HIGH-DEFINITION FIBER TRACKING STUDY OF THE EXECUTIVE CONTROL NETWORK IN BLAST-RELATED TRAUMATIC BRAIN INJURY

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Ashley L. Ware

August 2017

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ABSTRACT

Blast-induced traumatic brain injury (bTBI) is common in Iraq and Afghanistan war veterans. However, subtle neural alterations and lack of a definitive biomarker impede clinical detection. The current study evaluated structure and functional correlates of executive control network (ECN) white matter tracts in veterans with and without bTBI to investigate the clinical utility of using High Definition Fiber Tracking (HDFT) to identify a biomarker of chronic bTBI. For the current study, male veterans (N = 38) between 24 and 50 years old completed a standardized neuropsychological evaluation that included the Stop Signal Task (SST) and structural magnetic resonance imaging. HDFT was used to derive quantitative metrics of tracts between the dorsolateral prefrontal cortex (DLFPC) and the putamen, caudate, and thalamus. Groups had similar demographic characteristics, and medical histories. Relative to the comparison group, moderate to strong effects indicated that bTBI was associated with: elevated quantitative anisotropy (QA) and reduced right hemisphere volume across tracts; reduced right DLFPC-putamen tract count and greater generalized fractional anisotropy (GFA); greater right DLPFC-thalamus tract count. A strong Group×Age interaction effect was observed on DLPFC-caudate tract count, indicating worse outcomes with older age in the bTBI group. Groups had similar SST performance, which strongly correlated with HDFT metrics across tracts in the comparison group; go and stop signal reaction time correlated positively with QA and negatively with tract volume and count; errors of commission correlated negatively with QA. Overall results support anomalous density and integrity of ECN white matter tracts in bTBI, particularly in the right putamen and thalamus tracts. In line with the literature, veterans with bTBI showed worsening DLPFC-caudate density with older age. Although ECN dysfunction was not

apparent via behavioral testing, faster and more accurate task performance related to higher QA and lower tract count and volume in the comparison group, respectively. Spared ECN function, despite anomalous white matter microstructure, could indicate functional compensation in bTBI, although alternate interpretations are being explored.

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Traumatic Brain Injury

Traumatic brain injury (TBI) is the brain dysfunction and pathology that can occur in isolation or along with additional bodily injury subsequent to an injury or external force (Centers for Disease Control and Prevention, 2015; Marr, 2004). Head injuries occur across a broad, heterogeneous spectrum of severity that includes historical classification of injuries as being mild, moderate, or severe on the basis of post-resuscitation level of coma, neurological, and neuroimaging assessments. Mild TBI (mTBI) includes concussion as the mildest form (McCrory et al., 2009; Ruff et al., 2009) and is the most common TBI incurred by civilians (Cassidy et al., 2004; Coronado et al., 2011) and military personnel (see Helmick et al., 2015). The symptoms of mTBI are highly variable from one person to another, and understanding of the effects of mTBI, and perhaps especially concussion, are historically controversial (e.g., Lishman, 1988; Sandy Macleod, 2010). This controversy largely stems from the fact that a definitive biomarker of mTBI has not been identified (Bigler & Bazarian, 2010; Tate, Shenton, & Bigler, 2012; Tate, Wilde, Bouix, & McCauley, 2015). However, significant advances in neuroimaging, research methods, and clinical approaches to medical management have potentiated novel insights regarding general scientific understanding of the effects of mTBI through promotion of early identification and the promise of efficacious interventions.

Classification

Treatment and medical management of TBI necessitate accurate diagnosis and classification of injury severity. Historically, clinical classification of head injuries as being mild, moderate or severe historically focused on neurological, or behavioral, signs. However, advances in neuroimaging methodologies have promoted increased classification accuracy through the integration of both behavioral and neuroradiological examination as part of modern classification systems. Regardless, identification and classification of TBI remains relatively complicated, particularly of injuries at the mild end of the spectrum.

Behavioral approaches. TBI has historically been classified on the basis of the presence and duration of loss of consciousness, alteration of consciousness, and/or post-traumatic amnesia. Whereas loss of consciousness (LOC) describes a period of unconsciousness (blackout) as a result of the traumatic event, alteration of consciousness (AOC) involves marked confusion or ambiguity regarding the event itself or the period of time subsequent to the event. Post-traumatic amnesia (PTA) is the time interval during which loss of memory and/or confusion for the event itself as well as the events immediately following the injury is experienced.

The Glasgow Coma Scale (GCS) is the most widely used measure for the clinical classification of TBI. The GCS is a neurologic scale that assesses level of consciousness through three components: eye opening, verbal response, and motor response, and was adapted as a measure of LOC (Teasdale et al., 2014). Classification of injury severity is based on total GCS score, which defines mild injury as scores between 13-15, moderate injury as scores between 9-12, and severe injury as scores between 3-8 (Teasdale &

Jennett, 1974). The scale also provides mortality scoring, characterized by scores of 2 or less. However, the sensitivity of the GCS is somewhat limited. Variables related to injury characteristics, medical interventions, and standardization of scores can affect GCS ratings, leading to misclassification of injury severity when utilized in isolation (Edwards, 2001; Gabbe, Cameron, & Finch, 2003; Reith, Brennan, Maas, & Teasdale, 2016).

Post-traumatic amnesia (PTA) has also been investigated as a predictor of TBI severity. PTA is shown to predict functional outcomes and, except at the extremes, correlates well with GCS scores (Levin, O'Donnell, & Grossman, 1979; Sherer, Struchen, Yablon, Wang, & Nick, 2008). Clinical classification of injuries using PTA characterizes injuries with PTA up to 24 hours as mild, between 1-7 days as moderate, and more than 7 days as severe (Saatman et al., 2008). Despite greater accuracy than GCS scores in predicting long-term functional status (e.g., Nakase-Richardson et al., 2009), identification of occurrence and duration of PTA can be difficult to establish in clinical contexts. These considerations highlight why reliability of PTA has been questioned.

Neuroradiological approaches. Advanced neuroimaging findings have been used to classify severity of TBI. Computed tomography (CT) was historically and continues to be utilized more frequently than other neuroimaging techniques in emergency departments. CT is most often used to evaluate the need for immediate and, when applicable, neurosurgical intervention in the presence of injury-related hematoma, contusion, lesion, and hemorrhage (Saatman et al., 2008). However, TBI can result in wide ranging alterations of the central nervous system that can be subtle, and clinical CT

results do not always detect structural alterations and can underestimate extent of damage (Azouvi, 2000). These limitations extend to other modern neuroimaging techniques such as magnetic resonance imaging (MRI). Although MRI allows for increased signal contrast of different tissue types to be examined through superior spatial resolution, sensitivity to acute effects of TBI can be somewhat limited compared to chronic effects. This is particularly the case in mTBI. However, evolving neuroimaging technologies and refined approaches to neuroradiological assessment are beginning to enable the detection of even subtle alterations in TBI, promising future classification through the use of clinical biomarkers.

Mild injuries. Compared to moderate and severe injuries, mTBI is much more challenging to identify, classify and diagnose. The subtle and highly variable nature of acute signs and symptoms subsequent to mild head injuries has challenged traditional clinical detection through standard behavioral and radiological evaluation. As a result, clinical and research conceptualization of these injuries has been plagued by controversy during the last half-century.

Early controversy centered around the etiology of neurological disturbance in mTBI. Emphasis was placed on psychiatric as opposed to neurologic etiology of dysfunction (reviewed in Shenton et al., 2012). The commonly limited radiological evidence for frank central nervous system disruption in mTBI that resulted in increased clinical reliance on often transient and subjective behavioral symptoms provided support for this argument. Though not fully resolved, recent clinical and research findings in both patients and preclinical animal models have supported neurological etiology of cognitive and neurobehavioral impairments following mTBI. Although, it is noted that the

influence of both isolated and/or comorbid psychiatric disorder(s) on outcomes in mTBI continues as a research focus.

The spectrum of injuries encompassed by a "mild" severity classification has also been contentiously debated. A brief movement in the research literature distinguished patients with radiological evidence of an acquired lesion, defined as "complicated" mTBI, from those who lacked radiological findings, or "uncomplicated" mTBI (e.g., D. H. Williams, Levin, & Eisenberg, 1990). However, limited neurological or neuropsychological support for differential outcomes and recovery/prognostic trajectories of these subgroups has emerged (e.g., Iverson, 2006). In fact, groups generally appeared more similar than different. Thus, current research investigations typically collapse across these groups. Similarly, the spectrum of injuries considered as being "mild" in severity, particularly concussion, have been controversial (as discussed in Sandy Macleod, 2010) although modern research often uses "concussion" and "mTBI" interchangeably.

Unified approaches. It is noteworthy that modern classification systems have been developed for use in civilians (e.g., Ruff et al., 2009) and in veterans and military personnel (detailed review provided by Helmick et al., 2015). However, global acceptance and utilization of a single approach to classification of TBI, particularly of mild injuries, is still in progress.

Epidemiology

TBI is a global public health concern. In the United States, the annual economic burden of TBI alone is estimated to be in excess of $60 billion (Finkelstein, Corso, & Miller, 2006).

Incidence and prevalence. Global incidence and prevalence rates of TBI, particularly mild injury, have increased since 2000 (Cassidy et al., 2004). In the United States, incidence has somewhat plateaued in recent years although prevalence rates have increased (Centers for Disease Control and Prevention, 2015). This likely reflects improved clinical care and management of TBI, especially of moderate and severe cases. In 2010, the Centers for Disease Control and Prevention (CDC) estimated that TBI accounted for 2.5 million emergency department visits, hospitalizations, and deaths in the United States, either as an isolated injury or in combination with other injuries (Centers for Disease Control and Prevention, 2015). Approximately 87% (2,213,826) of these cases were treated in emergency departments and released, 11% (283,630) required hospitalization, and only 2% (52,844) were fatal. Mild TBI occurred in roughly 1.3 million individuals annually, accounting for 70 to 80% of all head injuries (Cassidy et al., 2004; Coronado et al., 2011).

Cited rates are likely underestimations. Published estimates have not accounted for individuals who did not receive medical care or who received care in an outpatient or private clinical setting or at a federal facility (e.g., United States military personnel or veterans) (Coronado et al., 2011; Faul, Xu, Wald, Coronado, & Dellinger, 2010). Substantial variability of incidence rates are further influenced by study location; urban centers report greater incidence than centers in rural areas, and significant heterogeneity exists across countries (Cassidy et al., 2004). Less conservative estimates within this context have suggested a world population incidence of mTBI that exceeds 4.2 million individuals annually.

TBI-related disability. An estimated 57 million people worldwide have been hospitalized with one or more TBI, although the proportion of individuals living with a subsequent disability is not known (Murray & Lopez, 1996). In the United States, limited data exists for the incidence of disability from TBI. This is particularly true for mTBI, given limited classification and diagnostic accuracy. National-level estimates are based on extrapolations of state-level data from South Carolina and Colorado have reported that in 2010, between 3.2 million to 5.3 million individuals were living with a TBI-related disability (Selassie et al., 2008; Thurman, Alverson, Dunn, Guerrero, & Sniezek, 1999; Zaloshnja, Miller, Langlois, & Selassie, 2008). The likely influence of injury severity, especially more severe injuries (e.g., moderate and severe TBI), on disability prevalence is unknown. As with general epidemiological estimates of TBI, rates likely underestimate disability prevalence. It is evident that more research in this area is greatly needed.

Causality and Risk

In civilians, falls (35%), motor vehicle accidents (17%), and strikes or blows to the head from or against an object (17%) such as those from sports injuries are the leading causes of non-fatal TBI in the United States (Faul et al., 2010) and the leading causes of emergency department visits for head injury (without admittance) (Coronado et al., 2011).

Identified risk factors. Heterogeneous injury mechanisms and evolving definitions of mTBI have resulted in limited understanding of causes and risks factors specific to mTBI in civilians as well as in veterans and military personnel (Cassidy et al., 2004). However leading risk factors for TBI in general have been identified, and include

variables related to demographic characteristics, recreational activities, and personality traits.

Age. In the United States, age represents the greatest risk factor for TBI. Children under 4 years, adolescents between 15–19 years, and adults over 75 years of age have the highest risk of TBI-related emergency department visits or hospitalizations (Faul et al., 2010; Isokuortti et al., 2016). Adults who are 65 years and older have the highest rates of TBI-related hospitalizations and deaths among all age groups, with those over the age of 75 years mainly resulting from falls (Faul et al., 2010). Bicycle- and sports-related injuries account for the greatest number of head injuries in youth between 5 and 14 years of age (Bazarian et al., 2005).

Sex. With the exception of adults over 65 years old, where women outnumber men, prevalence of TBI is higher in men than in women (e.g., Bazarian et al., 2005). Males account for approximately 59% of all reported TBI-related medical visits in the United States (Faul et al., 2010). However incidence in females has increased over the past decade (Bazarian et al., 2005).

Socioeconomic status. Lower socioeconomic status is associated with increased likelihood for TBI due to falls and violent assaults (Hanks et al., 2003).

Alcohol and substance use. Preexisting alcohol and substance use are risk factors for TBI, across injury severity (Olson-Madden, Brenner, Corrigan, Emrick, & Britton, 2012). However, greater than normal pre- and post-injury substance use is typical in individuals with TBI, making causality difficult to infer (Olson-Madden et al., 2012). Heavy drinkers have increased incidence rates of TBI (Isokuortti et al., 2016), which is more likely to result from violence (e.g., assault) in the presence of high blood alcohol

content levels (Hanks et al., 2003). It is possible that proclivity for risky behaviors results in similarly increased risk of alcohol (and substance) use disorders and TBI.

Ethnicity. Certain ethnicities such as Native American and Alaskan Natives have increased risk for TBI. This may reflect inherent demographic characteristics such as socioeconomic status (Bazarian et al., 2005) or elevated alcohol and substance use disorder rates that are culturally prevalent as opposed to ethnic or racial factors per se (e.g., Beauvais, 1998). However, more research is warranted.

Recreational activities and sports. According to the National Electronic Injury Surveillance System-All Injury Program (Centers for Disease Control and Prevention, 2011), activities associated with the greatest estimated number of emergency department visits due to TBI include bicycling, football, playground activities, basketball, and soccer among persons younger than 19 years of age. Several sports are specifically associated with increased risk for concussion. In high school, college, and amateur athletes, risk of concussion is highest in ice hockey and rugby players (Koh, Cassidy, & Watkinson, 2003). In recreational sports, female taekwondo participants and male boxers have the highest frequency of concussion (Koh et al., 2003), with roughly 6.2% having sustained a concussion in a three-year prospective study (Covassin, Swanik, & Sachs, 2003). The annual incidence of mTBI (i.e., concussion) in recreational, high school, collegiate, and professional American football players is substantial, with up to 20% of 1.5 million players incurring at least one head injury annually (Bailes & Cantu, 2001). Furthermore, modern tracking device data has indicated that football players, particularly professionals, sustain thousands of sub-concussive hits to the head during a single season (Crisco et al., 2010; Greenwald, Gwin, Chu, & Crisco, 2008). Selassie et al. (2013) indicated that most

head injuries resulted from being kicked, regardless of sport (Selassie et al., 2013). Nevertheless, studies of recreation- and sports-related mTBI are limited, and associated injury mechanisms and risk factors are still being identified.

Incarceration and delinquency. One study examined TBI histories in incarcerated adults (W. H. Williams et al., 2010). Approximately 65% of prisoners reported medical histories of at least one TBI (W. H. Williams et al., 2010). Of those cases, roughly 45% were consistent with mTBI. Prisoners with histories of TBI typically entered into the custodial system at an earlier age (i.e., younger age at initial enrollment) and had higher rates of repeat offenses compared to incarcerated peers (W. H. Williams et al., 2010).

Military and Veteran Populations

The evolution of warfare culminated in the highest rates of mild closed head injury among veterans and military personnel of the recent Iraq and Afghanistan conflicts than previous conflicts (Owens et al., 2008). Explosive blasts are the most common mechanism of injury among those who served in the United States military as part of Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND) (Maas et al., 2010; Owens et al., 2008). Since 2000, an estimated 300,000 to 500,000 deployed active duty service members acquired head injuries as the result of exposure to improvised explosive devices (IED). The majority (82.4%) involved mTBI (i.e., concussion), acquired as the result of blast exposure alone or in combination with blunt trauma (for further review see Helmick et al., 2015). The VA Polytrauma and Blast Related Injuries (PT/BRI) Quality Enhancement Research Initiative (QUERI) reported

that of the OIF/OEF veterans who received health care at the VA, 7% seen during a one-year period and roughly 10% seen over a three-year period carried a diagnosis of TBI.

The Department of Defense (DoD) has propagated several initiatives that successfully curtailed incidence rates of blast-induced TBI (bTBI). Enforced reduction of exposure to blast decreased the overall percentage of diagnosed concussion between August 2010 through June 2014 (DoDI 6490.11 2012; also reviewed in Helmick et al., 2015). However, identification and classification of bTBI in active duty military personnel is largely complicated by factors related to the mechanism of injury. The behavioral and neurologic symptoms necessitated in order to diagnose TBI by traditional classification systems are often unknown or absent in bTBI. Hoge et al. (2008) surveyed members of United States Army combat infantry brigades 3 to 4 months after returning from deployment. Whereas nearly 79% reported bTBI, a mere 4.9% of those with head injuries reported LOC (of 2 to 3 minutes in duration) at time of injury (TOI). Altered mental state without LOC (i.e., AOC) at TOI was more commonly endorsed (in approximately 10%), although less than 2% reported AOC lasting longer than 30 minutes (Hoge et al., 2008).

Within the DoD, however, the Defense and Veterans Brain Injury Center (DVBIC) indicated that the majority of head injuries in military personnel are acquired in garrison as the result of concussion, with only 1% classified as severe (Cassidy et al., 2004; Helmick et al., 2015). As in civilians, injuries frequently result from motor vehicle accidents, falls, and recreation- and sports-related activities. However, many also occur during military training (Helmick et al., 2015). History of deployment substantially increases the long-term risk for TBI in garrison and also more generally; nearly 20% of

active duty military personnel reported having at least one mTBI during deployment (Helmick et al., 2015).

Chronic Health Effects

Chronic health effects of mTBI are inherently heterogeneous, encompassing a broad range of neurological, neuropsychological, and psychiatric difficulties. Variability as well as differing onset, duration, and recovery trajectories of symptoms makes outcomes in mTBI difficult to predict (e.g., Silverberg et al., 2015).

Post-Concussive Syndrome

Post-concussive syndrome (PCS) describes persistent symptomatology that can occur subsequent to a (mild) head injury. PCS is defined by the onset of complaints from four symptom categories within one month post-injury (ICD-100, dg. F07.2). The number and specific pattern of symptoms experienced varies significantly between patients. Specific subsets of PCS symptoms are categorized as follows: cognitive, physical, psychiatric, or emotional dysregulation (Caplan et al., 2010). Specifically, cognitive symptoms are related to poor concentration, memory, and overall intellectual or functional abilities; physical symptoms include headache, dizziness, malaise, fatigue, noise intolerance; psychiatric symptoms assess anxiety, depression, and other mood disorders; and symptoms of emotional dysregulation include irritability, depression, anxiety, lability. Additional symptoms have been noted, including insomnia, reduced alcohol tolerance, and blurred vision. Irritability is possibly the most commonly occurring PCS symptom, with estimates suggesting that it occurs in 54.2 % of patients with mTBI (Sivak et al., 2016). Persistent complaints of headache, fatigue, emotional lability and cognitive problems can also occur in the majority (estimates ranging between

40-80%) of patients with mTBI. Though these symptoms typically only persist up to three months post-injury, approximately 10-15% of patients experience chronic symptoms during the first 12 months after TOI (Bigler, 2003; Blennow, Hardy, & Zetterberg, 2012).

Not all patients experience symptoms of PCS. Predicting the occurrence, onset, severity and chronicity, including recovery trajectory, of complaints has proven difficult, with limited consistency of results across studies. High subjectivity and variable severity of associated symptoms as well as the influence of psychiatric factors complicate understanding of PCS in mTBI. Development of PCS likely depends on different neurobiological and psychological factors, including pre-injury depression and anxiety, somatoform disorder, life stressors, pain, sex, age, coping style, cognitive biases of expected recovery, premature return to full training regime in athletes, litigation stress, exaggeration, and malingering (Broshek, De Marco, & Freeman, 2015). Risk factors for maintenance of PCS also include pre-injury factors (e.g., education, military rank, female, age), peri-injury factors related to mechanism and context of injury, and post-injury factors such as comorbid psychiatric distress, and secondary gain (Cooper et al., 2011; Lange et al., 2014). Litigation is particularly associated with significantly greater elevations of emotional and cognitive complaints in patients with TBI. Specifically, self-reported symptoms of anxiety and depression are elevated in patients with TBI who are also involved in litigation, and both are related to diminished cognitive performance upon standardized neuropsychological evaluation (Evered, Ruff, Baldo, & Isomura, 2003). Given the breadth of evidenced complexities, diagnosis of PCS must often include multidisciplinary problem-solving and consideration of differential diagnoses in order to

account for headache disorders, spinal cord injuries, visual and/or vestibular dysfunction, and psychiatric disorders, including those related to mood disorder, somatization, as well as malingering.

Neurologic Outcomes

Several neurological difficulties are frequently reported among patients with mTBI. Oculomotor deficits commonly occur in TBI (Kraus, Little, et al., 2007) and are observed in symptomatic patients with concussion (Heitger et al., 2006). In concussion, deficits in reflexive saccades are not typically observed, although specific disruptions like self-paced and anti-saccades have been shown (Johnson, Zhang, Hallett, & Slobounov, 2015). Oculomotor deficits can occur in all injury phases in mTBI (i.e., acute, post-acute, and chronic) and are observed in patients with and without intact neuropsychological function (Heitger, Anderson, & Jones, 2002; Heitger et al., 2004). However, altered oculomotor control is associated with cognitive difficulties, even after psychiatric comorbidity such as depression and malingering are considered (Heitger et al., 2009). Thus, deficits are distinct, yet associated with other functional outcomes in mTBI. Oculomotor deficits are also associated with structural white matter (Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010) and anterior executive control network cortical alterations in concussed athletes (Johnson et al., 2015). For some investigators, overall findings support the clinical utility of oculomotor dysfunction as a biomarker for the extent of cerebral dysfunction following mTBI (Heitger et al., 2002; Maruta et al., 2010).

Sleep disturbances are fairly common in mTBI. Though encompassed within PCS, some sleep difficulties may occur independently. Schreiber et al. (2008) indicated persistent disruption of sleep patterns in adults with mTBI compared to controls. Specific

anomalies were detected in sleep timing and also in the architecture of the sleep pattern; mTBI was related to atypical occurrence of non-rapid eye movement sleep and excessive daytime sleepiness (Schreiber et al., 2008).

Repetitive Head Injuries

Accumulating evidence supports greater risk of progressive forms of encephalopathy, termed chronic traumatic encephalopathy (CTE), subsequent to repetitive head injuries from sports-related concussion and bTBI (McKee et al., 2010; Omalu, Bailes, et al., 2011; Omalu, Hammers, et al., 2011; Sivak et al., 2016). Results have suggested that prolonged and long-term effects of mTBI may be synergistically exacerbated by repetitive injuries. For example, increased risk of dementia in professional football players is 5-19 times that in the general population (Gardner & Yaffe, 2015; Sivak et al., 2016). This is of particular concern as an epidemiologic study of collegiate and high school football players found that players who sustained one concussion were three times more likely to sustain a second concussion in the same season (Guskiewicz, Weaver, Padua, & Garrett, 2000). However, increased risk for dementia and accelerated cognitive decline with aging in mTBI have been debated and remain controversial. A national cohort study indicated increased risk of dementia in mTBI, that was even supported in patients with histories of a single injury (Lee et al., 2013). However, a recent systematic review concluded that evidence for this association was inconclusive (e.g., Godbolt et al., 2014).

Neuropsychological Outcomes

Neuropsychological consequences of mTBI have been particularly debated in the research literature (Bigler et al., 2013). Systematic reviews in civilians (Carroll et al.,

2014; Carroll et al., 2004; Schretlen & Shapiro, 2003) and athletes (Cancelliere et al., 2014) support acute onset of cognitive deficits in adults with full recovery to baseline-level performance during the first year since TOI. However, cognitive complaints and difficulties persist in some patients. Severity of deficits also varies widely, although most studies support declines that are still within normal limits.

Acute and subacute phase outcomes. Generally consistent results have supported cognitive deficits in acute and subacute phases of mTBI (e.g., Carroll et al., 2014). However, the specificity of affected cognitive domains and the magnitudes of associated deficits are not consistent across studies. Inconsistencies likely reflect methodological differences that exist between studies with regards to selected neuropsychological measures, cognitive domains, sample demographics, and injury characteristics (Carroll et al., 2014).

Diminished cognitive performance is observed in patients with mTBI as early as 48 hours after TOI, although results may be specific to patients who experienced LOC (Brewer, Metzger, & Therrien, 2002). More consistent findings suggest that typical onset of acute phase deficits of processing speed, memory, learning, and attention occurs within the first few days (Landre, Poppe, Davis, Schmaus, & Hobbs, 2006) and weeks post-injury (Carroll et al., 2014; Heitger et al., 2006; Shanmukhi & Panigrahi, 2003). Noted, however, is that deficits in the aforementioned cognitive domains are not supported by all studies (e.g., Heitger et al., 2006).

Given the largely mixed findings across individual studies, it not surprising that meta-analyses of acute phase onset neuropsychological impairments in mTBI have provided mixed results (see Karr, Areshenkoff, & Garcia-Barrera, 2014). In an initial

meta-analysis, Binder and colleagues (1997) indicated minimal effect of mTBI on cognitive performance across studies (Binder, Rohling, & Larrabee, 1997). However, in their follow-up meta-analysis, acute phase effects occurred across neuropsychological domains and lasted up to 30 days post-injury, with the largest deficits detected during the first 7 days post-injury (Rohling et al., 2011). Other meta-analyses have yielded similarly discrepant results (Carroll et al., 2014; Karr et al., 2014).

Post-acute phase outcomes. Although full recovery of acute and subacute phase neuropsychological deficits occurs within the first post-injury month (i.e., 30 days) in most (e.g., 68%) patients with mTBI (Losoi et al., 2015), recovery trajectories are variable (Bigler et al., 2013; McKee et al., 2009). In a systematic review, Cassidy et al. (2014) observed persistent PCS symptoms in roughly 14-26% of patients beyond 30 days, although generalizability of findings is cautioned given methodological limitations (Cassidy et al., 2014). Mechanism of injury may influence recovery. One meta-analysis of sports-related concussion reported that expedited recovery occurred in athletes as early as 7 days post-concussion (Belanger & Vanderploeg, 2005). Other injury characteristics can also influence onset. LOC is associated with slower cognitive processing speed (Brewer et al., 2002) and radiological abnormalities characteristic of complicated mTBI relate to generally poorer performance outcomes (Iverson, 2006). However, duration of PTA and history of previous TBI were not associated with cognitive performance after one month post-injury in one study (Tellier et al., 2009). Overall some prolongation of cognitive deficits after one month post-injury is supported, and may be largely dependent on variables related to the mechanism and characteristics of the injury.

Chronic phase outcomes. Few studies support prolongation of acute onset difficulties beyond 3 months post-injury in mTBI, yet a number of patients have persistent complaints (see McCrea & American Academy of Clinical Neuropsychology, 2008). While full recovery of neuropsychological deficits by 3 to 6 months post-injury is typical (Karr et al., 2014), great inter-person variability is supported (Bigler et al., 2013). de Boussard et al. (2005) indicated that up to 30% of patients exhibited at least 2 scores that were less than 1 SD below those obtained by controls 3 months after TOI (de Boussard et al., 2005).

Cognitive recovery may be domain specific. In Heitger et al. (2006), acute phase verbal memory deficits were not fully resolved until one year post- injury, whereas acute phase deficits in information processing speed typically resolved within the first 3 months (Heitger et al., 2006). A population-based longitudinal study also indicated limited deficits in attention, memory, and visuospatial abilities in individuals who reported histories of mTBI within the 5 years prior to study involvement relative to non-injured controls (Sundstrom et al., 2004). However, time since the injury was not taken into account, and results likely describe a wide range of injury phases (i.e., time since the injury).

Domains of neuropsychological impairment. With little consensus across studies, it is unclear whether specific cognitive domains are more susceptible to the deleterious effects of mTBI than others (Karr et al., 2014). Highly variable performance is reported within- and between-domains, leading some to question both the sensitivity and specificity of neuropsychological assessment measures for detecting effects of mTBI (Binder et al., 1997). However, consistent findings do exist in the literature. The most

commonly reported cognitive symptom of mTBI is poor memory, with an estimated 63% of patients exhibiting difficulties (Sivak et al., 2016). In particular, verbal, working and visual memory domains are shown to be particularly affected by the effects of mTBI (Rohling et al., 2011). Several meta-analyses have also supported susceptibility of higher-order cognitive functions to mTBI (Karr et al., 2014). For example, executive function deficits show dose-dependent declines with repetitive head injuries (Belanger, Spiegel, & Vanderploeg, 2010; Belanger & Vanderploeg, 2005).

Psychiatric Outcomes

Studies consistently associate mTBI with increased risk of psychiatric disorders and suicide (Carroll et al., 2014). In patients with no immediate pre-injury psychiatric histories, collective results support a roughly 3-fold increased risk of being diagnosed with a psychiatric disorder during the first 6 months since TOI (Carroll et al., 2014). This risk includes severe psychiatric disturbance. Patients with mTBI, particularly adult males, have elevated risk of developing schizophrenia up to 5 years after the traumatic event (Carroll et al., 2014).

Military Personnel and Veterans

As in civilian mTBI, determination of outcomes in veterans and military personnel is complicated.

Common outcomes. Advanced statistical modeling has facilitated understanding of outcomes in mTBI in veterans and military personnel, although inconsistent results have been reported. Using profile analysis, Bailie et al. (2016) identified common symptom profiles in male service members with histories of combat-related mTBI as relating to four general profiles of 1) good recovery (38%), marked by minimal

neurobehavioral and psychiatric symptoms and higher rates of non-head injuries with successful pain management; 2) cognitive symptoms (22%), indicated through cognitive and headache difficulties with few mood symptoms; 3) post-traumatic stress disorder (PTSD; 22%), marked primarily by symptoms associated with mood and/or PTSD with few cognitive or headache complaints; and 4) mixed neurobehavioral symptoms and PTSD (19%) (Bailie et al., 2016).

Latent class modeling has also been used to examine common profiles of mTBI in veterans and military personnel. Whereas Pugh et al. (2014) identified 6 classes relating to comorbidity in mTBI, Jaraimillo et al. (2015) more recently reported 7 latent classes that were specific to neurologic (i.e., physical and somatic distress), pain, mental health, and common comorbidities. While both studies indicated that a large subgroup experienced low-distress, Jaramillo et al. reported that over 50% of the veterans had been diagnosed with TBI, depression, and/or PTSD. In Jaramillo et al., TBI risk related to high rates of headaches and memory complaints (Jaramillo et al., 2015). High-distress related to comorbid TBI, PTSD, and depression, and included increased risk for somatic and psychological complaints (Jaramillo et al., 2015). Greater risk of PTSD and/or depression was also associated with elevated overall risk for substance use and anxiety disorders (Jaramillo et al., 2015). Greater complaints of pain were observed across subgroups in both studies (Jaramillo et al., 2015; Pugh et al., 2014).

Post-concussive syndrome. As in civilians, the majority of military personnel and veterans with mTBI experience PCS symptoms. Headache is the most debilitating clinical symptom associated with mTBI in post-deployed military personnel and is strongly correlated with injury characteristics (Hoge et al., 2008). In Hoge et al., 2008,

headaches occurred in nearly one third (32%) of active military personnel with LOC as opposed to AOC (18%) at TOI. These authors also indicated that headache remained significantly associated with injury severity to a greater extent than other predictors even after psychiatric symptoms (i.e., PTSD and depression) were considered. A systematic review provided through the NIH, indicated that 33% of all neurology referrals in veterans with mTBI are for headache (O'Neil et al., 2014).

Similarly, irritability, fatigue, and, though to a somewhat lesser extent, concentration and sleep disturbance, may be particularly consequential of mTBI in veterans and military personnel. Persistent complaints of this nature are not accounted for by symptoms of PTSD or other demographic or injury characteristics (Hoge et al., 2008). Nearly half of military personnel with mTBI, regardless of LOC (57%) or AOC (48%) at TOI, reported high levels of irritability in one study (Hoge et al., 2008). Moderate to severe sleep disturbance occurs in an estimated 13-23% of veterans and military personnel with mTBI, and may be exacerbated by injury characteristics like LOC (53; 54%) and AOC (40; 45%) (Hoge et al., 2008). These rates are substantially higher than what is typical of veteran and military populations, although further research could be beneficial (O'Neil et al., 2014). Symptoms of PCS are worsened by comorbid mTBI and PTSD diagnosis in military personnel (Polusny et al., 2011). This comorbidity is associated with exacerbated headache, irritability, and fatigue (Polusny et al., 2011).

Neurological outcomes. The most common physical health concerns in veterans and military personnel with mTBI include vestibular, headache, auditory and visual, and nausea-related complaints (O'Neil et al., 2014). Tinnitus co-occurs in 24% and 18% of veterans with LOC or AOC at TOI, respectively (Hoge et al., 2008; Polusny et al., 2011).

Increased risk of epilepsy with TBI generally, and particularly repetitive injuries, is elevated in veterans relative to civilians (Pugh et al., 2014). As with most outcomes in veterans and military personnel, psychiatric comorbidity is shown to influence neurologic outcomes of mTBI and must be considered during clinical decision-making (Polusny et al., 2011).

Neuropsychological outcomes. Domain-specific cognitive disabilities subsequent to mTBI in veterans and military personnel commonly include visuospatial, memory, executive function, and attention/concentration (O'Neil et al., 2014). Despite similar pre-deployment (baseline) scores, Adam et al. (2015) observed notably diminished post-deployment scores on simple reaction time, processing speed, associative learning, figure delayed memory, working memory, and visual spatial memory tests (from the Automated Neuropsychological Assessment Metrics; ANAM) in personnel with bTBI compared to those without histories of TBI, that predicted recovery time (Adam et al., 2015; Cernich, Reeves, Sun, & Bleiberg, 2007). Neuropsychological deficits in mTBI occur independently of psychiatric difficulties in veterans and military personnel (S. C. Miller et al., 2015). However, PTSD and depression comorbidity can worsen neuropsychological performance and elevate self-rated complaints (Verfaellie, Lafleche, Spiro, & Bousquet, 2014; American Psychiatric Association, 2000). For example, co-occurring mTBI and PTSD is associated with exacerbated memory and concentration difficulties in these populations (Polusny et al., 2011).

Injury characteristics show little influence on objective neuropsychological performance in veterans and military personnel with mTBI. Cognitive outcomes are apparently unaffected by blast load or proximity, or by LOC at TOI (Verfaellie et al.,

2014). However, self-report ratings of cognitive impairment, of which executive dysfunction and memory difficulties are the most frequent (Bailie et al., 2016), are significantly elevated with histories of additional injury, and LOC, AOC, and PTA at TOI (American Psychiatric Association, 2000; O'Neil et al., 2014). For example, subjective report of concentration and memory difficulties is negatively influenced to a greater extent in mTBI with LOC (31%; 27%) than with AOC (26%; 16%) at TOI (Hoge et al., 2008). However, there is less definitive evidence for frank neuropsychological deficits in bTBI in the overall literature.

Psychiatric outcomes. Consideration of mental health and psychiatric outcomes after mTBI is imperative in veterans and military personnel as incidence of difficulties are elevated in these populations relative to civilians (O'Neil et al., 2014). However, studies have provided inconclusive results as to whether or not risk in mTBI is elevated in comparison to already increased risk of psychiatric disorder in DoD samples (O'Neil et al., 2014). It may also be important to consider phase of recovery when assessing patients, as associated increased risk for development of PTSD symptoms as well as schizophrenia may be persistent up to 6 months after TOI (S. C. Miller et al., 2015). Alternatively, increased risk for the development of other mood disorders, generalized anxiety disorder, acute stress disorders, and attention-deficit/hyperactivity disorder symptoms may only occur in the first 30 days post-injury, and associated risk may be largely negligible after adjusting for PTSD and depression symptoms (S. C. Miller et al., 2015).

Post-traumatic stress disorder. In the DoD, mTBI is associated with high co-occurrence of PTSD (Adam et al., 2015). The Veterans Affairs and NIH have estimated

that 45% of veterans and military personnel who have histories of mTBI also have comorbid PTSD (O'Neil et al., 2014). Injury characteristics can influence development of PTSD, with LOC (44%) being associated with greater risk for this disorder than AOC (27%) (Hoge et al., 2008). However, development of PTSD following mTBI is not well understood. Other factors can influence occurrence and severity of PTSD in veterans and military personnel. For instance, regardless of head injury history, self-reported pre-military delinquent behavior in personnel with PTSD is greater relative to personnel without PTSD (Hoge et al., 2008).

Poorer outcomes can occur in veterans and military personnel who have comorbid PTSD and mTBI relative to mTBI alone (Barnes, Walter, & Chard, 2012; Polusny et al., 2011; Verfaellie et al., 2014). This comorbidity has resulted in worse PCS symptom development and persistence, cognitive difficulties, neurologic complaints, and physical pain (Polusny et al., 2011; Verfaellie et al., 2014). Elevated PTSD symptoms are also observed in veterans with comorbid PTSD and mTBI than with PTSD alone (Barnes et al., 2012).

Although independent effects of both mTBI and PTSD are observed on outcomes such as PCS symptoms and alcohol use and dependency, PTSD may negatively influence symptoms of depression, quality of life, social adjustment, risky behaviors (e.g., impulsivity), and somatic symptom severity to a greater extent than effects of head injury in post-deployed military personnel (James, Strom, & Leskela, 2014; Polusny et al., 2011). In veterans with and without bTBI, comorbid PTSD worsens lifetime alcohol dependence and symptoms of depression (Davenport, Lim, & Sponheim, 2015) as well as suicidality to a greater extent than mTBI (Miskey, Shura, Yoash-Gantz, & Rowland,

2015). Regardless of mTBI, PTSD is also associated with increased risky behaviors and greater impulsivity during negative affective states in this population (James et al., 2014). This association could explain the strong association among PTSD and suicidality in veterans and military personnel with histories of mTBI (James et al., 2014).

Mood disorders. In veterans and military personnel with mTBI, between 50-78% are estimated to have comorbid axis I disorder diagnosis (American Psychiatric Association, 2000; O'Neil et al., 2014). In a large sample of Airmen, Miller et al. (2015) indicated that mTBI resulted in the greatest risk for development of depression, even after adjusting for effects of PTSD (S. C. Miller et al., 2015). In veterans and military personnel depression is associated with worsened neuropsychological performance in mTBI (Verfaellie et al., 2014).

Other disorders. Other commonly occurring psychiatric disturbances in veterans and military personnel with mTBI include suicidal behaviors as well as alcohol and substance use disorders. The National Institute of Health has estimated that 25% of this population experiences suicidal ideation, with 7% having experienced intent and 4% having had past suicide attempts (O'Neil et al., 2014). Twenty-eight percent of veterans and military personnel with mild head injuries also have difficulties with alcohol use and dependencies and 9% using and or dependent upon other substances (O'Neil et al., 2014).

Protective factors. Personnel with non-central nervous system-related physical injuries have decreased neurobehavioral and stress symptoms than their head-injured peers (Kennedy, Cullen, Amador, Huey, & Leal, 2010). Though limited, results indicated that physical ailments potentially protect head-injured personnel from psychiatric comorbidity. Kennedy et al. (2010) interpreted findings to indicate reduced stress from

adequate medical attention and care for the physical injury decreased injury distress as opposed to increased distress incurred by the often "invisible" nature of and highly subjective deficits inherent to mTBI. Further research is warranted regarding this and other protective factors.

Pathogenesis

Outcomes and severity of TBI relate not only to the mechanical nature of the injury but also to the extent of disruption of central nervous system tissue. A growing number of post-mortem studies have demonstrated subtle brain pathology in mTBI (detail review in Bigler & Maxwell, 2012) and in sports related chronic traumatic encephalopathy (McKee et al., 2010; Omalu, Bailes, Hammers, & Fitzsimmons, 2010).

Biomechanical Influences

Goldsmith and Plunkett (2004) conceptualized the main biomechanical features of TBI as resulting from impulsive loading and impact loading. Impulsive loading describes the resultant head motion that emanates from other body regions, whereas impact loading occurs subsequent a direct strike of the head against a stationary or moving object. The nature of biomechanically distinct and separate features potentially leads to disparate pathological consequences that may not occur simultaneously, but are likely successive (Goldsmith & Plunkett, 2004). TBI generally, and specifically mTBI, is most commonly caused by a combination of impact and acceleration/deceleration forces like those of high-speed motor vehicle crashes (Ommaya, Goldsmith, & Thibault, 2002) or blast exposure (DePalma, Burris, Champion, & Hodgson, 2005; Moore, Radovitzky, Jerusalem, Nyein, & Jaffee, 2008), which often result in diffuse and widespread damage to brain tissue. This is in contrast to focal, or localized, injuries that result in specific,

isolated brain regions that occur at both the site of impact (coup) or opposite the side of impact (contrecoup) subsequent to a blow to the head (Adams, Graham, & Gennarelli, 1983).

Additionally, inertial forces can involve translational, rotational, or, the combination of the two, angular acceleration, that can lead to shearing and straining of axons. Angular acceleration of the brain is generally regarded as yielding resultant microstructural and metabolic alterations in neural tissue that occurs in mTBI, including concussion (see Bigler & Maxwell, 2012 for review). Given these deleterious outcomes, it is not surprising then that mechanism of injury influences post-injury outcomes (Bushnik, Hanks, Kreutzer, & Rosenthal, 2003).

Biomechanics of blast exposure. The biomechanics of bTBI are highly complex and can result in unpredictable patterns of injury in exposed individuals (DePalma et al., 2005). DePalma et al. (2005) have described four categories of blast exposure. Primary effects are related to atmospheric pressure including over- and under-pressurization effects. Subsequent injury can involve ruptured tympanic membranes and hollow viscera (e.g., abdominal cavity, gastrointestinal tracts) as well as pulmonary damage. Secondary effects are comprised of projectiles of explosive device fragments and casings. Projectiles inherently result in penetrating injuries and are the primary cause of death from explosions. Closed head brain injuries most likely occur during tertiary effects, or the effects of structural collapse such as that from buildings or vehicles. While crush injuries can result in high rates of fatalities, tertiary effects can also result in bodily displacement due to high-speed wind forces. Thus, closed head blast-induced injuries often occur

subsequent to a combination of blast wind force and blunt trauma. Lastly, heat and toxins comprise quaternary effects and can cause asphyxiation and burns.

Animal studies have furthered our understanding of blast-related head injuries. Important considerations in mTBI from exposure to blast must include specific factors that are specific to this mechanism and that can influence injury severity. Distance from the blast influences biomechanical effects of TBI (Sundaramurthy et al., 2012). Additionally, confinement in a small space, such as a motor vehicle, is associated with greater heterogeneity of injuries (Arnold, Halpern, Tsai, & Smithline, 2004).

Neuropathology

Diffuse axonal injury (DAI), the primary neural insult of TBI, leads to subsequent neurologic dysfunction through disconnection of functional brain networks. The neurochemical cascade of metabolic and pathophysiological changes that begin immediately at TOI as a result of biomechanical forces culminate in DAI, inciting the long-term disease process of TBI. In mTBI, DAI has been supported through histopathology findings indicating WM microstructural disruption in patients with mTBI who died from other causes (e.g., Adams et al., 1989; Bigler, 2004; Blumbergs et al., 1994; Oppenheimer, 1968).

Neuropathology of mTBI. MacFarlane et al. (2015) provided a detailed review of the neuropathological cascade in preclinical animal models of mTBI (i.e., concussion) (MacFarlane & Glenn, 2015). At the time of biomechanical injury, disruption of cellular homeostasis results in a cascade of neural alterations in brain tissue that leads to massive neural excitation and hyperglycolysis. Mass excitation is followed by widespread neuronal depression as a result of metabolic suppression. Subsequent attempts to restore

metabolism are disrupted by increased energy demands, increased glucose utilization, and hyperglycolysis. In the subacute phase of mTBI, metabolic changes persist, resulting in prolonged metabolic depression and hypometabolism.

Peri-acute and acute phase alterations. Mechanical tearing and sheering forces cause an efflux of intracellular potassium (K^+) through mechanoporation, or disruption of cellular membranes, and axonal stretching at the time of the injury (Giza & Hovda, 2001, 2014; Katayama, Becker, Tamura, & Hovda, 1990). These effects lead to subsequent cellular depolarization and resultant indiscriminant neuronal firing, causing an ongoing feedback loop of continuous depolarization, altered permeability of voltage-gate channels on the cellular membrane, increased K^+ flux, and subsequent indiscriminant release of excitatory neurotransmitters, primarily excitatory amino acids. Extracellular glutamate concentrations also increase significantly, further stimulating excitatory amino acids receptors (Giza & Hovda, 2001, 2014).

The increased release of excitatory amino acids coupled with stimulated excitatory receptors further influences cellular depolarization through direct and indirect routes. Stimulation of excitatory amino acid receptors in the cell membrane induces further K^+ efflux, directly propagating the depolarization cycle. Indirect effects of excitatory amino acids on the depolarization feedback loop occurs through N-methyl-D-aspartate (NMDA) and D-amino-3-hydrocy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. Through their relation with glutamate, these receptors influence K^+ and calcium (Ca^{2+}) flow. Resultant indiscriminant release of excitatory amino acids subsequent to random neuronal firing leads to massive excitation as well as an efflux of intracellular Ca^{2+} concentrations (Giza & Hovda, 2001, 2014). In animals, the period of

simultaneous massive excitation and hyperglycolysis has lasted between 2 to 120 minutes. Though Ca^{2+} influx may not solely account for DAI, it is directly linked with neurometabolic alterations in mTBI (MacFarlane & Glenn, 2015).

After massive excitation occurs, neuronal depression specific to head injury is induced (Giza & Hovda, 2001, 2014; MacFarlane & Glenn, 2015). Neuronal depression is thought to arise as the direct result of the substantial depolarization effects that are observed in mTBI. It is thought that neurologic and behavioral symptoms that occur at the time of the injury, e.g., LOC and traumatic amnesia, likely result from this widespread neuronal depression. In order to manage alterations of K^{+} concentration, glial cells begin to work in overdrive. This requires large amounts of energy. In order to restore homeostasis, the adenosine triphosphate (ATP) requirement by the sodium-potassium pump promotes accelerated ATP production through increased neuronal glucose metabolism (Bigler and Maxwell 2012). The resultant period of hyperglycolysis lasts between 30 minutes and up to 4 hours in animal models of concussion in cortical regions, the hippocampus, as well as in distal brain regions from initial contusion location. Increased lactate concentrations, occurring as the result of hyperglycolysis, lead to acidosis. Resultant effects can involve cellular membrane damage, cellular dysfunction, weakened blood-brain barrier, and cerebral edema. Deleterious outcomes related to increased lactate production are not always supported in mTBI, which could result from influences of oxidative metabolism among other metabolic factors (Giza & Hovda, 2001, 2014; MacFarlane & Glenn, 2015).

Subacute phase alterations. Subacute metabolic alterations include acidosis, accumulation and sequestration of Ca2+, reductions in magnesium, altered cerebral blood

flow, and prolonged depression and hypometabolism in mTBI. These effects cumulatively alter neural function, disrupt functional brain networks, and promote DAI, which occurs in all TBI regardless of severity. Extent of edema and other neuroimmunologic responses can have influential effects on neural recovery. It is also important to note that cumulative effects may be synergistic in repetitive head injury, particularly if additional head injuries occur during certain stages of recovery. For instance, repetitive injuries can further disrupt altered Ca2+ concentrations, cerebral blood flow, hypermetabolism, and neurotransmission (MacFarlane & Glenn, 2015).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an advanced neuroimaging modality that has enabled high definition brain images to be captured through numerous sequences that can be performed in both clinical and research contexts. Acquired MRI data is more sensitive than CT in detecting brain abnormalities, and can be obtained without risk of ionizing radiation. Data is acquired through the combination of safe high strength magnetic field, controllable magnetic field gradients, and radiofrequency pulses. Varied combinations of these variables produce image sequences that can detect differing pathologies in TBI. Common sequences typically include T_1-weighted, T_2-weighted, fluid attenuated inversion recovery (FLAIR), and T_2-gradient recalled echo (GRE) or susceptibility weighted images. T_1-weighted images contrast between basic tissue types (generally WM, gray matter [GM], and cerebrospinal fluid) to create high-resolution structural images that are most commonly used to evaluate and identify lesions, volumetric changes, and morphology of brain tissue. Macroscopic WM lesions, contusions and intracranial bleeds, and cerebrospinal fluid volume are generally more

sensitively detected through T_2-weighted and FLAIR sequences, which provide converse contrast of neural tissues from T_1-weighted sequences. Susceptibility weighted images are acquired through high-resolution gradient echo sequences, and allow for the visualization of venous blood, micro-bleeds, calcifications and other vasculature changes through increased sensitivity to density of underlying brain tissue.

Lesion Imaging

Though generally less subtle than the lesions observed in moderate and severe injuries, radiological evidence for lesions in mTBI does exist. More generous estimates have suggested that up to 30% of patients with mTBI exhibit lesions (e.g., B. A. Cohen et al., 2007), although generalizability of these findings is cautioned given limited sample sizes. Most studies in the published research literature of mTBI have reported lesion findings based upon examination using high definition T_1-weighted images. A few studies have examined hyperintensities evinced using FLAIR or susceptibility weighted imaging. Susceptibility weighted imaging has confirmed lesions in patients with TBI. WM hyperintensities are also observed, and volumes inversely relate to functional outcomes (Marquez de la Plata et al., 2007) and atrophy in adults with TBI (Ding et al., 2008), although it is not known whether these relations differ across severity of TBI (Ding et al., 2008).

Volumetric and Morphometric Analyses

A plethora of morphometric and volumetric studies of TBI have been published. However, few studies have exclusively examined mTBI separately from moderate and severe injuries.

Acute alterations. Acute phase alterations are observed in mTBI patients. In as early as 7 days post-injury, Dall'Acqua et al. (2016) observed altered cortical and subcortical morphology in patients with mTBI compared to controls. Alterations were reported in both GM and WM and were exacerbated by PCS symptom severity (Dall'Acqua et al., 2016). Although whole-brain analysis failed to show differences among patients and controls in cortical morphology, significantly reduced cortical surface area was observed in a subgroup of mTBI patients with severe PCS symptoms in ROIs including the lateral prefrontal cortex, central sulcus/postcentral gyrus, inferior temporal gyrus, and the insula compared to controls. Prefrontal cortical surface area correlated with indices of WM disruption and cognitive control in mTBI patients. Subcortical morphological alterations are also observed in acute mTBI. Holli et al. (2010) found greater asymmetry of left and right mesencephalon and WM of the corona radiata and corpus callosum in acute phase patients with mTBI compared to controls (Holli, Harrison, et al., 2010). The basal ganglia and thalamus are also reduced in acute and subacute phase mTBI (Zagorchev et al., 2016).

However, not all studies of mTBI support early injury phase morphologic alterations (e.g., da Costa, van Niftrik, Crane, Fierstra, & Bethune, 2016). This may be due to the regionally specific neural responses to mTBI that occur and may not be detectable until later, follow-up assessments (Killgore et al., 2016; Zagorchev et al., 2016). Zagorchev et al. (2016) observed subcortical alterations in acute and subacute phase patients with mTBI compared to controls in the caudate, putamen and thalamus that, though somewhat normalized (i.e., diminished), were persistent at one year post-injury, at which time atrophy of the hippocampus and amygdala was observed

(Zagorchev et al., 2016). Other recent findings denoted that altered GM volume in the ventromedial prefrontal cortex and right fusiform gyrus in mTBI patients at least two weeks post-injury relative to controls were more pronounced in patients assessed at longer post-injury intervals (Killgore et al., 2016). Thus, the most robust findings in mTBI have included either chronic phase patients (e.g., B. A. Cohen et al., 2007; Dean, Sato, Vieira, McNamara, & Sterr, 2015; Little et al., 2014) or longitudinal follow-up of acute phase patients (e.g., da Costa et al., 2016; Ross et al., 2012; Toth et al., 2013; Zagorchev et al., 2016; Zhou et al., 2013).

Chronic alterations. Global changes in GM, WM, and cerebrospinal fluid occur in chronic mTBI (Little et al., 2014). Increased global and GM atrophy is observed in subacute and chronic mTBI patients compared to controls regardless of whether or not lesions are present (B. A. Cohen et al., 2007). In mTBI, specific regional atrophy has been particularly evinced in the anterior cingulate, cingulate gyrus, and the right precuneus GM {Zhou, 2013 #3996}. GM differences are also shown in frontal, parietal, temporal, hippocampal, parahippocampal, and cerebellar regions in chronic phase mTBI patients relative to controls (Dean et al., 2015; Little et al., 2014; Maller et al., 2014). Injury characteristics predict chronic injury phase changes. GM density reductions are exacerbated in patients with histories of multiple as opposed to a single mTBI (Little et al., 2014). Greater GM atrophy in bilateral medial temporal lobe, inferior parietal lobe, and right precuneus is associated with more severe PCS symptoms (Dean et al., 2015). In chronic phase patients, altered WM/GM density in the posterior cingulate, internal capsule and temporal and parietal regions relate to respective aspects of cognitive control including executive dysfunction and inattention; and memory impairments are associated

with reduced density in the parahippocampal gyrus, anterior temporal lobe, and internal capsule (Little et al., 2014). Although Dean et al. (2015) did not observe altered cortical thickness in chronic phase mTBI patients (Dean et al., 2015), significantly reduced left inferior parietal and right insular cortices compared to controls has been observed (Maller et al., 2014). The latter study by Maller et al. (2014) further implicated reduced inferior temporal and parietal regions as well as reduced right lingual area in the development of subsequent major depressive disorder in chronic phase mTBI (Maller et al., 2014).

Longitudinal alterations. Atrophy following mTBI is largely supported by longitudinal studies, across varied injury phases. The presence of lesions 2-5 days post-injury related to longitudinal brain atrophy (Hofman et al., 2001). Significant longitudinal reductions in cortical GM volume and significant enlargements of cerebrospinal fluid and ventricular volumes are reported in patients as early as 1 month post-injury (Toth et al., 2013). Longitudinal GM atrophy is observed in mTBI patients after three months post-injury compared to controls and is correlated with concussion symptom ratings (da Costa et al., 2016). At one year post-injury, GM, WM, and global brain atrophy is reported in mTBI patients compared to controls (Zhou et al., 2013). Brain alterations show regionally and time-specific responses to mTBI (Zagorchev et al., 2016). Longitudinal WM and GM volumetric reductions in mTBI are particularly observed in anterior brain regions, including the cingulum and cingulate gyrus and right frontal regions (Zhou et al., 2013). Though normalization of subacute alterations in deep subcortical GM structures is supported, so is the emergence of amygdala and hippocampus volumetric reductions at 1 year post-injury (Zagorchev et al., 2016). Ongoing total brain, frontal, cerebral WM, and

cerebellum volume atrophy has been supported across chronic phases in mTBI and is related to functional outcomes (e.g., vocational status) (Ross et al., 2012).

Diffusion Tensor Imaging

Sensitization of the MR signal to water diffusion has enabled underlying WM anatomy to be investigated through diffusion-weighted imaging. Diffusion tensor imaging (DTI) is another MRI technique that allows for the measurement of water diffusion within single voxels to be estimated and modeled. Instead of exhibiting isotropic diffusion, defined as equitable diffusion that occurs similarly and freely in all directions (i.e., spherical), water diffusion in biological tissue is highly anisotropic. Anisotropic diffusion occurs in fiber bundles of cerebral WM wherein diffusion occurs more readily along fiber axes (i.e., less restrictive) than across them, which is more restrictive. Thus, water diffusion is restricted and, in contrast to that observed in isotropic (i.e., non-restricted) diffusion, diffuses along a preferential axis or axes that can be detected using DTI techniques. In mTBI, DTI techniques may be especially sensitive to DAI.

Mathematical modeling is used to specify and characterize diffusion through a representative 3-dimensional ellipsoid. The shape of the ellipsoid is metrically characterized by three eigenvalues, used to describe the lengths of the longest, middle and shortest axes, and by three eigenvectors that characterize orientation (i.e., direction). Since these metrics cannot be directly measured using MRI techniques, reconstruction of the ellipsoid is conducted through the calculation of a related diffusion tensor. The mathematical representation provides a resultant rank-2 symmetrical tensor wherein diffusion properties of the ellipsoid (i.e., size, shape, orientation) are quantitatively

estimated (Basser & Pierpaoli, 1996).

Of concern in biological tissue in that theoretical assumptions (i.e., Gaussian diffusion) pertaining to water diffusion are not met. Structures comprising neural tissue such as cell organelles, membranes and myelin sheaths create barriers that limit free water distribution and inherently reduce translational motion. Therefore, non-Gaussian diffusion properties are calculated and are then represented by the "apparent diffusion constant" (ADC) instead of the diffusion constant. Discrete characteristics of the diffusion tensors are typically quantified through several commonly utilized metrics in the research literature. Fractional anisotropy (FA), the most commonly reported metric, is a scalar value between 0 and 1 that is used to describe the degree of diffusion anisotropy, or the amount of diffusion occurring within the ellipsoid. Isotropic diffusion has an FA value of 0, indicating that diffusion is occurring equally in all directions. Anisotropy, when FA approaches 1, describes diffusion that occurs in a single orientation, or a line, as diffusion is otherwise restricted. In brain tissue, FA values are highest in WM as the result of the myelin sheath, which restricts water diffusion to a single direction, reflecting the cylindrical orientation of axons (Song et al., 2003), and are lowest in cerebrospinal fluid. Consistent with this theory, reduced FA values in WM has been used as a metric for integrity of myelin. Axonal and myelin degradation are indicated by FA reductions (Beaulieu, Does, Snyder, & Allen, 1996). Other commonly reported metrics include mean diffusivity (MD), the average diffusivity within a voxel (i.e., tensor size); axial diffusivity (AD), which reflects the largest eigenvalue of the tensor (i.e., ellipsoid length); and radial diffusivity (RD), the average of the smallest eigenvalues within the tensor.

Tractography is the most common analytic approach to DTI data analysis in

clinical populations (Ito, Mori, & Melhem, 2002). In this approach, major fiber pathways are reconstructed on the basis of tensor orientation. The literature has demonstrated the neuroanatomical accuracy of tractography methods in reconstructing major WM tracts (Catani, Howard, Pajevic, & Jones, 2002; Fernandez-Miranda et al., 2012).

General findings. DTI techniques have produced somewhat inconsistent results in mTBI (see review by Shenton et al., 2012). Reduced FA and elevated MD values within various WM regions have been consistently observed in both acute and chronic phase patients with mTBI (Bazarian et al., 2007; Mayer et al., 2010; Wilde et al., 2008), although this typical anomalous patterning is not observed in all studies of mTBI (e.g., Hasan et al., 2014; Zhang et al., 2010). Discrepancies likely reflect the considerable methodological heterogeneity among studies (e.g., magnetic strengths, data analysis, tractography approach, outcome measures, included brain regions of interest, selection and inclusion and exclusion criteria of participants, time since injury, injury characteristics, and demographic characteristics of included samples) (Shenton et al., 2012). However, some general consistencies exist and are described in more detail below.

Corpus callosum. DTI findings in acute (within 24 hours of injury) and chronic mTBI patients confirm corpus callosum microstructural alterations in mTBI (e.g., Arfanakis et al., 2002; Bazarian et al., 2007; Grossman et al., 2012; Henry et al., 2011; Holli, Waljas, et al., 2010; Inglese et al., 2005; Lipton et al., 2008; Lo, Shifteh, Gold, Bello, & Lipton, 2009; Maruta et al., 2010; Matthews et al., 2011; Mayer et al., 2010; McAllister et al., 2012; Messe et al., 2011; Miles et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008; Rutgers, Fillard, et al., 2008; Rutgers, Toulgoat, et al., 2008; Smits et al.,

2011). It is notable that differences were observed in patients and athletes who had negative CT and/or MRI findings at TOI (Henry et al., 2011; Lipton et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008).

In the first DTI study of mTBI, reduced FA was exhibited in the corpus callosum of patients within 24 hours of TOI relative to controls, although MD did not differ (Arfanakis et al., 2002). Reduced FA in the corpus callosum has since been observed in both acute and chronic (Inglese et al., 2005; Lipton et al., 2008) phases of mTBI (Rutgers, Toulgoat, et al., 2008). A later study also found elevated MD values in the corpus callosum of chronic phase patients (Lipton et al., 2008). However, Mayer et al. (2010) reported callosal alterations of increased FA values as well as reduced RD values in subacute (average assessment was 12 days post-injury) patients with mTBI compared to controls (Mayer et al., 2010). Henry and colleagues (2011) also indicated significant elevations of both FA and MD in the corpus callosum that were apparent in the days immediately after and at 6 months since TOI in concussed athletes (Henry et al., 2011).

Specific callosal regions may be particularly sensitive to mTBI. Altered diffusion characteristics are observed in the forceps minor and major (Messe et al., 2011), although the splenium and genu of the corpus callosum may be especially susceptible to deleterious effects of mTBI. Increased MD (Miles et al., 2008) and reduced FA values (Maruta et al., 2010; Miles et al., 2008; Rutgers, Fillard, et al., 2008) are observed in the genu of the corpus callosum in acute patients with mTBI when compared to controls. Increased radial diffusivity has also been observed in this anterior callosal structure, although patients with both mild and moderate injuries were examined (Rutgers, Fillard, et al., 2008). Alternatively, Bazarian et al. (2007) indicated that posterior callosal WM

abnormalities of increased median FA occurred more generally than anterior disruption in patients 72 hours post-injury compared to controls (Bazarian et al., 2007). Other studies have supported reduced FA (Matsushita, Hosoda, Naitoh, Yamashita, & Kohmura, 2011) and elevated MD values in the splenium of the corpus callosum, which occurred to a greater extent in patients with acute as opposed to chronic mTBI (Inglese et al., 2005).

Injury severity is related to callosal WM alterations. Reduced FA in moderate TBI in the genu, stem, and splenium were significantly greater in moderate TBI compared to mTBI (Matsushita et al., 2011). In patients with mild and moderate TBI, Rutgers et al. (2008) indicated greater FA reduction, increased ADC, and fewer fibers in the genu and splenium of the corpus callosum with more traumatic injuries. Amelioration of FA and ADC abnormalities in the genu of the corpus callosum were also observed after 3 months since TOI in these same patients (Rutgers, Fillard, et al., 2008).

Results collectively suggest that the corpus callosum may be especially susceptible to effects of mTBI, particularly in more severe injuries, and that these effects are more evident during acute and subacute injury phases. However, all studies do not support diffusion abnormalities in this brain region in patients with mTBI relative to controls (e.g., Lange, Iverson, Brubacher, Madler, & Heran, 2012; Zhang et al., 2010). This likely reflects methodological differences. For instance, studies that collapsed across patients with mTBI and other, more severe injuries did not observe diffusion differences in civilian (Huisman et al., 2004) or in military-related mTBI in this brain structure (e.g., Davenport, Lim, Armstrong, & Sponheim, 2012; Jorge et al., 2012; Levin et al., 2010).

Corticospinal tract. The corticospinal tract (CST) is disrupted in mTBI (Jang, 2011). However, results are inconsistent. Athletes with mTBI evinced increased FA and

decreased MD in dorsal CSTs at both baseline and at 6 month follow up in one study (Henry et al., 2011), although another study by Kraus and colleagues (2007) indicated that chronic mTBI patients exhibited reduced FA values in the CST (Kraus, Susmaras, et al., 2007).

Specific subregions of the CST may be more susceptible to the effects of mTBI than others. Significantly reduced FA values are reported in both the anterior and posterior internal capsule in acute (Arfanakis et al., 2002) and in chronic (Lipton et al., 2008) patients with mTBI (Inglese et al., 2005; Miles et al., 2008). Inglese et al. (2005) further indicated that significantly increased MD values in the internal capsule were lower in the posterior limb of the internal capsule in acute patients compared to chronic patients. Overall results support increased MD and reduced FA values in the internal capsule generally (Lipton et al., 2008) and, more specifically, in the posterior limb (Miles et al., 2008). Diffusion characteristics of the corona radiata, superficial to the internal capsule, are also disrupted in mTBI. In particular, FA values are reduced in this structure (Maruta et al., 2010; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008). Relations among FA alterations and functional disturbance in patients with mTBI are also observed. Maruta and colleagues (2010) suggested that altered FA values (i.e., reduced) related to oculomotor disruption (Maruta et al., 2010). Niogi et al. (2008) found reduced FA values in the anterior corona radiata in 41% of acute phase patients with PCS symptoms (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008) that related with later memory performance (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008). Increased MD and reduced FA values have also been observed in the centrum semiovale (the ventral aspect of the corona radiata) in acute mTBI patients (Miles et al.,

2008). However, not all studies support diffusion abnormalities in these brain regions following mTBI (see Shenton et al., 2012 for a more detailed review).

Lobular white matter. Altered cerebral lobar white matter (WM) is evinced in the frontal, parietal, temporal, and occipital lobes of patients with TBI (Lipton et al., 2009; Rutgers, Toulgoat, et al., 2008). Specific alterations are also observed in anterior regions such as the orbitofrontal (Mac Donald et al., 2011) and dorsolateral prefrontal areas (Lipton et al., 2009; Zhang et al., 2010).

Cerebellar connectivity. Reduced FA is observed in the cerebellar peduncles in mTBI (Mac Donald et al., 2011) as well as in the left superior cerebellar peduncle, particularly in patient with chronic PCS complaints (Maruta et al., 2010).

Major white matter tracts. Abnormal WM tracts in mTBI include the inferior longitudinal fasciculus (Cubon, Putukian, Boyer, & Dettwiler, 2011; Messe et al., 2011; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008), superior longitudinal fasciculus (Cubon et al., 2011; Geary, Kraus, Pliskin, & Little, 2010; Matthews et al., 2011; Mayer et al., 2010; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008), uncinate fasciculus (Geary et al., 2010; Mayer et al., 2010; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008), fronto-temporo-occipital association fiber bundles (Rutgers, Toulgoat, et al., 2008), and the acoustic radiation (Cubon et al., 2011).

Deep subcortical structures. DTI results have also indicated deep cortical (Brandstack, Kurki, Hiekkanen, & Tenovuo, 2011) and subcortical alterations subsequent

mTBI. Limbic system regions of the hippocampus, fornix, and cingulum are altered by mTBI (Zagorchev et al., 2016), but not in all studies (Corbo et al., 2014). The thalamus and thalamic radiations show particular vulnerability to mild head injuries (Cubon et al., 2011; Grossman et al., 2012; Messe et al., 2011). Additional alterations in the mesencephalon (Holli, Waljas, et al., 2010) as well as the sagittal stratum (Cubon et al., 2011; Geary et al., 2010) have been indicated.

Structural connections. Dall'Acqua (2016) utilized structural MRI and DTI techniques to examine structural connectivity disruption through connectome modeling in subacute (7 days post-injury) patients with mTBI relative to a group of healthy controls (Dall'Acqua et al., 2016). Connectome analytic approaches provide a graph-based approach to modeling complex brain connectivity that is based on maps of widely distributed networks of brain regions and axonal tracts (i.e., nodes and edges) (Zalesky, Fornito, & Bullmore, 2010). The strength of anatomical links between two nodes is determined by ratios that consider the total number of interconnecting fibers observed among the regions. Dall'Acqua (2016) observed altered connections that were primarily in intra-hemispheric networks, though some inter-hemispheric disruptions were observed, among specific networks including bilateral frontal lobes as well as the thalamus and caudate nucleus in mTBI. Furthermore, greater network disconnection was particularly related to reduced cortical surface area in specific prefrontal and fronto-parietal regions including that of the lateral prefrontal, medial prefrontal, orbitofrontal, and anterior cingulate cortices, along with the pre- and post-central gyri of the right hemisphere. Interpretation of these results suggested that reduced network connectivity (as observed through weakened neural connections) occurred subsequent to DAI in mTBI. Functional

support for this effect was also provided as morphometric and connectivity results were more anomalous in the patients who had greater severity of post-injury clinical symptomology (Dall'Acqua et al., 2016).

Limitations. Though DTI provides information regarding the extent and orientation of diffusion anisotropy, limitations must be considered. DTI only enables the macrostructural assessment of neural microstructure. The average resolution typically yields voxels between 1-5 mm^3. Thus, a single voxel contains largely heterogeneous environments that are comprised of various components of neural tissue (e.g., axons, neuroglia, small cells). This has complicated the differentiation of distinct WM tracts in regions of the brain that contain overlapping (i.e., crossing) or parallel fiber pathways. Limited accuracy of pathways obtained through common fiber reconstruction techniques is also problematic. Bifurcations of axons are difficult to detect given current limitations and tracking accuracy is hindered by degree of curvature of a given fiber pathway (usually subcortical). Other limitations include the signal to noise ratio and general assumptions of water diffusion that are violated in biological tissue. It is unlikely that water diffusion occurs in a predominant direction, even within brain tissue, or that diffusion estimates isolated to a single voxel would pertain to true characteristics of whole tracts.

High-Definition Fiber Tracking

Methodological limitations of DTI have been addressed through the development of alternative fiber mapping techniques (detailed review provided by Abhinav et al., 2014). High-definition fiber tracking (HDFT) has optimized alternative methodologies such as diffusion spectrum imaging (DSI) to create a novel processing approach that

utilizes advanced data sampling, reconstruction and tractography methods (Fernandez-Miranda et al., 2012). Specifically, this high directional DSI technique combines generalized Q-sampling imaging (GQI) and constrained spherical convolution (CSC) to estimate fiber orientation diffusion function (fODF) in each voxel. The resultant maximized resolution of HDFT enables comparable anatomical precision of WM fiber tracts derived from deterministic tractography to histology in both typical and pathological tissues that exceeds that of other diffusion-weighted imaging techniques including DTI (Fernandez-Miranda et al., 2012). Specifically, this approach permits precise tracking and visualization of multiple fiber crossings, termination end points in (multiple) cortical and subcortical regions, subcortical segmentation based on the organization of structural and somatotopic connectivity, decussated fiber pathways, fibers with complex architecture (i.e., angularizations), branches of fiber pathways, and pathology in human brain tissue (Fernandez-Miranda et al., 2012). In addition to providing traditional diffusion metrics such as generalized fractional anisotropy (GFA), greater anatomical accuracy of HDFT tractography also provides indexed measurements of independent fiber tract spread and left-and right hemisphere tract homologue asymmetry that can be compared at an individual patient level (Presson, Krishnaswamy, et al., 2015; Shin et al., 2012).

HDFT tractography has confirmed clinical utility in civilian (Presson, Krishnaswamy, et al., 2015) as well as in veteran and military-related TBI (Presson, Beers, et al., 2015). HDFT can sensitively detect small, specific WM fiber alterations that are caused by TBI in heterogeneous brain regions intra-individually (Shin et al., 2012). Exploratory findings indicated that specific metrics that can be derived from HDFT (i.e.,

tract spread and homologue asymmetry) are better indices of specific WM microstructural abnormalities and neuropsychological deficits in patients with TBI than conventional anisotropy metrics (Presson, Beers, et al., 2015; Presson, Krishnaswamy, et al., 2015). Although preliminary findings have included patients across a range of injury severities, there is substantial promise that HDFT may provide a clinical biomarker of DAI in mTBI.

Magnetic Resonance Imaging in Military Personnel and Veterans

Lesion Imaging

Lesions are observed in veterans and military personnel with mTBI (e.g., Levin et al., 2010; Raymont et al., 2010), although the majority of injuries in this population go undetected upon radiological MRI examination, even when combined with moderate injuries (Levin et al., 2010).

Volumetric and Morphometric Alterations

Cortical gray matter. Thinning of cortical GM is observed in veterans and active duty service members, although it is not clear whether causation can be attributed to the effects of mTBI specifically. Tate et al. (2014) demonstrated significant thinning in left Heschl's gyrus (but not the right hemisphere) in a small cohort of blast injured service members who had substantial hearing/auditory loss (Tate et al., 2014). Veterans with comorbid PTSD and mTBI showed greater and more diffuse thinning that was associated with elevated measures of stress (Corbo et al., 2014). Overall findings suggest that mTBI may exacerbate the vulnerability of the brain to stressful events, although it is clear that additional studies are warranted.

Subcortical gray matter. In veterans with histories of chronic mTBI, Lopez-Larson et al. (2013) observed disproportionately larger thalamic volumes bilaterally in veterans with suicidal behaviors relative to controls. Disproportionate enlargement of the left thalamus was somewhat accounted for by depression symptom severity, and, though to a lesser extent, especially in veterans with histories of chronic mTBI who did not have suicidal behaviors. However, in the veterans with suicidal behaviors, right thalamus volume was significantly correlated with anxiety score (Lopez-Larson et al., 2013). Mac Donald et al. (2013) further indicated that military personnel with bTBI showed altered volume of the medulla compared to military personnel with blast exposure that did not result in subsequent symptoms of head injury, although specifics of this difference were not provided (Mac Donald et al., 2013). Depue et al. (2014) observed disproportionately reduced bilateral amygdala volume in veterans with mTBI and PTSD compared to comparison veterans without PTSD or histories of head injury. Disproportionate reductions in left amygdala volume related with increased commission errors during go/no-go task and increased impulsivity ratings and disproportionate right amygdala reductions associated with symptoms of PTSD in the veterans with PTSD and mTBI, which was not observed in comparisons (Depue et al., 2014).

Magnetization Transfer Imaging

A whole-brain analysis in veterans with bTBI indicated reduced macromolecular proton fraction, based on magnetization transfer effect, in several cortical-subcortical, interlobar, as well as subgyral WM pathways that was exacerbated by repetitive exposure to blast (Petrie et al., 2014). Specifically, reductions included WM of the right hemisphere external capsule and anterior limb of the internal capsule, interlobar right

superior longitudinal fasciculus, frontal and parietal subgyral alterations in the right precentral, superior and middle frontal gyri, medial parietal gyrus/precuneus, and left superior parietal lobule. Cortical GM structures such as the right superior and middle frontal, precentral, and anterior cingulate as well as the left lingual and subcallosal gyri also evinced reductions. Thus, the right hemisphere was particularly more affected than the left hemisphere.

Diffusion Tensor Imaging

As with civilian mTBI, DTI has been utilized to detect mTBI-related effects on cerebral WM alterations in Military service members and veterans. In particular, studies have often focused on the specific effects of bTBI. Results have indicated discrete and distinguishable effects of biomechanical forces of blast compared to other mechanisms of injury that are demonstrable through DTI techniques.

Blast specific diffusion abnormalities. Effects of blast on diffusion properties of WM result in demonstrably heterogeneous patterning of diffusion alterations (e.g., D. R. Miller, Hayes, Lafleche, Salat, & Verfaellie, 2016). Injuries subsequent to biomechanical forces of blast are discrete and distinguishable from other mechanisms of injury. For instance, results from a pothole analysis, which provides a standardized comparison for detecting regions of abnormally low FA values, showed significantly greater number of potholes in veterans with probable bTBI and possible bTBI relative to veterans without histories of blast exposure (Jorge et al., 2012). These results also indicated differences between bTBI and other mechanisms of mTBI in veterans and civilians.

Blast exposure independently alters diffusion metrics of cerebral WM. In previously deployed veterans with histories of blast exposure that did not result in

diagnosed or suspected TBI, Taber et al. (2015) reported significantly lower FA in diffuse cortical and subcortical tracts in the right hemisphere including the forceps major, superior and inferior longitudinal fasciculus, radiations of the anterior thalamic nucleus, inferior fronto-occipital fasciculus, and the CST relative to controls with no histories of blast exposure or TBI; a pattern that was not observed in left hemisphere. Furthermore, blast exposure but not mTBI history related to elevated RD and AD values compared to controls (Taber et al., 2015). It is noteworthy, however, that not all studies have observed differences in diffusion characteristics in veterans with bTBI relative to comparisons (e.g., Levin et al., 2010).

Acute and subacute phase alterations. Studies of blast-related diffusion alterations in military and veteran populations mostly examined chronic patients, although two studies examined acute phase effects of bTBI (Adam et al., 2015; Mac Donald et al., 2011). In the first study, Mac Donald et al. (2011) compared deployed service personnel with histories of blast exposure with and without mTBI at baseline (within 90 days post-injury) and follow-up (between 6 to 9 months after baseline) assessments. Reduced anisotropy in the cingulum bundle, uncinate fasciculus, and anterior limb of the internal capsule in addition to expected alterations in WM of the orbitofrontal area and cerebellar peduncle were observed at baseline in service members with mTBI compared to those without histories of head injury. However groups exhibited similar diffusion in the corpus callosum and posterior limb of the internal capsule, which are sensitive to mTBI in civilians (as discussed above), in addition to other diffusion metrics such as MD and RD. The lack of significant group differences in callosal diffusion properties was interpreted as being indicative of the sparing of these brain

regions in bTBI. Sensitivity of DTI metrics to bTBI was also stable over time (Mac Donald et al., 2011).

Adam et al. (2015) compared military service members with acute (within 7 days) bTBI to service members who had not sustained a head injury within the 12 months prior to study enrollment. While differences between groups were not observed for MD, AD or RD values, FA values were reduced in the right superior longitudinal fasciculus in the service members with bTBI compared to the overall comparison group, but not relative to a subset of age-matched males from the comparison group. Neither recovery time nor neurocognitive performance correlated with FA values in any of the examined regions of interest (ROIs) (Adam et al., 2015).

Chronic phase alterations. Reduced FA is the most prevalent finding in service members and veterans with chronic bTBI (e.g., Bazarian et al., 2013; Davenport et al., 2012; Jorge et al., 2012; Mac Donald et al., 2013; Taber et al., 2015). One study indicated that blast-induced head injury may be especially associated with reduced FA in the forceps major and minor, bilateral anterior thalamic radiations, right CST, bilateral inferior frontal occipital fasciculus, bilateral inferior longitudinal fasciculus, left superior longitudinal fasciculus, and, once civilian TBI history is taken into account, the superior longitudinal fasciculus and right cingulum (Davenport et al., 2012).

Mac Donald et al. (2013) observed other diffusion abnormalities specific to blast in cerebellar WM in 3 of 4 veterans with histories of a single bTBI that occurred several years prior to assessment. The four veterans with bTBI exhibited decreased relative anisotropy in the middle cerebellar peduncle as well as significantly reduced FA values

relative to a comparison group of service members with histories of blast exposure that did not result in symptoms of mTBI (Mac Donald et al., 2013).

Loss of consciousness at TOI can worsen FA reductions. For veterans exposed to blasts within a 100 m range, Miller et al. (2016) indicated that veterans who had mTBI with LOC exhibited significantly greater number of clusters with reduced FA relative to veterans with mTBI without LOC and veterans without histories of TBI, which did not differ. Number of clusters with reduced FA related to PCS severity, even after significant effects of traumatic stress were taken into account (D. R. Miller et al., 2016), and were identified as a significant mediator between LOC and physical PCS severity in bTBI (D. R. Miller et al., 2016). Although an earlier study by Hayes et al. (2015) that also examined mTBI acquired as the result of exposure to blast within 100 m failed to find differences in FA in several ROIs at a conservative alpha, veterans with bTBI with LOC were 2.36 times more likely than controls and 3.36 times more likely than veterans with bTBI without LOC, which showed similar likelihood, to have one or more ROIs that were considered abnormal (Hayes, Miller, Lafleche, Salat, & Verfaellie, 2015). LOC also exacerbated the association among blast load and reduced FA values, whereby higher blast load with LOC was associated with lower FA in the left retrolenticular part of internal capsule and in the right sagittal stratum in veterans with mTBI (Hayes et al., 2015).

Interactive effects between age and bTBI on diffusion abnormalities is supported. In a cross-sectional study, Trotter et al. (2015) indicated negative age-related neural trajectories at the microstructural tissue level subsequent to bTBI. Blast-induced TBI resulted in the greatest reduction of diffusion-related neural integrity (e.g., FA) in older

military veterans and service members than in younger personnel. This interaction was particularly evident subsequent repetitive exposure (Trotter, Robinson, Milberg, McGlinchey, & Salat, 2015). Time since injury also negatively correlated with FA in bTBI, although this relation was independent of age and symptoms of PTSD (Trotter et al., 2015).

Psychiatric comorbidity. Diagnosis, treatment, and general understanding of the biological underpinnings of mild head injuries in the DoD are complicated by overlapping symptoms with other diagnoses that frequently co-occur in this population, particularly PTSD, depression, and suicidal behaviors (e.g., Hoge & Castro, 2006, 2011; Hoge et al., 2008). Researchers have utilized DTI techniques to distinguish effects of common psychiatric comorbidities of military-related mTBI from the physical effects of trauma.

***Post-traumatic stress disorde*r.** Since exposure to blast is associated with polytrauma, the relation between PTSD and bTBI has been particularly investigated (Bazarian et al., 2013). Davenport et al. (2015) found differential, independent effects of PTSD and blast exposure on diffusion properties in recently deployed service members with and without mTBI. Whereas PTSD increased likelihood of abnormally high number of (i.e., first percentile) MD values, blast exposure was associated with increased likelihood of having greater number of regions with reduced (i.e., first percentile) FA. Having at least one region of abnormally high MD related to PTSD, regardless of the presence or absence of mTBI. In particular, PTSD related to altered diffusion metrics in ROIs including the inferior cerebellar peduncle, corticospinal tract, medial lemniscus, anterior limb of the internal capsule, caudate nucleus and pons. In this study, blast

exposure was associated with altered FA in the inferior cerebellar peduncle and MD in the caudate nucleus, with both mTBI and PTSD showing effects on superior cerebellar peduncle MD, and FA in the fornix, midbrain, and splenium of the CC. However, none of the relations survived correction for multiple comparisons. Davenport et al. (2015) also supported differential effects of PTSD and TBI on WM in veterans with and without histories of blast exposure. Voxel-wise comparisons indicated that PTSD was associated with higher GFA in one large cluster of voxels encompassing generally right hemisphere regions of the corpus callosum, cingulum, superior longitudinal fasciculus, CST, internal capsule, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus, as well as 8 additional clusters encompassing bilateral external capsule, bilateral middle cerebellar peduncle, right anterior thalamic radiation, and left superior cerebellar peduncle (Davenport et al., 2015). PTSD was consistently associated with elevated GFA in specific ROIs, increased likelihood for regions with voxels with reduced diffusion (low MD) and greater number of voxels with elevated FA values. TBI history was associated with fewer regions with voxels with elevated MD values.

PTSD is not always related to altered diffusion properties. In veterans from the Iraq and Afghanistan conflicts, PTSD and mTBI related to diffusion alterations in the caudate nucleus and the inferior cerebellar peduncle that were not maintained after corrections for multiple comparisons were applied (Bazarian et al., 2013). Trotter and colleagues (2015) indicated no effects of PTSD on diffusion abnormalities in veterans with bTBI (Trotter et al., 2015). Two other studies also indicated minimal, non-statistically significant effects of PTSD on FA values once LOC was taken into account (Hayes et al., 2015; D. R. Miller et al., 2016). This effect is also observed in heavy

drinkers with mTBI. Heavy drinking is associated with reduced FA values in fronto-subcortical WM regions in veterans (Maksimovskiy et al., 2014) even after PTSD and indicators of alcohol use are taken into account (Jorge et al., 2012; Taber et al., 2015).

Depression. Effects of comorbid depression have also been examined in veterans with histories of mTBI. Matthews et al. (2011) examined chronic bTBI in veterans of the Iraq and Afghanistan conflicts who had current diagnosis of major depression relative to those without current or lifetime histories of depression. A diagnosis of depression was associated with significantly lower FA values in the corona radiata, corpus callosum, and superior longitudinal fasciculus, regardless of mTBI history. Although, comorbid mTBI and depression related to lower FA values in the superior longitudinal fasciculus related to greater depression symptom severity (Matthews et al., 2011). Isaac et al. (2015) compared veterans with chronic mTBI and PTSD with veterans who had chronic mTBI with comorbid PTSD and depression. FA values were significantly greater in the group without depression in the left uncinate and right cingulum fiber tracts (Isaac et al., 2015). However, there were no observed group differences on RD or AD values.

Suicidal behavior. Lopez-Larson et al. (2013) investigated the relation between suicidal behavior and neural microstructure in veterans with mTBI. Suicide behaviors related to greater FA values in bilateral anterior thalamic radiations than mTBI alone (i.e., without suicidal behaviors) and also relative to controls without histories of psychiatric disruption or head injury (Lopez-Larson et al., 2013).

Functional correlates. Diffusion properties of WM are purported to provide an estimate of WM integrity. Functional correlates of WM integrity have hence been supported by a number of studies. FA and MD values are related to severity of PCS and

PTSD symptoms in post-deployed veterans with mild to moderate TBI (Davenport et al., 2015; Levin et al., 2010). Associations between neuropsychological performance AND LOC are also supported. Extent of diffusion abnormalities mediated the relation between LOC and poorer verbal memory performance, which was maintained above PTSD severity in one study (Hayes et al., 2015). Levin et al. (2010) also indicated relations among FA and ADC values and verbal learning and memory and nonverbal learning, and aspects of executive control (Levin et al., 2010). Taber et al. (2015) also observed relations among FA (voxel clusters) and tests of executive function (e.g., set-shifting) and simple reaction time that existed above the effects of psychiatric comorbidity and demographic characteristics (Taber et al., 2015).

Limitations. Achieving cohesive understanding of how, specifically, blast exposure disrupts cerebral WM has proven to be highly complex as a result of methodological differences across studies in the published literature. For instance, participant inclusion criteria for military and veteran populations differed substantially across studies. Most military studies utilizing DTI have limited participants to include only those who sustained injuries during the Iraq and Afghanistan conflicts (e.g., Bazarian et al., 2013; Davenport et al., 2012; Hayes et al., 2015; Jorge et al., 2012; Mac Donald et al., 2011; Maksimovskiy et al., 2014; Matthews et al., 2011; D. R. Miller et al., 2016; Morey et al., 2013), although Isaac et al. (2015) also included veterans from various, earlier conflicts as well (Isaac et al., 2015).

Injury characteristics have also differed tremendously across studies. Although most studies have only examined mTBI, some have included a range of injury severities (Trotter et al., 2015; Yurgelun-Todd et al., 2011) in their investigations, including

patients with moderate (Levin et al., 2010) and even severe injuries (Yurgelun-Todd et al., 2011). Mechanism of injury is also heterogeneous across studies with some including only bTBI (e.g., Adam et al., 2015; Davenport et al., 2012; Davenport et al., 2015; Hayes et al., 2015; Jorge et al., 2012; Levin et al., 2010; Mac Donald et al., 2013; Mac Donald et al., 2011; Matthews et al., 2011; D. R. Miller et al., 2016; Taber et al., 2015) and others including mTBI groups comprised of patients with histories of mTBI from various mechanisms (Bazarian et al., 2013; Isaac et al., 2015; Lopez-Larson et al., 2013; Trotter et al., 2015), such as blast, blunt, and combination injuries (Maksimovskiy et al., 2014; Yurgelun-Todd et al., 2011), as well as those from impact-related injuries only (Morey et al., 2013). Of the studies that were specific to blast exposure, some only included participants with histories of exposure to blast within 100 m (Hayes et al., 2015; D. R. Miller et al., 2016). Several studies limited inclusion criteria of participants to only patients with injuries sustained during deployment (e.g., Hayes et al., 2015) or during combat (Adam et al., 2015; Matthews et al., 2011), with some excluding individuals with pre-deployment histories of TBI (Levin et al., 2010; D. R. Miller et al., 2016; Taber et al., 2015). Some studies also excluded women in overall (e.g., Lopez-Larson et al., 2013; Yurgelun-Todd et al., 2011) and specific (e.g., follow-up) analyses (Adam et al., 2015), as well as non-right-handed individuals (Levin et al., 2010; Yurgelun-Todd et al., 2011).

Length of time since injury varied greatly between studies. Adam et al. (2015) only included acute patients who were assessed within 7 days post-injury (Adam et al., 2015) whereas other studies have assessed acute patients up to 90 days post-injury (e.g., Mac Donald et al., 2011). Similarly, studies of chronic military-related mTBI patients have greatly varied in assessment periods from those including assessments as early as 6

months since TOI (Mac Donald et al., 2011), to those including later assessments of within 42 months (Levin et al., 2010) and as late as 4 (Jorge et al., 2012; Mac Donald et al., 2013) and 5 (Davenport et al., 2015) years since TOI.

Comparison groups also varied wildly across studies. Individuals with histories of blast exposure who were not considered to have sustained subsequent mTBI were included in some studies as comparison controls (Hayes et al., 2015; Mac Donald et al., 2013; Mac Donald et al., 2011; D. R. Miller et al., 2016), which may be particularly problematic when comparing results across studies as blast exposure alone can account for alterations of diffusion in WM (Taber et al., 2015). Whereas one study included only healthy controls (Lopez-Larson et al., 2013) as comparisons, the comparison groups of other studies included were more variable, comprising individuals with bodily injuries not considered to affect the central nervous system (Levin et al., 2010); without histories of head injury (Morey et al., 2013; Yurgelun-Todd et al., 2011); without histories of blast exposure or head injuries (Davenport et al., 2012; Jorge et al., 2012); without histories of bTBI or PTSD (Davenport et al., 2015); without histories of pre-deployment TBI or blast exposure (Taber et al., 2015); without histories of blast exposure, deployment-related TBI or PTSD (D. R. Miller et al., 2016); without histories of TBI within the past 12 months (Adam et al., 2015); with civilians (Yurgelun-Todd et al., 2011). Furthermore, studies have included individuals with histories of concussion and head injury in comparison control groups (Bazarian et al., 2013; Davenport et al., 2012; Davenport et al., 2015; Maksimovskiy et al., 2014; Taber et al., 2015; Trotter et al., 2015), and not all studies have included comparison groups (e.g., Isaac et al., 2015; Matthews et al., 2011).

Functional Magnetic Resonance Imaging

Most functional MRI (fMRI) studies in mTBI have examined aspects of executive control given the frequency of complaints and observed deficits in this cognitive domain (Mayer, Bellgowan, & Hanlon, 2015; McDonald, Flashman, & Saykin, 2002). Although memory has also been examined given the similarly high occurrence of memory complaints and difficulties incurred by patients with mTBI (Heitger et al., 2006; Sivak et al., 2016; Sundstrom et al., 2004). In the majority of studies, results indicated altered neural function, even in chronic phase patients who evinced full recovery from PCS symptoms (McDonald et al., 2002). Results have been suggested as providing direct evidence that persistent alterations in neural tissue occur and persist beyond evidenced recovery of neurological and neuropsychological function. Thus, results have provided evidence for the deleterious effects of mTBI on neural tissue and functional brain networks that persists beyond recovery and above psychiatric comorbidity in some patients.

Working memory. To determine outcomes specific to bTBI, Newsome et al. (2015) compared fMRI task performance during working memory among veterans with mild and moderate bTBI, a civilian cohort with mild to moderate TBI, and two control groups comprised of veterans and civilians who had no histories of TBI, respectively (Newsome et al., 2015). The task involved encoding of 1, 3, or 5 items. The civilian TBI group and both control groups demonstrated a monotonic, positive relationship between working memory set size and activation in the right caudate during encoding that was not observed in the veterans with blast TBI. Blast-induced TBI also related to worse task performance relative to all other groups, which did not relate to activation in any region

in the group with bTBI but was related to reaction time in the civilian TBI group. Results were thought to reflect specific vulnerability of the caudate to blast injury.

Executive function. An event-related fMRI task examined activation patterns during a stimulus-response compatibility task (i.e., conflict resolution) in veterans with chronic mTBI relative to controls. Veterans with mTBI exhibited greater activation in the anterior cingulate gyrus, medial frontal cortex, and areas within the posterior visual attention network relative to controls (Scheibel et al., 2012). The authors interpreted hyperactivation in these anterior and posterior attention networks as being compensatory for inefficient processing subsequent deafferentiation from DAI.

Response inhibition. Anomalous neural activation during response inhibition in veterans with bTBI is also supported. Matthews et al. (2011) examined fMRI activation patterns during the stop signal task in veterans with bTBI who had experienced LOC or AOC. Though groups performed similarly on the task, activation patterns differed during the easy inhibitory trials. Compared to AOC, LOC was associated with less activation in the middle frontal gyrus of the ventromedial prefrontal cortex, which related to severity of somatic symptoms. Reduced somatic complaints with hypoactivation in these regions was interpreted as potential indication of poor self-awareness following LOC.

In a later study, Fischer et al. (2014) compared active duty service members and veterans with mTBI from exposure to blast and civilians with histories of mTBI from traditional injury mechanisms such as blunt force trauma to two comparison control groups comprised of veterans or civilians with no histories of TBI, respectively. During the stop-signal task, greater activation was observed in individuals with histories of bTBI in bilateral inferior and left superior temporal, caudate, and cerebellar regions during

errors related to failure to inhibit response tendencies relative to veterans with no TBI (Fischer et al., 2014). Blast-induced TBI also resulted in a distinct pattern of greater activation in the anterior cingulate and orbital gyri during successfully inhibited trials from that of civilian mTBI and in the civilian controls. Thus, bTBI may result in discrete injury outcomes. Since the military mTBI groups also differed from the civilians with mTBI, results provided support for differential outcome in military-related mTBI compared to civilian mTBI.

Emotional processing. Given high rates of emotional and psychiatric problems in military-associated mTBI, fMRI has been used to examine neural activation patterns during processing of emotional stimuli. When responding to emotional faces, differences in amygdala activation was observed in veterans with bTBI with and without comorbid major depression (Matthews et al., 2011). fMRI results indicated decreased bilateral amygdala activation in veterans with comorbid mTBI and depression that related to anomalous WM diffusion indices. This comorbidity also related with lower activation in regions associated with the cognitive control network including the dorsolateral prefrontal cortex (DLPFC) relative to veterans with mTBI without comorbid depression. Overall results supported additive effects of depression on amygdala function during emotional processing in veterans with bTBI.

Functional Connectivity Magnetic Resonance Imaging

Reduced functional connectivity is also observed in mTBI. Detailed results have been comprehensively provided in reviews of civilian mTBI (e.g., Mayer et al., 2015; McDonald et al., 2002) as well as veteran and military-related mTBI (see Wilde et al., 2015). To briefly summarize, most studies emphasized default mode network function

through resting state fMRI. Altered connectivity within the default mode network has been consistently evidenced in civilians and athletes with mTBI (e.g., Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; Zhou et al., 2012) and military mTBI (Wilde et al., 2015). Reduced connectivity is generally observed in acute and subacute mTBI, and may be worsened by repetitive head injuries. However, increased anterior connectivity among prefrontal and anterior cingulate cortices has been observed in subacute phase mTBI as well as in chronic phase mTBI, suggesting relative stability (Mayer et al., 2011). Posterior default mode network regional connectivity is generally reduced in civilians with mTBI, but was increased in one study of active duty service members (Nathan et al., 2015). Examination of bTBI has also supported reduced functional connectivity (Vakhtin et al., 2013), and proximity to blast explosion influences connectivity alterations within the default mode network (Robinson et al., 2015). Blast-specific findings support susceptibility of the caudate to this mechanism of injury in addition to PTSD, as less efficient neural connectivity was observed in a network that surrounded the caudate (Spielberg, McGlinchey, Milberg, & Salat, 2015).

Connectivity within other neural networks is also altered in mTBI. Subcortical GM connections may be particularly susceptible to deleterious effects of DAI in mTBI, including connections among thalamic (Tang et al., 2011; Zhou et al., 2014) and basal ganglia (Shumskaya, Andriessen, Norris, & Vos, 2012) nuclei. In support of previously observed connectivity alterations of the thalamus in mTBI (Tang et al., 2011), Zhou et al. (2014) observed decreased thalamo-thalamo, thalamo-frontal, and thalamo-temporal connectivity during resting state fMRI and reduced thalamo-motor cortex connectivity during a motor task in patients with mTBI (Zhou et al., 2014). Veterans with bTBI have

also exhibited decreased connectivity in the motor-striatal network that was observed along with other network pairs that also included the default mode and basal ganglia networks (Vakhtin et al., 2013).

Rationale for the Current Study

Blast-induced TBI is among the most common injury sustained by veterans and military personnel of the recent Iraq and Afghanistan conflicts (Helmick et al., 2015), although the subtlety of subsequent neural alterations and the lack of a definitive biomarker of DAI impede clinical identification and intervention of bTBI. With evidence for heightened vulnerability of the recently injured brain, return to duty guidelines within the DoD have been revised to enhance recovery and prevent severe brain injury due to re-injury from further exposures to blast (Helmick et al., 2015). However, guidelines rely on subjective symptom reporting, neurological testing, and conventional clinical neuroimaging techniques that lack a strong basis in pathophysiology. Preliminary results have indicated high sensitivity of HDFT to small, specific WM fiber alterations in TBI that occur intra-individually in heterogeneous brain regions. While HDFT may provide a clinical biomarker of DAI, the sensitivity of this approach for detecting bTBI remains unknown.

Mounting neuropsychological and functional neuroimaging evidence supports susceptibility of the executive control network (ECN) to effects of bTBI (Bailie et al., 2016; Fischer et al., 2014; Mayer et al., 2015; McDonald et al., 2002; Newsome et al., 2015; O'Neil et al., 2013; Scheibel et al., 2012; Spielberg et al., 2015). The ECN subserves and facilitates stimulus-response associations in order to facilitate context-based, goal-driven, and expected behaviors within evolving environments through

cortico-striatal connections among prefrontal cortical regions and nuclei of the basal ganglia and thalamus (Chambers, Garavan, & Bellgrove, 2009; McNab et al., 2008; E. K. Miller & Cohen, 2001; Rubia et al., 2010; Rubia et al., 2001; Sebastian et al., 2013; Swick, Ashley, & Turken, 2011). Response inhibition (RI), or the ability to withhold an ongoing prepotent response tendency, is a distinct domain of executive control that is distinguishable from other higher-order cognitive domains such as working memory and attention (McNab et al., 2008; Wager & Smith, 2003). Distinct frontal cortico-striatal connections of the ECN subserve differential and distinguishable aspects of higher-level information processing (Middleton & Strick, 2000, 2002). Cortico-striatal projections first terminate in the striatum (i.e., caudate and putamen) of the basal ganglia, and enable or inhibit selected responses determined by the prefrontal cortex while suppressing additional, non-adaptive behaviors (reviewed in M. X. Cohen & Frank, 2009). The pallidum, through cortico-thalamic projections, then initiates projections back to prefrontal cortical regions, particularly to the DLFPC. Thus, separate but connected cortico-striatal circuits moderate motoric and cognitive behavior through regulation of action selection and action inhibition (e.g., Alexander, DeLong, & Strick, 1986).

Though deleterious effects of bTBI on ECN function can be highly specific and discernable from other injury mechanisms (Fischer et al., 2014; Mayer et al., 2015; McDonald et al., 2002; Newsome et al., 2015; Scheibel et al., 2012; Spielberg et al., 2015), the microstructural basis for executive dysfunction is unknown. This has largely been due to limitations of traditional structural neuroimaging techniques (Verstynen, Badre, Jarbo, & Schneider, 2012). However, HDFT results of discrete neural networks are promising. Superior resolution of HDFT to traditional diffusion MRI methods

enabled precise tracking of specific cortico-striatal pathways of the ECN in a typical adult sample (Fernandez-Miranda et al., 2012; Verstynen et al., 2012). It is possible that understanding microstructural alterations of the ECN in bTBI using HDFT could help to elucidate a clinical biomarker of bTBI.

Aims and Hypotheses

The current study addressed gaps in the research literature including the sparse number of brain imaging studies of mTBI in veterans and military personnel and the need to identify and validate biomarkers of bTBI, which have prognostic utility. Identifying and validating the proposed biomarkers of bTBI could provide demonstrable clinical utility for early and accurate identification of affected veterans that would bolster injury prevention efforts of return to duty guidelines and medical decision-making for injured personnel. The current study examined microstructural and functional outcomes of the ECN in veterans with chronic symptoms of bTBI relative to a comparison group of veterans with no histories of blast exposure through the following aims:

1. To examine dorsolateral prefrontal cortico-striatal and cortico-thalamic WM fiber pathways of the ECN in veterans with and without bTBI utilizing HDFT.

   ***Hypothesis*:** Quantitative metrics derived from HDFT will be significantly altered in veterans with bTBI compared to veterans in the comparison group.

2. To examine functional correlates of ECN microstructure in veterans with and without bTBI.

   ***Hypothesis*:** Given the topographic and parallel, looped organization of the dorsolateral prefrontal cortico-striatal and cortico-thalamic projections (Alexander et al., 1986; Verstynen et al., 2012), difficulties in executive aspects of RI (i.e.,

action withholding as indexed by RI reaction time) will relate to projections among the dorsolateral prefrontal cortex (DLPFC) and the putamen whereas deficits in motor responding (i.e., reaction time and response selection) will relate to the pathways among DLPFC and the caudate and thalamus. Specifically, greater alteration of HDFT tract metrics were expected to correlate with less efficient RI performance (i.e., slower and inaccurate).

METHOD

The current retrospective, dual cohort observational study evaluated structural alterations of ECN WM in 38 male veterans with (n = 23) and without (n = 15) histories of bTBI from exposure to primary blast to establish the clinical utility of utilizing quantitative HDFT metrics to identify a biomarker of chronic bTBI (Aim 1). The functional correlates of ECN microstructure were also examined in a secondary aim (Aim 2). ECN structure and functions were respectively assessed through HDFT image acquisition and fiber reconstruction and a standardized paradigm of RI, the Stop Signal Task (SST).

Participants

Male veterans (N = 38) between the ages of 24 and 50 years were recruited from clinics at the Michael E. DeBakey VA Medical Center (MEDVAMC), veteran organizations, social media, and community and friend referral in Houston, TX.

The Blast-induced TBI group. Veterans (n = 23) with documented histories of primary blast exposure that resulted in bTBI at least 3 months prior to enrollment were included in the bTBI group. Inclusion criteria for the bTBI group included exposure to blast that resulted in AOC and/or LOC lasting less than 30 minutes, PTA lasting less than

24 hours, a GCS score between 13-15 at 30 minutes post-injury, transient neurological abnormalities such as focal signs and focal lesions on neuroimaging when applicable, and/or other neurological or neuropsychological dysfunction (e.g., PCS) that significantly impaired aspects of daily functioning (e.g., social, academic, or employment impairments). Exclusion criteria for the bTBI group included penetrating head injuries or injuries requiring subsequent surgical intervention, history of head injury within 90 days prior to study enrollment, or any history of moderate or severe TBI, i.e., GCS < 13 and/or PTA > 24 hours.

The comparison group. Veterans (n = 15) without histories of blast exposure were included in the comparison group. The rationale for including a veteran comparison group was to control for psychiatric and demographic characteristics typical of post-deployed veterans that can influence structural and functional outcomes such as PTSD and alcohol use disorders (Hoge et al., 2008; Wilde et al., 2015). Efforts were made to ensure similarity of the comparison group to the bTBI group on demographic characteristics such as age and education, military and deployment history, and psychiatric symptoms related to PTSD and alcohol use disorders. In order to help partial out specific effects of exposure to primary blast, some of the veterans in the comparison group had prior mTBI histories that resulted from common mechanisms in garrison (e.g., sports-related concussion, motor vehicle accidents), military training, and on deployment (e.g., blunt injuries). All injuries were mild in severity, per the same criteria as that used in the bTBI group (described above). Exclusion criteria for the comparison group included penetrating head injuries or injuries requiring subsequent surgical intervention, history of head injury within 90 days prior to study enrollment, or any history of

moderate or severe TBI, i.e., GCS < 13 and/or PTA > 24 hours.

Overall exclusionary criteria for both groups included female sex, any MRI contraindications (e.g., implanted ferrous metal, pacemakers, body weight > 125 kg, or claustrophobia), medical history of neurologic disability (i.e., not related to TBI), severe psychiatric (i.e., psychosis, bipolar disorder) or neurodevelopmental disorder (e.g., autism spectrum disorder), any physical disability that would preclude study participation (e.g., paralysis of the upper extremities), and/or inability to provide consent for study participation.

General Procedure

Participant recruitment and enrollment followed the procedures of the overall, larger HDFT study initiative (detailed in Presson, Beers, et al., 2015). All procedures were conducted in agreement with the ethical standards for research with human subjects set forth by the Institutional Review Boards at E. DeBakey VA Medical Center (MEDVAMC), Baylor College of Medicine, and University of Houston, in Houston, TX.

Screening. Screening of potential participants for study eligibility was conducted in person or by telephone through a series of yes or no questions (i.e., inclusion/exclusion criteria) that lasted approximately 15 minutes. Once eligibility was determined, scheduling and participants were enrolled into the study.

Enrollment. At initial study enrollment, all participants underwent a formal written consent process. Subsequently, information regarding demographic and medical history was obtained from each participant. Head injury history was also obtained, including severity, frequency, mechanism(s), and characteristics (e.g., duration of PTA, and AOC or LOC at TOI). A polytrauma interview was also conducted at this time to aid

in determining specifics of explosive blast exposure history, and to assess for the occurrence of primary blast exposure and PTSD.

Data acquisition. Enrolled participants completed a standardized neuropsychological battery (detailed in Presson, Beers, et al., 2015) prior to completion of the MRI scan (discussed below). Efforts were made to complete neuropsychological testing in a single day.

Participant incentive. Participants received compensation for study participation.

Neuropsychological Assessment

Each participant completed a standardized neuropsychological battery that lasted between 2 to 2.5 hours (for a detailed summary see Presson, Beers, et al., 2015). Symptoms of PCS as well as symptoms of PTSD and alcohol use disorders were evaluated using multiple neuropsychological measures that have strong psychometric properties, satisfactory normative comparison data, and are widely used in both clinical and research settings for assessing outcomes in TBI (detailed in Presson, Beers, et al., 2015). Symptoms of PCS were measured using the Rivermead Post Concussion Symptoms Questionnaire (King, Crawford, Wenden, Moss, & Wade, 1995). The PTSD CheckList-Civilian (PCL-C) was used to assess symptoms and overall severity of PTSD (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996). Current and past alcohol use and disorder history was examined using the AUDIT: Alcohol Use Disorders Identification Test (Saunders, Aasland, Babor, de la Puente, & Grant, 1993).

The Stop Signal Task. ECN functions were assessed using the Stop Signal Task (SST) (Schachar & Logan, 1990), a computerized choice reaction-time task that provides a more direct measure of RI than other paradigms (Eagle, Bari, & Robbins, 2008; Rubia

et al., 2001; Sebastian et al., 2013; Swick et al., 2011; Zheng, Oka, Bokura, & Yamaguchi, 2008). The SST is well validated in neurological populations including TBI (Dimoska-Di Marco, McDonald, Kelly, Tate, & Johnstone, 2011).

During the SST, participants are instructed to respond as quickly and as accurately as possible to 'go' stimuli while simultaneously withholding these responses in the presence of a 'stop' stimulus. 'Go' trials consist of a randomized series of 'X's or 'O's that are visually presented in the middle of the computer screen (as shown in Figure 1). During the 'stop' trials, an audible tone is presented after the go stimulus appears on the screen that serves as a prompt to withhold the response to the presented "go" stimuli. Timing of the 'stop' stimulus presentation is adaptive, based on the independent horse-race model (Logan, Cowan, & Davis, 1984). The adaptive nature of the task is based on each participant's reaction time in order to ensure that accuracy during 'stop' trials will occur 50% of the time for each participant. Consequently, correctly inhibited responses during stop signal trials decreases the delay between the go signal (i.e., "X" or "O") and the stop signal (beep) for subsequent stop trials by 50 ms, increasing the difficulty of stop trial response inhibition. Conversely, incorrect responses during a stop trial, (i.e., participant presses the button) increases the delay of the following stop signal trial by 50 ms, resulting in increasingly easier inhibition responses to stop trials. The sequence of 'stop' and 'go' stimuli presentation is randomized across trials. Participants completed one practice block and four test blocks consisting of 24 trials each. A 10 s pause follows each block during which the examiner checks participant readiness before continuing. The entire task takes about 10 minutes to complete.

Multiple dependent variables can be generated from the SST. Outcome variables

are summarized in Figure 2. Scores are calculated within a horse-race framework whereby stopping (inhibition) and ongoing response processes compete for the first completion time (Logan et al., 1984). The stop signal reaction time (SSRT) score, conceptualized as the mean latency for successful stop trials, was computed using the stop signal delay score minus the mean go reaction time. In addition, several accuracy and reaction time (RT) scores were respectively calculated for several trial types: (a) Go: correct response, (b) Go: no response (i.e., omission errors), (c) Stop: failed inhibition (i.e., commission errors), and (d) Stop: correct inhibition (i.e., no response). For the current study, derived accuracy and speed scores for each of the four trial types were calculated across all trials and blocks (i.e., total scores).

[Insert Figure 2 Here]

With the exception of two participants in the bTBI group, all participants completed the task with valid performance on the day of the MRI. For the participants with missing SST data, one participant had invalid performance (i.e., discontinuation due to poor performance), and the other participant's data was excluded because of technical issues with the laptop.

Magnetic Resonance Imaging

Microstructure of the ECN was examined using the HDFT acquisition, processing, and image reconstruction pipeline (detailed in Fernandez-Miranda et al., 2012).

Data acquisition. Diffusion and structural MRI data was acquired on a research dedicated, 3 Tesla Siemens Trio System using a 32-channel head coil (Wedeen, Hagmann, Tseng, Reese, & Weisskoff, 2005) at the Baylor College of Medicine Core for

Advanced MR Imaging (CAMRI) in Houston, TX. A multi-shell diffusion spectrum imaging (DSI) protocol (Wedeen, Hagmann, Tseng, Reese, & Weisskoff, 2005) using simultaneous multi-slice (SMS) optimization with multiband acceleration factor of 3 (Setsompop, Gagoski, et al., 2012). A total of 279 diffusion volumes were collected: b = 1000 with 64 directions, using repetition time/echo time (TR/TE) = 2900/94 ms; b = 3000 with 64 directions, using TR/TE = 3500/122 ms; b = 5000 with 128 directions, using TR/TE = 3900/140 ms. Twenty-three non-gradient (b = 0) weighted images were also acquired. For each shell, voxel size = 2.4 mm^3 (isotropic); field of view (FoV) = 230.4 mm^2; and 63 axial slices were collected. The total procedure was completed in approximately 22 min. Anatomical data was acquired using a 7 min T_1-weighted axial magnetization-prepared rapid gradient-echo (MPRAGE) sequence; TR/TE = 1,500/3.19 ms, flip angle = 8°, 176 slices, voxel size = 1.0 mm^3, FoV = 256 mm^2.

Image reconstruction. Data reconstruction was conducted using an HDFT algorithm that combines generalized Q-sampling imaging (GQI) (Yeh, Wedeen, & Tseng, 2010) and constrained spherical deconvolution (CSD) (Tournier, Clamante, Gadian, & Connelly, 2004) to estimate the fiber oriented distribution function (fODF) in each voxel. The b = 1000 shell was excluded from the reconstruction to better estimate fiber geometry. Orientated distribution function (ODF) peak finding was performed to obtain measures of quantitative anisotropy and direction of multiple, modeled diffusion directions (or fibers) in each brain voxel. A map of generalized fractional anisotropy (GFA), a measure of the standard deviation of the ODF divided by the mean of the ODF (Tuch, 2004) was computed.

All scans were analyzed blind to group status. MRI data was reviewed for quality assurance prior to performing morphometric or HDFT tracking analyses.

Atlas segmentation. FreeSurfer (http://surfer.nmr.mgh.harvard.edu) (Fischl, 2012) was used to automatically segment cortical and subcortical regions from the T_1-weighted anatomical image to create a region of interest (ROI) within the ECN for each participant (Verstynen et al., 2012; Verstynen, Jarbo, Pathak, & Schneider, 2011). Individual ROIs were isolated from the template image (aparc.a209s+aseg.mgz output file from FreeSurfer) and saved as separate NIfTI files. Each ROI was subsequently co-registered to the b_0 image and resliced with a linear, rigid body transformation procedure using FSLMaths from the FMRIB Toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL; Smith et al., 2002) to match the voxel and matrix dimensions of the DSI data. All ROI masks were expanded by 2 voxels to account for any distortion artifacts and partial-volume effects (using the FSLMaths dilation command). Gray matter masks are illustrated in Figure 3.

[Insert Figure 3 Here]

Since the ECN is comprised of distinct, but interconnected cortico-subcortical circuits that moderate motoric and cognitive behavior through regulation of action selection and action inhibition (Alexander et al., 1986), discrete cortical ROIs in each hemisphere were selected and categorized as belonging to the DLPFC per Lopez-Paniagua & Seger (2011) and Fischl et al. (2004). The selected ROIs included the middle frontal gyrus, inferior frontal sulcus, and superior frontal sulcus. In addition to cortical ROIs, subcortical ROI masks for the caudate, putamen, and thalamus were extracted for each hemisphere.

Tractography. All fiber tracking was performed using DSIStudio (http://dsi-studio.labsolver.org). Track streamlines for each tract were modeled using a multi-FACT deterministic tractography algorithm with trilinear interpolation of diffusion direction (Basser et al., 2000; Lazar et al., 2003; Yeh, Wedeen, & Tseng, 2010). Fiber tracking was constrained within a brain mask that was produced by applying the FMRIB Software Library (FSL) brain extraction tool (BET) (Smith et al., 2002) to the non-gradient weighted diffusion image (b_0), and, subsequently, an in-house Matlab code to refine misclassified edge voxels (detailed in Presson, Beers, et al., 2015). In order to account for relative signal to noise ratio during scanning, quantitative anisotropy (QA) thresholds were determined for each participant in DSIStudio prior to tractography by expert HDFT tractographers, blinded to group, and therefore differed between subjects. The groups did not differ on assigned threshold values, $F(1, 35) < 1.00$, $p = .474$.

Separate fiber tracking was conducted between the DLPFC ROI and each subcortical ROI mask (i.e., caudate, putamen, thalamus) for the left and right hemispheres separately so that only ipsilateral ECN connections were examined. Using an ODF-streamline ROI-based approach (Yeh, Wedeen, & Tseng, 2010) tracking was initiated using a randomized, whole-brain seed mask approach with randomly assigned initial step direction that enabled maximum detection of cortico-striatal and cortico-thalamic projections. With this approach, each brain voxel was given equal probability of being seeded 25 times (with number of seeds based on total number of brain mask voxels). In this approach, only the fibers that pass through both the DLPFC and the subcortical ROIs were included as part of the tract. Tractography was conducted with the following parameters: step size of 0.5 mm, 60° maximum turning angle, smoothing

weighting of 0.2, and streamline length between 20-100 mm. Once tracked, all streamlines were saved for further quantification and analyses.

Quantification. Tractography metrics were quantified for analysis. Average generalized fractional anisotropy (GFA), quantitative anisotropy (QA), number of tracts (tract count), and tract volume (in mm^3) were calculated for the ECN fiber projections between the DLPFC and each subcortical gray matter ROI, i.e., the caudate (Caudate-DLPFC), putamen (Putamen-DLPFC) and thalamus (Thalamus-DLPFC) in both hemispheres using DSIStudio (Yeh, Wedeen, & Tseng, 2010).

Reliability. The current tractoragraphy approach is considered highly reliable given that the ROI-based approach utilizes ROI masks derived from FreeSurfer, which has strong reliability (Fischl, 2012).

General Statistical Approach

To ensure similarity of groups on demographic, medical, and military variables, group comparisons were conducted using chi-square tests for categorical variables and one-way analysis of variance (ANOVA) for categorical and continuous variables, respectively.

Each study aim was addressed in separate analyses. To determine whether dorsolateral prefrontal cortico-striatal and cortico-thalamic WM pathways of the ECN differed between the veterans with bTBI relative to the comparison veteran group (Aim 1), the effect of Group on quantitative HDFT-derived tract metrics (i.e., GFA, QA, number of tracts, and tract volume) for each of the DLPFC-subcortical fiber tracts (Caudate-DLPFC, Putamen-DLPFC, and Thalamus-DLPFC) was examined using multiple linear regression techniques. A similar approach was used to compare the bTBI

and comparison groups on total SST accuracy and RT performance as part of Aim 2; the effect of Group on (a) Go Accuracy (%) and correct trial RT (Go Correct RT, (b) Go: no response total (Omission Errors), (c) Stop: failed inhibition total (Commission Errors), and (d) Stop signal RT (SSRT) was examined. To evaluate functional correlates of ECN microstructure in the veterans with bTBI and in the comparison group (Aim 2), Spearman's rank correlation coefficients (r_s) were examined between HDFT-derived tract metrics (i.e., GFA, QA, tract count, and volume) and SST outcome variables separately for each group.

Effect sizes were examined and described for each analysis to account for the current sample size. Measures of magnitudes of effects for Aim 1 included R^2, η^2, and η_p^2, respectively, and the squared Spearman rank order correlation coefficient (r_s) was used to assess magnitudes of the structure-function relations for Aim 2. Because criteria for interpreting magnitude of correlation coefficients are somewhat arbitrary and vary depending on the context (Cohen, 1988), the following set of criteria was used to assess effect size in the current study: (a) values < .06 were considered weakly related (i.e., $r_s < |.25|$; small effect), (b) values between .06 and .16 were considered moderately related (i.e., $|.25| < r_s < |.40|$; moderate effect), and (c) values > .16 being considered strongly related (i.e., $r_s > |.40|$; large effect).

Prior to final analyses, preliminary analyses were examined to ensure distribution normality of all primary outcomes was examined and ensured by identifying and subsequently excluding any significant outliers from further analyses. Hemispheric differences were also examined in preliminary analyses using separate 2 (Group)×2 (Hemisphere) mixed model, repeated measures ANOVAs. With the exception of number

of tracts and tract volume for the Putamen-DLPFC [number of tracts: $F(1, 34) = 11.21$, $p = .002$, $\eta_p^2 = .25$; tract volume: $F(1, 35) = 3.35$, $p = .080$, $\eta_p^2 = .08$] and Thalamus-DLPFC [number of tracts: $F(1, 35) = 4.38$, $p = .044$, $\eta_p^2 = .11$; tract volume: $F(1, 35) = 4.26$, $p = .046$, $\eta_p^2 = .109$], none of the Group×Hemisphere interaction terms were statistically significant, ps $\geq .203$. Thus, HDFT metrics were examined for average (across left and right hemisphere) tracts in final analyses, except for separately conducted analyses for left and right hemisphere Putamen-DLPFC and Thalamus-DLPFC tract volume.

Additionally, model covariates were determined and included on the basis of their theoretical and statistical relevance to each specified outcome measure in preliminary models. Effects of Age (i.e., age at the time of assessment), Injury Age (i.e., age at TOI), PTSD Rating (per the PCL-C), and Blunt Injuries (i.e., number of blunt TBIs, including combination blunt/blast injuries) were examined as potential covariates. Covariates with unrelated main effects and/or two-way interaction terms with Group were trimmed from the final models. In the interest of space only the final models are reported below.

RESULTS

Sample Characteristics

Military history and demographic characteristics for the current sample are shown in Table 1. With regards to military history, groups had similar years of active military service and number of combat deployments. There were more Army and US Marine Corps veterans in the bTBI group relative to the comparison group. The bTBI and comparison groups were similar in age at assessment, sex, ethnicity, handedness, and educational attainment. In the comparison group, 8 veterans (53.3%) had histories of

mTBI from various causes, e.g., military training accidents, falls, recreation and sports activities, and motor vehicle accidents. The veterans with bTBI also had histories of blunt mTBI from similar causes and/or from combined blast and blunt injuries. Although the rate of blunt injuries was similar between the groups, bTBI generally occurred at a younger age and more frequently involved LOC at the TOI than the blunt injuries sustained in the comparison group. However, groups were similar on self-reported symptoms of PCS, PTSD or alcohol use/alcohol use disorders.

[Insert Table 1 Here]

Aim 1: Executive Control Network Structure

Descriptive data for HDFT metrics for each of the examined ECN tracts is provided in Table 2. Tractography results are illustrated in Figure 4.

[Insert Table 2 Here]

[Insert Figure 4 Here]

Caudate-DLPFC white matter. Relative to the comparison group, the bTBI group had largely elevated QA and moderately reduced tract volume in the Caudate-DLPFC (averaged across hemispheres), respectively. A strong Group×Age interaction effect on tract volume indicated that age strongly, negatively related to Caudate-DLPFC tract volume in the bTBI group, but not in the comparison group. However, groups had similar Caudate-DLPFC GFA and tract count.

The overall model for QA included the predictor Group, $F(1, 34) = 6.51$, $p = .015$, $R^2 = .16$. A large Group effect indicated that QA was elevated in the bTBI group relative to the comparison group, $B = -.02$, $\eta^2 = .16$.

For Caudate-DLPFC tract volume, the overall model included the predictor Group, the covariate Age, and the two-way Group×Age interaction, $F(3, 33) = 2.56$, $p = .072$, $R^2 = .19$. A moderate Group effect, $B = -28356.53$, $p = .022$, $\eta_p^2 = .15$, indicated that tract volume was reduced in the bTBI group relative to the comparison group, controlling for the minimal effect of Age, $B = -133.53$, $p = .407$, $\eta_p^2 = .02$. There was a large Group×Age interaction effect on Caudate-DLPFC tract volume, $B = 829.32$, $p = .014$, $\eta_p^2 = .17$. Follow-up analyses indicated a strong, negative relation between Age and Caudate-DLPFC tract volume in the bTBI group, $r_s = -.51$, $p = .016$, but not the comparison group, $r_s = .33$, $p = .227$.

The overall model for GFA, $F(1, 33) < 1.00$, $p = .608$, $R^2 = .01$, and tract count, $F(1, 34) < 1.00$, $p = .856$, $R^2 < .01$, with predictor Group, indicated minimal effect of Group.

Putamen-DLPFC white matter. Relative to the comparison group, the bTBI group had moderately elevated GFA and QA (averaged across hemispheres) and largely reduced tract count and volume in the right hemisphere Putamen-DLPFC. However, groups had similar left Putamen-DLPFC tract count and volume.

The overall model for Putamen-DLPFC GFA included the predictor Group and the covariate Age, $F(2, 32) = 4.15$, $p = .025$, $R^2 = .21$. A moderate Group effect, $B = -.003$, $p = .056$, $\eta_p^2 = .11$, indicated that GFA was elevated in the bTBI group relative to the comparison group, controlling for the effect of Age. A moderate Age effect, $B = -.0002$, $p = .046$, $\eta_p^2 = .12$, indicated that age negatively related to GFA, across Group.

The overall model for Putamen-DLPFC QA included the predictor Group, $F(1, 35) = 4.46$, $p = .042$, $R^2 = .11$. A moderate Group effect indicated that QA was elevated in the group with bTBI relative to the comparison group, $B = -.029$, $\eta^2 = .11$.

Separate models for left and right hemisphere Putamen-DLPFC tract count and tract volume were examined to account for significant Group×Hemisphere interaction effects (see preliminary analyses). The overall models for left hemisphere Putamen-DLPFC tract count, $F(1, 34) = 1.74$, $p = .196$, $R^2 = .05$, and tract volume, $F(1, 35) < 2.00$, $p = .682$, $R^2 = .01$, with predictor Group, indicated minimal effect of Group.

The overall model for right Putamen-DLPFC tract count included the predictor Group and the covariate Blunt Injuries, $F(2, 34) = 10.75$, $p < .001$, $R^2 = .39$. A large Group effect, $B = 567.34$, $p = .002$, $\eta_p^2 = .25$, indicated that right hemisphere tract count was reduced in the bTBI group relative the comparison group, controlling for the effect of Blunt Injuries. A large Blunt Injuries effect, $B = 82.05$, $p = .001$, $\eta_p^2 = .28$, indicated that number of blunt injuries positively related to tract count, across Group.

The overall model for right hemisphere Putamen-DLPFC tract volume included the predictor Group and the covariate Blunt Injuries, $F(2, 34) = 4.73$, $p = .015$, $R^2 = .22$. A large Group effect, $B = 5467.83$, $p = .012$, $\eta_p^2 = .17$, indicated reduced right hemisphere tract volume in the bTBI group relative to the comparison group, controlling for the effect of Blunt Injuries. A moderate Blunt Injuries effect, $B = 535.37$, $p = .059$, $\eta_p^2 = .10$, indicated that number of blunt injuries positively related to tract volume, across Group.

Thalamus-DLPFC white matter. Relative to the comparison group, the bTBI group had moderately elevated QA (averaged across hemispheres) and moderately

reduced right hemisphere tract count in the Thalamus-DLPFC. However, groups had similar Thalamus-DLPFC GFA (averaged across hemispheres), left hemisphere tract count and volume, and right hemisphere tract volume.

The overall model for Thalamus-DLPFC QA included the predictor Group, $F(1, 35) = 5.42$, $p = .026$, $R^2 = .13$. A moderate Group effect indicated that QA was elevated in the bTBI group relative to the comparison group, $B = -.024$, $\eta^2 = .13$.

The overall model for Thalamus-DLPFC GFA, with predictor Group, $F(1, 35) = 1.03$, $p = .318$, $R^2 = .03$, indicated minimal effect of Group.

Separate models for left and right hemisphere Thalamus-DLPFC tract count and tract volume were examined to account for significant Group×Hemisphere interaction effects (see preliminary analyses). The overall models for left hemisphere tract count, $F(1, 35) < 1.00$, $p = .461$, $R^2 = .02$, and volume, $F(1, 35) < 1.00$, $p = .571$, $R^2 = .01$, with predictor Group, indicated minimal effect of Group.

The overall model for right hemisphere Thalamus-DLPFC tract count included the predictor Group, $F(1, 35) = 3.09$, $p = .087$, $R^2 = .08$. A moderate Group effect indicated that tract count was reduced in the group with bTBI relative to the comparison group, $B = 346.32$, $\eta^2 = .08$.

The overall model for right hemisphere Thalamus-DLPFC tract volume included the predictor Group, $F(1, 35) = 2.11$, $p = .155$, $R^2 = .06$. A moderate Group effect indicated that tract volume was reduced in the group with bTBI relative to the comparison group, $B = 3514.28$, $\eta^2 = .06$.

Aim 2: Executive Control Network Function

Stop Signal Task performance. Average accuracy and RT performance for each of the four SST trials are presented in Table 3. SST performance was generally similar between the groups. For Go Accuracy, only 5 (23.8%) veterans in the bTBI group and 4 (26.7%) veterans in the comparison group had less than perfect (i.e., < 100% accuracy) performance during Go trials, and veterans in both groups had accuracy scores of at least 94%. Relatedly, only 4 of the veterans in the bTBI (19.0%) and comparison (26.7%) groups had errors of omission (failed to provide a response during Go trials).

[Insert Table 3 Here]

Relations between HDFT metrics and Stop Signal Task performance. Spearman rank correlation coefficients (r_s) were used to examine relations among HDFT-derived metrics and SST task performance, and are presented separately for each group in Table 4. Given that RI is predominantly lateralized to the right ECN (Chambers, Garavan, & Bellgrove, 2009; McNab et al., 2008; E. K. Miller & Cohen, 2001; Rubia et al., 2010; Rubia et al., 2001; Sebastian et al., 2013; Swick, Ashley, & Turken, 2011), functional correlates of Putamen- and Thalamus-DLPFC tract count and volume, for which hemispheric differences of HDFT metrics were observed, were only examined in the right hemisphere. Given that restricted range of Go Accuracy and Omission Errors scores (see above), neural correlates of these outcome were not examined in the between-Group correlation analyses. In the interest of space, only relations considered to be robust, i.e., those with large effect sizes (i.e., $r_s > |.40|$), are discussed below.

[Insert Table 4 Here]

Contrary to expectations, none of the HDFT metrics in the ECN pathways robustly correlated with SST performance variables in the bTBI group. However, as shown in Table 4, robust brain-behavior correlations were observed in the comparison group. Specifically, Go Correct RT strongly, positively correlated with Caudate-DLPFC QA; strongly, negatively correlated with Caudate-DLPFC and Thalamus-DLPFC tract count; and strongly, negatively correlated with tract volume in all of the ECN pathways. SSRT strongly, negatively correlated with Putamen-DLPFC and Thalamus-DLPFC tract count. Commission Errors strongly, negatively correlated with Caudate-DLPFC and Putamen-DLPFC QA.

As expected, these results indicated slower correct go trial responses with higher Caudate-DLPFC tract QA and with lower tract count and volume in the DLPFC-subcortical pathways, respectively, in the comparison group. Whereas slower response inhibition was associated with lower Putamen-DLPFC and Thalamus-DLPFC tract count, less accurate response inhibition performance was associated with lower Caudate-DLPFC and Putamen-DLPFC tract QA in the comparison group.

DISCUSSION

Blast-induced TBI is common among Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND) war veterans (Maas et al., 2010; Owens et al., 2008). Although neuropsychological and functional neuroimaging findings support particular susceptibility of ECN substrates to the deleterious effects of bTBI (e.g., Bailie et al., 2016; Fischer et al., 2014; Mayer et al., 2015; McDonald et al., 2002; Newsome et al., 2015; O'Neil et al., 2013; Scheibel et al., 2012; Spielberg et al., 2015), limitations of traditional structural neuroimaging techniques (Verstynen, Badre,

Jarbo, & Schneider, 2012) restricted comprehensive understanding of whether structural alterations occurred in this network in bTBI. The current retrospective, dual cohort study of male veterans with and without histories of bTBI from primary blast exposure utilized HDFT to investigate whether bTBI disrupted the structure and/or associated functional correlates of specific DLPFC-subcortical WM pathways of the ECN. Structure and function of the ECN were respectively assessed through HDFT image acquisition and fiber reconstruction and a standardized paradigm of RI, the Stop Signal Task (SST).

High Definition Fiber Tracking

HDFT is a relatively novel approach to advanced diffusion MRI data acquisition and analysis that enables *in vivo* examination of brain tissue through tractography based on anatomically precise spatial anisotropy and fiber volume estimates (i.e., tract count and volume) and volume. QA is a density-based measure representing the quantity of anisotropic spins diffusing along a fiber orientation (Yeh, Verstynan, et al., 2013). This relatively novel metric defines each fiber orientation on the basis of peak orientations on a spin distribution function (SDF), which is the density of diffusing water at different directions, of water diffusion calculated during HDFT data reconstruction (Fernandez-Miranda et al., 2012). Unlike QA, GFA provides a voxel-based measure of the rate of water diffusion and is related to fractional anisotropy (FA) and other tensor-derived metrics of diffusivity (Tuch, 2004). The use of QA as a termination index as opposed to GFA during fiber tracking improves spatial resolution and increases anatomical accuracy of deterministic tractography approaches like HDFT (Yeh, Verstynan, et al., 2013). This likely reflects the greater tolerance of QA to partial volume effects from various sources such as crossing fibers compared to GFA (Yeh et al., 2013).

Aim 1: Executive Control Network Structure

As expected, bTBI was associated with altered WM in the examined DPFC-subcortical pathways of the ECN. The most consistent findings across tracts were moderately to largely elevated QA and reduced tract volume in the veterans with bTBI relative to the comparison veteran group, respectively. Number of fibers in the right hemisphere DLPFC-putamen and -thalamus projections also differed between groups, with moderate reductions observed in the veterans with bTBI. GFA was moderately elevated in the bTBI group, although this was only observed in the DLPFC-putamen pathway (averaged across hemispheres). It is noteworthy that these moderate to large group differences were not accounted for by factors related to sociodemographic and military background as well as symptoms of PCS and alcohol use/abuse, and persisted above the effects of assessment age, number of blunt head injuries (acquired in isolation and in combination with blast), and PTSD. Results maintain susceptibility of thalamic (Tang et al., 2011; Zhou et al., 2014) and striatal (Shumskaya, Andriessen, Norris, & Vos, 2012) nuclei structure and network connectivity to the deleterious effects of DAI. Specific to bTBI is that functional connectivity of fronto-striatal (Davenport, Lim, & Sponheim, 2015; Newsome et al., 2015; Fischer et al., 2014; Spielberg, McGlinchey, Milberg, & Salat, 2015; Vakhtin et al., 2013) and fronto-thalamic (Zhou et al., 2014) networks are reduced in veterans with bTBI compared to controls.

In line with initial HDFT findings in both civilians (Presson, Krishnaswamy, et al., 2015) and veterans (Presson, Beers, et al., 2015) with TBI, tract QA, count and volume more robustly differed across ECN pathways in the veterans with bTBI relative to the comparison group, whereas moderate GFA differences were only observed in the

projection fibers of the DLPFC-putamen tract. Anomalies in multiple HDFT metrics may reflect different aspects of tract damage subsequent to bTBI. Limited research has suggested that measures of diffusivity such as GFA show sensitivity to WM structural integrity, whereas density metrics (i.e., QA, volume, count) show greater sensitivity to inter-individual physiological heterogeneity and characteristics of density such as fiber compactness (Yeh, Vettel, et al., 2016). Thus, overall results support generally anomalous connectivity (i.e., elevated QA; reduced tract count and volume) and integrity (i.e., elevated GFA) of DLPFC-subcortical WM pathways of the ECN in bTBI. In WM disease (e.g., amyotrophic lateral sclerosis), the observed pattern of increased QA in the presence of reduced tract volume in the veterans with bTBI has been interpreted as an indication of functional compensatory mechanisms of spared fibers (e.g., Abhinav et al., 2014). However, it is important to consider the complexity of relations among discrete metrics and neuropathology. Though unknown, it is unlikely that individual HDFT-derived metrics measure isolated pathologies.

The veterans with bTBI evinced particularly disrupted (i.e., reduced tract count and volume) DLPFC-putamen and -thalamus pathways that was lateralized to the right hemisphere. Concordant findings in the bTBI literature (Taber et al., 2015) as well as in the more general literature in mTBI indicate heightened vulnerability of the right hemisphere to the effects of TBI (e.g., Narayama et al., 2015; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008). In mTBI, hemispheric asymmetry has been attributed to greater right hemisphere susceptibility to biomechanical forces of head injury due to reduced density of axonal branches compared to the left hemisphere (Klingberg et al., 1999; Narayana et

al., 2015). There is also support for heightened involvement of the right prefrontal cortex and striatum in bTBI. Whole-brain magnetic transfer imaging (MTI) analysis indicated reduced macromolecular proton fraction in the right hemisphere WM of the external capsule and anterior limb of the internal capsule as well as in subgyral WM of the right precentral, superior and middle frontal gyri in bTBI (Petrie et al., 2014). Although not directly examined, respective proximity of reported disruptions to the putamen and subcortical WM of the DLPFC supports likely involvement of these structures, especially in the right hemisphere. Taber, et al. (2015) reported altered anisotropy (i.e., FA) in the radiations of the right anterior thalamic nucleus in post-deployed war veterans with histories of blast exposure that did not result in diagnosed or suspected bTBI; a pattern that was not observed in the left hemisphere (Taber et al., 2015). However, whether the current neuroimaging findings represent neuropathological disruption of axonal composition remains to be determined, particularly concerning the DLPFC-putamen and -thalamus tracts.

Interactive effects between age and bTBI on volumetric abnormalities in the DLPFC-caudate tract was expected. In a cross-sectional study, Trotter et al. (2015) similarly indicated negative age-related neural microstructural trajectories subsequent to bTBI that was worse in older military veterans and service members than in younger personnel and especially subsequent to repetitive exposure (Trotter, Robinson, Milberg, McGlinchey, & Salat, 2015). Risk of neurodegenerative disease is also elevated by extensive concussion histories in civilians, athletes, and veterans (McKee et al., 2010; Omalu, Bailes, et al., 2011; Omalu, Hammers, et al., 2011; Sivak et al., 2016) Microstructural alterations occur with normal aging as the result of degenerative

processes (Kalaria, 2010). Neuronal and axonal degeneration can result from lost connectivity due to myelin sheath degradation that can cause apoptosis in cells that do not regenerate or, when regeneration does occur, thinner myelin sheaths with aging (Peters, 2009). Degeneration of the vascular system also influences brain tissue and function (Kalaria, 2010). Although the specific mechanism(s) by which blast force induces central nervous system disruption is being debated, deleterious effects on neuronal and axonal structure as well as on cerebral vasculature are supported (as detailed in: Hicks et al., 2010). Vulnerability of caudate structure and function to bTBI is also consistently supported in neuroimaging studies (Davenport et al., 2015; Newsome et al., 2015; Fischer et al., 2014; Spielberg, McGlinchey, Milberg, & Salat, 2015). This may result from the proximity of this structure to the ventricles given the likeliness that shear strain disrupts periventricular tissue, although the extent of brain deformation in bTBI is still under investigation (Hicks et al., 2010). Nonetheless, current results maintain caudate involvement in bTBI and further implies that the resultant disruption is potentially worsened in older age as the result of the degenerative processes of normal aging.

Current findings of elevated GFA in the DLPFC-putamen pathway fibers was somewhat surprising since reduced FA is the most prevalent DTI finding in service members and veterans with chronic bTBI (e.g., Bazarian et al., 2013; Davenport et al., 2012; Jorge et al., 2012; Mac Donald et al., 2013) and is negatively correlated with time since injury independent of age and symptoms of PTSD (Trotter et al., 2015). In brain tissue, FA values are highest in WM as the result of the myelin sheath, which restricts water diffusion to a single direction, reflecting the cylindrical orientation of axons (Song et al., 2003), and are lowest in cerebrospinal fluid. Consistent with this theory, reduced

FA values in WM has been used as an indicator of axonal and myelin degradation (Beaulieu, Does, Snyder, & Allen, 1996). However, in line with current results, increased FA is observed in patients with mTBI from other mechanisms, especially during acute and subacute stages of injury (e.g., Mayer et al., 2010; Henry et al., 2011). This has led some investigators to conclude that increased FA reflects initial axonal swelling with DAI (see Shenton et al., 2012). Sports-related concussion is particularly associated with elevated FA (Bazarian et al., 2011). Bazarian et al. (2011) observed both increases and decreases in FA in athletes with repetitive concussive and subconcussive blows to the head that directly related to injury severity, i.e., whether injury resulted in a concussion or was subconcussive. In this population, Kou et al. (2009) suggested that decreased FA may represent vasogenic edema, which likely resolves, whereas increased FA could reflect cytotoxic edema, or axonal swelling that results in more restricted water diffusion (Song et al., 2003). Similar neuroinflammatory responses are observed in preclinical rodent models of bTBI, which indicate widespread activation of microglia in white and gray matter (Kaur, Singh, Lim, Ng, Yap, & Ling, 1995) in addition to neuronal, axonal, and glial disruption (Bauman et al., 2009). As previously stated, however, current understanding is limited by the relative novelty of HDFT as a diffusion MRI data acquisition and analysis technique.

Achieving cohesive understanding of how, specifically, blast exposure disrupts cerebral WM is further challenged by methodological differences across studies in the published literature. For example, participant inclusion criteria (e.g., Bazarian et al., 2013; Davenport et al., 2012; Hayes et al., 2015; Jorge et al., 2012; Mac Donald et al., 2011; Maksimovskiy et al., 2014; Matthews et al., 2011; D. R. Miller et al., 2016; Morey

et al., 2013) has substantially differed across studies. Although most studies have only examined mTBI, some have included the full range injury severities (Trotter et al., 2015; Yurgelun-Todd et al., 2011; Levin et al., 2010; Yurgelun-Todd et al., 2011). Mechanism of injury is heterogeneous across studies with some including only bTBI (e.g., Adam et al., 2015; Davenport et al., 2012; Davenport et al., 2015; Hayes et al., 2015; Jorge et al., 2012; Levin et al., 2010; Mac Donald et al., 2013; Mac Donald et al., 2011; Matthews et al., 2011; D. R. Miller et al., 2016; Taber et al., 2015) and others including mTBI from various injury mechanisms (Bazarian et al., 2013; Isaac et al., 2015; Lopez-Larson et al., 2013; Trotter et al., 2015; Maksimovskiy et al., 2014; Yurgelun-Todd et al., 2011; Morey et al., 2013). Of the studies that were specific to blast exposure, some only included participants with histories of exposure to blast within 100 m (Hayes et al., 2015; D. R. Miller et al., 2016), or to patients with injuries sustained during deployment (e.g., Hayes et al., 2015) or during combat (Adam et al., 2015; Matthews et al., 2011). Similarly, studies of chronic military-related mTBI patients have greatly varied in assessment periods from those including assessments as early as 6 months since TOI (Mac Donald et al., 2011), to those including later assessments as late as 4 (Jorge et al., 2012; Mac Donald et al., 2013) and 5 (Davenport et al., 2015) years since TOI. Comparison groups also varied wildly across studies (e.g., Hayes et al., 2015; Mac Donald et al., 2013; D. R. Miller et al., 2016; Lopez-Larson et al., 2013; Morey et al., 2013; Yurgelun-Todd et al., 2011; Davenport et al., 2012; Jorge et al., 2012; Bazarian et al., 2013; Davenport et al., 2012; Davenport et al., 2015; Maksimovskiy et al., 2014; Taber et al., 2015; Trotter et al., 2015), and not all studies have included comparison groups (e.g., Isaac et al., 2015; Matthews et al., 2011).

Aim 2: Executive Control Network Function

The functional significance of observed ECN WM pathway alterations was examined in the second study aim. RI was investigated given the frequency of complaints and observed executive control deficits in this population (Mayer, Bellgowan, & Hanlon, 2015; McDonald, Flashman, & Saykin, 2002). However, veterans with bTBI and the veterans in the comparison group performed similarly on the Stop Signal Task in the current study. Although this is the first study to specifically examine RI utilizing this task, differences were expected given documented deficits across executive function domains (O'Neil et al., 2014). It is possible that the included, conservative comparison group minimized between-group differences. The current comparison group comprised veterans both with and without histories of mTBI from non-blast mechanisms who had similar demographic and medical (i.e., injury severity and symptoms) characteristics, military and combat deployment history, as well as severity and symptoms of alcohol use/abuse and PTSD. Other studies that examined response inhibition reported subtle impairments in veterans with bTBI compared to civilian mTBI, which is also associated with poorer performance, as well as veteran and civilian control groups (Verfaellie, Lafleche, Spiro, & Bousquet, 2014; DeHaan et al., 2007). During Stop Signal Task performance, Shu and colleagues (2014) observed greater response-inhibition-specific functional alterations (i.e., event-related potentials [ERP]) in veterans with comorbid mTBI and PTSD compared to mTBI without PTSD that was particularly evidenced in the dorsal anterior cingulate. Behavioral findings also support impaired response inhibition during a go/no-go task in veterans with PTSD, regardless of mTBI history (Shu, O'Connell, Simmons, & Matthews, 2014). Thus, the null results for group differences on

inhibitory control in the current study could be attributable to the similarity of PTSD symptoms and severity. It is also possible that bTBI does not result in frank RI impairments per se, but may occur secondary to deficits in other cognitive domains like attention, processing speed, and working memory, which can also be affected by PTSD (Verfaellie, Lafleche, Spiro, & Bousquet, 2014; Adam et al., 2015; Cernich, Reeves, Sun, & Bleiberg, 2007). Continuing to investigate the modal neuropsychological profile of bTBI could be beneficial.

Contrary to expectations, none of the HDFT metrics in the ECN pathways robustly correlated with SST performance in the bTBI group. This was unexpected given previous results. For example, Taber et al. (2015) observed relations among FA (voxel clusters) and tests of executive function (e.g., set-shifting) and simple reaction time that existed above the effects of psychiatric comorbidity and demographic characteristics in veterans with bTBI (Taber et al., 2015). Levin et al. (2010) also indicated relations among FA and ADC values and verbal learning and memory and nonverbal learning, and aspects of executive control in veterans (Levin et al., 2010). As expected, however, strong (i.e., large effect size) ECN structure-function relations were observed in the comparison group. Specifically, faster reaction times for correct go and stop signal trials (i.e., SSRT) corresponded to higher QA and lower tract count and volume in the ECN pathways, respectively; less number of commission errors also related to increased QA in the DLPFC-caudate and -putamen pathways. Thus, increased density (i.e., QA) was associated with more efficient and accurate RI performance, whereas tract connectivity (i.e., tract count and volume) was associated with greater efficiency. The inclusion of veterans with and without histories of mTBI in the comparison group complicates

definitive interpretation of current relations. This is the first study to directly examine the underlying structural deficits that likely contribute to dysfunction of this pathway in mTBI. Inclusion of a healthy veteran control group for normative comparison could potentially clarify the exact nature of this finding.

In line with previous studies of HDFT, quantitative metrics of the spatial properties of fiber tracts derived from HDFT increased detection of WM microstructural abnormalities associated with DAI and neuropsychological deficits in veterans beyond what was captured by estimates of diffusion anisotropy (i.e., GFA) (Presson, Beers, et al., 2015; Presson, Krishnaswamy, et al., 2015). HDFT tractography has confirmed clinical utility in civilian (Presson, Krishnaswamy, et al., 2015) as well as in veteran and military-related TBI (Presson, Beers, et al., 2015). HDFT can sensitively detect small, specific WM fiber alterations that are caused by TBI in heterogeneous brain regions intra-individually (Shin et al., 2012). Although preliminary findings included patients across a range of injury severities, results indicated that specific metrics related to spatial properties of WM tracts can be derived from HDFT (i.e., tract spread and homologue asymmetry), and provide better indices of specific microstructural abnormalities and neuropsychological deficits in patients with TBI than conventional anisotropy metrics (Presson, Beers, et al., 2015; Presson, Krishnaswamy, et al., 2015). Current results that spatial tract-based metrics were more sensitive to aberrant WM microstructure and more robustly correlated with neuropsychological performance than GFA values supports the benefits of utilizing this approach and further suggests that HDFT can distinguish among different injury mechanisms of mTBI in veterans.

Limitations

Data related to primary blast and blunt mTBI was based on retrospective self-report, which could have influenced data reliability. This may be particularly the case for variables related to events where polytrauma could be reasonably suspected, including prior history of head injury and exposure to blast, as well as to characteristics of the injury mechanisms, e.g., blast proximity and loading, and injury outcomes such as the presence and/or duration of LOC, AOC and/or PTA. This illustrates the need for prospective and longitudinal studies of bTBI, which could promote greater understanding of how specifically this mechanism disrupts neural tissue.

The biomechanics of blast are complex and can be exacerbated by dynamic environmental and contextual variables (see Connolly & Clutter 2010). The current sample of veterans typically incurred bTBI due to IED detonation while in a vehicle. There was great inter-individual variability in vehicle type (i.e., unarmored or armored vehicle), location within the vehicle, and gear worn at the TOI that could have potentially influenced outcomes. Future work is greatly needed to determine the influence of these factors on blast-induced neuropathology. In addition, bTBI rarely results from isolated effects of primary blast exposure (for further review see Hicks et al., 2010). Blast-related concussion (i.e., bTBI) is acquired as the result of blast exposure alone or in combination with other head trauma, including blunt injuries (for further review see Helmick et al., 2015). The current retrospective study sought to account for co-occuring bTBI and bunt injury effects through the inclusion of a comparison group of veterans with similar histories of mTBI from blunt force. However, it is likely that biomechanical forces of blast and non-blast mechanisms varied both within and between the groups.

Many of the veterans with bTBI had histories of repetitive exposure to blast, incurred across several deployments and/or within a single deployment. Repetitive exposure may exacerbate outcomes in this population. Accumulating evidence supports greater risk of progressive forms of encephalopathy, termed chronic traumatic encephalopathy (CTE), subsequent to repetitive head injuries from concussive and subconcussive insults, including blast (McKee et al., 2010; Omalu, Bailes, et al., 2011; Omalu, Hammers, et al., 2011; Sivak et al., 2016). Results suggest that prolonged effects of DAI may be synergistically exacerbated by repetitive injuries. Although the current sample size limited our ability to examine interactive effects of repetitive blast exposure, future research into the effects of repetitive compared to single bTBI could potentially benefit general understanding of this injury mechanism.

Conclusions and Future Directions

Current findings underscore currently limited understanding of the highly complex, dynamic pathophysiological mechanisms of bTBI. Although pathology of DAI, or the cascade of deleterious effects that propagate neuronal, axonal and astroglial disruption in mTBI, can persist in bTBI (Mac Donald et al., 2017; MacFarlane & Glenn, 2015), mechanism-specific effects of blast on brain tissue remains largely unknown. As reviewed in Hicks et al. (2010), proposed means of primary blast transduction include (a) direct transcranial propagation, (b) the vascular system, including through disruption of the blood brain barrier, and (c) cerebrospinal fluid in the spinal cord to the foraman magnum. However, support for each hypothesis has been variable. Understanding of the pathophysiology of bTBI has proven complicated. Highly heterogeneous outcomes are reported, and although blast is considered a distinct injury mechanism of closed head

TBI, especially mTBI, the neuropathological consequences show substantial overlap with other injury mechanisms.

The HDFT metrics were sensitive to altered DLPFC-subcortical WM of the ECN in bTBI. Although all pathways exhibited increased WM density, results provided further evidence of susceptibility of putamen and thalamus connectivity to the deleterious effects of bTBI. Susceptibility of the caudate was supported by current results, which also indicated that consequent alterations induced by blast force may be additionally influenced by neural changes related to aging. However, the underlying neuropathology of these alterations in bTBI is unknown. This is somewhat attributable to the relative novelty of HDFT as an approach to quantification of WM integrity, as well as to the generally limited understanding of specific pathology in bTBI. Results highlight how future research in both areas could be beneficial.

The SST may have provided a limited evaluation of the ECN. Identifying the modal neurocognitive profile of bTBI through assessment using a broader number of measures, across greater number of cognitive domains is warranted and should be emphasized as gained understanding could have clinical and prognostic utility. Although unrelated to aspects of RI performance in the group of veterans with bTBI, density (i.e., increased QA; reduced tract count and volume) related to more efficient and accurate RI performance in the comparison group. Evidence of generally intact RI performance in light of reduced WM integrity could support functional compensation processes in bTBI, particularly since the pattern of observed ECN structural alterations of increased QA with decreased volume was previously interpreted being indicative of functional compensation of spared fibers in patients with white matter degeneration (e.g., Abhinav et al., 2014).

Finally, the study was retrospective and cross-sectional. There is a strong need for longitudinal neuroimaging studies of acute and chronic bTBI. In more traditional studies of TBI outcomes, important results have emerged from studies that track patients from the acute stage and provide long-term follow-ups (e.g., Mac Donald et al., 2015). Such studies would be especially useful for bTBI. Sampling should begin with exposure and recruit participants irrespective of initial effects based on exposure. Such a framework, coupled with neuropsychological and neuroimaging investigations, would illuminate the effects of bTBI in this critical population.

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Table 1

Descriptive Data for the Current Sample

	Group		Statistical Results	
	Blast TBI (n = 23)	Comparison (n = 15)	Statistic	p-value
Military Branch (N [%])			$x^2(3) = 8.74$	.033
Army	16 (69.6)	8 (53.3)		
Navy	1 (4.3)	4 (26.7)		
Air Force	0 (0)	2 (13.3)		
Marines	6 (26.1)	1 (6.7)		
Years in Military (M [SD])	8.52 (4.95)	10.07 (7.31)	$F(1, 36) < 1.00$	.442
Number of Combat Deployments (M [SD])	1.91 (1.16)	1.4 (0.91)	$F(1, 36) = 2.08$	.158
Age (M [SD])	35.78 (6.77)	36.47 (9.02)	$F(1, 36) < 1.00$	.791
Sex (N [% Male])	23 (100)	15 (100)	-	-
Ethnicity (N [% Hispanic])	8 (34.8)	4 (26.7)	$x^2(2) < 1.00$	.599
Handedness (N [% Right])	18 (78.3)	10 (66.7)	x^2 (2) = 1.05	.592
Years of Education (M [SD])	14.35 (1.43)	14.40 (1.50)	$F(1, 36) < 1.00$	.915
Age at Time of Injury (M [SD])	25.39 (5.30)	29.70 (6.83)	$F(1, 31) = 3.87$	.058
LOC (N [% Positive])	16 (69.6)	4 (26.7)	x^2 (2) = 6.75	.034
Total Number of Blunt Injuries (M [SD])	1.82 (2.8)	1.82 (1.17)	$F(1, 26) < 1.00$	.995
Alcohol Use Rating Score (M [SD])	6.82 (6.63)	6.40 (7.78)	$F(1, 36) < .031$	.862
PTSD Rating Score (M [SD])	54.30 (16.98)	47.93 (22.03)	$F(1, 36) < 1.00$	.322
PCS Rating Score (M [SD])	29.65 (13.17)	23.27 (17.37)	$F(1, 36) = 1.66$	.206

Note. LOC = loss of consciousness; PCS = post-concussive syndrome; PTSD = post-traumatic stress disorder.

Table 2

HDFT Diffusion Metrics of Executive Control Network Cortical-Subcortical White Matter Pathways

Metric	Hemisphere	Group		Statistical Results	
		Blast TBI	Comparison	Effect of Group	Pairwise
		M (*SD*)	*M* (*SD*)		
GFA					
Caudate-DLPFC	Average	.077 (.004)	.076 (.004)	-	-
	Right	.077 (.006)	.076 (.004)		
	Left	.076 (.004)	.074 (.005)		
Putamen-DLPFC^{+}	Average	.085 (.004)	.082 (.006)	Moderate	Blast TBI > Comparison
	Right	.083 (.007)	.081 (.008)		
	Left	.084 (.005)	.081 (.006)		
Thalamus-DLPFC	Average	.086 (.006)	.084 (.008)	-	-
	Right	.087 (.006)	.084 (.009)		
	Left	.086 (.007)	.085 (.007)		
QA					
Caudate-DLPFC	**Average**	**.184 (.029)**	**.162 (.018)**	**Large**	**Blast TBI > Comparison**
	Right	.181 (.031)	.160 (.017)		
	Left	.188 (.030)	.164 (.021)		
Putamen-DLPFC	Average	.212 (.046)	.183 (.032)	Moderate	Blast TBI > Comparison
	Right	.206 (.046)	.181 (.029)		
	Left	.218 (.048)	.186 (.036)		
Thalamus-DLPFC	Average	.205 (.034)	.181 (.026)	Moderate	Blast TBI > Comparison
	Right	.204 (.040)	.175 (.027)		
	Left	.206 (.035)	.187 (.027)		

Tract Count					
Caudate-DLPFC	Average	1303.73 (994.53)	1365.54 (981.79)	-	-
	Right	1195.18 (1114.28)	1457.80 (1294.37)		
	Left	1412.27 (1084.46)	1239.29 (738.13)		
Putamen-DLPFC	**Right**	**514.68 (505.98)**	**982.07 (661.83)**	**Large**	**Blast TBI < Comparison**
	Left	803.77 (629.91)	553.86 (400.87)	-	-
Thalamus-DLPFC	Right	645.68 (514.62)	992.00 (683.45)	Moderate	Blast TBI < Comparison
	Left	864.86 (321.95)	773.00 (427.42)	-	-
Tract Volume					
Caudate-DLPFC	Average	22469.97 (7439.05)	24149.86 (8249.47)	Moderate	Blast TBI < Comparison
	Right	20718.54 (8400.84)	22732.31 (9879.27)		
	Left	24221.40 (7323.04)	25567.42 (8453.44)		
Putamen-DLPFC	**Right**	**13397.20 (5298.15)**	**18212.85 (7522.49)**	**Large**	**Blast TBI < Comparison**
	Left	17868.15 (4911.23)	18657.35 (6712.96)	-	-
Thalamus-DLPFC	Right	21897.01 (7313.91)	25411.29 (7075.43)	Moderate	Blast TBI < Comparison
	Left	25869.53 (3847.70)	24980.55 (5624.99)	-	-

Note. Large effect sizes are boldface. Tract volume reported in mm^3. The overall model for Caudate-DLPFC tract volume included the covariate Age and the two-way Group×Age interaction term; the overall model for Putamen-DLPFC GFA included the covariate Age; the overall model for right Putamen-DLPFC tract count included the covariate Blunt Injuries; the overall model for right Putamen-DLPFC tract volume included the covariate Blunt Injuries. GFA = generalized fractional anisotropy; DLPFC = dorsolateral prefrontal cortex; QA = quantitative anisotropy.

Table 3

Stop Signal Task Performance

Trial Type	Group		Statistical Results		
	Blast TBI	Comparison	$F(1, 34)$ Statistic	Group Effect (R^2)	p-value
	M (*SD*)	*M* (*SD*)			
Go Trials					
Correct Accuracy (%)	99.27 (1.56)	99.41 (1.08)	< 1.00	.003	.754
Correct Reaction Time	688.51 (101.60)	679.61 (134.55)	< 1.00	.002	.822
Omission Errors	0.33 (0.80)	0.80 (2.08)	< 1.00	.025	.353
Stop Trials					
Stop Signal Reaction Time	306.35 (69.89)	282.66 (66.58)	1.76	.030	.314
Commission Errors	10.33 (1.88)	9.6 (2.29)	1.11	.021	.300

Table 4

Spearman Rank Correlation Coefficients between HDFT Diffusion and Stop Signal Task Performance

Group	HDFT Metric	Trial Type		
		Go Correct Reaction Time	Stop Signal Reaction Time	Commission Errors
Blast TBI				
Caudate-DLPFC	GFA	.19	.29	.05
	QA	.09	.22	-.07
	Count	.12	-.09	.30
	Volume	-.03	-.14	-.03
Putamen-DLPFC	GFA	-.14	.24	.24
	QA	-.09	.15	-.16
	Count	-.24	.18	.03
	Volume	-.29	-.01	-.09
Thalamus-DLPFC	GFA	-.29	.33	.18
	QA	-.18	.17	-.02
	Count	-.28	-.12	.07
	Volume	-.19	-.24	-.13
Comparison				
Caudate-DLPFC	GFA	.03	-.17	.17
	QA	**.41**	.12	**-.51**
	Count	**-.51**	-.02	.06
	Volume	**-.61**	.12	.22
Putamen-DLPFC	GFA	.25	-.06	-.30
	QA	.28	.02	**-.46**
	Count	-.39	**-.40**	.04

	Volume	**-.45**	-.25	-.15
Thalamus-DLPFC	GFA	.39	-.11	-.02
	QA	.39	< .01	-.37
	Count	**-.53**	**-.52**	.20
	Volume	**-.43**	-.18	.19

Note. Large effect sizes are boldface. Correlations with the Putamen-DLPFC and Thalamus-DLPFC tract count and volume analyses were conducted for the right hemisphere. GFA = generalized fractional anisotropy; DLPFC = dorsolateral prefrontal cortex; QA = quantitative anisotropy.

Figure 1. Stop Signal Task Stimuli and Instructions.

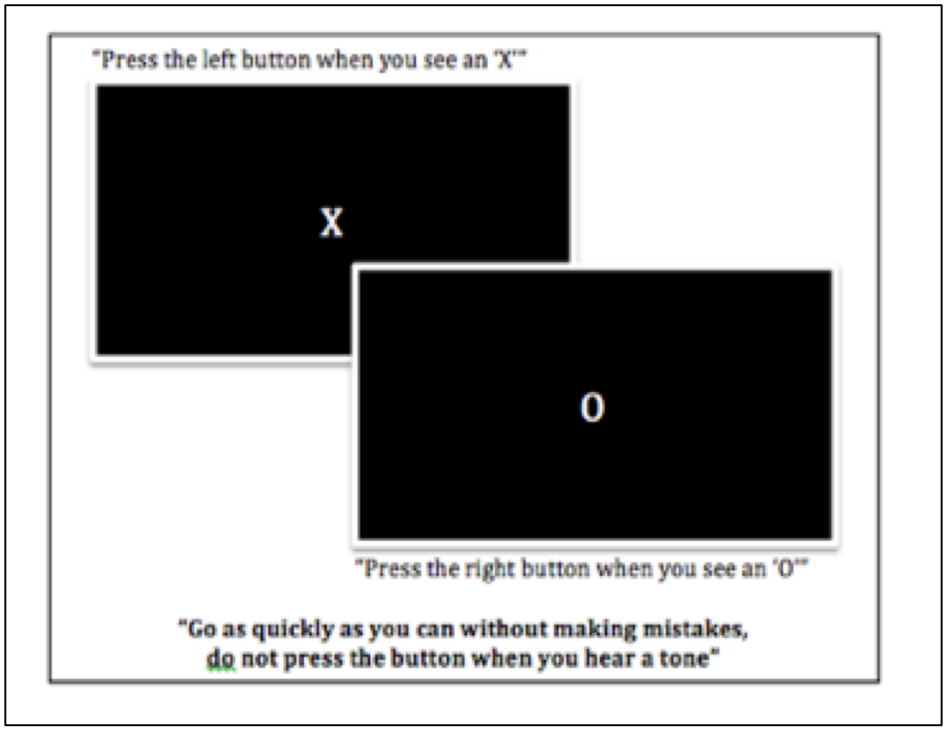
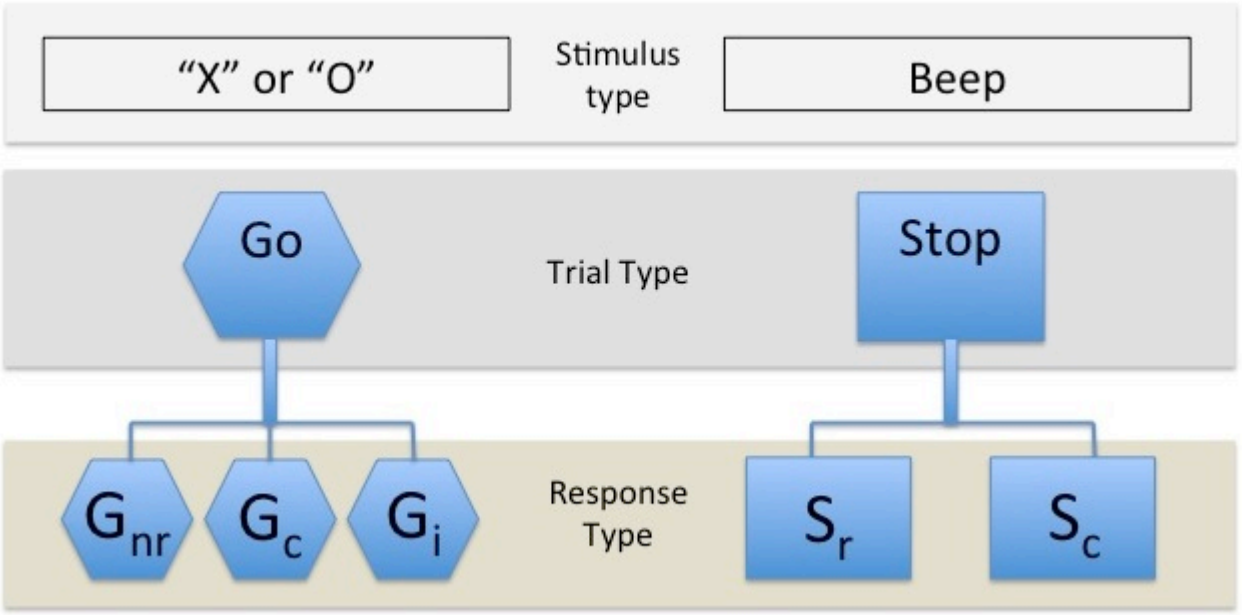
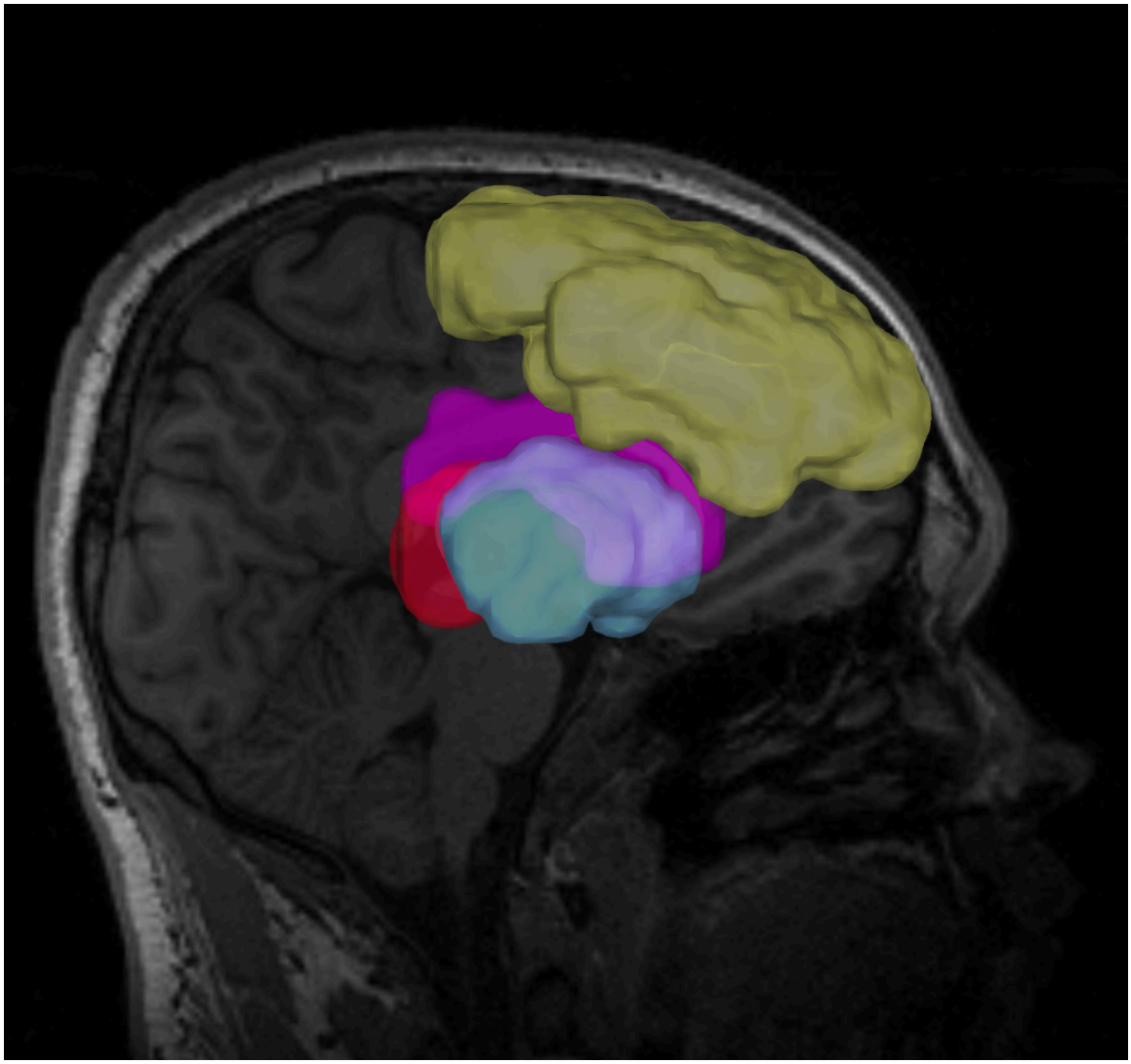


Figure 2. Depiction of Stop Signal Task Outcome Variables.



Note. G_{nr} = no response; G_c = correct response; G_i = incorrect response; S_f = failed inhibit; S_c = correct inhibit.

Figure 3. Example of Gray Matter Masks.



Note. Yellow, dorsolateral prefrontal cortex (DLPFC); purple, caudate; blue, putamen, red, caudate.

Figure 4 Executive Control Network Pathways Between the Dorsolateral Prefrontal Cortex and the Putamen (Blue), Thalamus (Red), and Caudate (Purple).