysis used. One potential factor contributing to these mixed findings is the fact that these studies used techniques that focused on white matter alterations that were spatially consistent across subjects. Recent studies have shown that white matter abnormalities in blast-related mTBI are spatially heterogeneous (Davenport et al., 2011; Hayes et al., 2015; Jorge et al., 2012). These studies raise the possibility that methods that capture diffuse and spatially non-overlapping white matter abnormalities may be better suited to assess the relationship with PCS. Consistent with this notion, the only longitudinal study to find an association between changes in PCS severity and white matter integrity in civilians used a methodology that captured the spatial heterogeneity of mTBI (Ling et al., 2012).

In this study, I used voxel-wise cluster-based methods that have been shown to be sensitive to white matter abnormalities in blast-related mTBI (Jorge et al., 2012) to examine the relationship between white matter integrity and chronic PCS in a large cohort of OEF/OIF veterans with and without mTBI. The goals of this study were: 1) to examine the presence of white matter abnormalities in blast-related mTBI; 2) to assess the association between these white matter abnormalities and the severity of PCS, after accounting for traumatic stress; and 3) to examine whether white matter integrity mediates the relationship between mTBI and PCS, after accounting for traumatic stress symptoms.
Methods

Participants

Participants were 90 OEF/OIF veterans who reported exposure to blast within 100 meters. Individuals were recruited through the VA Boston Polytrauma Network and through flyers and outreach events in the community. Exclusion criteria for the study were a history of pre-deployment TBI with LOC or with symptoms persisting longer than three months post-injury, high levels of current alcohol use (>25 drinks per week), questionable effort with raw scores below 45 on the retention trial of the Test of Memory Malingering (TOMM; Tombaugh & Tombaugh, 1996), and structural brain abnormalities (e.g., hemorrhages, hematomas, skull fractures, tumors, excessive hyperintensities, hemispheric asymmetries) on T2-FLAIR, susceptibility weighted imaging (SWI), or T1-weighted sequences as determined by a board-certified neuroradiologist. Participants were also excluded if more than 10 weeks has elapsed between their behavioral assessment and neuroimaging.

Individuals were further subdivided into three groups (no-TBI, mTBI without LOC [mTBI-LOC], mTBI with LOC [mTBI+LOC]) using the definition of mTBI put forth by the ACRM (1993). Evaluation of TBI was based on an extensive clinical interview, which is described in detail in Verfaellie et al. (2013). Briefly, participants were questioned about their blast exposure(s) to determine the index event, which was the most severe exposure. Then, individuals were asked for an in-depth description of the index event including their memory for events preceding, during, and subsequent to the blast in order to infer the presence and duration of PTA and LOC. Participants were also
questioned about the presence of neurological symptoms immediately after the blast. Last, we inquired whether TBI could be corroborated by medical examination or witness reports. For individuals in the mTBI+LOC group, in all but two cases information regarding the presence and duration of LOC was based on information the participant obtained from a medic or combat peers who had witnessed the event. Interviews were transcribed and evaluated by two investigators who sought consensus as to whether a minimal biomechanical threshold for mTBI had been met as well as any reported disorientation was the result of mTBI rather than situational chaos and confusion.

Of the 90 blast-exposed veterans, 37 were in the no-TBI group, 29 in the mTBI-LOC group, and 24 in the mTBI+LOC group. The no-TBI group consisted of individuals who had been exposed to deployment-related blast but reported no subsequent symptoms suggestive of TBI. Individuals were excluded from this group if they reported TBI from any other mechanism of injury during their deployment. Furthermore, because the goal of this study was to examine blast-related mTBI, participants with mTBI not associated with blast during their deployment were excluded from the mTBI-LOC and mTBI+LOC groups. A subset of mTBI participants (n = 16) reported having tertiary injuries (e.g., being thrown against an object). Thus, any reference to blast-related injuries in this study refers to blast mechanisms with the inclusion of additional tertiary injury in some cases. Groups did not significantly differ in gender, age, education, premorbid IQ (as assessed by the Wechsler Test of Adult Reading [WTAR]; Wechsler, 2001), number of alcoholic drinks per week, number of blast exposures, or interval between time of injury and MRI scan. A summary of the demographic characteristics can be found in Table 1.
Table 1. Summary of demographic and clinical characteristics of participants in Study 1.

Note: For ease of interpretation, mean (M) and standard deviation (SD) reflect non-transformed data for non-normal variables. WTAR is listed as z-score. *=significantly different from other groups. mTBI= mild traumatic brain injury; LOC=loss of consciousness; WTAR=Wechsler Test of Adult Reading; CAPS=Clinician-Administered PTSD Scale; PCS=postconcussion symptoms.

An additional 14 OEF/OIF Veterans (age, mean [standard deviation] = 30.2 [7.4]) without a history of blast exposure or deployment-related TBI, who did not meet diagnostic criteria for PTSD as assessed by the Clinician-Administered PTSD scale (CAPS) for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; Blake et al., 1995), were also scanned and formed the reference group for the purpose of neuroimaging analyses. Of these 14 reference group participants, 10 were male.
Behavioral and Neuropsychiatric Assessments

Assessments were administered by a trained licensed clinical neuropsychologist. PCS were evaluated in the blast exposed sample using the Rivermead Postconcussion Questionnaire (RPQ; King, Crawford, Wenden, Moss, & Wade, 1995). The RPQ is a 16-item checklist that requires participants to rate the severity of their current physical, emotional, and cognitive symptoms in comparison to pre-injury functioning. Participants rated severity for each item on a scale from 0 to 4. An average score for each domain (physical, emotional, and cognitive) was calculated.

PTSD was assessed using the CAPS for DSM-IV (Blake et al., 1995). CAPS scores were used as a measure of PTSD symptom severity.

Image Acquisition and Processing

Data were acquired on a 3-Tesla Siemens Trio whole-body MRI scanner located at the VA Boston Healthcare System, Jamaica Plain campus. Two T1-weighted scans were collected for each participant. The first 22 participants had T1-weighted anatomical scans collected with the following parameters: FOV=256, Matrix=240 x 256, 160 slices, 1 x 1 x 1.2 mm voxels, TR=2300 ms, TE=2.98 ms, flip angle=9º and thereafter, a slightly modified sequence was used: FOV=256, Matrix=256 x 256, 176 slices, 1 x 1 x 1 mm voxels, TR=2530 ms, TE=3.32 ms, flip angle=7º. DTI scan parameters for the first 22 participants consisted of two acquisitions of 30 directions averaged for a total of 60 diffusion weighted images, FOV=256, Matrix=128 x 128, TR=8000 ms, TE=83 ms, 2 x 2 x 2 mm voxels, b value = 700 s/mm². Thereafter, a slightly modified DTI sequence was used consisting of one acquisition of 60 directions, FOV=256, Matrix=128 x 128,
TR=10000 ms, TE=103 ms, 2 x 2 x 2mm voxels, b value = 700 s/mm². The sequences were modified in order to align them with the pulse sequence of a separate study protocol for data sharing. Eight of the 14 reference group participants were scanned with both DTI sequences and all analyses were corrected by sequence (see below) to account for any potential sequence differences.

Imaging data were analyzed using the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu) and The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl). Images were first corrected for motion and eddy currents and then brain-extracted using the Brain Extraction Tool (BET) to remove non-brain voxels from the analysis (Smith, 2002). Using FreeSurfer, FA images were created by fitting a tensor model using linear least squares to the raw diffusion data. Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) was used to align all FA images to a standard space. A FA threshold of 0.20 was used to restrict the white matter skeleton to voxels comprising only white matter and to reduce partial volume effects.

To identify clusters of abnormal FA, I used a procedure similar to White, Schmidt, and Karatekin (2009), in which the FA standard space skeletonized images produced by TBSS were used to calculate z-score maps. First, average and standard deviation values for each voxel were created using the FA skeletonized images of the reference group. Next, the statistical images were used to generate a z-score map for each individual, in which each voxel of the skeletonized image was converted into a z-score. To correct for potential sequence differences, z-score maps for individuals scanned with
the original DTI sequence were based on reference group participants who were scanned with the original sequence (n = 8), and z-score maps for individuals scanned with the modified sequence were based on reference group participants who were scanned with the modified sequence (n = 14). To find clusters with reduced FA relative to the reference group, z-score maps were thresholded at $z = -3.0$. Next, FreeSurfer’s `mri_volcluster` was used to find clusters of z-scores of $z = -3.0$ in at least 5 contiguous voxels. The total number of clusters for each individual was calculated.

**Statistical Analysis**

Statistical analyses were performed using SPSS, version 19 (IBM Corp., Armonk, NY). Age and total number of clusters were square root transformed to account for the positive skew of the data before entering into group analyses.

To examine whether blast-related mTBI was associated with the number of clusters with reduced FA, a hierarchical linear regression analysis was performed, in which number of clusters with reduced FA was the dependent variable. Age was added as a covariate in the first step of the model and mTBI group status (no-TBI, mTBI-LOC, and mTBI+LOC coded as dummy variables) was added in the second step. To examine the contribution of PTSD to clusters with reduced FA, CAPS total score was added in the third step.

To examine the association between number of clusters with reduced FA and PCS, a multivariate analysis was performed in which the three PCS domains (physical, emotional, and cognitive) were the dependent variables. Age was added as a covariate. CAPS scores were added into the model to account for traumatic stress symptoms and
number of clusters was added to determine whether white matter abnormalities accounted for additional variance in PCS severity. In order to determine which particular domain of PCS was most associated with white matter abnormalities, follow-up univariate hierarchical linear regression analyses were performed for each PCS domain (physical, emotional, and cognitive).

Finally, a mediation analysis was performed to examine whether the number of clusters with reduced FA influenced the relationship between mTBI and PCS. In simple mediation models, the independent variable (mTBI group status) can exert an indirect effect on the dependent variable (PCS severity) through an intermediate variable (number of clusters with reduced FA). Age and CAPS scores were included as covariates. Groups were compared with simple indicator coding, in which the no-TBI group was the reference group. Direct and indirect effects were examined with the Mediate macro for SPSS (Hayes & Preacher, 2014). Bootstrapping was used to estimate the sampling distribution (n=5000) and 95% confidence intervals for the indirect effect. Because only severity of physical PCS was significantly associated with the number of clusters with reduced FA, a mediation analysis was performed for physical PCS only.

**Results**

Groups did not significantly differ in PTSD symptom severity. Individuals in the no-TBI group had significantly fewer physical PCS than individuals in the mTBI-LOC and mTBI+LOC groups, but there were no group differences in emotional or cognitive PCS (see Table 1).
Hierarchical linear regression showed an effect of group on the number of clusters with reduced FA, with a significant overall model \( R^2 = 0.10, F(3,86) = 3.22, P = 0.03 \) and a significant change in the model when group was added \( \Delta R^2 = 0.08, \Delta F(2,86) = 3.58, P = 0.03 \). Compared to the no-TBI group, the mTBI+LOC group had a greater number of clusters with reduced FA \( \beta = 0.30, P = 0.01 \); see Figure 1), suggesting that mTBI, and in particular LOC, has an effect on white matter integrity. The no-TBI and mTBI-LOC groups did not significantly differ from each other \( \beta = 0.19, P = 0.11 \).

PTSD symptom severity had no effect on clusters with reduced FA \( \Delta R^2 = 0.02, \Delta F(1,85) = 1.97, P = 0.16 \). The spatial distribution of clusters with reduced FA in each group is shown in Figure 2, demonstrating that the abnormalities are dispersed throughout the brain and are not constrained to any particular location across individuals.

**Figure 1.** Mean number of clusters with reduced FA for each group in Study 1.

*Note:* Figure displays number of clusters with reduced FA that have been square root transformed.

*=significant group difference from the no-TBI group, \( P = 0.011 \). Error bars refer to standard error of the mean. FA=fractional anisotropy; mTBI=mild traumatic brain injury; LOC=loss of consciousness.
Visual inspection of the data revealed a multivariate outlier in the mTBI+LOC group for number of clusters with reduced FA and physical PCS. Examination of Cook’s distance (Cook’s $D > 0.04$) confirmed that this subject was a statistical outlier and was thereby removed from all further analyses. Results revealed an effect of clusters with reduced FA on PCS severity, even after accounting for traumatic stress, with a significant multivariate model ($F(3,83) = 3.00, P = 0.04$, Wilks’ $\Lambda = 0.90$, partial $\eta^2 = 0.10$). Follow-up analyses revealed that as expected, CAPS had a significant effect on all three symptom domains (physical: $\Delta R^2 = 0.27$, $\Delta F(1,86) = 32.18$, $\beta = 0.52$, $P < 0.001$;
emotional: $\Delta R^2 = 0.32$, $\Delta F(1,86) = 41.32$, $\beta = 0.57$, $P < 0.001$, cognitive: $\Delta R^2 = 0.34$, $\Delta F(1,86) = 44.20$, $\beta = 0.58$, $P < 0.001$). Adding number of clusters with reduced FA to the model accounted for significant variance in physical PCS, with a significant overall model ($R^2 = 0.34$, $F(3,85) = 14.64$, $P < 0.001$) and a significant change in the model when number of clusters was added ($\Delta R^2 = 0.07$, $\Delta F(1,85) = 8.80$, $\beta = 0.27$, $P = 0.004$). However, there was no significant change in the model when number of clusters was added for emotional ($\Delta R^2 = 0.01$, $\Delta F(1,85) = 1.37$, $\beta = 0.10$, $P = 0.25$) or cognitive ($\Delta R^2 = 0.003$, $\Delta F(1,85) = 0.39$, $\beta = 0.06$, $P = 0.53$) symptoms. The association of physical PCS severity with number of clusters with reduced FA is shown in Figure 3.

A mediation analysis was performed to determine if the number of abnormal white matter clusters mediates the relationship between mTBI and PCS after accounting
for PTSD symptom severity. This analysis revealed that the number of clusters with reduced FA was a significant mediator between mTBI+LOC and physical PCS severity (see Figure 4). Individuals in the mTBI+LOC group had a greater number of abnormal white matter clusters (\(a = 1.05, P = 0.02\)), which in turn, was associated with increased physical PCS severity (\(b = 0.10, P = 0.02\)). A bias-corrected bootstrap confidence interval for the indirect effect for PCS severity did not encompass zero for number of clusters (\(ab = 0.10; 95\% \text{ CI} [0.01, 0.28]\)). As expected, number of clusters with reduced FA was not a significant mediator for the mTBI-LOC group. These results suggest that the association between mTBI that resulted in LOC and physical PCS complaints is mediated in part by the degree to which individuals have alterations in white matter.

Figure 4. The number of clusters with reduced FA mediates the relationship between mTBI+LOC and physical PCS in Study 1. Individuals in the mTBI+LOC group had a greater number of clusters with reduced FA, which in turn was associated with greater physical PCS severity. Note: Numbers shown represent unstandardized coefficients. Solid lines indicate significance (\(P < 0.05\)). Gray indicates covariates in the model. FA=fractional anisotropy; PCS=postconcussion symptoms; mTBI=mild traumatic brain injury; LOC=loss of consciousness; CAPS=Clinician Administered PTSD Scale.
Discussion

I used a voxel-wise cluster-based technique to examine the association between white matter integrity, chronic PCS severity, and blast-related mTBI in a large sample of OEF/OIF Veterans. Blast-related mTBI with LOC was associated with more extensive white matter abnormalities than blast exposure without mTBI. These white matter abnormalities were spatially heterogeneous, with very little overlap in the distribution of clusters across individuals. Further, I found that white matter abnormalities were associated with physical PCS severity, even after accounting for traumatic stress symptoms. Finally, I found that for individuals who suffered LOC, these white matter abnormalities mediated the relationship between mTBI and physical PCS severity.

My results add to an emerging literature pointing to the importance of LOC in white matter abnormalities across varying methodologies (Hayes et al., 2015; Jorge et al., 2012; Matthews et al., 2012; Sorg et al., 2013). One possibility for these results is that LOC may represent a more significant white matter injury than mTBI without LOC. LOC is thought to result from more widespread brain disruption, and thus may be more likely to lead to disconnection of cortical and subcortical structures from deeper structures such as the brainstem (Ommaya & Gennarelli, 1974). Additionally, LOC may be a more reliable indicator of the presence of mTBI than other alterations in consciousness such as PTA and confusion, which may also occur in the context of a psychologically traumatic event.

The finding that LOC was a marker for white matter abnormalities contradicts the claim by Xydakis, Ling, Mulligan, Olsen, and Dorlac (2012) that retrospective self-report
of LOC may not be a useful indicator of TBI-related neuropathology. Their conclusion was based on the fact that in their study, individuals with LOC had fewer neuroimaging abnormalities on CT or MRI than those without LOC. The discrepancy in findings may be due to the fact that white matter disruptions are a more sensitive marker of TBI-related brain abnormalities than clinical abnormalities found on CT and MRI (Borg et al., 2004; Lee et al., 2008; Niogi & Mukherjee, 2010). Additionally, there were important differences in study population. While participants in this study were evaluated following completion of deployment, Xydakis et al.’s (2012) findings pertained to individuals with extensive injury requiring immediate stateside evacuation. In the latter case, LOC may be more likely to reflect a neurophysiologic response to extracranial bodily injuries.

I found that in blast-exposed OEF/OIF veterans, physical PCS severity was associated with the number of white matter abnormalities even after accounting for PTSD symptom severity. These findings support and extend those of two previous studies investigating the association between white matter integrity and chronic PCS following blast exposure (Levin et al., 2010; Yeh et al., 2014). While these studies did not take into account the contribution of mental health symptoms, my results demonstrate that the link between white matter abnormalities and physical PCS is independent of PTSD symptom severity. Furthermore, these findings suggest a specific relationship between mTBI-related white matter abnormalities and physical symptoms. Physical symptoms include complaints that may be more directly linked to traumatic axonal injury (e.g., blurred vision, light sensitivity) than cognitive and emotional symptoms and thus, may be more likely to be associated with diffuse white matter alterations (Landre et al., 2006).
longitudinal study in civilians similarly found that recovery from white matter injury was associated selectively with a reduction in physical symptoms (Ling et al., 2012).

For the first time, I demonstrated that the number of white matter abnormalities mediates the relationship between blast-related mTBI with LOC and physical PCS severity, even after accounting for traumatic stress symptoms. Thus, these results suggest that spatially heterogeneous white matter abnormalities may constitute an independent mechanism accounting for chronic PCS in mTBI. It is well established that mTBI transiently disrupts neural function, and as such, contributes to acute PCS (Bazarian et al., 2007; Bigler, 2008; Macciocchi, Barth, Alves, Rimel, & Jane, 1996; McCrea et al., 2003). Here, I demonstrate that even in the chronic stage, residual mTBI-related white matter alterations continue to be associated with physical symptoms.

These findings should not overshadow the fact that mental health factors including PTSD have an important role in the maintenance of chronic PCS. In the present study, PTSD symptom severity was significantly associated with PCS severity in all three domains, a finding that has been observed in a number of other studies (Belanger, Kretzmer, et al., 2010; Lippa et al., 2010; Verfaellie et al., 2013). However, PTSD symptom severity was not associated with white matter alterations. Several other studies have reported similar negative findings (Jorge et al., 2012; Morey et al., 2012; Taber et al., 2015), although two studies using different diffusion metrics suggest white matter involvement in PTSD (Bazarian et al., 2012; Davenport, Lim, & Sponheim, 2015). Nonetheless, PTSD-related neuropathology appears to be associated primarily with changes in gray matter volume (Bremner et al., 1995; Corbo, Clement, Armony,
Pruessner, & Brunet, 2005; Kasai et al., 2008; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015; Smith, 2005) and functional alterations (Bremner et al., 1999; Daniels, et al., 2010; Hayes, LaBar, et al., 2011; Milad et al., 2009; Sadeh, et al., 2015; Shin & Liberson, 2010; Shin et al., 2004; St Jacques, Kragel, & Rubin, 2013; van Wingen et al., 2012). Further research is needed to determine if PTSD-related neuropathology independently mediates the relationship between PTSD and PCS severity. These open questions notwithstanding, these findings reinforce the notion that chronic PCS are multi-determined, and reflect at least in part TBI-associated axonal injury.

These results should be considered within the context of the limitation that mTBI group assignment was dependent on retrospective self-reports long after the injury occurred. Therefore, these reports are potentially subject to misremembering or reporting bias. However, mTBI assessment was conducted using a guided in-depth structured interview, which is currently the gold standard for diagnosis (Corrigan & Bogner, 2007). Another limitation is the small sample size of the reference group used for the purposes of neuroimaging analyses. Difficulty enrolling participants in this group reflects the strict inclusion criteria, which required absence not only of blast exposure, but also of deployment-related TBI and current PTSD. Future studies would benefit from a larger reference group.

In summary, spatially heterogeneous white matter abnormalities was observed in individuals with a history of blast-related mTBI, particularly when accompanied by LOC. While multiple factors contribute to chronic PCS, the current findings provide evidence for a direct association between white matter abnormalities and reports of physical
symptoms such as headaches, nausea, dizziness, and fatigue. PTSD symptom severity was not related to white matter abnormalities, but it was highly associated with severity of PCS in all three domains. These results suggest that white matter abnormalities are an additional, unique mechanism for chronic physical PCS in blast-related mTBI with LOC. It will be important to validate these findings with other measures that are equally sensitive to spatially heterogeneous white matter abnormalities in mTBI. Furthermore, it will be of interest to determine in longitudinal studies whether changes in white matter integrity are associated with changes in PCS.
CHAPTER THREE: White Matter Abnormalities are Associated With Overall Cognitive Status in Blast-Related mTBI

Introduction

Due to the high incidence of blast-related mTBI in the Iraq and Afghanistan wars, there has been increased attention to the negative long-term consequences of blast-related mTBI, both at the neural and behavioral level. At the neural level, accumulating evidence from DTI studies suggests that blast-related mTBI is associated with changes in white matter microstructure, putatively reflecting traumatic axonal injury (Hayes et al., 2015; Mac Donald et al., 2013; Mac Donald et al., 2011; Matthews et al., 2012; Morey et al., 2012). These studies indicate that mTBI is associated with acute white matter abnormalities that persist chronically, years following the initial injury.

At the behavioral level, blast-related mTBI has been associated with persistent cognitive difficulties (Karr et al., 2014; Kontos et al., 2013; Levin et al., 2010). Although often attributed to psychiatric comorbidities (Campbell et al., 2009; Nelson et al., 2009; Nelson et al., 2012; Storzbach et al., 2015; Vasterling et al., 2012; Verfaellie et al., 2014), cognitive impairment has also been linked to TBI-related white matter injury. However, there is inconsistency in the particular cognitive domain implicated in the association between cognitive performance and TBI-related white matter abnormality. Some studies report associations with verbal memory (Hayes et al., 2015; Levin et al., 2010), whereas others report associations with executive function (Jorge et al., 2012; Sorg et al., 2013; Taber et al., 2015).
The divergent findings in the cognitive correlates of white matter abnormalities may reflect the spatial variability of white matter injury observed in mTBI. Recent work has suggested that the location of white matter abnormalities differs from one individual to another following blast-related mTBI (Davenport et al., 2011; Hayes et al., 2015; Jorge et al., 2012; Miller, Hayes, Lafleche, Salat, & Verfaellie, 2016; Taber et al., 2015). It is conceivable that the nature of the cognitive sequelae also may differ across individuals and that the cognitive profile will vary based on the pattern of neural injury. Consistent with this notion, a recent study found that individuals with mTBI who were given a battery of neuropsychological tests were more likely than would be expected by chance to have abnormal performance on two or more neuropsychological tests, even though at a group level no consistent pattern of impairment on any test was observed (Mac Donald et al., 2015). Thus, heterogeneity of cognitive impairment may be an important factor to consider when examining the impact of blast-related mTBI on neurocognitive functioning. Yet, there are currently no studies examining the association between spatially variable white matter abnormalities in mTBI and overall cognitive status.

In the present study, I examined in a large group of OEF/OIF veterans whether spatially variable white matter abnormalities are associated with a measure of overall cognitive impairment that accommodates heterogeneity of cognitive sequelae across individuals. Building on Chapter 2 (Miller et al., 2016) in which I found that individuals who suffered mTBI with LOC had more spatially variable white matter abnormalities than a blast-exposed group without TBI, the goals of the current study were 1) to assess the relationship between number of white matter abnormalities and overall cognitive
impairment, after accounting for PTSD symptom severity and 2) to examine whether number of white matter abnormalities mediates the relationship between blast-related mTBI and cognitive impairment.

Methods

Participants

Participants of this study overlap with participants described in the study of Chapter 2. Inclusion and exclusion criteria were the same as those described Chapter 2. For some individuals excluded in the study described in Chapter 2, neuropsychological testing was repeated at the time of imaging and therefore, these subjects are included in the current study. Thus, there were 37 no-TBI, 31 mTBI-LOC, 28 mTBI+LOC, and 14 reference individuals. A summary of demographic information can be found in Table 2.

Neuropsychological and Neuropsychiatric Assessments

Premorbid IQ was estimated using the WTAR (Wechsler, 2001). Participants were administered a battery of neuropsychological tests selected based on their sensitivity to mTBI. Table 3 provides an overview of these tests.

PTSD was assessed using the CAPS for DSM-IV (Blake et al., 1995) by a trained licensed clinical neuropsychologist. CAPS scores were used as a measure of PTSD symptom severity. CAPS scores were unavailable for three participants and were estimated based on their score on the PTSD Checklist-Military version (PCL-M; Weathers, Litz, Herman, Huska, & Keane, 1993). Linear regression was used to generate an equation using the remaining dataset’s CAPS and PCL-M scores. Then, the three
individual’s PCL-M scores were entered into this equation to calculate their estimated CAPS scores.

Table 2. Summary of demographic and clinical characteristics of participants in Study 2.

<table>
<thead>
<tr>
<th></th>
<th>no-TBI (n = 37)</th>
<th>mTBI-LOC (n = 31)</th>
<th>mTBI+LOC (n = 28)</th>
<th>Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, $M (SD)$</td>
<td>30.2 (6.3)</td>
<td>29.6 (7.7)</td>
<td>27.9 (4.2)</td>
<td>$F(2, 93) = 1.07, P = 0.35$</td>
</tr>
<tr>
<td>Males, no. (%)</td>
<td>35 (94.6)</td>
<td>30 (96.8)</td>
<td>28 (100.0)</td>
<td>$\chi^2(2) = 1.54, P = 0.46$</td>
</tr>
<tr>
<td>Education in years, $M (SD)$</td>
<td>13.8 (2.1)</td>
<td>13.0 (1.6)</td>
<td>12.9 (1.4)</td>
<td>$F(2, 93) = 2.27, P = 0.11$</td>
</tr>
<tr>
<td>WTAR, $M (SD)$</td>
<td>0.3 (0.8)</td>
<td>0.5 (0.7)</td>
<td>0.3 (0.8)</td>
<td>$F(2, 93) = 0.53, P = 0.59$</td>
</tr>
<tr>
<td>Blast exposures, $M (SD)$</td>
<td>8.4 (11.7)</td>
<td>11.6 (12.2)</td>
<td>6.2 (8.6)</td>
<td>$F(2, 93) = 1.85, P = 0.16$</td>
</tr>
<tr>
<td>Injury to scan interval in months, $M (SD)$</td>
<td>49.8 (36.3)</td>
<td>43.8 (27.2)</td>
<td>56.3 (23.2)</td>
<td>$F(2, 93) = 1.84, P = 0.17$</td>
</tr>
<tr>
<td>Current alcoholic drinks per week, $M (SD)$</td>
<td>4.6 (6.4)</td>
<td>3.4 (4.6)</td>
<td>3.4 (7.2)</td>
<td>$F(2, 93) = 0.63, P = 0.53$</td>
</tr>
<tr>
<td>CAPS total score, $M (SD)$</td>
<td>48.8 (27.8)</td>
<td>58.4 (24.6)</td>
<td>63.2 (23.7)</td>
<td>$F(2, 93) = 2.72, P = 0.07$</td>
</tr>
</tbody>
</table>

Image Acquisition and Processing

Image acquisition and analysis were the same as those described in Chapter 2.

Statistical Analyses

Statistical analyses were performed using SPSS, version 19 (IBM Corp., Armonk, NY). Age and number of clusters with reduced FA were square root transformed to
account for the positive skew of the data. For similar reasons, WTAR was arcsin transformed.

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-KEFS Trail Making Test</td>
<td>Number + letter sequencing, number-letter switching, motor speed</td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency Test</td>
<td>Letter fluency total correct</td>
</tr>
<tr>
<td>D-KEFS Color-Word Interference</td>
<td>Color naming speed, word reading speed, inhibition</td>
</tr>
<tr>
<td>Digit Span (Wechsler Adult Intelligence Scale – III)</td>
<td>Digits backward score</td>
</tr>
<tr>
<td>Digit Symbol-Coding (Wechsler Adult Intelligence Scale – III)</td>
<td>Total correct responses</td>
</tr>
<tr>
<td>Auditory Consonant Trigrams</td>
<td>Total number correct averaged over 9, 18, and 36 second delays</td>
</tr>
<tr>
<td>California Verbal Learning Test</td>
<td>Trials 1-5 total, long delay free recall, total recognition discriminability</td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test</td>
<td>Total recall, delayed recall, recognition discrimination index</td>
</tr>
<tr>
<td>Finger Tapping Test</td>
<td>Mean number of taps for dominant and non-dominant hand</td>
</tr>
<tr>
<td>Purdue Pegboard Test</td>
<td>Completion time for dominant and non-dominant hand</td>
</tr>
</tbody>
</table>

Table 3. Neuropsychological tests and measures in Study 2.

To examine the association between blast-related mTBI and number of clusters with reduced FA, a hierarchical linear regression analysis was performed in which number of clusters with reduced FA was the dependent variable. Age was added as a nuisance variable in the first step of the model and mTBI group status (no-TBI, mTBI-LOC, and mTBI+LOC coded as dummy variables) was added in the second step. CAPS
total score was added in the third step to examine the contribution of PTSD to clusters with reduced FA.

Next, to identify the primary domains of neuropsychological functioning and for data reduction of cognitive tests, a factor analysis with promax rotation was performed. Digit Span Backwards data was not available for 11 subjects, and there were several other instances where data on a particular test were missing for at most four subjects. I used the EM algorithm with the open source program R (http://www.R-project.org) and the norm package (http://www.stat.psu.edu/~jls/missoftwa.html#aut) to impute missing data on these cognitive measures. Factor scores were estimated as z-scores using regression. Individuals were considered to have normal cognition if no z-score fell below -2. In contrast, if z-scores for one or more factors fell below -2, they were deemed to have evidence of clinically significant cognitive impairment. A z-score of -2 and below is generally accepted as an indicator of clinically significant cognitive impairment (Lezak, 2004).

To examine the association between number of clusters with reduced FA and cognitive status, a hierarchical logistic regression analysis was performed. Age and WTAR were added as nuisance variables. CAPS total score was added into the model to account for PTSD symptoms. Lastly, number of clusters was added to determine the additional contribution of number of white matter abnormalities to cognitive impairment.

Finally, a mediation analysis was performed to examine whether number of clusters with reduced FA influenced the relationship between mTBI and cognitive status. In a mediation model, the causal variable (mTBI group) can exert an indirect effect on the
outcome variable (cognitive status) through a mediating variable (number of clusters with reduced FA). Group was dummy coded so that the effect of each mTBI group could be examined with reference to the no-TBI group. The mTBI group not included as the independent variable was added as a covariate. Age, WTAR, and CAPS total score were also included as covariates. Direct and indirect effects were examined with the Process macro for SPSS (Hayes, 2013). Bootstrapping was used to estimate the sampling distribution (n = 5000) and 95% confidence intervals for the indirect effect.

Results

*mTBI Associations with White Matter Abnormalities*

Hierarchical linear regression revealed an effect of group on the number of clusters with reduced FA, with a significant overall model ($R^2 = 0.13$, $F(3,92) = 4.69$, $P = 0.004$) and a significant change in the model when group was added ($\Delta R^2 = 0.11$, $\Delta F(2,92) = 5.57$, $P = 0.005$). Specifically, the mTBI+LOC group had significantly more clusters with reduced FA than the no-TBI group ($\beta = 0.36$, $P = 0.001$; see Figure 5), suggesting that individuals with LOC have more extensive white matter injury than those without mTBI. The no-TBI and mTBI-LOC groups did not significantly differ from each other ($\beta = 0.19$, $P = 0.09$), nor did the mTBI-LOC and mTBI+LOC groups when directly compared to each other ($\beta = 0.20$, $P = 0.12$). PTSD symptom severity was not significantly associated with the number of clusters with reduced FA ($\Delta R^2 = 0.003$, $\Delta F(1,91) = 0.29$, $P = 0.60$). The spatial distribution of clusters with reduced FA is shown in Figure 6, which demonstrates that these white matter abnormalities are spatially variable across individuals and do not consistently occur in any particular location.
Figure 5. Mean number of clusters with reduced FA for each group in Study 2.

Note: For interpretation purposes, figure displays untransformed number of clusters with reduced FA. *=significant group difference from the no-TBI group, $P = 0.001$. Error bars reflect standard error of the mean. FA=fractional anisotropy; mTBI=mild traumatic brain injury; LOC=loss of consciousness.

Relationship Between White Matter Abnormalities and Cognition

Based on the scree plot from the factor analysis, six factors were extracted (see Table 4), which accounted for 69% of the common variance. These factors were labeled as processing speed, verbal memory, visual memory, motor speed, working memory, and manual dexterity.

Using a measure of overall cognitive impairment based on performance in each of these domains, there were 15 individuals who met criteria for impaired cognition. Of these 15, 12 had clinical evidence for impairment in a single factor, while the remaining three had impairments in multiple factors. Figure 7 shows the number of subjects who had impairment in each factor, demonstrating that cognitive impairment was heterogeneous and did not consistently affect one particular cognitive factor.
Hierarchal logistic regression revealed an effect of number of clusters with reduced FA on cognitive status, even after accounting for PTSD symptom severity (see Table 5). PTSD symptom severity was also significantly associated with the likelihood of cognitive impairment (see Table 5).

Because odds ratios are difficult to interpret when the independent variable is transformed, I also ran a logistic regression using untransformed number of clusters. The analysis yielded a similar pattern of results and revealed that with each additional abnormal white matter cluster, individuals were 1.03 times more likely to have evidence of cognitive impairment.
<table>
<thead>
<tr>
<th>Neuropsychological Tests</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Processing Speed</td>
</tr>
<tr>
<td></td>
<td>Verbal Speed</td>
</tr>
<tr>
<td></td>
<td>Visual Speed</td>
</tr>
<tr>
<td></td>
<td>Motor Speed</td>
</tr>
<tr>
<td></td>
<td>Working Speed</td>
</tr>
<tr>
<td></td>
<td>Manual Dexterity</td>
</tr>
<tr>
<td>Trails number letter switching</td>
<td>.843</td>
</tr>
<tr>
<td>Trails letter + number sequencing</td>
<td>.683</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>.670</td>
</tr>
<tr>
<td>Stroop color + word naming</td>
<td>.424</td>
</tr>
<tr>
<td>Stroop inhibition</td>
<td>.386</td>
</tr>
<tr>
<td>Consonant trigrams</td>
<td>-.224</td>
</tr>
<tr>
<td>Digit span backwards</td>
<td>.079</td>
</tr>
<tr>
<td>Digit Symbol-Coding</td>
<td>.361</td>
</tr>
<tr>
<td>CVLT total trials 1-5</td>
<td>.099</td>
</tr>
<tr>
<td>CVLT delayed recall</td>
<td>.133</td>
</tr>
<tr>
<td>CVLT delayed recognition</td>
<td>-.116</td>
</tr>
<tr>
<td>BVMT-R total trials 1-5</td>
<td>.169</td>
</tr>
<tr>
<td>BVMT-R delayed recall</td>
<td>.207</td>
</tr>
<tr>
<td>BVMT-R delayed recognition</td>
<td>-.307</td>
</tr>
<tr>
<td>Trails motor speed</td>
<td>.754</td>
</tr>
<tr>
<td>Finger tapping dominant</td>
<td>.180</td>
</tr>
<tr>
<td>Finger tapping non-dominant</td>
<td>-.082</td>
</tr>
<tr>
<td>Grooved pegboard dominant</td>
<td>.111</td>
</tr>
<tr>
<td>Grooved pegboard non-dominant</td>
<td>-.234</td>
</tr>
</tbody>
</table>

Table 4. Factor loadings in Study 2.

*Note:* Factor loadings > 0.35 for each test are shown in bold. CVLT=California Verbal Learning Test; BVMT=Brief Visuospatial Memory Test.
A mediation analysis revealed that mTBI+LOC indirectly influenced cognitive status through its effect on the extent of white matter abnormalities, after accounting for PTSD symptom severity (see Figure 8). Individuals in the mTBI+LOC group had a greater number of clusters with reduced FA ($a = 1.63, P = 0.001$), and, in turn, number of abnormal clusters was significantly associated with cognitive status ($b = 0.40, P = 0.02$). The direct effect of mTBI+LOC on cognitive status was not significant. A bias-corrected
bootstrap confidence interval for the indirect effect of cognitive impairment did not encompass zero ($ab = 0.66$, 95%CI [0.03, 1.8]). As expected, the extent of white matter abnormalities was not a significant mediator for mTBI-LOC. These results suggest that as white matter abnormalities accumulate in mTBI+LOC individuals, the likelihood of having cognitive impairment increases.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>0.55</td>
<td>-0.82</td>
<td>-1.31</td>
</tr>
<tr>
<td>Age</td>
<td>-0.39</td>
<td>-0.41</td>
<td>-0.73</td>
</tr>
<tr>
<td>WTAR</td>
<td>-7.01</td>
<td>-7.42*</td>
<td>-8.76*</td>
</tr>
<tr>
<td>CAPS total score</td>
<td>0.02*</td>
<td>0.01</td>
<td>0.03*</td>
</tr>
<tr>
<td>Number of abnormal clusters</td>
<td></td>
<td>0.39*</td>
<td>0.17</td>
</tr>
<tr>
<td>Negelkerke $R^2$</td>
<td>0.08</td>
<td>0.15</td>
<td>0.24</td>
</tr>
<tr>
<td>Model $\chi^2$ (df)</td>
<td>4.50 (2)</td>
<td>8.69 (3)*</td>
<td>14.63 (4)**</td>
</tr>
<tr>
<td>Block $\chi^2$ (df)</td>
<td>4.50 (2)</td>
<td>4.19 (1)*</td>
<td>5.94 (1)*</td>
</tr>
</tbody>
</table>

Table 5. Logistic regression for cognitive impairment in Study 2.

Note: *=significance $P < 0.05$; **=significance $P < 0.001$. Age is square root transformed. WTAR is an average z-score and is arcsin transformed. Number of abnormal clusters is square root transformed. SE=standard error; $e^B$=odds ratio; CAPS=Clinician-Administered PTSD Scale; WTAR=Wechsler Test of Adult Reading.
mTBI+LOC indirectly influences the likelihood of having cognitive impairment through its effect on the number of clusters with reduced FA in Study 2.

Note: Numbers shown represent unstandardized coefficients. Solid lines indicate significance ($P < 0.05$). Gray indicates covariates in the model. FA=fractional anisotropy; mTBI=mild traumatic brain injury; LOC=loss of consciousness; CAPS=Clinician Administered PTSD Scale; WTAR=Wechsler Test of Adult Reading.

**Discussion**

To my knowledge, this is the first study to examine the association between spatially variable white matter abnormalities and overall cognitive status in individuals with a history of blast exposure. Using a voxel-wise cluster-based technique in a large cohort of OEF/OIF veterans, I found that, consistent with the findings of Chapter 2 (Miller et al., 2016), individuals with mTBI and LOC had a significantly greater number of white matter abnormalities than individuals without mTBI. Importantly, I found that these spatially variable white matter abnormalities were associated with a measure of...
overall cognitive impairment that accommodates variable patterns of cognitive deficiency across individuals. Additionally, number of white matter abnormalities indirectly influenced the relationship between mTBI with LOC and the likelihood of having clinically significant cognitive impairment.

My results revealed that cognitive impairment was heterogeneous, with impairment seen across a range of factors in different individuals. These results support recent work by MacDonald et al. (2015) who found evidence for impairment at the individual subject level in veterans with blast-related mTBI despite lack of consistent impairment at the group level. My findings go beyond this work in demonstrating that cognitive impairment defined at the individual subject level was associated with the neural sequelae of blast injury. Specifically, as the number of abnormal white matter clusters increased, the odds of cognitive impairment also increased.

Whereas previous studies have examined the link between global white matter disruption and performance in specific cognitive domains (Hayes et al., 2015; Taber et al., 2015), here I took into account not only heterogeneity of neural injury but also heterogeneity in cognitive impairment across individuals. The finding that cognitive impairment, regardless of its specific nature, could be linked to diffuse white matter injury is in keeping with the notion that blast-related neural injury has direct consequences for cognition. However, given the heterogeneity of cognitive impairment, such associations may not be consistently observed in any particular domain.

Further, I demonstrated that number of white matter abnormalities indirectly influences the relationship between blast-related mTBI with LOC and cognitive status.
Specifically, as white matter abnormalities accumulate in individuals with blast-related mTBI with LOC, the odds of having cognitive impairment increases, even after taking PTSD into account. These results suggest that heterogeneous cognitive sequelae in this sample reflect to some degree mTBI-related injury. Importantly, I showed that cognitive impairment in blast-related mTBI with LOC is associated with mTBI-related white matter abnormalities when both the variability of injury and heterogeneity of cognitive impairment are considered. These findings suggest that blast-related mTBI is a heterogeneous injury, producing unique patterns of brain injury and associated cognitive sequelae for each individual.

Consistent with previous studies suggesting that mental health, including PTSD, is an important contributor to neuropsychological performance (Campbell et al., 2009; Hayes et al., 2015; Nelson et al., 2012; Vasterling et al., 2012; Verfaellie et al., 2014), I found that PTSD symptom severity was also significantly associated with cognitive status, such that as PTSD symptom severity increased, the likelihood of having cognitive impairment increased. However, PTSD was not associated with white matter abnormalities, a finding that is consistent with several other studies (Jorge et al., 2012; Miller et al., 2016; Morey et al., 2012; Taber et al., 2015). It will be important for future studies to determine whether PTSD-related neuropathology is a mediator in the relationship between PTSD and cognitive impairment.

These results should be interpreted within the context of the limitation that mTBI group assignment was based on retrospective self-report years after the injury occurred and may be subject to misremembering or reporting bias. However, participant reports
were guided by an in-depth structured clinical interview, which is the gold standard for diagnosis (Corrigan & Bogner, 2007). Another limitation was the small sample size of the reference group for neuroimaging analyses. This group required strict inclusionary criteria including absence of blast exposure, deployment-related TBI, and current PTSD. Future studies would benefit from a larger reference group in neuroimaging analyses.

In summary, I report a greater number of spatially variable white matter abnormalities in individuals with blast-related mTBI with LOC in comparison to individuals without mTBI. Importantly, these white matter abnormalities were directly associated with overall cognitive status that takes into account heterogeneity across individuals. PTSD symptom severity was also associated with cognitive status, but it was not related to white matter abnormalities. The heterogeneity in neural injury as well as in cognitive impairment is an important consideration in examining brain-behavioral correlations in blast-related mTBI.
CHAPTER FOUR: Cognitive Control in Blast-Related mTBI

Introduction

The use of more sensitive cognitive probes such as experimental tasks suggests that mTBI-related behavioral impairment may be apparent in higher-order cognitive processing such as cognitive control (Pontifex, O'Connor, Broglio, & Hillman, 2009; Seignourel et al., 2005). Cognitive control is the process by which an individual flexibly guides goal-directed behavior in accordance with continuously changing and evolving states and environments. This relies on the ability to select task relevant information, inhibit inappropriate responses, and maintain relevant contextual information (Botvinick, Braver, Barch, Carter, & Cohen, 2001). Cognitive control is comprised of two processes referred to as evaluative and regulative control. The evaluative process monitors salient events and initiates compensatory adjustments in top-down control, whereas the regulative process actively implements top-down control during information processing in order to flexibly guide behavior (see Botvinick et al., 2001 for review).

Neuroimaging studies have shown that cognitive control strongly relies on several prefrontal areas, including the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (DLPFC), as well as the insula and posterior parietal cortex (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Kerns et al., 2004; MacDonald, Cohen, Stenger, & Carter, 2000). Interestingly, these regions are often identified as part of larger networks that typically co-activate during tasks, including the salience network (SN) and central executive network (CEN). The insula and dACC are two core hubs of the SN, whereas the DLPFC and posterior parietal cortex are key hubs of the CEN. Research has
suggested that the SN, particularly the insula and dACC, is involved in the evaluative aspect of cognitive control (Botvinick et al., 2001). The insula is thought to be important for detecting salient stimuli and initiates control signals for additional stimulus and response processing in order to guide behavior. Once stimuli are marked as salient, the dACC is engaged to modulate responses in the sensory, motor, and association cortices (Ham, Leff, de Boissezon, Joffe, & Sharp, 2013; Menon & Uddin, 2010).

The regulative process of cognitive control is rooted in the CEN, particularly the DLPFC and posterior parietal cortex. The DLPFC maintains goal representations and initiates top-down control during information processing, which allows for flexible online adjustments as choices are weighed against changing conditions (Botvinick et al., 2001). This top-down control allows for selective enhancement of processes that depend on posterior brain areas such as the posterior parietal cortex until the appropriate actions are selected (Botvinick et al., 2001; Seeley et al., 2007). Thus, successful cognitive control not only depends on the functional integrity of these brain regions separately but also on the dynamic interaction between these regions. Studies have supported the importance of the interaction between brain regions in cognitive control using both functional (Cole, Yarkoni, Repovš, Anticevic, & Braver, 2012; Nomura et al., 2010; Spielberg, Miller, Heller, & Banich, 2015) and structural (Bonnelle et al., 2012) connectivity measures. Using these methods, evidence supports models that suggest that the prefrontal cortex is critical for modulating activity in posterior regions in response to control demands (Botvinick et al., 2001; Miller & Cohen, 2001).
Several experimental tasks can be used to measure cognitive control in the laboratory. One popular measure is the flanker task, in which participants are required to respond to the direction of a center arrow surrounded by four flanker arrows. These flanker arrows can be congruent with the center arrow (i.e., in the same direction) or incongruent (i.e., in the opposite direction). Incongruent stimuli require an individual to inhibit the flanker arrows (task irrelevant stimuli) in order to correctly respond to the direction of the center arrow (task relevant stimuli). Thus, individuals are typically slower and less accurate on incongruent trials than congruent trials (interference effect) as it requires response inhibition of task irrelevant information. Other common tasks used to measure cognitive control are the Stroop task and stimulus-response compatibility task, both of which also use stimuli that actively recruit cognitive control by requiring an individual to inhibit inappropriate responses and select task relevant information.

Aside from the interference effect, cognitive control also manifests in the response to errors (i.e., performance monitoring). One influential theory suggests that errors generate high response conflict, which is the result of competition between a correct response and a strong response tendency for an incorrect response, and therefore requires increased cognitive control (Botvinick et al., 2001). A number of studies suggest that error detection concerns not only the identification of the error (evaluative control) but also the correction of differences between the intended task goal and executed response (regulative control; Menon, Adleman, White, Glover, & Reiss, 2001; Taylor, Stern, & Gehring, 2007; Ullsperger & von Cramon, 2001). According to Rabbitt (2002), after an incorrect response individuals engage regulative control by slowing down their
response on the subsequent trial to increase the chance of making a correct response. Thus, post-error slowing serves as a behavioral modulation in response to previous erroneous responses. Therefore, error-related processing and performance serve as additional measures of cognitive control in experimental tasks.

Studies support the notion that experimental tasks of cognitive control may be more sensitive to mTBI-related cognitive impairment than standard neuropsychological testing. Pontifex and colleagues (2009) found that individuals with chronic mTBI did not significantly differ from controls in performance on standardized testing (i.e., Immediate Post-Concussion Assessment and Cognitive Testing; ImPACT), but did show increased interference reaction time and decreased response accuracy for incongruent stimuli on a flanker task. However, groups did not differ on post-error reaction time or accuracy. Importantly, they found that mTBI was associated with reduced responsiveness in the anterior cingulate cortex (ACC) during errors, which is an area associated with the evaluative process of cognitive control. The fact that Pontifex et al. (2009) did not find any associated behavioral error-related deficits with this reduced responsiveness in the ACC points to the possibility that mTBI-related cognitive control deficits in error processing may be limited to the evaluative process of cognitive control and that the regulative process governing behavior may still be intact through compensatory mechanisms.

Other studies have also suggested that individuals with mTBI have performance deficits in cognitive control tasks (Seignourel et al., 2005) and altered brain activity in regions important for cognitive control (Fischer et al., 2014). Recently, Scheibel and
colleagues (2012) demonstrated that patients with chronic blast-related mTBI have residual impairments in cognitive control. Using a stimulus-response compatibility task, Scheibel et al. (2012) examined 15 blast-related mTBI subjects and 15 controls without blast exposure or TBI. They found that when controlling for PTSD, the mTBI group had increased reaction time to incompatible stimuli compared to controls. Moreover, individuals with mTBI had greater activation in the ACC, medial frontal cortex, and posterior cerebral areas in response to incompatible stimuli.

Despite several studies pointing to the sensitivity of experimental tasks, some research suggests that individuals with mTBI do not show performance deficits on these tasks (Killam, Cautin, & Santucci, 2005; Larson, Clayson, & Farrer, 2012; Larson, Farrer, & Clayson, 2011; Larson, Perlstein, Demery, & Stigge-Kaufman, 2006). However, this does not necessarily mean a return to pre-injury brain function for individuals with mTBI. There is some evidence for brain differences even in the absence of behavioral impairment on cognitive control tasks, suggesting that these tasks may still elicit mTBI-related brain changes (Broglio, Pontifex, O'Connor, & Hillman, 2009; Fischer et al., 2014). This may in part be explained by specific alterations to the evaluative component of cognitive control. The regulative process of cognitive control that governs behavior may still be intact in mTBI thereby limiting behavioral differences across groups. However, more research is needed to determine if mTBI is associated with disruptions specific to the evaluative process of cognitive control and whether mTBI is associated with compensatory mechanisms that then help engage regulative control.
In this study, I use the flanker task to examine the associations between cognitive control performance and brain function and connectivity using fMRI in a cohort of OEF/OIF veterans with and without blast-related mTBI. The goals of this study are to examine whether individuals with chronic blast-related mTBI: 1) exhibit behavioral differences in a task that makes high demands on cognitive control and 2) show altered brain activation and connectivity during cognitive control performance, and whether such alterations, if observed, are selective to regions associated with evaluative or regulative control.

Methods

Participants

Participants of this study were a subsample (n = 35) of OEF/OIF veterans who participated in the studies described in Chapters 2 and 3. Thus, all participants who participated in this study underwent a clinical TBI interview as part of the earlier studies. Participants were divided into two groups according to ACRM criteria (1993), a blast-exposed no-TBI group and a blast-related mTBI group. The no-TBI group (n = 17) consisted of individuals who were exposed to deployment-related blast but reported no subsequent changes suggestive of TBI. Participants were excluded from this group if they reported TBI from any other mechanism of injury during deployment. The mTBI group consisted of 7 individuals with LOC and 11 without LOC. Because the goal of this study was to examine blast-related mTBI, participants with mTBI not associated with blast during their deployment were excluded from the mTBI group.
Participants were excluded from this study if they reported a history of pre-deployment TBI with LOC or with symptoms persisting longer than three months post-injury, demonstrated questionable effort with raw scores below 45 on the retention trial of the TOMM (Tombaugh & Tombaugh, 1996), had structural brain abnormalities (e.g., hemorrhages, hematomas, excessive hyperintensities) on T2-FLAIR, SWI, or T1-weighted sequences as determined by a board-certified neuroradiologist, demonstrated alcohol abuse as determined by scores above 20 on the Alcohol Use Disorder Identification Test (AUDIT), or had a diagnosis of or used medication suggestive of attention deficit hyperactivity disorder (ADHD). One no-TBI individual and one individual with mTBI without LOC were excluded from this study because they were unable to stay awake during the task, making the final sample 33 OEF/OIF veterans. A summary of demographic characteristics can be found in Table 6.

<table>
<thead>
<tr>
<th></th>
<th>no-TBI (n = 16)</th>
<th>mTBI (n = 17)</th>
<th>Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, M (SD)</td>
<td>33.1 (5.6)</td>
<td>31.7 (6.8)</td>
<td>t(31) = 0.7, P = 0.5</td>
</tr>
<tr>
<td>Males, no. (%)</td>
<td>14 (87.5)</td>
<td>17 (100.0)</td>
<td>χ²(1) = 2.3, P = 0.1</td>
</tr>
<tr>
<td>Education in years, M (SD)</td>
<td>15.6 (2.4)</td>
<td>14.7 (1.6)</td>
<td>t(31) = 1.2, P = 0.2</td>
</tr>
<tr>
<td>Injury to scan interval in months, M (SD)</td>
<td>91.3 (34.7)</td>
<td>82.9 (40.8)</td>
<td>t(31) = 0.6, P = 0.5</td>
</tr>
<tr>
<td>PCL-M score, M (SD)</td>
<td>37.6 (12.6)</td>
<td>40.2 (13.2)</td>
<td>t(31) = -0.6, P = 0.6</td>
</tr>
<tr>
<td>Individuals with LOC, no. (%)</td>
<td>7 (41.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Summary of demographic and clinical characteristics of participants in Study 3.
Note: mTBI=mild traumatic brain injury; PCL-M=PTSD Checklist-Military version.

Neuropsychiatric Assessments

The PCL-M (Weathers et al., 1993) was used as a measure of PTSD symptom severity.
Flanker Task

The flanker task was administered in the scanner as an event-related fMRI paradigm. Visual stimuli were presented with E-Prime 2.10 Software (Psychology Software Tools, Pittsburg, PA) and were projected to a screen at the back of the scanner, which participants viewed with a mirror attached to the head coil. Stimuli were presented for 200ms, immediately followed by a crosshair presented for a mean of 4300ms that was randomly jittered between 1800ms and 7800ms (see Figure 9). Fifty percent of the stimuli were incongruent and fifty percent were congruent. Additionally, on half of each type of trial (incongruent or congruent), the central stimulus was pointing in the left direction and on the other half it was pointing in the right direction. The stimuli were pseudo-randomized to ensure that no more than three incongruent stimuli appeared in a row or that no more than three stimuli were pointing in the same direction. Individuals were required to use their right index finger for arrows pointing left and their right middle finger for arrows pointing right. Responses were collected up to 2000ms after stimulus onset\(^2\). There were four runs in total with 80 trials per run, equating to 320 trials across all four runs. Instructions and practice were given outside the scanner a half hour before scanning took place. During fMRI data acquisition, response accuracy, onset time, and reaction time were recorded for each stimulus and only trials with a response were included in analyses.

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\(^2\) For the first 5 participants, responses were only recorded up to 1000ms. Two of these participants were in the mTBI group and three were in the no-TBI group.
**Image Acquisition**

Data were acquired with a 32-channel head coil on a 3-Tesla Siemens Trio whole-body MRI scanner located at the VA Boston Healthcare System, Jamaica Plain campus. One T1-weighted scan was collected for each participant (FOV=256, Matrix=256 x 256 x 176 slices, 1 x 1 x 1 mm voxels, TR=2530 ms, TE=3.32 ms, flip angle=7º). A T2-FLAIR image was also collected (FOV=256, Matrix=512 x 512 x 160 slices, 0.49 x 0.49 x 1 mm voxels, TR=6000ms, TE=388ms, flip angle=120º) for each participant. Four blood oxygen level dependent (BOLD) T2*-weighted echo-planar imaging runs were acquired (FOV=192, TR=2000ms, TE=30ms, 2.67 x 2.67 x 3.75 mm voxels, interleaved acquisition). The first five volumes of each run collected before stimulus presentation began were discarded to allow for signal magnetization equilibrium.

![Figure 9. Flanker Task in Study 3](image)

Stimuli were presented for 200ms followed immediately by a cross hair with presentation duration randomly jittered between 1800ms-7800ms.
Image Analysis

All preprocessing procedures and analyses were carried out using The Oxford Centre for FMRIB FSL software package (version 4.15; http://www.fmrib.ox.ac.uk/fsl). FMRI data were processed using fMRI Expert Analysis Tool (FEAT; Version 5.98). Data were preprocessed with the following pre-statistics: motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of full-width/half-max (FWHM) 5mm, and grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor. To remove head motion artifact, I used a data-driven independent component analysis (ICA) method to identify and remove motion-related components from the data (ICA-based stratgey for Automatic Removal of Motion Artifact [ICA-AROMA]; Pruim et al., 2015). After removing these motion components, I removed signal from white matter and CSF using nuisance regression. Recent evidence suggests that removing signal from white matter and CSF further helps minimize noise-related artifact in functional data (Prium, Mennes, Buitelaar, & Beckmann, 2015). Next, I applied linear detrending and a highpass temporal filter (σ = 45.0s). Registration to high-resolution structural and standard space images was carried out using FMRIB’s Linear Image Registration Tool (FLIRT) and further refined using FMRIB’s Nonlinear Image Registration Tool (FNIRT).

Functional analyses were performed using a design matrix of an incongruent > congruent correct contrast. A separate analysis examining error processing was conducted in which the contrast included incorrect > correct. Higher-level analyses were
carried out using FMRIB’s Local Analysis of Mixed Effects (FLAME) stage 1 (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). To examine each contrast, runs were combined for each participant and statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$. To determine activation differences across groups, group level activation maps were generated for each contrast using FLAME stage 1. Age and PTSD symptom severity were entered into the model as regressors. In order to examine group differences at the significance level of $P = 0.05$, $Z$ statistic images were thresholded using clusters determined by $Z > 1.96$ and a corrected cluster significance threshold of $P = 0.05$.

To examine whether groups differed in the functional network involved in cognitive control, I performed psychophysiological interactions (PPI) analysis (Friston et al., 1997). PPI analysis is a whole brain analysis method to find regions whose activity is modulated both by the task and activation in the seed ROI. Therefore, PPI analysis serves as a method to identify brain regions differentially correlated with a ROI as a function of task condition. The model involves a psychological regressor, which is the task regressor (incongruent vs. congruent or incorrect vs. correct responses), a physiological regressor, which is the timecourse of the seed ROI, and the PPI term, which is the interaction between the psychological and physiological regressors. Group level PPI maps were generated to determine group differences in brain regions that were modulated by the interaction of the task and activation of the seed ROI. To determine if disruptions in functional activity during the cognitive control task were also associated with disruptions
in functional connectivity, I used regions in which I found a significant group difference from the activation map of interest (i.e., incongruent > congruent or incorrect > correct) as seed regions. I extracted the time course of these seed regions from all participants. Higher-level analyses for the PPI regressor were carried out using FLAME stage 1. Runs were combined for all participants and Z statistic images were thresholded using clusters determined by \( Z > 2.3 \) and a corrected cluster significance threshold of \( P = 0.05 \). To determine group differences, age and PTSD symptom severity were entered into the model as regressors and group PPI maps were generated. Z statistic images were thresholded using clusters determined by \( Z > 1.96 \) and a corrected cluster significance threshold of \( P = 0.05 \). The maps of the PPI analysis represented the effects of the interaction that were over and above the main effects of the BOLD response to the task contrast and correlations with the seed region.

Finally, to identify brain regions that were associated with behavior, I performed a mixed effects (FLAME stage 1) group-level analysis for both congruency and error-related performance. For congruency, I calculated an interference score by subtracting congruent reaction time from incongruent reaction time. For error-related performance, I calculated a post-error slowing score in which reaction time on trials immediately following a correct response (post-correct) was subtracted from reaction time on trials immediately following an error (post-error). This is indicative of the amount of post-error slowing an individual exhibits. Next, I identified brain regions that were positively and/or negatively associated with the interference or post-error slowing scores within the incongruent > congruent or incorrect > correct contrasts, respectively, by using the scores
as regressors in each analysis. Additionally, to determine whether these brain-behavior associations differed across groups, I conducted a continuous covariate interaction analysis. The behavioral scores (interference and post-error slowing) were entered as separate regressors for each group. Age and PTSD symptom severity were entered as regressors in all analyses. Z statistic images were thresholded using clusters determined by $Z > 1.96$ and a corrected cluster significance threshold of $P = 0.05$.

**Behavioral Statistical Analysis**

Statistical analyses were performed with SPSS, version 19 (IBM Corp., Armonk, NY). PCL-M scores and age were entered as covariates in all analyses. However, because the variables did not contribute significant variance, they are not reported in the results section.

To examine how increased demands for cognitive control associated with incongruent trials affected the two groups, a 2 x 2 repeated measures analysis of covariance (ANCOVA) was performed on accuracy and reaction time. Congruency was the within subjects factor and group was the between subjects factor. Furthermore, to examine if there were group differences in the type of errors, a 2 x 2 x 2 repeated measures ANCOVA was performed in which congruency and type of error (i.e., omission vs. commission) were the within subjects factors and group was the between subjects factor.

To determine whether there were behavioral differences in post-error performance, an ANCOVA was performed, in which the post-error slowing score (post-error reaction time – post-correct reaction time) was the dependent variable and mTBI
group was the fixed factor. Additionally, to determine whether groups differed in the proportion of incongruent trials post-error, an independent samples t-test was performed.

**Results**

**Behavioral Performance**

To assess cognitive control associated with processing incongruent information, I examined both accuracy and reaction time data for congruent and incongruent conditions. Analysis of accuracy data revealed that accuracy did not significantly differ in the congruent and incongruent conditions \(F(1,29) = 0.003, P = 0.96\) or across groups \(F(1,29) = 0.58, P = 0.45\). Moreover, the group by congruency interaction was also not significant \(F(1,29) = 0.04, P = 0.85\). A direct comparison of the nature of the errors (i.e., omission or commission) revealed that there was no significant difference in the frequency of omission and commission errors \(F(1,29) = 1.75, P = 0.20\). Numerically commission errors, but not omission errors, were more frequent in the incongruent than congruent condition across both groups. However, the type of error by condition interaction was not significant when age and PCL-M scores were added to the model \(F(1,29) = 0.005, P = 0.95\). The interaction between type of error and group \(F(1,29) = 2.13, P = 0.16\) and type of error, condition, and group \(F(1,29) = 0.19, P = 0.67\) were also not significant. Mean accuracy data are presented in Table 7.

Analysis of reaction time data revealed that reaction time was not significantly different in the congruent and incongruent conditions \(F(1,29) = 2.93, P = 0.10\), although numerically performance was slower in the incongruent condition than congruent condition (see Table 7). Neither the effect of group \(F(1,29) = 0.46, P = 0.50\)
nor the group by congruency interaction were significant ($F(1,29) = 0.21, P = 0.65$), suggesting that mTBI and no-TBI groups performed similarly in both conditions.

<table>
<thead>
<tr>
<th>Performance as a function of congruency</th>
<th>no-TBI ($n=16$)</th>
<th>mTBI ($n=17$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congruent accuracy, $M \ (SD)$</td>
<td>92.3 (9.2)</td>
<td>94.0 (6.0)</td>
</tr>
<tr>
<td>Incongruent accuracy, $M \ (SD)$</td>
<td>83.0 (10.8)</td>
<td>85.1 (8.8)</td>
</tr>
<tr>
<td>Congruent omission errors, $M \ (SD)$</td>
<td>3.0 (4.5)</td>
<td>3.2 (4.5)</td>
</tr>
<tr>
<td>Congruent commission errors, $M \ (SD)$</td>
<td>4.6 (7.5)</td>
<td>2.8 (3.4)</td>
</tr>
<tr>
<td>Incongruent omission errors, $M \ (SD)$</td>
<td>3.6 (4.8)</td>
<td>4.0 (4.7)</td>
</tr>
<tr>
<td>Incongruent commission errors, $M \ (SD)$</td>
<td>13.4 (7.3)</td>
<td>10.8 (5.5)</td>
</tr>
<tr>
<td>Congruent RT, $M \ (SD)$</td>
<td>590.3 (122.5)</td>
<td>558.9 (117.7)</td>
</tr>
<tr>
<td>Incongruent RT, $M \ (SD)$</td>
<td>697.4 (133.6)</td>
<td>649.8 (159.8)</td>
</tr>
<tr>
<td>Interference score, $M \ (SD)$</td>
<td>107.1 (92.0)</td>
<td>90.9 (81.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Performance as a function of accuracy of the preceding trial</th>
<th>no-TBI ($n=16$)</th>
<th>mTBI ($n=17$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-correct RT, $M \ (SD)$</td>
<td>637.7 (116.0)</td>
<td>599.5 (130.8)</td>
</tr>
<tr>
<td>Post-error RT, $M \ (SD)$</td>
<td>661.4 (121.1)</td>
<td>622.8 (140.4)</td>
</tr>
<tr>
<td>Post-error slowing score, $M \ (SD)$</td>
<td>23.7 (61.1)</td>
<td>23.3 (47.4)</td>
</tr>
</tbody>
</table>

**Table 7. Congruency and error-related performance by group in Study 3.**
*Note: Accuracy and errors are in percent. Reaction times are in milliseconds. mTBI=mild traumatic brain injury; RT=reaction time.*

Next, I examined cognitive control associated with error processing, using a post-error slowing score as the dependent variable. The post-error slowing score is the difference in reaction time on trials following a correct (post-correct) response and on trials following an incorrect (post-error) response. Results revealed that there were no significant group differences in post-error slowing score ($F(1,29) = 0.001, P = 0.97$), suggesting that groups did not differentially slow down after errors. Additionally, reaction time was not significantly different in post-correct and post-error trials ($F(1,29) = 0.28, P = 0.60$), although, numerically, both groups were slower after incorrect responses than correct responses (see Table 7). Because reaction time slowing on post-error trials will also vary as a function of congruency, it was important to determine
whether the frequency of incongruent vs. congruent post-error trials was similar across groups. Results showed that the proportion of incongruent trials after an error was not significantly different across groups ($t(31) = 0.60, P = 0.56$).

**Imaging Results**

*Cogntive Control Associated with Processing of Incongruent Information*

The incongruent > congruent contrast was examined to determine if there were significant group differences in brain activation associated with processing of incongruent information. Both groups showed increased activation in the dACC and right superior parietal lobe, two areas associated with the SN and CEN, respectively (see Table 8). There were no significant group differences in cognitive control regions in the incongruent > congruent contrast. However, the mTBI group showed increased activation in the left occipital lobe compared to controls (see Table 9).

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Cluster Size</th>
<th>Peak Voxel (MNI coordinates)</th>
<th>Z-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no-TBI group map of Incongruent &gt; Congruent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right dACC</td>
<td>5547</td>
<td>8 28 20</td>
<td>3.5</td>
</tr>
<tr>
<td>Right Superior Parietal Lobe</td>
<td>5344</td>
<td>28 -62 58</td>
<td>3.4</td>
</tr>
<tr>
<td>Right Supplementary Motor Area</td>
<td>1573</td>
<td>32 8 58</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>mTBI group map of Incongruent &gt; Congruent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Superior Parietal Lobe</td>
<td>14462</td>
<td>22 -60 60</td>
<td>3.9</td>
</tr>
<tr>
<td>Left dACC</td>
<td>7350</td>
<td>-8 48</td>
<td>4.5</td>
</tr>
<tr>
<td>Left Superior Parietal Lobe</td>
<td>4720</td>
<td>-28 -58 56</td>
<td>3.8</td>
</tr>
<tr>
<td>Left Occipital Cortex</td>
<td>3175</td>
<td>-48 -70 -6</td>
<td>4.0</td>
</tr>
<tr>
<td>Left Precentral Gyrus</td>
<td>2649</td>
<td>-32 -6 68</td>
<td>3.1</td>
</tr>
<tr>
<td>Left Inferior Frontal Gyrus</td>
<td>2352</td>
<td>-46 6 14</td>
<td>3.3</td>
</tr>
<tr>
<td>Right Insula</td>
<td>1176</td>
<td>34 26 -10</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Table 8. Significant brain regions for incongruent > congruent contrast in each group in Study 3.  
*Note: mTBI=mild traumatic brain injury; dACC=dorsal anterior cingulate cortex.*
In an exploratory analysis, I examined the uncorrected maps of the incongruent > congruent contrast at a $z$ threshold of 1.96. In comparison to controls, individuals with mTBI had increased activation in the left dACC (see Table 9), an area of the SN and associated with evaluative control.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Cluster Size</th>
<th>Peak Voxel (MNI coordinates)</th>
<th>Z-Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTBI &gt; no-TBI for Incongruent &gt; Congruent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Occipital Cortex</td>
<td>2500</td>
<td>-16 -90 -6</td>
<td>3.3</td>
</tr>
<tr>
<td>Left dACC/Supplementary Motor Area (from uncorrected map)</td>
<td>1490</td>
<td>-4 -6 60</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Table 9. Significant group differences in brain regions for incongruent > congruent contrast in Study 3.

*Note:* mTBI=mild traumatic brain injury; dACC=dorsal anterior cingulate cortex.

In light of the uncorrected group difference in dACC activation, I next examined whether there were regions where greater functional connectivity for incongruent (vs. congruent) trials differed across groups. To do this, I performed a PPI analysis using the dACC as a seed. Results showed that there were no significant group differences in dACC functional coupling as a function of congruency.

In the incongruent > congruent contrast, age was positively correlated with activation in the right angular gyrus and right frontal pole and negatively associated with activation in the right superior parietal lobe, right precentral gyrus, and left superior temporal gyrus. PCL-M scores were negatively associated with activation in the left cerebellum. However, there were no positive associations between PCL-M scores and activation in the incongruent > congruent contrast.
Cognitive Control Associated with Error Processing

The incorrect > correct contrast was examined to determine if there were significant group differences in brain activation associated with error processing. Both groups showed increased activation in the right insula and left inferior parietal lobes (see Table 10), regions that are part of the SN and CEN, respectively.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Cluster Size</th>
<th>Peak Voxel (MNI coordinates)</th>
<th>Z-statistic</th>
</tr>
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<tbody>
<tr>
<td>no-TBI group map of Incorrect &gt; Correct</td>
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<tr>
<td>Right dACC</td>
<td>59673</td>
<td>4 24 42</td>
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</tr>
<tr>
<td>Right Insula</td>
<td>13382</td>
<td>42 24 -8</td>
<td>4.1</td>
</tr>
<tr>
<td>Left Precuneus</td>
<td>8835</td>
<td>-8 -74 50</td>
<td>3.8</td>
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<td>Right Superior Temporal Gyrus</td>
<td>5154</td>
<td>48 -52 36</td>
<td>3.3</td>
</tr>
<tr>
<td>Right Cerebellum</td>
<td>3438</td>
<td>38 -76 -30</td>
<td>3.4</td>
</tr>
<tr>
<td>Left Thalamus</td>
<td>2372</td>
<td>-8 -4 4</td>
<td>3.4</td>
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<tr>
<td>Left Inferior Parietal Lobe</td>
<td>2372</td>
<td>-56 -36 50</td>
<td>3.2</td>
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<tr>
<td>Right Caudate</td>
<td>2298</td>
<td>10 8 8</td>
<td>3.6</td>
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<tr>
<td>mTBI group map of Incorrect &gt; Correct</td>
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<td></td>
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<tr>
<td>Right Insula</td>
<td>61973</td>
<td>42 22 -6</td>
<td>5.2</td>
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<td>Left Occipital Cortex</td>
<td>22507</td>
<td>-8 -86 8</td>
<td>4.5</td>
</tr>
<tr>
<td>Left Insula</td>
<td>16268</td>
<td>-32 20 4</td>
<td>5.1</td>
</tr>
<tr>
<td>Right Inferior Parietal Lobe</td>
<td>14753</td>
<td>52 -40 50</td>
<td>4.6</td>
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<tr>
<td>Left Inferior Parietal Lobe</td>
<td>7231</td>
<td>-36 -50 38</td>
<td>4.3</td>
</tr>
<tr>
<td>Left Superior Parietal Lobe</td>
<td>1036</td>
<td>-26 -66 52</td>
<td>3.4</td>
</tr>
<tr>
<td>Right Middle Frontal Gyrus</td>
<td>104</td>
<td>32 54 -6</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Table 10. Significant brain regions for incorrect > correct contrast in each group in Study 3. Note: mTBI=mild traumatic brain injury; dACC=dorsal anterior cingulate cortex.

There were significant group differences in regions outside the SN and CEN in the incorrect > correct contrast. Specifically, compared to controls, individuals with mTBI showed greater deactivation of the left ventromedial prefrontal cortex (vMPFC), left posterior cingulate cortex (PCC) and left precuneus, areas part of the default mode network (DMN) that are typically deactivated during cognitive control tasks (see Table 11, Figure 10). Additionally, controls had greater activation than mTBI participants in
the left dorsomedial prefrontal cortex (dMPFC), another region of the DMN (Table 11, Figure 10), whereas the mTBI group showed deactivation in this region in incorrect vs. correct trials.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Cluster Size</th>
<th>Peak Voxel (MNI coordinates)</th>
<th>Z-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>no-TBI &gt; mTBI for Incorrect &gt; Correct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left PCC*</td>
<td>11041</td>
<td>-4 -30 36</td>
<td>4.0</td>
</tr>
<tr>
<td>Left Precuneus*</td>
<td>7156</td>
<td>-36 -70 40</td>
<td>4.3</td>
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<tr>
<td>Right Cerebellum</td>
<td>7129</td>
<td>40 -76 -50</td>
<td>3.8</td>
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<tr>
<td>Left dMPFC</td>
<td>1177</td>
<td>-4 42 40</td>
<td>3.7</td>
</tr>
<tr>
<td>Left vMPFC*</td>
<td>751</td>
<td>-2 46 -12</td>
<td>3.6</td>
</tr>
</tbody>
</table>

| mTBI > no-TBI for Incorrect > Correct |              |                              |             |
| Occipital Cortex       | 9304         | -6 -84 10                    | 3.9         |

Table 11. Significant group differences in brain regions for incorrect > correct contrast in Study 3. Note: *=for these regions, no-TBI > mTBI for Incorrect > Correct represents greater deactivation in mTBI. mTBI=mild traumatic brain injury; PCC=posterior cingulate cortex; dMPFC=dorsomedial prefrontal cortex; vMPFC=ventromedial prefrontal cortex.

Figure 10. The mTBI group had significant deactivation in DMN regions for the incorrect > correct contrast in Study 3.
The no-TBI group had increased activation in the left dMPFC for the incorrect > correct contrast. The mTBI group had greater deactivation in the left vMPFC and left dMPFC for the incorrect > correct contrast. Note: dMPFC=dorsomedial prefrontal cortex; vMPFC=ventromedial prefrontal cortex; mTBI=mild traumatic brain injury.
In light of the deactivation of the DMN in the mTBI group, I next examined whether there were regions where greater functional connectivity with the DMN for incorrect (vs. correct) trials differed across groups. To do this, I used the vMPFC and dMPFC as seeds in two separate PPI analyses and examined group differences. Using the vMPFC as a seed, I found that functional coupling with the right dACC for incorrect vs. correct trials was greater in the mTBI group than the no-TBI group. Upon further inspection, results showed that there was increased negative coupling between these regions such that the dACC is active when the vMPFC is deactivated (see Table 12; Figure 11A). These results suggest that the differential functional coupling between

<table>
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<th>Brain Region</th>
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<th>Peak Voxel (MNI coordinates)</th>
<th>Z-statistic</th>
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</thead>
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<td></td>
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<tr>
<td>Right Caudate</td>
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<td>Left Caudate/Insula</td>
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<td>3.4</td>
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<tr>
<td>Right dACC</td>
<td>2136</td>
<td>4 28 26</td>
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</tr>
<tr>
<td>Left Thalamus</td>
<td>243</td>
<td>-22 -22 2</td>
<td>2.8</td>
</tr>
<tr>
<td>mTBI &gt; no-TBI for dMPFC seed</td>
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<td></td>
<td></td>
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<tr>
<td>Right dACC</td>
<td>10488</td>
<td>6 24 42</td>
<td>3.8</td>
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<tr>
<td>Right Inferior Frontal Gyrus</td>
<td>7229</td>
<td>48 12 22</td>
<td>3.6</td>
</tr>
<tr>
<td>Left Inferior Frontal Gyrus</td>
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<td>-44 2 28</td>
<td>3.8</td>
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<tr>
<td>Right Caudate</td>
<td>5528</td>
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<td>Right Inferior Parietal Lobe</td>
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<td>Right Middle Frontal Gyrus</td>
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<td>Left Cerebellum</td>
<td>2405</td>
<td>-8 -82 -32</td>
<td>3.6</td>
</tr>
<tr>
<td>Left Insula</td>
<td>1884</td>
<td>-32 20 0</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Table 12. Significant group differences in functional connectivity with seed regions in the incorrect > correct contrast as determined by PPI analyses in Study 3.

Note: mTBI=mild traumatic brain injury; dMPFC=dorsomedial prefrontal cortex; dACC=dorsal anterior cingulate cortex; vMPFC=ventromedial prefrontal cortex.
regions of the SN and DMN as a function of response accuracy is greater in individuals with mTBI than no-TBI controls. Similarly, I found that differential negative coupling between the vMPFC and left insula for incorrect vs. correct trials was greater in the mTBI group than the no-TBI group (Table 12; Figure 11B). There were no regions where the no-TBI group showed greater differential functional connectivity for incorrect vs. correct trials than the mTBI group. Taken together, these results suggest enhanced negative coupling between the DMN and SN in individuals with mTBI during cognitive control associated with error processing.

Figure 11. The mTBI group had enhanced functional connectivity between the vMPFC of the DMN and regions of the SN for the incorrect > correct contrast in Study 3. A. Differential negative functional connectivity between the left vMPFC seed and the right dACC for incorrect vs. correct trials was greater for the mTBI group than the no-TBI group. B. Differential negative functional connectivity between the left vMPFC and left insula for incorrect vs. correct trials was greater for the mTBI group than the no-TBI group. Note: The hemodynamic response functions are plotted to the right of the figures to show coupling. mTBI=mild traumatic brain injury; dACC=dorsal anterior cingulate cortex; vMPFC=ventromedial prefrontal cortex.
Similar to the vMPFC, the mTBI group showed deactivation in the dMPFC for the incorrect > correct contrast. To determine if this deactivation was also associated with group differences in functional connectivity as a function of response accuracy, I used the dMPFC as a seed in a PPI analysis. Results suggested that differential functional coupling with bilateral DLPFC and bilateral insula for incorrect vs. correct trials was greater in the mTBI group than the no-TBI group (Table 12, Figure 12). Further inspection revealed that both of these findings were the result of enhanced negative coupling, such that with enhanced suppression of a DMN region (i.e., dMPFC) for incorrect vs. correct trials, regions of the CEN (i.e., DLPFC) and SN (i.e., insula) were more engaged in the mTBI group. There were no brain regions where the no-TBI group showed greater functional connectivity for incorrect (vs. correct) trials than the mTBI group. These findings provide further evidence that mTBI participants had increased negative functional connectivity between the DMN and SN, and suggest similarly increased negative functional connectivity with the CEN.

I observed a significant negative association between age and activation in the left cerebellum in the incorrect > correct contrast. There were no significant positive associations between age and functional activation. Analysis of PCL-M scores in the incorrect > correct contrast revealed that with increased PTSD symptom severity there was reduced activation in the left precentral gyrus, right dACC, and right frontal pole. There were no significant positive associations between PCL-M scores and brain activation.
Figure 12. The mTBI group had enhanced functional connectivity between the dMPFC of the DMN and regions of the SN and CEN for the incorrect > correct contrast in Study 3. A. Negative functional connectivity between the left dMPFC seed and bilateral insula for incorrect vs. correct trials was greater in the mTBI group than the no-TBI group. B. Negative functional connectivity between the left dMPFC seed and bilateral DLPFC for incorrect vs. correct trials was greater in the mTBI group than the no-TBI group. Note: The purple circles represent the brain region for which the hemodynamic response functions are plotted against the dMPFC to show coupling. The left insula and DLPFC hemodynamic response functions are not shown but reveal a similar pattern. mTBI=mild traumatic brain injury; dMPFC=dorsomedial prefrontal cortex; DLPFC=dorsolateral prefrontal cortex.

Correlations Between Behavioral and Functional Activation Measures of Cognitive Control

To determine whether brain activation reflecting cognitive control was associated with behavioral measures of cognitive control, as indexed by the interference score and post-error slowing score, I performed two regression analyses – one using the interference score as a regressor and the other using the post-error slowing score as the regressor. Additionally, I examined whether group interacted with each regressor to
determine whether group moderated any observed brain association with behavior. The first analysis suggested that the interference score was positively associated with activation in the right dACC, bilateral superior parietal lobe, and right DLPFC, and negatively associated with activation in the right dMPFC and right occipital cortex (see Table 13) for incongruent vs. congruent trials. The group interaction revealed that group significantly moderated the association between the interference score and activation in the left superior parietal lobe and right DLPFC, such that the interference score was positively associated with activation in these regions in individuals with mTBI, but not in no-TBI controls (Table 13, Figure 13A). Group also moderated the association between the interference score and left paracentral lobule activation, with a positive association in the mTBI group and a negative association in the no-TBI group (Table 13, Figure 13B).

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Cluster Size</th>
<th>Peak Voxel (MNI coordinates)</th>
<th>Z-statistic</th>
</tr>
</thead>
<tbody>
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<td><strong>Positive associations with the interference score – main effect</strong></td>
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<tr>
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<td>-28 -62 52</td>
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<td>Right Superior Parietal Lobe</td>
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<td>32 -44 42</td>
<td>5.0</td>
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<td>Right DLPFC</td>
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<td>4.6</td>
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<td>Right dACC</td>
<td>5364</td>
<td>6 26 40</td>
<td>3.9</td>
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<td><strong>Negative associations with the interference score – main effect</strong></td>
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<td>Right Occipital Cortex</td>
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<td>12 -92 18</td>
<td>3.2</td>
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<td><strong>Group interaction with the interference score</strong></td>
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<td>4.0</td>
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<td>50 6 44</td>
<td>4.0</td>
</tr>
<tr>
<td>Left Paracentral Lobule</td>
<td>2008</td>
<td>-2 -4 58</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Table 13. Significant brain regions associated with interference score in Study 3.

Note: dACC=dorsal anterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex; dMPFC=dorsomedial prefrontal cortex.

The second analysis revealed a significant negative association between the post-error slowing score and activation in the left precentral gyrus, right postcentral gyrus, and
left medial temporal lobe for incorrect vs. correct trials (see Table 14). There were no significant positive associations with the post-error slowing score. Group moderated the association between the post-error slowing score and activation in the precuneus and right DLPFC (see Table 14). Further inspection revealed that greater post-error slowing was associated with greater deactivation of the precuneus in individuals with mTBI, but not in no-TBI controls (Figure 14A). Additionally, greater post-error slowing was associated with greater recruitment of the right DLPFC in individuals with mTBI, but not in no-TBI controls (Figure 14B).

![Graphs showing neural activity and interference scores](image)

Figure 13. Greater experience of conflict was significantly associated with activity in CEN regions in mTBI in Study 3.
A. Greater activation of the left superior parietal lobe and right DLPFC was associated with higher interference scores in the mTBI group. B. Greater activation of the left paracentral lobule was associated with higher interference scores in the mTBI group and lower interference scores in the no-TBI group. Note: Activation is represented as contrast of parameter estimate values. mTBI=mild traumatic brain injury; DLPFC=dorsolateral prefrontal cortex.
Table 14. Significant brain regions associated with the post-error slowing score in Study 3.

Note: Only significant contrasts are shown. DLPFC=dorsolateral prefrontal cortex.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Cluster Size</th>
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<th>Z-statistic</th>
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</thead>
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<tr>
<td><strong>Negative associations with the post-error slowing score – main effect</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left Precentral Gyrus</td>
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<td>Right Postcentral Gyrus</td>
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<td>58 -6 16</td>
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<td>Left Middle Temporal Gyrus</td>
<td>326</td>
<td>-56 -18 -6</td>
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<td><strong>Group interactions with the post-error slowing score</strong></td>
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<td></td>
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<tr>
<td>Right DLPFC</td>
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<td>46 38 26</td>
<td>3.7</td>
</tr>
<tr>
<td>Precuneus</td>
<td>2895</td>
<td>0 -78 40</td>
<td>3.5</td>
</tr>
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</table>

Figure 14. Increased cognitive control was significantly associated with activity in DMN and CEN regions in mTBI in Study 3.

A. Greater deactivation of the precuneus was associated with greater cognitive control in the mTBI group.
B. Greater activation of the right DLPFC was associated with greater cognitive control in the mTBI group.

Note: Activation is represented as contrast of parameter estimate values. mTBI=mild traumatic brain injury; DLPFC=dorsolateral prefrontal cortex.
Lastly, I wanted to examine whether the uncorrected group difference in dACC activation for incongruent (vs. congruent) trials was associated with the interference score. To determine if there were significant associations between activation and the interference score, I extracted the activation of the dACC for each individual’s incongruent > congruent contrast map and correlated it with the interference score. Results revealed that in participants with mTBI, a higher interference score was associated with increased activation in the dACC (Figure 15).

Figure 15. Activity in the dACC significantly correlates with the interference score in the mTBI group in Study 3.

There was no significant correlation for the no-TBI group. Note: Activation is represented as contrast of the parameter estimate values. mTBI=mild traumatic brain injury; dACC=dorsal anterior cingulate cortex.
Discussion

I used fMRI and the flanker task to examine cognitive control in blast-exposed OEF/OIF veterans and report several main findings. First, I did not find performance differences between mTBI and no-TBI groups. Second, there was suggestive evidence for increased recruitment of the dACC in individuals with mTBI. This was associated with performance such that mTBI individuals with greater dACC activity had higher interference scores. Third, I found that with increased demand for cognitive control, there was greater deactivation of DMN regions in mTBI than no-TBI. Further inspection revealed that this was associated with enhanced negative coupling with SN and CEN regions.

Surprisingly, I found no evidence for behavioral differences in cognitive control. Several studies investigating performance on cognitive control tasks in chronic civilian-related mTBI have found that mTBI is associated with behavioral impairment (Pontifex et al., 2009; Seignourel et al., 2005). However, several other studies report no behavioral impairment associated with cognitive control in chronic mTBI (Killam et al., 2005; Larson et al., 2012; Larson et al., 2011; Larson et al., 2006). The reason for the discrepancy in these findings is unclear, as neither the chronicity of injury nor the choice of experimental task offers an explanation of these discrepant findings.

Studies investigating cognitive control in chronic blast-related mTBI have been limited, but a recent study using the stimulus-response compatibility task found that participants with mTBI had significantly slower responses for incompatible stimuli than a no-TBI control group (Scheibel et al., 2012). These findings suggest impaired cognitive
control in blast-related mTBI. However, my behavioral findings provide no evidence for this notion. The discrepancy in findings between Scheibel et al.’s (2012) study and the current one may be because the stimulus-response compatibility task places higher demands on cognitive control than the flanker task. During the incompatible condition in the stimulus-response compatibility task, individuals are required to respond to the opposite direction of the arrow. This generates a high level of response conflict, as a correct response requires inhibition of the strong tendency to respond to the direction of the arrow. In contrast, in the incongruent condition of the flanker task, response conflict occurs as a result of the competing tendencies to respond to the direction of the flanker arrows and the direction of the target arrow. As such, inhibition of the flanker arrows can mitigate response conflict. Thus, unlike on the stimulus-response compatibility task, successful performance on the flanker task may be possible with strong regulative processes of perceptual selection. Therefore, it may be that individuals with blast-related mTBI only show impairment on cognitive control tasks that pose a strong demand on regulation of response selection.

Alternatively, the discrepant outcomes may be due to the use of different control groups. Scheibel and colleagues (2012) used a non-blast exposed control group, which leaves open the possibility that the reported behavioral differences between mTBI and controls are associated with blast exposure and/or mTBI. In contrast, I used a blast-exposed control group to isolate the contribution of mTBI to performance. The absence of group differences in my study suggests that mTBI is not associated with behavioral deficits in cognitive control. Therefore, the behavioral differences reported in Scheibel et
al. (2012) may be due to blast exposure. Recent evidence suggests that blast-exposure itself is associated with neural changes (Robinson et al., 2014; Taber et al., 2015) and thus, may significantly contribute to performance decrements.

There is some evidence for mTBI-related differences in brain function in the absence of behavioral impairment in cognitive control (Broglio et al., 2009; Fischer et al., 2014). Yet, in contrast to what I expected, I did not find significant group differences in activation in brain regions associated with evaluative or regulative control. Instead, when the incongruent condition was compared to the congruent condition, both groups activated the dACC and parietal lobe, which are areas involved in evaluative and regulative control, respectively (Botvinick et al., 2001).

However, in an exploratory analysis, I found suggestive evidence for increased activity in the dACC for incongruent vs. congruent trials in the mTBI group. The dACC is a hub of the SN and is important for evaluative control. It is involved in monitoring for salient events and initiating output signals to motor and sensory areas (Menon & Uddin, 2010; Seeley et al., 2007). These preliminary results are consistent with the findings of previous studies that have shown alterations in the recruitment of evaluative control regions in mTBI (Pontifex et al., 2009; Scheibel et al., 2012). I extend these findings by showing that activation of the dACC in mTBI was associated with a behavioral measure of interference. I interpret these findings to suggest that there is increased recruitment of the SN in mTBI when there is greater experience of conflict. The finding of an association between interference scores and activation in key nodes of the CEN in mTBI
further suggests that in addition to SN regions, recruitment of CEN regions is also increased in mTBI when there is greater experience of conflict.

Whereas group differences in brain activation related to congruency were only suggestive, differences related to error processing were robust. However, contrary to my hypothesis, these alterations were not located within evaluative or regulative control regions but were instead isolated to DMN regions, including the PCC, vMPFC, and dMPFC. The DMN is a well-established resting state network that is most active at rest and is suggested to be involved in autobiographical memory retrieval, mind-wandering, and other internally directed thoughts (Gusnard, Akbudak, Shulman, & Raichle, 2001; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Raichle et al., 2001). During tasks that require externally oriented attention, the DMN is deactivated (Fox et al., 2005; Fransson, 2006; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009). Here, I found evidence for greater deactivation in the PCC, vMPFC, and dMPFC in the mTBI group than the no-TBI group under increased demands on cognitive control. Several other studies investigating DMN activity during cognitive control tasks also report DMN deactivation (Greicius, Krasnow, Reiss, & Menon, 2003; Sridharan, Levitin, & Menon, 2008). However, my findings suggest that DMN deactivation is greater in mTBI. The finding of an association between post-error slowing and DMN deactivation in mTBI suggests that this deactivation may facilitate the implementation of cognitive control.

Further evidence to support this notion is provided by the finding that the negative coupling between the vMPFC and regions of the SN associated with incorrect responses is enhanced in mTBI. The SN has been hypothesized to be a “switching” network in
cognitive control and may be especially important in switching between the DMN and CEN (Menon & Uddin, 2010). Work by Sridharan and colleagues (2008) shows that the SN is engaged to relay critical information to suppress DMN regions and to engage CEN regions. Studies suggest that this switching between endogenous and exogenous cognitive processing may facilitate access to working memory and attentional resources necessary for successful task performance (Fransson, 2006; McKiernan et al., 2003). In this study, I provide evidence for increased negative functional coupling between the DMN and SN in mTBI with increased cognitive control demands. In light of the fact that individuals with mTBI did not show behavioral impairments, this enhanced negative coupling between the DMN and SN in mTBI may serve as a compensatory mechanism for successful task performance.

One region of the DMN showed divergent patterns of activation in mTBI and no-TBI groups with increased demands on cognitive control. Whereas the mTBI group deactivated the dMPFC for incorrect vs. correct trials, the no-TBI group showed increased activation in the dMPFC during error processing. The dMPFC is involved with self-referential thought and attending to one’s current mental state (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Gusnard et al., 2001; Northoff & Bermpohl, 2004; Northoff et al., 2009). It is possible that the increased activation in the no-TBI group is associated with heightened awareness of or reflection upon errors. However, more research is needed to determine this possibility. The deactivation in the mTBI group may reflect the need for additional cognitive resources to implement enhanced cognitive
control. This notion was supported by the finding of greater negative functional coupling between the dMPFC and regions of the SN and CEN in mTBI in error processing.

While both the vMPFC and dMPFC nodes of the DMN showed greater functional connectivity with the SN associated with processing of errors in mTBI, only the dMPFC showed enhanced connectivity with the CEN in mTBI. Evidence from the animal literature has shown that areas homologous to the dMPFC have direct anatomical connections to lateral frontal and parietal regions (i.e., CEN nodes), whereas areas homologous to the vMPFC are more anatomically connected to limbic regions (Bates & Goldman-Rakic, 1993; Heidbreder & Groenewegen, 2003). Research suggests that functional connectivity largely reflects and is constrained by structural connectivity (Greicius, Supekar, Menon, & Dougherty, 2009; van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009). Thus, the finding that the increased functional connectivity between the DMN and CEN is specific to the dMPFC may be related to the anatomical connections between these regions.

Moreover, the dMPFC and vMPFC have been proposed to be involved in two distinct DMN subsystems subserving different cognitive functions (Andrews-Hanna et al., 2010) and therefore may differ in their functional interactions with networks outside of the DMN. Accumulating research suggests that the vMPFC plays an important role in integrating emotional and cognitive processes whereas the dMPFC is crucial for monitoring and appraising self-related information (Gusnard et al., 2001; Mitchell, Banaji, & Macrae, 2005; Northoff & Bermpohl, 2004). Therefore, functional connections to a subsystem involved in monitoring the self may play a larger role for successful
engagement in regulative control in error processing than a subsystem involved in integrating emotional and cognitive processes.

The results reported in this study should be considered within the context of the limitation that mTBI group assignment was based on self-report. However, mTBI assessment was conducted with an in-depth structured clinical interview, which is currently the gold standard of diagnosis (Corrigan & Bogner, 2007). Another limitation is the inability to examine LOC-associated effects on cognitive control. As shown in Chapters 2 and 3, LOC may be particularly important in the neural changes associated with blast-related mTBI, but my sample size was too small to allow for a direct comparison between individuals who suffered mTBI with and without LOC. Because of a shut down of the scanner due to a mandatory scanner upgrade, I was unable to enroll additional participants. Future studies will need to examine whether there are differences in cognitive control in individuals with mTBI as a function of presence of LOC.

In summary, I report robust brain differences associated with error processing in chronic mTBI. In particular, individuals with mTBI exhibited increased deactivation in regions of the DMN. Further, these deactivations were associated with greater negative functional connectivity with the SN and CEN during the processing of errors. Importantly, I did not observe any performance impairments in mTBI. Taken together, these results suggest that deactivation of DMN regions and associated enhancements of negative coupling between regions of the DMN and regions of the SN and CEN with increased cognitive control demand in mTBI may act as a compensatory mechanism for successful task performance.
CHAPTER FIVE: General Discussion

The goal of this dissertation was to explore the neural and behavioral sequelae of chronic blast-related mTBI. In Chapter 1, I provided a broad overview of the literature, which demonstrated that there are residual neural changes in chronic blast-related mTBI. Yet, the behavioral consequences of these changes are unclear. The work presented in this dissertation shows that even years after the injury, mTBI is associated with both structural and functional neural alterations. Additionally, this work suggests that these structural and functional neural changes are associated with report of behavioral symptoms and with cognition in chronic mTBI.

In Chapters 2 and 3, I found that mTBI with LOC was associated with white matter abnormalities, which in turn were associated with behavioral symptoms and cognitive outcome. Prior research that has investigated behavioral consequences in individuals with chronic blast-related mTBI has found that behavioral and cognitive sequelae are primarily associated with mental health factors such as PTSD (Belanger, Kretzmer, et al., 2010; Hoge et al., 2008; Lippa et al., 2010; Verfaellie et al., 2014; Verfaellie et al., 2013). However, mTBI is associated with white matter abnormalities (Davenport et al., 2011; Hayes et al., 2015; Mac Donald et al., 2013; Mac Donald et al., 2011; Morey et al., 2012). Yet, evidence that these white matter changes are associated with behavioral symptoms is limited (Levin et al., 2010; Yeh et al., 2014) and findings with regards to their association with cognition are mixed (Hayes et al., 2015; Jorge et al., 2012; Levin et al., 2010; Sorg et al., 2013). My studies show that the extent of white matter abnormality is associated with physical PCS severity and overall cognitive status.
In addition, white matter abnormality mediates the relationship between chronic mTBI with LOC and physical PCS and cognitive impairment. These results suggest that white matter injury may constitute a unique mechanism for behavioral and cognitive consequences in mTBI. Additionally, the finding that PTSD was not associated with white matter abnormalities suggests that the shared behavioral difficulties observed in mTBI and PTSD are mediated through different neural pathologies. Further research is needed to determine the mechanism mediating the relationship between PTSD and behavior, but prior work has shown that PTSD is primarily associated with changes in gray matter volume (Bremner et al., 1995; Corbo et al., 2005; Kasai et al., 2008; O'Doherty et al., 2015; Smith, 2005) and functional alterations (Bremner et al., 1999; Daniels et al., 2010; Hayes, LaBar, et al., 2011; Milad et al., 2009; Sadeh et al., 2015; Shin & Libezon, 2010; Shin et al., 2004; St Jacques et al., 2013; van Wingen et al., 2012). This open question notwithstanding, the work presented here suggests that mTBI-related structural connectivity changes have significant behavioral and cognitive consequences for individuals with mTBI particularly when accompanied by LOC.

Findings from Chapter 4 suggest that in addition to the structural connectivity abnormalities found in Chapters 2 and 3, mTBI is also associated with alterations in brain function. Results of Chapter 4 revealed that mTBI was associated with greater deactivation of regions in the DMN and enhanced negative coupling between regions of the DMN and regions of the SN and CEN in the absence of behavioral impairment. I interpreted these findings to suggest that deactivation of DMN regions and associated enhancements in functional connectivity allow for the up-regulation of regions important
for task performance and thereby may facilitate implementation of cognitive control in mTBI. Thus, these changes in brain function in mTBI may be compensatory for difficulties implementing cognitive control. This is supported by findings that, in individuals with mTBI but not in controls, deactivation in a DMN region as well as activation in a CEN region were associated with post-error slowing - a measure of successful implementation of cognitive control. Although prior research has also suggested that chronic mTBI elicits brain changes in the absence of behavioral impairment (Broglio et al., 2009; Fischer et al., 2014), this dissertation is the first to provide evidence that these changes are compensatory.

Chapter 4 provided evidence for increased task-related functional connectivity between regions of the DMN and regions of the SN in mTBI, but an outstanding question is whether these functional connectivity changes map onto structural connectivity changes in pathways connecting the DMN and SN, such as the cingulum bundle and superior longitudinal fasciculus. One possibility is that only individuals with intact white matter fiber pathways pertaining to the DMN and SN can deactivate the DMN and up-regulate the SN. This would suggest that the extent of white matter injury in these pathways limits the ability to functionally up-regulate connectivity between regions of the DMN and SN. Another possibility is that even with damage to relevant white matter fiber pathways, enhanced functional connectivity is possible, but is mediated through alternate white matter pathways such as the corona radiata. Research in severe TBI is consistent with the former possibility (Bonnelle et al., 2012; Sharp et al., 2011). However, it is unclear whether these findings would translate to mTBI, where the extent
of white matter damage is less severe. It will be important for future studies to examine these possibilities further in chronic mTBI.

Because the focus of my dissertation was on mTBI, I used a control group that was blast-exposed but had no evidence of mTBI. This allowed me to examine the direct effects of mTBI while keeping blast exposure constant across groups. Of importance, recent evidence suggests that blast exposure in the absence of mTBI may also be associated with white matter abnormalities (Bazarian et al., 2012; Taber et al., 2015) and functional connectivity changes (Robinson et al., 2014). Whether these changes are associated with behavioral symptoms or cognitive alterations is currently unknown. Nonetheless, it is possible that my studies underestimate the changes veterans with blast-related mTBI experience in comparison to their premorbid function, as observed changes would reflect the combined effects of blast exposure and mTBI. Indeed, recent work that took into account both the effects of blast exposure and mTBI by using a non-blast exposed control group suggests that blast exposure in combination with mTBI is associated with reduced cognitive control (Scheibel et al., 2012). Future work would benefit from the inclusion of both blast-exposed and non-blast exposed control groups to further understand outcome in blast-exposed veterans with and without mTBI.

Given the neural changes in chronic blast-related mTBI, an important question is whether these persistent changes have implications for pathology later in life. While research on this topic is still in its infancy, recent work has suggested that blast exposure is associated with accelerated aging of the white matter (Trotter, Robinson, Milberg, McGlinchey, & Salat, 2015). However, whether there are similar processes associated
with brain function is currently unknown. Evidence from healthy aging suggests that age is associated with a decline in brain function (Cabeza, 2001; Raz, 2000), which raises the question as to whether mTBI-associated functional compensation also declines with age. Given the link between both white matter and cognition as well as between functional reorganization and cognition (Bartzokis, 2004; Cabeza, Anderson, Locantore, & McIntosh, 2002), it is possible that these pathological burdens in blast-related mTBI increase the risk for cognitive decline at an earlier age. Continued understanding of these persistent neural changes in blast-related mTBI and their implications for aging will be an important area of future research.
# BIBLIOGRAPHY

**List of Abbreviated Journal Titles**

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CURRICULUM VITAE

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