NEURAL CORRELATES OF ATTENTION AND COGNITIVE PERFORMANCE VARIABILITY FOLLOWING MILD TRAUMATIC BRAIN INJURY IN A MILITARY SAMPLE

by

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DEDICATION

I dedicate this dissertation to my family for their tireless encouragement, and for inspiring my scientific curiosity and passion for helping others. Additionally, I dedicate this dissertation to my friends for lightening the journey with laughter and hugs and for always believing in me, and also to all the other members of the Armed Forces past and present for their dedicated service to our country.

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ABSTRACT

Neural correlates of attention and cognitive performance variability following mild traumatic brain injury in a military sample

Lyn Reinhardt, M.S., 2016

Thesis initiated under the direction of Mark Ettenhofer, Ph.D., Assistant Professor

Thesis completed under the direction of Jeffrey Goodie, Ph.D., Associate Professor, MPS

Traumatic brain injury (TBI) has been recognized as one of the "signature wounds" of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) (Tanielian & Jaycox, 2008; Vanderploeg, Belanger, & Curtiss, 2009) with prevalence rates in OEF/OIF combat veterans around 20% (Hoge et al., 2008; Tanielian & Jaycox, 2008). While the majority of these TBIs are considered to be "mild," cognitive, emotional and physical symptoms may be reported following injury of any severity (Brown et al., 2010). Most patients who have suffered a mild TBI (mTBI) recover within days to weeks. For a small subset of patients symptoms persist and affect quality of life well beyond the acute recovery timeframe. For example, mTBI patients commonly report subjective complaints and subtle objective deficits in attention. Such deficits can impact personal and occupational functional abilities, which may be critical to job performance and military readiness. "Attentional efficiency" is a composite conceptual measure of how consistently the brain is able to engage finite resources for effective decision-making and behavioral responses. As a cognitive processing variable, this "attentional efficiency" construct is hypothesized to play a fundamental role in successful functional outcomes. Due to a

potentially higher neurobehavioral symptom burden following TBI, patients with a history of at least one mTBI may be particularly sensitive to increased task-related attentional demands. Greater knowledge of the neural correlates of altered cognitive performance associated with attention efficiency after mTBI is a critical next research step. These neurobehavioral symptoms following mTBI are currently not well predicted, and the mechanisms of altered cognitive performance are not completely understood (Brown et al., 2010). This research project investigated the impact of brain resource utilization and cognitive performance on attentional efficiency in a sample of active duty military service members. Results are discussed within a framework of neural networks most vulnerable to the impact of mTBI. Consistent with existing literature, differences in brain activation patterns were observed between mTBI patients and controls related to this novel task of visual attention. Study results are grouped into three major categories: the relevance of a unique subgroup of multiple mTBI patients; the importance of distinguishing between the effects of PTSD and mTBI; and the impact of education as a potential moderator. Additionally, study results lend support for use of a novel analysis method in neuroimaging analyses. Findings suggest there are meaningful subgroups within mTBI. Specifically, important differences appear to exist between patients who have experienced multiple mTBIs and those who have experienced a single mTBI or no prior mTBIs. Results also indicate certain neural correlates of behavioral performance-related differences among these groups which may influence later stages in the visual attention process. In particular, the impact of mTBI may be statistically differentiated from the effects of PTSD. This study provides initial support for the utility of advanced analysis methods to better-understand interactions among mTBI and additional biopsychosocial factors which may impact attentional efficiency.

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CHAPTER 1: INTRODUCTION

Traumatic Brain Injury (TBI) has been classified as one of the "signature wounds" of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) (Tanielian & Jaycox, 2008). TBI symptoms may include difficulties with attention and performance of cognitive tasks that can significantly disrupt daily life and impact quality of life both acutely and long-term. There is limited knowledge of how brain structures and networks are specifically impacted by various brain injuries, and how a history of such injuries impacts cognitive functioning. It is critical to improve understanding of the impact of TBI on brain functioning in order to enhance diagnostic capabilities and to inform the development of more effective treatments. The objective of this dissertation is to advance our understanding of the effects of mild TBI (mTBI) on the visual attention network. Ultimately, the purpose of this study is to improve knowledge of brain structures and processes implicated in neurocognitive performance in a military sample of patients who have sustained at least one mTBI.

To contextualize the rationale and aims of the proposed study, a literature review addressing neural correlates of TBI pathophysiology as well as attention and cognitive performance will be presented within a biopsychosocial framework. First, an overview of TBI will be presented including definitions, prevalence, classification, mechanisms of injury, pathophysiology, cognitive outcomes, and related psychosocial factors. Next, a more in-depth review of neurological and cognitive sequelae associated with a specifically mild brain injury subgroup will be described. This review will include a focus on clinical and functional outcomes, neurobehavioral symptoms, neurocognitive performance, diffuse axonal injury in mTBI and brain activation. Finally an introduction to the concept of "attentional efficiency" and

the brain structures and networks associated with visual attention will be presented in the context of an integrated model of attentional impairment in mTBI.

This dissertation will build on extant literature with an examination of cognitive performance and brain activation in a sample of military service members with mTBI. This study will use a visual attention task and neuroimaging to investigate correlations between brain activation patterns in specific regions with cognitive performance measures. Results of this study are expected to elucidate how a history of mild brain injuries may correlate with differences in cognitive task performance and associated underlying neurocircuitry.

TRAUMATIC BRAIN INJURY: AN OVERVIEW

Definition, Prevalence and Impact of TBI

Traumatic brain injury (TBI) is defined as a physiological disruption of normal brain functioning resulting in focal and/or diffuse damage to the brain from biomechanical and/or inertial forces to the head or skull (e.g. concussive blow to the head such as during sports, motor vehicle accident, explosive blast) (LaPlaca, Simon, Prado, & Cullen, 2007; Silver, McAllister, & Arciniegas, 2009). Every year approximately 3.5 million Americans suffer a TBI (Coronado et al., 2012). In addition to direct effects of TBI – to include possible permanent disability or even death (CDC, 2014; Faul, Xu, Wald, & Coronado, 2010) – patients often report subsequent symptoms including pain and somatic complaints, cognitive difficulties, attention and memory problems, and mood disturbance (Ciurli, Formisano, Bivona, Cantagallo, & Angelelli, 2011; Lundin, de Boussard, Edman, & Borg, 2006). While acute medical care for TBI is primarily based on symptom presentation at the time of injury, brain injuries of any severity may be associated with a wide range of immediate and long-term sequelae. Symptoms that persist

beyond the acute recovery phase may impact quality of life, health outcomes, functional status, and successful community reintegration (Tanielian & Jaycox, 2008). The annual cost of TBI in the United States (U.S.) is estimated to be approximately $1 billion through medical expenses and lost productivity (McCrea, 2008). Taken together, the high cost of TBI to individuals and society is a critical public health concern.

TBI exposure rates among military service members during their career – and especially during recent combat deployments – are higher than in the civilian population (Chapman & Diaz-Arrastia, 2014; DVBIC, 2015; MacGregor, Dougherty, Morrison, Quinn, & Galarneau, 2011; M. W. Reid & Velez, 2015; Terrio et al., 2009; Warden, 2006). Put another way, there were approximately 25,000 reported cases of TBI in the military in 2014 (DVBIC, 2015) equivalent to approximately 1.2% annually, while civilian incidence estimations of TBI range from 1.7m to 3.5m annually for the entire US population (Coronado et al., 2012; Faul et al., 2010), equivalent to a rate of 0.5-1.1%. For OEF/OIF combat Veterans, prevalence has been estimated at 15.8% (MacGregor et al., 2010), while the lifetime exposure rate for civilians is close to 12% (Frost, Farrer, Primosch, & Hedges, 2013). However, although these numbers may represent similar incidence rates among each population, because the timeframe of reported incidence is condensed for military to exposure during active duty service status they are comparable to those on the order of lifetime exposure in a civilian population. Therefore, these higher rates of exposure represent increased risk for TBI within the military population. Unfortunately, a history of multiple TBIs has also been shown to predict poorer health and psychological outcomes (Belanger, Kretzmer, Vanderploeg, & French, 2009; MacGregor et al., 2010).

For civilians the most frequent causes of TBI are motor vehicle crashes, interpersonal violence and falls (Galarneau, Woodruff, Dye, Mohrle, & Wade, 2008) whereas for OEF/OIF combat operations TBIs are more frequently caused by explosive blasts than in the civilian population (M. W. Reid & Velez, 2015; Warden, 2006). The majority of TBIs sustained in the military are non-deployment related and therefore similar to injuries sustained in the civilian population (Galarneau et al., 2008). However, given this population's high risk for exposure, as well as significantly higher rates of persistent symptoms among military vs. civilian cases (Chapman & Diaz-Arrastia, 2014), examining TBI sequelae in the military is particularly critical.

TBI Classification

TBI severity classification for acute assessment and treatment purposes is typically based on observable signs immediately post-injury. These signs include duration or presence of loss of consciousness (LOC), posttraumatic amnesia (PTA), and may also be informed by available clinical imaging (DoD, 2015). While standards for classification have evolved over time, those presented here will be used for determinations in the present study.

Mild TBI (mTBI) is typically classified by LOC duration from 0-30 minutes, PTA ranging from 0-24 hours post injury, and, although paradoxically, frequently normal clinical imaging findings (see Table 1). For patients with mild TBI (as indicated by LOC, PTA and alterations of consciousness (AOC)) severity can be further classified as uncomplicated (no abnormal findings on neuroimaging), or complicated (complicated by brain lesion or depressed skull fracture; (Williams, Levin, & Eisenberg, 1990). Moderate TBI is defined as a confused/disoriented state lasting greater than 24 hours or LOC greater than 30 minutes but less than 24 hours, PTA lasting greater than a day but less than a week, and structural brain imaging

that may be normal but typically includes abnormal findings. Severe TBI is graded by a confused or altered state lasting greater than 24 hours, LOC greater than 24 hours, PTA lasting longer than seven days, as well as standard clinical imaging that may be normal but frequently indicate abnormal findings (DoD, 2015).

	Mild	**Moderate**	**Severe**
Loss of Consciousness (LOC)	≤ 30 minutes	> 30 minutes to 24 hours	> 24 hours
Posttraumatic Amnesia (PTA)	≤ 24 hours	1-7 days	> 7 days
Alteration of Consciousness (AOC)	< 24 hours	*> 24 hours - Severity based on other criteria*	*> 24 hours - Severity based on other criteria*
Clinical Imaging (CT)	*CT scan not indicated for most**	Normal or abnormal	Normal or abnormal

Table 1. TBI Severity Classification DoD (2015).

The majority of TBIs are classified as "mild" and are associated with relatively rapid recovery. Unfortunately TBI severity classifications – while potentially helpful for acute medical treatment – have little prognostic utility (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Brown et al., 2010). In particular, a small subset of mTBI patients experience persistent symptoms and impairments beyond what would be expected given the relative severity of their injuries (Lundin et al., 2006; Schretlen & Shapiro, 2003). These "chronic" cases present a significant challenge for assessment and treatment. For example, standard neuropsychological testing is typically not able to detect differences in performance between healthy controls and patients who experience even chronic mTBI symptoms (Bigler, 2013). However, there is some evidence for measures such as eye-tracking for detecting subtle

deficits (Heitger et al., 2009; Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010). While there is also some evidence for similarities between these "chronic" and/or "complicated" mTBI cases with TBIs of a higher severity, controversy in the literature exists regarding best classification (Borgaro, Prigatano, Kwasnica, & Rexer, 2003; Kashluba, Hanks, Casey, & Millis, 2008; Kushner, 1998; Lange, Iverson, & Franzen, 2009).

Prior literature has noted inconsistencies in the application of diagnostic criteria (Jeter et al., 2013; Pogoda et al., 2014). In fact, there is debate among clinicians and researchers regarding the diagnostic criteria itself (Pape et al., 2013), including a recent change in DoD TBI diagnostic criteria to no longer incorporate Glasgow Coma Scale scores (DoD, 2015). For example, disagreements exist as to whether mTBI with AOC and mTBI with LOC should be combined into a single mTBI injury class, or if they represent different injury severity classes. Recent evidence suggests that psychological and executive functioning, as well as underlying brain injury may differ between patients who experienced AOC v. LOC (S. Matthews, Simmons, & Strigo, 2011; S. Matthews, Spadoni, Lohr, Strigo, & Simmons, 2012; Sorg et al., 2014). Moreover it appears that differences among mTBI patients labeled as "complicated" (with significant neuroimaging findings) versus "uncomplicated" (without neuroimaging findings) may predict differential outcomes (Lingsma et al., 2015; Panenka et al., 2015). These diagnostic classification and outcome differences likely contribute to the heterogeneity observed within mTBI clinical applications and research (Jeter et al., 2013; Rosenbaum & Lipton, 2012), and this controversy in the literature also likely underlies some of the inconsistencies in prior results and failure in the field to consistently predict outcomes for patients with mTBI (Jeter et al., 2013; Pape et al., 2013).

Mechanisms of Injury (MOI)

While brain injury is usually classified by acute effects and observable signs, the extent of damage is primarily related to factors of how the injury was sustained. Injury-related trauma may be from blunt contact (e.g. blow to the head such as during an accidental fall, physical violence, or a sports impact/collision), inertial forces (e.g. rapid acceleration-deceleration such as in a motor vehicle accident), or penetrating (e.g. from a gunshot) mechanisms (Galarneau et al., 2008; Gean, 2014; LaPlaca et al., 2007; M. W. Reid & Velez, 2015; Warden, 2006; Werner & Engelhard, 2007). Blunt linear or rapid acceleration-deceleration inertial forces may result in coup-contrecoup injuries in which the brain impacts the skull causing focal contusions (localized injury). Coup and contrecoup brain injuries are localized to the site of impact, and generally occur when the head abruptly decelerates in response to an outside force (e.g. being struck, or in a motor vehicle collision). The sudden force may cause the brain to collide with the inside of the skull (LaPlaca et al., 2007). Rapid acceleration-deceleration and/or rotational forces may apply spatiotemporal gradients that strain subcortical neural tissue, resulting in more diffuse injuries (Andriessen, Jacobs, & Vos, 2010; Greve & Zink, 2009). Both linear and rotational forces may occur concurrently with any initial direct impact trauma during an injury event leading to physiological and/or mechanical tissue damage (Greve & Zink, 2009). Velocity, location, and other physical properties of the event may also play important roles in specifics of resulting injuries.

Notably, some incidents may be a combination of several types of injury forces and mechanisms, as with motor vehicle crashes and/or explosions (see (Granberg & Schmidt, 2010) for illustration). For example, combat events (e.g. improvised explosive devices (IED) or rocket propelled grenades (RPG)) may involve multiple types of injury forces and mechanisms related solely to the blast (including injury sustained from primary blast over-pressure wave, injuries

from shrapnel and other debris, injuries from hitting objects subsequent to blast wave, and quaternary injuries such as respiratory burns and/or eye trauma). While the literature on TBI includes studies indicating that blast-related TBI causes a distinctly unique pattern of injury and functional impairment relative to non-blast injuries (Davenport, Lim, Armstrong, & Sponheim, 2012; Mendez et al., 2013), several other studies show little to no correlation between symptom reports and blast mechanism of injury (Levin et al., 2010; Luethcke, Bryan, Morrow, & Isler, 2010). While the mechanism of injury plays an important role in determining extent and location of damage, the specific pathology of how these mechanisms relate to clinical and functional outcomes is yet unknown (Azouvi, 2000).

TBI Pathophysiology

The forces and factors involved in a brain injury event play major roles in determining specific pathophysiological sequelae. However, the relationships between these mechanisms of injury and neuronal damage remain unclear (LaPlaca et al., 2007; Warden, 2006). Pathological sequelae of a TBI result from both the physiological injury event itself, as well as the body's biochemical response to this injury. Primary injury refers to physiological damage to cerebral tissue incurred though initial physiological and mechanical forces; secondary injury occurs as a result of a pathological "cascade" of cellular and biological processes in response to this primary injury (Andriessen et al., 2010). Primary injury damage is often well-described by mechanism, location and other physical aspects of the event.

Following the primary injury, the body's pathophysiological response starts with a first stage characterized by direct tissue damage and poor regulation of cerebral blood flow and metabolism (e.g. ischaemia and hyperaemia) (Greve & Zink, 2009; Werner & Engelhard, 2007).

This second stage of injury is characterized by the body's pathophysiological response process, which in the literature may be referred to by various terms including a pathophysiological response, neural pathology process, or a biochemical or neuropathological cascade. For purposes of clarity, these various descriptions will be referenced as a "pathophysiological response" which is characterized by the increased release of excitatory neurotransmitters, catabolic intracellular processes and biological changes to vascular and cellular structures resulting in progressive damage which may continue to propagate neuronal injury during the acute recovery process (Greve & Zink, 2009; LaPlaca et al., 2007; Rao & Lyketsos, 2000; Silver et al., 2009; Werner & Engelhard, 2007). In summary, a traumatic brain injury results in a primary injury, characterized by the initial stage of mechanical forces, with limited opportunities for treatment and prevention. In addition, TBI is also associated with a second stage of injury, comprising a neurometabolic process referred to as a pathophysiological response to the initial (or primary) injury. Although this second stage process may be less well understood, it currently represents an important focus for potential interventions.

Long-term Implications of Multiple Brain Injuries

While there is preliminary evidence that direction and mechanism of impact may influence the development of specific post-concussive symptoms (Silver et al., 2009), unfortunately, the specific link between pathophysiological processes and clinical presentation remains unclear (Andriessen et al., 2010). Several studies have found that a history of multiple TBIs, in particular, is associated with decrements in cognitive performance including delayed memory and executive functioning (Belanger, Spiegel, & Vanderploeg, 2010; Halbauer et al., 2009; Schretlen & Shapiro, 2003; Vanderploeg, Curtiss, & Belanger, 2005). These findings are especially concerning, given that OEF/OIF combat veterans frequently report exposure to

multiple TBIs during deployments (Chapman & Diaz-Arrastia, 2014; MacGregor, Dougherty, Morrison, et al., 2011), and the impact of multiple mTBI on long-term functioning is still unclear. To better understand the potential dangers of repeated head injuries, animal studies have shown that repetitive mild closed head injuries can be linked to deficits in spatial recognition, visuospatial memory, complex learning as well as performance consistency and accuracy (Creeley, Wozniak, Bayly, Olney, & Lewis, 2004; DeRoss et al., 2002; Hylin et al., 2013).

A number of studies have begun to identify the long-term potential risk of sustaining multiple TBIs on later development of neurodegenerative disease (Baugh et al., 2012; Gavett, Stern, Cantu, Nowinski, & McKee, 2010; McKee et al., 2009; T. Stein, Alvarez, & McKee, 2014). For example, chronic traumatic encephalopathy is a neurodegenerative disease that is suspected to be linked to repetitive brain injury (Baugh et al., 2012; Gavett et al., 2010; McKee et al., 2009; T. Stein et al., 2014). Chronic traumatic encephalopathy is associated with cognitive, behavioral and emotional changes (e.g. irritability, aggression, depression, short-term memory deficits, personality changes, impulsivity, and heightened suicidality) initially progressing to more severe cognitive deficits and possible dementia (McKee et al., 2009; T. Stein et al., 2014). Given their high rates of exposure to multiple TBIs, there is concern that athletes and military personnel are particularly at risk for development of chronic traumatic encephalopathy (T. Stein et al., 2014). While the dangers of chronic traumatic encephalopathy are increasingly researched, unfortunately a diagnosis can only be confirmed post mortem at this time. Current research into an in vivo marker for chronic traumatic encephalopathy has led to the use of neuroimaging, with promising results allowing for the study of underlying structural and pathophysiological disturbances thought to be associated with degenerative brain disease

(Ng et al., 2014). Given the heterogeneity of potential outcomes for those who have suffered a TBI, it will be important to consider the number of brain injuries in a patient's history as a potential variable in future models of TBI pathology and recovery.

Biopsychosocial Context

Understanding the interactions between TBI pathophysiology and clinical outcomes is critical to providing timely and appropriate therapeutic interventions. TBI pathophysiology potentially affects a broad range of brain structures and networks. However, clinical outcomes likely depend on factors in addition to the speed, force, location and mechanism of injury, as well as state of the brain at time of injury.

Silver and colleagues developed a model of biopsychosocial factors (Silver et al., 2009) in which pre-injury factors (e.g. age, baseline cognitive function, psychiatric conditions, and risk-taking behaviors), injury characteristics, as well as post-injury factors are proposed to play an important role in predicting neuropsychiatric problems (including cognitive, emotional, behavioral, and physical functioning). For example, environmental variables such as availability of social support, medical and rehabilitative treatments, and socioeconomic status impact TBI outcomes (Silver et al., 2009). This model provides a useful context for how factors in addition to MOI and injury severity may moderate TBI outcomes. Incorporating psychosocial and demographic factors within a biopsychosocial model may help elucidate correlations and neuroanatomical mechanisms moderating neurocognitive performance following TBI.

Cognitive Outcomes

While the specific mechanisms may not yet be fully understood, TBI can result in cognitive performance deficits in attention, memory, executive functioning, processing speed, visuospatial and language skills (Andriessen et al., 2010; Belanger et al., 2010; Gosselin et al., 2012; McDonald, Saykin, & McAllister, 2012; Schretlen & Shapiro, 2003; Silver et al., 2009). Recovery in domains such as processing speed and semantic memory are fairly typical following a TBI (Daneshvar et al., 2011; Kinsella, 1998; Lezak, Howieson, Bigler, & Tranel, 2012). However, deficits in visuospatial memory and attention may remain even years after the injury (Dougherty, MacGregor, Han, Heltemes, & Galarneau, 2011; Halterman et al., 2006; Himanen et al., 2005; Slovarp, Azuma, & Lapointe, 2012).

Previous research has demonstrated limited utility for manual reaction time (RT) as a marker for recent TBI. However, especially for those who have suffered a less severe injury, TBI patients make relatively few errors on these simple measures of manual RT and other standard neuropsychological tasks beyond the acute recovery phase. The literature also suggests that more prolonged effects on task performance may be seen in intra-subject reaction time variability for patients with a history of brain injury (Hill, Rohling, Boettcher, & Meyers, 2013; Stuss, Murphy, Binns, & Alexander, 2003; Stuss et al., 1989) when compared to control subjects. Therefore, as a metric of task performance consistency, a higher degree of variability may reflect inefficient cognitive processing following a TBI. Previous studies also suggest that visual attention tasks specifically may more accurately capture subtle cognitive performance deficits. For example, a review paper by Hafed and colleagues (Hafed, Chen, & Tian, 2015) indicated that microsaccades are influenced by attention and affect reaction times. Importantly, the literature suggests that manual reaction times may reflect early visual system processes (Hafed et al., 2015). Additionally, a study by Tomasi and colleagues (Tomasi, Ernst, Caparelli, & Chang,

2004) demonstrated that attentional load modulation impacted various visual attention network brain regions, and that these differences correlated with behavioral measures such as task performance accuracy. These results support a model of visual attention in which early attentional variance impacts behavioral performance measures. Furthermore, higher saccadic error rates (Diwakar et al., 2015; Heitger et al., 2009) and generally larger RT standard deviations have been found among chronic mTBI (Heitger et al., 2009). Moreover, poorer eye movement function has been correlated with higher self-reported symptoms (Heitger et al., 2009). Together, these results suggest that for patients with more chronic symptoms, behavioral performance measures on visual attention tasks may better capture subtle deficits in cognitive outcomes for mTBI.

A history of multiple prior TBIs has also been associated with poor neuropsychological outcomes (Belanger et al., 2005; MacGregor, Dougherty, Morrison, et al., 2011). In particular multiple mTBIs have been associated with worsened attentional performance, deficits in executive functioning and delayed memory (Belanger et al., 2010). Considering this previous research, a patient's history of prior TBIs may be an important factor moderating neurocognitive performance, as well as reflecting underlying pathological processes. Therefore, a patient's history of prior TBIs may represent an important "pre-injury" factor affecting recent brain injury outcomes. Utilizing a biopsychosocial framework, foundational work for this dissertation research included analysis of a dataset of over 450 participants who reported experiencing a TBI (including mild, moderate and severe) and incorporating prior injury characteristics and symptoms. The results suggested that a greater number of reported lifetime TBIs moderated the relationship between most recent TBI severity and neurobehavioral symptom scores (Reinhardt & Ettenhofer, 2011). After controlling for the effects of additional biopsychosocial factors

(including age, time since injury, biological sex, and psychiatric comorbidities), history of prior TBIs appears to moderate the relationship between most recent TBI severity and some neurobehavioral symptoms. Specifically, among those with a history of two or more TBIs, greater severity of the most recent TBI was associated with higher reported severity of postconcussive headache, dizziness, and memory problems (Reinhardt & Ettenhofer, 2011). As in previous literature, the measure of current TBI severity yielded rather weak results, while the inclusion of prior number of TBIs in the analysis strengthened and highlighted an interaction with severity. Generally these results lend support for a model of TBI that includes pre-injury interactions with injury characteristics on post-injury neuropsychiatric functioning (Silver et al., 2009), toward a better understanding of potential risk factors in developing higher neurobehavioral symptoms scores. Clinically, these findings suggest that patients with a history of prior TBIs may report 'dose-dependent' increases in current symptoms following a subsequent TBI. While the pathophysiology of this effect is unknown, these findings provide further evidence that a history of prior TBIs may influence the state of the brain either at the time of injury or during recovery. Specifically, the results of the analysis support the inclusion of prior TBIs as a measure in future models examining neurobehavioral symptoms and cognitive functioning following TBI (Reinhardt & Ettenhofer, 2011).

Together, these results suggest that patients with a history of single and multiple TBIs may comprise clinically distinct groups (Reinhardt & Ettenhofer, 2011), and that subtle differences in their cognitive functioning may be demonstrated by inconsistent task performance and increased likelihood for errors in visual attention. Further research into performance differences between patients with a history of single and multiple TBIs, therefore, represents an

important next step in elucidating the heterogeneity in symptoms and outcomes seen among TBI patients within the literature.

Psychosocial Influences on TBI Outcomes

When considering psychosocial context in recovery from TBI, it is also important to include differences between military and civilian populations. For example, active duty service members in military combat settings are at higher risk for incurring a TBI than their civilian counterparts (Chapman & Diaz-Arrastia, 2014; Gean, 2014; Tanielian & Jaycox, 2008). Specifically, deployed military personnel are more likely to experience repeated TBIs over a relatively short timeframe (MacGregor, Dougherty, & Galarneau, 2011) embedded as part of continuous missions and operations, rather than as discrete events such as in civilian settings (Chapman & Diaz-Arrastia, 2014; Gean, 2014). In addition to the risk for multiple injuries within a deployment, military TBIs may be somewhat unique with regard to comorbidities (e.g. PTSD and other mental health diagnoses, and visual dysfunction or other injuries from blast mechanisms) as well as typical MOIs (Dougherty et al., 2011; Gean, 2014). For example, a comorbid diagnosis of PTSD is more common among military combat veterans than among civilian population, as well as higher rates of depression and substance use (Chapman & Diaz-Arrastia, 2014; Hoge et al., 2008). Higher rates of exposure to trauma and generally high levels of operational stress (e.g. sleep deprivation, physiological stress) during deployment are also important differences between military and civilian contexts for TBI exposure (Chapman & Diaz-Arrastia, 2014; Gean, 2014). Blast-related TBI mechanisms are also highly related to multiple additional injuries, including ocular or visual disorders (Dougherty et al., 2011; Gean, 2014). Military population-specific risks also include the potential for return to duty before all

effects have been fully resolved, as well as other combat-related practical challenges for diagnosis, treatment and recovery (Gean, 2014). Together, these differences suggest the need for evaluation of TBI within a military-focused biopsychosocial context. While civilian research into causes and consequences of TBI are important to inform research and clinical care for military TBI, given known differences in prevalence and risk factors as well as outcomes points to the need for additional research focused within this population.

NEUROLOGICAL AND COGNITIVE SEQUELAE OF MILD TBI

Clinical and Functional Outcomes

Existing research supports distinct stages of recovery from TBI typically associated with improvement across cognitive, physical and emotional domains (Hammond-Tooke, Goei, du Plessis, & Franz, 2010). For mTBI, the acute recovery process is typically expected to be on the order of hours to up to three months for full resolution of symptoms (Belanger et al., 2010; Lundin et al., 2006; Schretlen & Shapiro, 2003). While recovery from TBI may be characterized by evolving symptoms that decrease over time, the exact timing of the underlying associated neural process is not well understood (Kou et al., 2010). In addition, research has yet to determine why prognosis may be complicated and marked by a number of adverse clinical outcomes for some while relatively symptom-free for others.

Patients who have sustained an mTBI are more likely to have higher cost of associated medical and mental healthcare treatment even beyond acute effects of the brain injury itself (Tanielian & Jaycox, 2008). In addition, these persistent symptoms can affect a person's ability to perform daily functions, or delay reintegration to environments with more cognitively challenging tasks such as work or school (Daneshvar et al., 2011; Kinsella, 1998). For example,

athletes may delay or fail to return to play depending on the nature and severity of their symptoms. Military members and athletes who have sustained a mTBI, however, may also return to duty before full resolution of symptoms, placing them at increased risk for additional injury (Chapman & Diaz-Arrastia, 2014; Gean, 2014; MacGregor, Dougherty, & Galarneau, 2011).

Neurobehavioral symptoms

Many patients who have sustained a TBI report cognitive (e.g., attention and memory problems, impulsivity, and difficulty with decisions), emotional (e.g. irritability or anger management problems as well as symptoms of psychiatric disorders including depression and anxiety) and physical symptoms (e.g. headaches, dizziness, fatigue) (Ettenhofer, Reinhardt, & Barry, 2013; Potter, Leigh, Wade, & Fleminger, 2006). Although most patients who have experienced an mTBI typically recover within days to months (Belanger et al., 2009; Daneshvar et al., 2011; Lundin et al., 2006; Schretlen & Shapiro, 2003), persistent neurobehavioral symptoms have also been reported in a subset of patients well beyond this acute injury time-frame (Daneshvar et al., 2011; Ettenhofer et al., 2013; Lundin et al., 2006; Slobounov et al., 2010). MTBI patients whose symptoms persist beyond the expected acute recovery window may be referred to as having "chronic" mTBI, and this subset of patients may experience worse outcomes than their severity classification would have predicted (Belanger et al., 2005; Mooney & Speed, 2001; Vanderploeg et al., 2005), including impairments in neuropsychological functioning (e.g. concentration and memory difficulties) (Belanger et al., 2005; Vanderploeg et al., 2005). Beyond cognitive impairments, there is also evidence of impaired ocular motor and vision functioning following TBIs of all severity levels (Goodrich, Flyg, Kirby, Chang, &

Martinsen, 2013; Goodrich, Martinsen, et al., 2013; Hafed et al., 2015; Heitger et al., 2009). Evidence also suggests that eye-movements and other measures of visual attention may correlate with neurocognitive processes (Hafed et al., 2015; Heitger et al., 2009; Suh, Kolster, Sarkar, McCandliss, & Ghajar, 2006). For example, reported visuospatial attention difficulties following mTBI (Halterman et al., 2006) may be linked to initial deficits in visual processing (Hafed et al., 2015). Interestingly, the impact of attention at various stages in the visual process may be highly correlated with type of task and cognitive load (Kanwisher & Wojciulik, 2000).

The severity of disruptive cognitive, emotional and behavioral symptoms may be further complicated by comorbid mental disorders often seen following TBI (such as major depressive disorder (MDD) and PTSD (Amick et al., 2013; MacGregor, Dougherty, Tang, & Galarneau, 2013; Scheibel et al., 2012). Given higher rates of these diagnosed comorbid emotional disorders following TBI, it is important to consider that the literature suggests these higher reports of depression may be correlated with decreased fractional anisotropy (FA) in white matter tracts connecting frontal and emotion processing brain regions (S. Matthews, Strigo, et al., 2011). Additionally, there is evidence of altered brain activity in these brain regions for cognitive and emotion-processing control for patients with a history of TBI (Gosselin et al., 2011; Lipton et al., 2009; S. Matthews, Strigo, et al., 2011). Essentially, better understanding of the causes and differential diagnostic categories of frequently overlapping symptoms of TBI with other psychiatric disorders is necessary in order to better predict and tailor individualized treatments (M. Stein & McAllister, 2009).

Furthermore, previous research has shown that comorbid PTSD can impair response inhibition and affect executive functioning among military veterans with mTBI (Amick et al., 2013; Swick, Honzel, Larsen, Ashley, & Justus, 2012). Previous literature has also shown that

patients with compromised attentional capacity (e.g. TBI) are particularly sensitive to tasks which increase demand for processing resources (Azouvi, 2000; Dockree et al., 2006). Additionally, affective symptoms such as anxiety can be conceptualized as a type of cognitive load (I. Chen & Chang, 2009). Patients with comorbid neuropsychiatric symptoms will, therefore, likely exhibit larger performance effects than would be predicted by having a history of TBI alone. This investigation aims to help clarify which brain regions are associated primarily with TBI-based neurobehavioral symptoms, as well as specific structures and networks which overlap those involved in other psychiatric disorders.

Neurocognitive Performance

The timeline for recovery from TBI is typically split into acute and chronic stages, related to injury severity and resolution of symptoms (Chapman & Diaz-Arrastia, 2014; Daneshvar et al., 2011; Mayer et al., 2010). Reaction time has been used as an acute measure of neurocognitive deficits, while assessment of longer-term functioning frequently relies on measures of specific persistent cognitive domain performance deficits (i.e. neuropsychological tests of verbal and visuo-spatial abilities, attention, motor skills, and memory) (Belanger et al., 2005; Kinsella, 1998; Lezak et al., 2012).

Working memory is the ability to hold and manipulate information, and is an important dimension of successful cognitive functioning frequently affected by TBI (McAllister, Flashman, McDonald, & Saykin, 2006; McDowell, Whyte, & D'Esposito, 1997; Perlstein et al., 2004). Tasks designed to assess working memory capacity often use what is referred to as an "N-back" paradigm to study this aspect of attention. During an N-back task, participants are required to match a presented stimulus with one presented "N" number of steps previously (i.e. targets

presented 1 trial or 2 trials back). Larger N-back steps present increasingly more challenging cognitive load, and represent higher degrees of difficulty. Prior studies have shown significant differences in performance on these measures between patients with TBI compared with controls (Perlstein et al., 2004). While a majority of studies highlighting cognitive deficits have focused predominantly on moderate-severe TBI, studies of the effects of TBI on sustained attention (Dockree et al., 2006; Slovarp et al., 2012) and working memory capacity (Perlstein et al., 2004) inform our understanding of neurocognitive performance across all severities.

While some cognitive and performance deficits may resolve fairly quickly following mTBI (Belanger et al., 2005; McAllister et al., 2006; Stuss et al., 1989) – with task overall performance remaining typically comparable between mTBI and control participants – other symptoms may persist (Chapman & Diaz-Arrastia, 2014; Daneshvar et al., 2011). Interestingly, altered brain activation patterns may still be found among patients with a history of mTBI despite similar task performance to controls (Azouvi, 2000; McAllister et al., 2006). A better characterization of the sources and specific deficits in neurocognitive performance following mTBI is essential to informing more precise diagnoses and improved individualized treatment. Previous literature has revealed significant variability of injury characteristics, imaging findings and symptoms in mTBI patient populations (Goldstein, Allen, & Caponigro, 2010; Lee et al., 2008; Rosenbaum & Lipton, 2012). Given this high degree of heterogeneity in pathology and symptom presentations following mTBI, as well as frequently minimal pre-injury functionality information, explicit quantification of neurocognitive deficits has proven difficult in the past (Kinsella, 1998; Rosenbaum & Lipton, 2012).

While traditional neuropsychological assessment is helpful in identifying and categorizing severe deficits, the majority of patients with mTBI continue to score within normal

ranges on most measures (Belanger et al., 2005; Bigler, 2013; Cicerone & Azulay, 2002). Importantly, the timescale of measurements for behavioral performance (e.g. reaction time) and related error variability of traditional neuropsychological assessment may differ from real world challenges and experiences. Clinical assessments are measured on the order of seconds, while subtle deficits on the order of milliseconds may still significantly impact neural processing and subsequently impair cognitive functioning (Bigler, 2013). Additionally, these tests are only able to compare a person's current functioning to that of similar peers and are therefore relatively insensitive to subtle intra-individual deficits following mTBI (Bigler, 2013; Cicerone & Azulay, 2002). Unless an individual happens to have a valid previous baseline established, neuropsychological assessments may miss degradations in functioning compared with their own pre-injury state of functioning. Additionally, neuropsychological tests designed to incorporate baseline measures, such as the Automated Neuropsychological Assessment Metrics (ANAM; (Reeves, Kane, Elsmore, Winter, & Bleiberg, 2002)), have unfortunately proven to have low test-retest reliability in a military sample (Coldren, Kelly, Parish, Dretsch, & Russell, 2010; Coldren, Russell, Parish, Dretsch, & Kelly, 2012; Cole et al., 2013).

Measuring variability has proven helpful in characterizing some deficits in other disorders (Ettenhofer et al., 2010), and there are some data to suggest that performance inconsistency (measured as variability in reaction times) may persist even among those with a history of mTBI (Hill et al., 2013). For example, frontal lobe lesions have been correlated with increased reaction time (RT) variability (Stuss et al., 2003). Neuroimaging studies of intra-individual performance variability have shown correlations with a distributed network of frontal, parietal and thalamic brain regions even for healthy control participants (Bellgrove, Hester, & Garavan, 2004). Task-performance variability has also been shown to correlate with severity of

brain injury (Hill et al., 2013). Additionally, poorer task reaction times and greater memory errors among patients with a history of mTBI may correlate with greater severity of microstructural cortical damage in certain frontoparietal regions involved in attentional control and memory performance (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008). Together these findings suggest that the neural networks underlying mechanisms of intra-individual variability might be particularly vulnerable to the effects of TBI, especially at frontal regions.

Diffuse Axonal Injury in mTBI

Research into the underlying mechanisms of primary and secondary pathological injury following TBI as well as the recovery process includes a number of techniques. While neuroscience research continues to better elucidate the underlying pathological processes, neuroimaging techniques are useful for *in vivo* investigation of neurocognitive processes. Successful daily functioning requires a multitude of integrated cognitive processes including orienting/alerting; perception; attention; memory encoding, storage and retrieval; social and emotional processing; and language motor and executive outputs (Corbetta & Shulman, 2002; Lezak, Howieson, & Loring, 2004). These processes rely on various brain regions and networks for proper execution (Beauchamp, Petit, Ellmore, Ingeholm, & Haxby, 2001; Gitelman et al., 1999; Lezak et al., 2004).

Diffuse axonal injury (DAI) may occur during TBI of any severity. In this type of injury, the physiological disruption caused by varying linear and rotational forces across the brain is thought to create spatiotemporal gradients resulting in microstructural tissue damage to cerebral white matter axons (Greve & Zink, 2009). Structural imaging studies have shown that DAI

significantly contributes to neuropsychological dysfunction after TBI (Kumar et al., 2009). For example, DAI has been correlated with altered cognitive task performance and reaction times (Lo, Shifteh, Gold, Bello, & Lipton, 2009; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar, et al., 2008), and may also correlate with persistent symptom pathology across TBI of any severity (Gosselin et al., 2011; Kumar et al., 2009; Wilde et al., 2008). In addition to the adverse pathological effects of TBI leading to DAI, focal pathology may contribute to specific deficits as well. Damage at prefrontal regions has been shown to adversely affect executive control for attention and emotional regulation (Gosselin et al., 2011; Mohanty et al., 2007; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008). Focal damage to the corpus callosum has been linked to increased reporting of neurobehavioral symptoms (Wilde et al., 2008), and altered white matter integrity connecting frontal and temporal regions has been shown to affect attention and memory (Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008).

In mTBI, standard clinical imaging infrequently reveals any acute lesions or contusions. Instead, it is thought that the primary mechanism of injury in mTBI involves DAI. Such damage, however, is not typically captured with traditional clinical neuroimaging as it falls below the level of detection of routine CT and MRI methods.

Research studies using diffusion tensor imaging (DTI) suggest that DAI may be a possible mechanism linking clinical symptoms of mTBI with cognitive impairment and task performance (Maruta et al., 2010; S. Matthews et al., 2012; S. Matthews, Strigo, et al., 2011; Mayer et al., 2009; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008). Several studies indicate that differences in white matter integrity and functional activation patterns at various brain regions are correlated with neuropsychological difficulties following TBI (Gosselin et al., 2011; Hammond-Tooke et al., 2010). For example, attention and cognitive control of

emotion have been associated with compromised connections among prefrontal brain regions (Mohanty et al., 2007). Additionally, damage to the corpus callosum has been found to correlate with increased neurobehavioral symptom expression and distress (Wilde et al., 2008).

DTI is a promising experimental imaging technique for investigating and quantifying the extent of underlying structural neuropathology in mTBI (Inglese et al., 2005). However, currently the link between DAI and clinical outcomes in mTBI is not clearly established and the literature continues to be somewhat mixed (Azouvi, 2000; Miles et al., 2008). Additionally, it remains unclear how DAI and quantification of structural damage relates specifically to cognitive performance. Because of this insufficiency as well as its technically demanding processing requirements, DTI is not yet an approved clinical tool for diagnosis of brain injury. Furthermore, neuroimaging is currently a financially impractical solution for clinical diagnostics as well as an insufficient tool to meet the mobile needs of military applications. While experimental neuroimaging techniques such as DTI show promise for improved knowledge of mTBI, additional research and alternative assessment techniques are needed to better understand associated clinical outcomes.

Brain Activation Patterns following TBI

Both DAI and focal pathology following TBI contribute to neurocognitive deficits (Andriessen et al., 2010; Werner & Engelhard, 2007). While the timeline of recovery typically shows improvement, a number of studies show persistent symptoms and task performance alterations following TBI (Belanger et al., 2005; Chapman & Diaz-Arrastia, 2014; Daneshvar et al., 2011; Schretlen & Shapiro, 2003; Vanderploeg et al., 2005). Functional neuroimaging research has corroborated several neuropsychological and structural imaging studies by

providing associated task-related brain activation differences which may persist beyond the acute recovery phase following TBI (Azouvi, 2000; S. Matthews, Strigo, et al., 2011). For example, TBI has been associated with differential brain activation patterns predominantly in frontal-parietal regions during attention and memory tasks (Ashman et al., 2008; Dockree et al., 2006; Larson, Clayson, & Farrer, 2012; S. Matthews, Strigo, et al., 2011; McAllister et al., 2006; McDonald et al., 2012; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008; Scheibel et al., 2012), and sometimes poorer task performance (Dockree et al., 2006; Perlstein et al., 2004; Scheibel et al., 2012), relative to controls.

Given the high percentage of TBIs classified as mild, there are surprisingly relatively few neuroimaging studies to date (McDonald et al., 2012). Moreover, available neuroimaging studies of mTBI include limited longitudinal samples and restricted inclusion of military samples, and provide incomplete understanding of brain regions and networks affected and their relationship to task performance and underlying pathology (McDonald et al., 2012). Also, there is a significant amount of variability between studies with regard to activation patterns at various brain regions and networks, task-related performance differences, demographic covariates including other mental health dx, as well as time since injury (McDonald et al., 2012; Rosenbaum & Lipton, 2012). Furthermore, our current understanding of the mechanisms and causes of this heterogeneity in mTBI samples is inadequate (McDonald et al., 2012).

Additionally, patients with a history of mTBI have shown altered brain activation (in bilateral frontal-parietal regions) in response to increasing cognitive load aspects of working memory tasks (McAllister et al., 2006; McAllister et al., 2001), as well as slower task reaction times (Hammond-Tooke et al., 2010). Interestingly, while mTBI patients may demonstrate similar behavioral performance with respect to cognitive load in a working memory N-back task

(McAllister et al., 2001), decreased functional and structural connections among brain regions integral to successful cognitive performance have also been shown to correlate with increased cognitive load (Sharp et al., 2011). Specifically, while mTBI patients show increased task-related brain activation at lower cognitive load levels relative to healthy controls, they subsequently utilize great and more diverse brain region recruitment at higher load, reflective of decreased efficiency in monitoring and allocating processing resources (McAllister et al., 2001).

In fact, damage to neuroanatomical structures involved in working memory or to the subcortical white matter connections supporting this network have been linked neurobehavioral symptoms (Kasahara et al., 2011). Although task performance differences have not consistently been demonstrated between mTBI and control participants, a number of studies reflect altered brain activation patterns including a distributed network of brain regions (including prefrontal regions) supporting working memory (Kasahara et al., 2011; Perlstein et al., 2004; Sanchez-Carrion et al., 2008). Together, these results suggest a reduced cognitive efficiency requiring TBI patients to work harder to maintain comparable levels of performance (Azouvi, 2000; Larson et al., 2012; McAllister et al., 2006).

A neuroimaging study by Gosselin and colleagues (Gosselin et al., 2011), found altered task-related brain activation patterns and increased reported neurobehavioral symptoms correlated with a history of mTBI relative to healthy controls, even after controlling for comorbid neuropsychiatric pathology. Their findings suggest that injury-related neuropathology underlies altered working memory processing following mTBI, not otherwise accounted for by psychological diagnosis (Gosselin et al., 2011). Furthermore, a longitudinal study by McAllister and colleagues found that participants with mTBI showed persistent deficits in reaction time at one year post injury which correlated with increased right frontal task-related brain activation

patterns, despite reported resolution of neurobehavioral symptoms (McAllister et al., 2006). Preliminary evidence reported in this study show that catecholaminergic dysregulation following mTBI and genetic polymorphisms may play fundamental roles in the mechanisms of altered attentional task processing and working memory dysfunction (McAllister et al., 2006). These findings are in line with more recent studies of mTBI, suggesting inter-individual heterogeneity in the range and severity of symptom presentations and clinical outcomes is likely related to variability across many biopsychosocial factors including pre-injury functioning and brain state, injury-related factors, and post-injury pathophysiological and psychosocial factors (Goldstein et al., 2010; Rosenbaum & Lipton, 2012).

Regarding the mechanisms and underlying neuroanatomical pathology responsible for these differences in cognitive outcomes, Mayer and colleagues demonstrated that attentional abnormalities following mTBI, including impaired abilities to disengage and inhibit attention, correlated with hypoactivation at attentional network brain regions (Mayer et al., 2009). A study by Witt and colleagues found decreased activation of dorsolateral prefrontal cortex and altered deactivation of the Default Mode Network mTBI relative to healthy controls, interpreted to suggest that prefrontal dysfunction may be involved in attention and executive functioning dysregulation seen following mTBI (Witt, Lovejoy, Pearlson, & Stevens, 2010).

Consistent with these reported cognitive deficits and compensatory activation patterns, other neuroimaging studies have identified fronto-parietal and temporo-occipital brain structures and networks involved in various aspects of spatial attention (Corbetta & Shulman, 2002; Gitelman et al., 1999). Further, brain activation patterns across a prefrontal-cingulate task-specific network have been identified among patients with mTBI which demonstrate altered response patterns to increasingly difficult cognitive processing (Azouvi, 2000). Moreover, mTBI

patients “at rest” (i.e. not performing a directed cognitive task), have been shown to exhibit altered patterns of neural activation as well (Bonnelle et al., 2012; Bonnelle et al., 2011; Sharp et al., 2011).

While the majority of mTBI research has utilized civilian samples, studies with military and Veteran samples are primarily consistent with research suggesting altered patterns of brain activation (S. Matthews et al., 2012; S. Matthews, Strigo, et al., 2011; McDonald et al., 2012). For example, a study of active duty military personnel and Veterans following OEF/OIF deployment similarly showed increased task-related activation across distributed network and slower reaction times to produce equivalent task performance accuracy in patients who had experienced a mTBI (Scheibel et al., 2012). Specifically results showed higher and more diffuse task-related activation following mTBI while completing a visual response task compared to post-deployment healthy controls (Scheibel et al., 2012). Importantly, inclusion of PTSD and additional self-report neurobehavioral symptoms as covariates among this group of post-deployment participants heightens the generalizability of these findings to a military population.

Preliminary findings from a recent collaborative neuroimaging analysis of over 100 military participants suggest that altered activation patterns on an emotional working memory task may be related to certain injury factors as well as to neurobehavioral symptoms (Reinhardt, Graner, Oakes, Ettenhofer, & Riedy, 2014). Specifically, areas associated with executive function and attention, emotion and memory, and regions of the default mode network (including right anterior cingulate cortex, cerebellum, left caudate, left temporal pole) demonstrated altered brain activation patterns which correlated with aspects of cognitive and emotional task-performance. These findings are consistent with prior structural and functional imaging studies of neurocognitive deficits following TBI (Azouvi, 2000; Kumar et al., 2009; S. Matthews,

Strigo, et al., 2011; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008) and extend this literature to an emotional working memory task in a military population. Results also showed that cognitive performance variability was significantly associated with activation differences in frontal and limbic regions. More specifically, decreased reactivity to differences between difficulty levels of the cognitive task was found to be correlated with higher intra-subject variability in primarily frontal regions associated with attention, error-detection, and decision-making (Reinhardt et al., 2014).

Additionally, increased neurobehavioral symptoms were correlated with altered activation patterns on both cognitive difficulty (higher task difficulty burden) and emotional response aspects of the task (Reinhardt et al., 2014), suggesting that results of this study support prior civilian literature noting particular difficulties among mTBI for dual-tasks or those with increased cognitive load demand (McAllister et al., 2006; McAllister et al., 2001).

Together, these results suggest that future studies should include additional biopsychosocial factors (including history of prior TBI and neuropsychiatric diagnoses) to better understand heterogeneity. Also, manipulation of cognitive load may be utilized to better understand underlying mechanisms and activation patterns (especially in frontal networks subserving attention and executive functioning) of cognitive task performance and neurobehavioral symptoms. Finally, results of this study suggest that individual task performance variability may be an important and useful behavioral marker of underlying neuropathology and may correlate with neurobehavioral symptom expression.

ATTENTIONAL EFFICIENCY IN MILD TBI

Attention

Because brain systems are only able to process a limited amount of information at one time, networks to identify and filter selected targets for additional processing and responses have been described (Cohen, 2014). Attention can be conceptualized as a mechanism for selecting physical or internal targets for focus and prioritization of behavioral responses (Posner & Petersen, 1990; Raz & Buhle, 2006), and is critical to cognitive performance. Given these limited attentional resources, effective and successful neurobehavioral functioning demands brain processing to be consistent and accurate. Therefore, cognitive impairment such as from neurological insult (e.g. TBI, epilepsy, or stroke), psychiatric disorders (e.g. depression, PTSD, or Attention Deficit/Hyperactivity Disorder) or other health-related factors (e.g. medications, sleep-deprivation, pain or aging) may compromise efficient attentional processing (Lezak et al., 2012).

Posner's neuroanatomical model of the attention system describes mechanisms for the selection of internal and environmental data for cognitive processing (Posner & Petersen, 1990). Within this model, separate but integrated networks for alerting, orienting, and executive functioning decisions (Petersen & Posner, 2012; Pierrot-Deseilligny, Muri, Nyffeler, & Milea, 2005; Rueda, 2004) interact and mutually influence one another. These systems may also be conceptualized as comprising a "top-down" (goal-directed) network for inhibition, prediction and executive decisions, and a "bottom-up" (stimulus-driven) network for alerting, orienting, and identification (Corbetta & Shulman, 2002; Pierrot-Deseilligny et al., 2005). Posner's model of attention has been further investigated with cognitive tasks examining these underlying network typologies (Ghajar & Ivry, 2008; Hill et al., 2013) including evidence for specific brain

structures and neurotransmitter systems involved (Petersen & Posner, 2012; Pierrot-Deseilligny et al., 2005; Rueda, 2004).

Brain systems/networks supporting Attention

Studies of the structural and functional organization of the brain reveal complex dynamic networks, which interact toward the goals of efficient behavioral initiation and responses (Fox et al., 2005; Power et al., 2011; Sporns, Chialvo, Kaiser, & Hilgetag, 2004; van den Heuvel, Mandl, Kahn, Pol, & Hilleke, 2009). There is some debate regarding specific delineations and organization of the brain's structural and functional networks. However, general consensus is that cortical areas are neuronally connected to form three major functional networks consisting of a "task-negative" or "Default Mode Network" (DMN), a "Saliency Network" (SN), and a central/executive network, although sometimes these latter networks are referentially combined into a "task positive" network for saliency and executive control.

The Default Mode Network is engaged during the brain's "resting state" and social cognitive tasks, but exhibits decreased activation during higher-level cognitive tasks (Bonnelle et al., 2012). Default Mode Network brain structures include posterior cingulate cortex, precuneus, ventromedial prefrontal cortex, as well as medial, lateral and inferior portions of the parietal cortex (Bonnelle et al., 2012; Raichle et al., 2001). Default Mode Network functional connectivity has been found to correlate with both white matter structural integrity and task activation (Sharp et al., 2011).

Activation of the Saliency Network primarily serves to orient attention to tasks and events, and comprises structures including anterior insula, dorsal anterior cingulate cortex, presupplementary motor area, amygdala, substantia nigra/ventral tegmental area and thalamus

(Bonnelle et al., 2012). While the literature is mixed as to whether the Saliency Network and central/executive networks may be considered part of the same "task positive" network or represent separate entities, this "task positive" network of brain structures may alternatively be understood to comprise five core functional networks related to the specific task being performed. These five functional networks include a Spatial Attention Network (primarily located in posterior parietal cortex and frontal eye fields), a Language Network (concentrated at Wernicke's and Broca's areas), an Explicit Memory Network (including hippocampal-entorhinal complex and inferior parietal cortex), a Face-Object Recognition Network (comprising midtemporal and temporopolar cortex), and a Working Memory/Executive-Function Network (involving primarily prefrontal and inferior parietal cortex regions) (Bonnelle et al., 2012).

Within the attention literature, a number of studies have also begun documenting specific brain structures associated with various aspects of attention. Albeit conceptualized somewhat differently, these studies provide converging evidence for the importance of structural integrity and functionality of certain brain regions in optimal task performance. Previous research has demonstrated that a ventral frontoparietal (primarily right lateralized) network of brain regions is involved in stimuli detection, particularly for salient/unexpected events (Corbetta & Shulman, 2002). A "Posterior Attention Network" comprising posterior parietal lobe, thalamic areas and portions of midbrain colliculus has been shown to be principally responsible for orienting attention (Kinsella, 1998). Another network of brain regions primarily located in prefrontal and parietal regions including anterior cingulate cortex (ACC) and supplementary motor areas (SMA) and basal ganglia is responsible for selection and supervisory attentional control (Kanwisher & Wojciulik, 2000; Kinsella, 1998), and shifts of attentional focus appear to activate temporo-occipital cortex and anterior insula in response to spatial attention tasks (Gitelman et al.,

1999). Sustained attention is believed to heavily involve right hemisphere structures; in particular the locus coeruleus (Kinsella, 1998). Finally, goal-directed (aka "top-down") attention has been demonstrated to involve intraparietal cortex and superior frontal cortex (Corbetta & Shulman, 2002).

These attentionally-related networks are highly interdependent and may be particularly sensitive to the effects of TBI during cognitive task performance. Importantly, following a TBI, patients often report difficulties with attention (Daneshvar et al., 2011; Kinsella, 1998; MacGregor et al., 2013) including poor working memory (Slovarp et al., 2012) and difficulties with sustained attention especially under dual-task load conditions (Dockree et al., 2006). In particular, typical injury patterns of fronto-temporal region damage suggest that increased deficits in sustained and selective attention may be a particularly likely consequence of TBI (Kinsella, 1998).

Specific to mTBI, neuroimaging findings reveal attention and memory difficulties including deficits in performance monitoring and regulation of cognitive processing tasks (Azouvi, 2000; Bonnelle et al., 2012; Larson et al., 2012), as well as orienting and executive aspects of visuospatial attention (Halterman et al., 2006). Tasks of visual attention reflect its important role in selecting and processing visual information, given limited capacity of the attentional network (Desimone & Duncan, 1995). There is considerable support in the literature for neuroanatomical overlap in visuospatial attention networks and brain regions which activate to support eye movements (Beauchamp et al., 2001; Corbetta et al., 1998; Corbetta & Shulman, 2002; Nobre, Gitelman, Dias, & Mesulam, 2000). From a structural perspective, fronto-parietal regions appear to be particularly vulnerable to the effects of mTBI (Eierud et al., 2014; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee, et al., 2008). Together, these findings also support

differential effects of mTBI on various components of attention. In one study, Halterman and colleagues found that mTBI had a significant impact on particularly the executive component of visuospatial attention (Halterman et al., 2006). Additional research into the attentional components and networks most impacted by mTBI is subsequently essential in improving diagnosis and better understanding causation and prognosis for neurobehavioral symptoms.

Conceptualization of "Attentional Efficiency"

One explanation for variations in task performance and brain activation patterns between patients with a history of TBI and healthy controls is differential attentional capacity following TBI, especially under increasing task difficulty (Manly et al., 2003; McAllister et al., 2006) or "cognitive load". Cognitive load reflects increased demand (or simultaneous processing) during complex learning activities and especially during executive control over working memory and attention processing (I. Chen & Chang, 2009). Essentially, while TBI patients may be able to initially recruit additional brain areas to meet needs of increased task difficulty, there are limits to available resources to meet increased task demands.

This attentional "bottleneck" may have significant clinical implications. In fact, prior research has shown that attention and cognitive performance deficits may correlate with neurobehavioral symptom severity (Canli et al., 2005; Demenescu et al., 2011; S. Matthews, Strigo, et al., 2011). Differences in brain activation patterns have also been correlated with certain post-TBI neurobehavioral symptoms (Gosselin et al., 2011). Moreover, neuroimaging studies have indicated roles for attentional capacity (Vuilleumier, Armony, Driver, & Dolan, 2001) and cognitive load (Van Dillen, Heslenfeld, & Koole, 2009) on performance. Particularly certain brain structures including ACC, dorsolateral prefrontal cortex (dlPFC), insula,

supramarginal gyrus (SMG), and superior/posterior parietal cortex (Bush, Luu, & Posner, 2000; Pierrot-Deseilligny et al., 2005) have been implicated, which may be adversely impacted by TBI.

"Attentional efficiency" is a concept describing the efficiency of brain resource utilization, as well as accuracy and consistency, in making successful decisions and behavioral responses. This concept may represent an important initial cognitive step in successful "bottom-up" information processing. Attentional efficiency may also play a role in successful "top-down" decision-making as well as subsequent emotional and behavioral outcomes. TBI may disrupt these processes through damage to structures and neural networks involved in attentional efficiency. Because available clinical neuroimaging and neuropsychological testing measures may currently be limited, detection of more subtle deficits often seen following mTBI requires alternative methods.

Task performance measures, including error rates and consistency of response times, provide quantitative data regarding the efficiency of these attentional networks, and are particularly useful metrics in TBI (Ghajar & Ivry, 2008; Hill et al., 2013; Sharp et al., 2011). Specifically "attentional efficiency," may provide a valuable marker in the quantification and characterization of cognitive performance. Task performance variability reflects the consistency of an individual's responses, and subsequently may prove to be an important biomarker to identify alterations in cognitive processing following TBI (Bellgrove et al., 2004; Ghajar & Ivry, 2008; Hill et al., 2013; Stuss et al., 2003; Stuss et al., 1989). Given the complexity and heterogeneity of task performance and brain activation patterns among mTBI patients, that a more in-depth investigation of subgroups (e.g. history of single or multiple TBIs, comorbid mental health diagnoses, and additional psychosocial factors which may differentiate among mTBI patients) within this population is indeed warranted. In particular, further study of the

common elements and differentiation among brain networks (such as attention) will be important to clarify unique pathophysiological contributions to task performance, symptom expression, and clinical outcomes for patients with a history of mTBI.

Model of reduced attentional efficiency following mTBI

Overall the literature suggests neurocognitive sequelae consistent with a diagnosis of mTBI include impairment in performance consistency (Azouvi, 2000; McAllister et al., 2001), as well as errors in attention and memory. Specifically, neuroimaging literature suggests that altered structure and functioning in fronto-parietal regions are involved in these attention and memory impairments following mTBI. FMRI research has also demonstrated significant overlap of these attentional systems with brain structures involved in processing eye movements (Corbetta et al., 1998; Nobre et al., 2000). There is also evidence of impaired ocular motor and vision functioning following TBIs of all severity levels (Goodrich, Martinsen, et al., 2013), including deficits in visuospatial abilities following mTBI (Halterman et al., 2006). Previous findings further suggest that eye-movements and other measures of visual attention may correlate with neurocognitive processes and brain activation (Corbetta et al., 1998; Kanwisher & Wojciulik, 2000; McColeman et al., 2014). Given evidence of oculomotor and visual attention deficits following TBI (Contreras, Ghajar, Bahar, & Suh, 2011; Dougherty et al., 2011; Goodrich, Flyg, et al., 2013; Suh, Basu, et al., 2006; Suh, Kolster, et al., 2006), the integration of neuroimaging with a visual attention task provides a valuable and unique opportunity to better investigate attentional processes and networks which may be disrupted by mTBI.

Following from Posner's model of attention and prior neuroimaging support for structural and functional vulnerability to mTBI in fronto-parietal "task-positive" brain regions, the

following model will be tested for the proposed dissertation research. MTBI causes structural damage to attention networks (through a mechanism such as DAI), resulting in attentional inefficiency in completion of neurocognitive tasks. This impairment in attentional resource utilization may be further compromised by additional biopsychosocial factors, including a history of multiple brain injuries. Deficits in neurocognitive functioning resulting from attentional inefficiency may be observed through sensitive measures of task performance including consistency and accuracy, especially under various levels of cognitive load *(see figure 1 below)*.

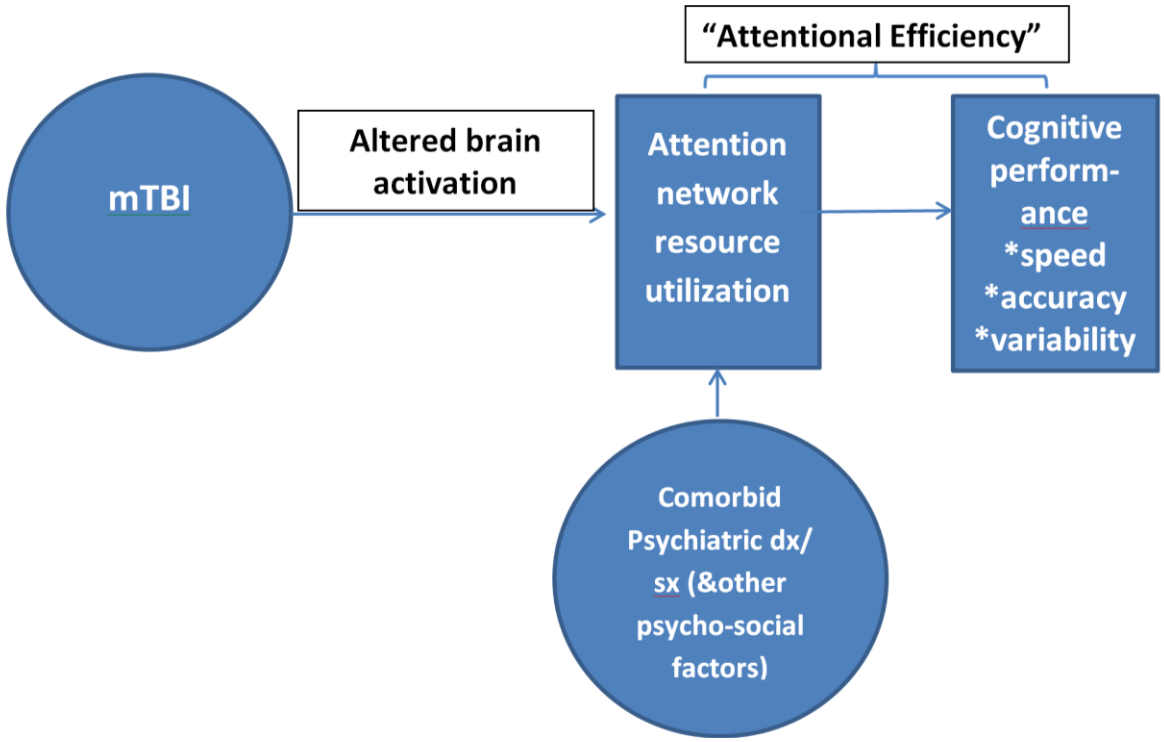


Figure 1. Theoretical model for study. MTBI proposed to cause structural damage (through a mechanism such as DAI), which impacts Attentional Efficiency comprised of attention network resource utilization (measured with BOLD signal) and cognitive performance (measured as speed, accuracy and variability). Additional psychosocial factors may also impact attention network resource utilization.

SUMMARY AND STUDY RATIONALE

Summary

Military service members are a population at high risk for TBI, particularly multiple mTBI due to the nature of combat deployment environment and operational factors (Gean, 2014; MacGregor, Dougherty, Morrison, et al., 2011). The exact relationship between mTBI pathophysiology and other biopsychosocial factors determining outcomes remains unclear. Controversy regarding authoritative classification for mTBI (e.g. whether AOC and LOC injuries should be included within the same injury severity, debate regarding differences among chronic and/or complicated mTBI diagnoses) and impact of various pre-injury factors (e.g. impact of history of prior TBIs) have impacted heterogeneity in classification and outcomes in previous studies in the literature. Additionally, the underlying brain structures and functional networks affected by mTBI may be diffuse and difficult to detect with traditional clinical imaging and neuropsychological measures. Nonetheless, a significant number of service members who have sustained an mTBI report neurobehavioral symptoms which may have long-term impact (Chapman & Diaz-Arrastia, 2014; MacGregor et al., 2013). Deficits in performance, measured by attentional inefficiency, may play a critical role in understanding the clinical and functional impacts of mTBI. Inclusion of biopsychosocial factors involved in brain injury, as well as current models of attentional control may help to elucidate the contextual framework of chronic neurobehavioral symptoms following mTBI in a military sample.

Rationale and Significance

Although previous literature suggests that mTBI patients often demonstrate comparable task performance to healthy controls, the proposed study utilizes performance metrics that may

be more sensitive to individual variability and deficits. Furthermore, increased attentional demand of differing cognitive load levels may stress an injured brain to a higher degree thereby presenting a greater challenge as measured by performance metrics. Specifically, the burden of additional cognitive demands of the various task conditions may impact performance consistency and accuracy through limitations in attentional resources. For patients with a history of mTBI, attentional network capacity limits may present subtle markers of decreased performance accuracy and consistency, which may also be observed as altered patterns of neuronal signal activation relative to the unstressed state. These alterations may be correlated with specific aspects of the brain injury itself, as well as other previously established patient characteristics and biopsychosocial factors including a history of prior TBIs (Reinhardt & Ettenhofer, 2011) and demographic factors (Ettenhofer et al., 2013) identified in previous research. Inclusion of these individual covariates may help elucidate sources of heterogeneity within the mTBI population.

Attentional efficiency may be investigated via measures of task performance consistency (e.g. reaction time variability) and accuracy (e.g. task errors), while also examining resource utilization with fMRI. Understanding how neural attention processing is related to these task performance metrics may help clarify the contributions of mTBI to altered cognitive performance and symptom expression. Neuroimaging investigation of these networks may also highlight brain areas most vulnerable to damage, potentially yielding targets for future therapeutic intervention.

This dissertation study builds on prior research demonstrating the importance of biopsychosocial factors in recovery from TBI, as well as cognitive task performance and neuroimaging among military patients with a history of mTBI. Patients with a history of mTBI have demonstrated historically inconsistent results in studies regarding task performance

variability. Standard neuropsychological measures typically do not adequately explain symptom reports of patients with mTBI. Moreover, military mTBI represents a unique subset of the TBI patient population with regard to biopsychosocial factors including exposure risks, demographics, and community resources. This study, therefore, presents an opportunity to advance our knowledge of chronic mTBI in a relatively healthy sample of military participants. The purpose of this dissertation research is to examine potential underlying brain structures and networks associated with heterogeneity in visual attention and cognitive processing in mTBI, as well as to investigate the relationship of potentially altered activation patterns with reported neurobehavioral symptoms.

Studies of the underlying neural circuitry involved in clinically relevant measures of attention are an essential next step to inform more precise diagnostic procedures and improved treatment planning. The proposed research is expected to expand existing knowledge of mechanisms of cognitive deficits and symptom burden following mTBI as well as the specific roles and vulnerabilities of attentional networks. These structures and processes may serve as potential targets in the development of future interventions and individualized treatment following mTBI.

SPECIFIC AIMS

Aims & Hypotheses

The overarching aim of this research is to identify brain regions and neural networks associated with poor attentional efficiency among patients who have sustained one or more mild TBIs compared with healthy controls. The central hypothesis for the proposed study is that neural networks involved in attentional processes are vulnerable to disruption following mTBI,

and fMRI may represent a more sensitive marker for damage to these brain networks. Given overlapping brain networks and symptoms, tasks that increase demand for processing resources, especially among patients with compromised attentional efficiency, will suffer detrimental performance effects. Subsequently, history of prior TBIs as well as task-related cognitive demands are expected to impact task performance through the mechanism of reduced attentional efficiency. Data will be collected using a novel fMRI task of visual attention. Specifically, in line with the proposed study model for examining attentional efficiency, whole-brain activation patterns will be analyzed to identify brain resource utilization across task conditions and their associations with performance measures for task accuracy and consistency.

Specific Aim 1

To examine patterns of neural activation associated with cognitive processing of specific types of visual attention demands and attentional efficiency after mTBI. Participants will complete a cued "Go/No-Go" visual attention task administered in the fMRI environment (*see Methods section for additional task description, including Figure 2 cue examples*). Main effects of task condition, mTBI history, and the interaction of condition with mTBI history will be examined in terms of their association with brain activation, as well as demographic and patient characteristics for improved model prediction.

Hypothesis 1a)

Task condition for "Go" trials (directional cue, misdirectional cue, and uncued trials) will correlate with whole brain voxel-wise blood oxygen level dependent (BOLD) activation patterns in the overall sample.

Hypothesis 1b)

A main effect of group (mTBI history: none vs. single vs. multiple) will be associated with voxel-wise whole brain BOLD activation patterns across "Go" trials.

Hypothesis 1c)

Task condition for "Go" trials (directional cue, misdirectional cue, and uncued trials) will be associated with significantly different patterns of voxel-wise whole brain BOLD activation between groups with different mTBI history (none vs. single vs. multiple).

Hypothesis 1d)

Beyond the effects of cognitive load and mTBI history on brain activation patterns, certain individual characteristics are expected to account for additional sources of heterogeneity in attentional efficiency. Significant predictors in the model analysis including main effects for task condition, mTBI history and their interaction, as well as PCL and NSI scores, and demographic covariates will add to the initial model to account for significant additional variance in BOLD response.

Specific Aim 2

To examine patterns of neural activation associated with performance measures of attentional efficiency after mTBI. Performance accuracy ("inattention" omission errors and "disinhibition" commission errors; for "Go" and "No-Go" trials separately), as well as speed (reaction time (RT)) and consistency (measured as Intraindividual Coefficient of Variation (ICV) *adapted from (Bellgrove et al., 2004)* and RT standard deviation (SD) for comparison) for "Go" trials will be analyzed for potential relevance as biomarkers of attentional efficiency.

Hypothesis 2a)

There will be a significant main effect of performance accuracy (manual error ratio on the No-Go task condition) on voxel-wise whole brain BOLD activation patterns. If a sufficient proportion of errors in performance exists to support analysis of variability, accuracy of saccadic performance (partial and full errors of disinhibition and inattention divided by total valid inhibition trials) will also be examined as an indicator of performance accuracy.

Hypothesis 2b)

There will be a significant main effect of group (mTBI history: none vs. single vs. multiple) on voxel-wise whole brain BOLD activation patterns on the No-Go task condition.

Hypothesis 2c)

Performance accuracy (manual error ratio) on the "No-Go" task condition will be associated with significantly different patterns of voxel-wise whole brain BOLD activation between groups with different mTBI history (none vs. single vs. multiple prior mTBIs).

Hypothesis 2d)

There will be a significant main effect for each attentional efficiency performance measure including speed (RT), consistency (ICV or SD), and accuracy (manual errors) on whole brain voxel-wise BOLD activation patterns across "Go" trial conditions.

Hypothesis 2e)

Performance speed (RT), consistency (ICV or SD), and accuracy (errors) for "Go" trials will be associated with significantly different patterns of voxel-wise whole brain BOLD activation between groups with different mTBI history (none vs. single vs. multiple prior mTBIs).

Secondary Aim

To examine relationships of attentional efficiency to key demographic and clinical factors relevant to primary aims. Univariate relationships will be examined between cognitive load (task conditions), performance variables (RT, ICV, SD, and errors), demographic variables (including age, education and biological sex), self-report questionnaire scores (PCL-C and NSI), and TBI history (prior number of mTBIs, with none for control participants). These variables, utilized in previous analyses, will be investigated for correlations with one another to provide better neuropsychological context within which to interpret differential brain activation patterns.

CHAPTER 2: METHODS

STUDY DESIGN OVERVIEW

A cross-sectional study of participants with a history of mTBI and healthy controls was conducted as an extension of a collaborative project between the Ettenhofer Neurocognitive Research Lab at Uniformed Services University of the Health Sciences (USUHS) and the Neuroimaging Department at the National Intrepid Center of Excellence (NICoE). This neuroimaging study leveraged the direct relationship between attention and visual processes. Specifically, this project used a novel functional neuroimaging task that also measures behavioral performance and eye movement metrics to investigate attentional efficiency (based on the "BEAM" (Barry, Lunsford, & Ettenhofer, 2013). The "I-BEAM" (an event-related visual attention fMRI task, detailed further in the Measures section below) examined relationships among task performance, brain activation patterns, medical history (including TBI), and reported neurobehavioral symptoms. Measures of visual attention were used to assess cognitive processing performance in mTBI participants. The study aimed to further identify underlying neural circuitry involved in altered brain activation patterns observed in mTBI patients during performance of a visual attention task.

Participants were military service members with a history of mTBI and healthy controls. The study was part of a larger neuroimaging project examining symptom presentations and differential diagnostics for wounded warriors with predominantly mTBI and psychological health conditions not responsive to current therapy (e.g., "chronic mTBI"). This study utilized a cross-sectional correlational neuroimaging design. Measures included clinical interviews, self-report questionnaires, as well as neuroimaging incorporating a novel research measure of visual attention.

PARTICIPANTS

Sample Size Determination

Neuroimaging literature indicates that an experimental group of 40 is preferable to obtain statistically interpretable results (Desmond & Glover, 2002), therefore a target sample size of 40 mTBI participants and 10 healthy controls was proposed for this study. Per dissertation committee request, additional power analysis was performed. Based on a study by Heitger and colleagues (Heitger et al., 2009) that used a similar visual attention task, effect sizes for velocity (proxy for speed) and error measurements from the study were used to estimate the required study sample size for this dissertation project. Building on this project's proposed model and these statistical power calculations, a minimum sample size of 3 participants per group for errors and 23 participants per group for speed measurements would be needed to detect expected task effects. These calculations would suggest that a sample of 23 mTBI and 23 healthy controls should be used in this study. Given logistical constraints for collecting healthy control data, a smaller healthy control sample was necessary for the purposes of this study. Additionally, given the expected relative heterogeneity of the mTBI population, a ratio with higher mTBI patients to control participants may optimize detection of effect sizes. The intended sample size was also adjusted to account for data loss issues (e.g. excessive movement or task failure) in order to yield a sample size with sufficient power to detect true significant results. Therefore, based on these power calculations and considerations from Desmond and Glover (Desmond & Glover, 2002), a final sample size goal of 50 mTBI patients and 12 healthy controls was set for this study in order to provide sufficient statistical power to detect significant main effects (Desmond & Glover, 2002).

Participant Selection

Due to unanticipated changes in resources and mentorship beyond this author's control, data collection for this project was not able to proceed as intended. The larger neuroimaging protocol to which it was tied was halted during the intended time of data collection, and given incompatibility of any additional data gathered after subsequent upgrades to the neuroimaging scanner equipment and software were made, the decision was made in consultation with the dissertation committee chair not to resume data collection and to allow project analysis with the already collected sample. Participants included in this study therefore were 14 patients at NICoE with a history of mTBI and 7 healthy control volunteers who were all Defense Enrollment Eligibility Reporting System (DEERS)-eligible Active Duty military participants enrolled in the parent research protocol. Study eligibility was verified by research staff from patient medical records (including NICoE clinician determinations of mTBI history) prior to enrollment in the parent research project.

Inclusion/Exclusion Criteria

Participants for this study were active duty military service members and DEERS-eligible former service members seen at NICoE recruited as part of a larger neuroimaging project. Specific inclusion criteria included eligibility and enrollment in primary NICoE study including: 1) 18 years of age or older; 2) DEERS-eligible; as well as 3) history of at least one mTBI with LOC (as determined by NICoE clinicians and research study team clinical interviews) or no history of TBI for healthy controls. Exclusion criteria include: 1) females who are or who might be currently pregnant; 2) individuals who are unable to be scanned due to safety or other risk issues (e.g. ferrous metal/ medical device implants, claustrophobia); 3) individuals with a history

of AOC-only or a history of moderate/severe TBI for mTBI group participants, or any history of TBI for healthy control participants; 4) visual impairments which impede a participant's ability to accurately view the stimuli through MRI-compatible goggles; 5) inability to respond to stimuli in the MRI scanner using the button response paddles.

Human Subjects and Procedures

Participants who consented to participate in the NICoE parent neuroimaging study underwent initial screening procedures for MRI safety, as well as completing self-report questionnaires (see Measures below). For purposes of recruitment, participants for this study were a subset of those participating in the larger protocol including only those who met additional Inclusion/Exclusion criteria. For those eligible and assigned to this sub-study, participants completed a brief practice I-BEAM task in preparation for the scan, as well as self-report questionnaires (PCL and NSI) before undergoing the neuroimaging scan. This protocol presented no more than minimal risk, and complied with WRNMMC IRB approved protocol and regulations.

EXPERIMENTAL METHODS

Neuroimaging

Anatomical and functional MRI images were obtained as part of the larger IRB-approved imaging research protocol at NICoE including an initial localizer scan to prescribe subsequent scans, as well as high-resolution anatomical scans and B0 field maps. Scans were acquired on a GE 3.0 Tesla MR750 scanner (General Electric, Milwaukee, WI) at the NICoE Neuroimaging Department at the Walter Reed National Military Medical Center (WRNMMC). All subjects

also underwent the study's functional MRI task utilizing blood oxygenation level dependent (BOLD) imaging to detect changes in regional blood oxygenation associated with hemodynamic response to brain functioning. Anatomical imaging included high resolution T1- and T2-weighted images (160 sagittal slices with 0.47x0.47x1.2 mm^3 spatial resolution. T1: TR= 6.7 ms, flip angle= 12 degrees; T2: TR= 2200 ms, flip angle= 90 degrees). Functional images for the I-BEAM task were obtained using an echoplanar imaging (EPI) sequence (40 sagittal slices, slice thickness at 3.75 x 3.75 x 4.0 mm^3 in-plane resolution, 64 x 64 voxel FOV, TR= 2000ms, flip angle= 60 degrees), with cardiac pulsation and respiration recorded during scans via finger pulse oximeter and respiratory belt, respectively.

Additional Measures

Participants completed a 2 hour scanning session at the NICoE neuroimaging lab. During this visit, consented participants underwent a battery of structural and functional scans including the I-BEAM task, and completed self-report questionnaires (including PTSD Checklist (PCL) and Neurobehavioral Symptom Inventory (NSI)).

PTSD Checklist (PCL-C)

The PCL is a standard 17-item self-report screening questionnaire comprising the 17 DSM-IV symptoms of PTSD rated for severity (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996; Wilkins, Lang, & Norman, 2011). Scores range from 17-85, with higher scores representing higher severity of symptoms. This measure is estimated to take approximately 5 to 10 minutes to complete. PCL total score was used as an index of PTSD symptoms for analyses examining additional individual characteristics associated with BOLD activation patterns (Hypothesis 1d and secondary aim).

Neurobehavioral Symptom Inventory (NSI)

The NSI is a 22-item self-report measure of commonly reported post-concussive symptoms (Meterko et al., 2012). Items use Likert-type scale ratings for each symptom experienced since the time of their injury, including "feeling dizzy," "headaches," "poor concentration, can't pay attention, easily distracted," "feeling depressed or sad" with ratings ranging from 0 = "none" to 4 = "very severe". NSI symptom subdomains include: cognitive (e.g., problems with concentration, memory, decision-making, speed), affective (e.g., depression, fatigue/insomnia, anxiety, irritability/frustration, headaches), and somatic (e.g., dizziness, numbness, poor balance/coordination, vision/hearing difficulty, light/noise sensitivity, changes in taste/smell or appetite). From this measure a post-concussive symptoms total score, as well as totals for each of the subscales (affective, cognitive, and somatic) were computed from raw scores of relevant items. This measure is estimated to take approximately 5 to 10 minutes to complete. NSI total score was used as an index of neurobehavioral symptoms for analyses examining additional individual characteristics associated with BOLD activation patterns (Hypothesis 1d and secondary aim).

fMRI I-BEAM task

The imaging BEAM (I-BEAM) attention task is an event-related adaptation of the BEAM attention task (Barry et al., 2013), designed based on prior research on attention and TBI. The I-BEAM is a visual attention task requiring participants to look at target circles following different cue types. Different cue types vary location and timing information, thus changing the cognitive load level of each trial type (*see Figure 2 below for cue types included in I-BEAM)*. Wearing MRI-compatible goggles (Nordic NeuroLab Inc., Milwaukee, WI), participants were asked to look at target circles, and press buttons on hand-held MRI-compatible response paddles (Nordic

NeuroLab Inc., Milwaukee, WI) to indicate targets appearing to the right or left side of the screen to produce behavioral data (including reaction times and errors). The task objective is for participants to look at the target circle as quickly as possible, while correctly navigating false cues and inhibiting trial types where they are instructed not to move their eyes or press the response button. Specifically, the I-BEAM task is able to test performance in both cued and uncued attentional eye-tracking responses as well as testing visual and manual inhibition.

The I-BEAM task design varies these visual attentional processing demands (including directional, misdirectional and no cues, as well as inhibition reaction trials) using E-Prime software (Psychology Software Tools, Inc.). The I-BEAM utilizes a pseudo-randomized set of cues (arrows and fixation cross, as well as colored inhibitory signal) and targets (circles presented to left and right), with the same stimuli presented in the same order for all participants (*see Figure 2 below for cue types included in I-BEAM*). This task assesses cognitive performance (measured by RT, response errors and individual response variability (ICV or standard deviation)) as well as brain activation patterns associated with each of the task conditions and associated behavioral metrics. The I-BEAM task requires approximately 10 minutes to complete in the MRI scanner. Additionally, participants were trained on the task prior to scanning, to allow for any questions to be answered and to ensure proper understanding of the task. This pre-task training outside of the MRI scanner took approximately 3-5 minutes including instructions and time to answer questions.

Results from this fMRI-adapted I-BEAM measure were used to investigate visual attention and cognitive processing differences among participants with a history of mTBI compared to healthy controls. Specifically, the study examined event-related neural activation and behavioral response to I-BEAM within a military sample of participants with chronic mTBI

and healthy controls. Statistical analysis of this multi-modal dataset is expected to help elucidate neural underpinnings of visual attention deficits and neurobehavioral symptoms commonly seen following mTBI.

Metrics used to evaluate attention and task performance for the I-BEAM included reaction times (RT) and intra-individual coefficient of variability (ICV) calculated as RT_{SD}/RT_{Mean} (*adapted from (Bellgrove et al., 2004)*) as well as standard deviation (SD) for comparison to ICV as a performance metric. Additionally, errors (including "inhibitory" or commissions, and "inattention" or omissions), were collected to evaluate error rates. Due to logistical challenges, visual metrics (including saccadic RT and all visual errors) were unable to be included in analyses. Due to low manual error rates among participants, a categorical variable for errors made (yes or no) was included in analyses as an alternative to some of the initially proposed error rates. Software used in this study did not operate as planned for capturing required analysis metrics for participants' manual behavioral responses. Although participants were initially instructed to press both left and right buttons for each "Go" task target circle to minimize laterality effects in the task, due to these unanticipated software issues in data collection the task directions were changed to have participants press only a single "left" or "right" response for each task trial. Preliminary analysis between participants with the two types of task directions indicated no significant differences in brain activation patterns or behavioral performance measures on the I-BEAM task.

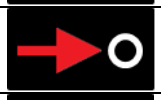
Cue type	Trial type	Example
Direct cue (DC)	Go	
Direct cue RED (DC-R)	No-Go	
Misdirectional Cue (MDC)	Go	
Uncued (UC)	Go	

Figure 2. I-BEAM fMRI task cue types, trial types and example stimuli for each task condition. Participants were asked to look at the target circle and press a button unless they see a red arrow.

DATA ANALYSIS

The study design and methods used for neuroimaging research follow from the inherent complexity of this field. Typical neuroimaging studies use a series of steps to process images from the initial data collection at the individual subject level through group analysis, although the exact parameters and procedures may vary from one study to another. The data analysis plan for this study involved first completing individual level fMRI pre-processing and QA before conducting group level analyses related to each of the specific aims. The image-processing software used and order of these steps are detailed below for general processing for this study, as well as choices in this pathway specific to the specific aims and hypotheses. Below are descriptions of analyses conducted for these more general fMRI procedures followed by a description of choices and procedures applied for the specific aims analyses.

fMRI Individual Analysis

Subject fMRI images were processed using a combination of standard scanner manufacturer software as well as software written either in-house or sourced from other

institutions. In addition to initial scanner processing and data anonymization, functional imaging sequences were pre-processed using FMRIB Software Library (FSL) including automated skull-strip procedure, in-house B0 field inhomogeneity corrections, and Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Initial EPI data pre-processing for each participants' data included: removal of the first three volumes (3dtcat); acquisition slice-timing correction (3dtshift); B0 field inhomogeneity corrections (in-house and FSL software); and physiology corrections (FSL and in-house software). Subsequently, pre-processed time series data steps for each participant were completed using AFNI software suite (Cox, 1996) including afni_proc.py for sub-brick to base-brick registration as well as alignment of EPI and T1 anatomical images and Montreal Neurological Institute (MNI)-152 standard space transformation calculations (3dvolreg), and general linear model analysis using time series data convolution with a gamma-variate hemodynamic response function (3dDeconvolve), smoothing with 6mm FWHM Gaussian blur, and transformation of EPI signal values to voxel-wise % means using afni_proc.py pre-processing scripts for each individual subject level analysis with statistical significance outputs of task weight contribution to changes in BOLD signal. Anatomical T1 data for each subject underwent spatial normalization to MNI152-2009c brain template standard stereotactic space. The resulting transform was also applied to each subject's fMRI data for transformation of co-registered functional images into standard space. After individual subject level processing and analysis was completed as well as quality and data integrity checks, group functional image analyses were conducted in accordance with the data analytic plan. In particular, because the I-BEAM is a novel task of visual attention and part of the analyses involve confirmation of the brain regions and associated networks activated by the task, whole-brain analyses were conducted to determine significant voxel-wise clusters of

activation. Although one mTBI group participant's neuroimaging data was removed for excessive movement, missing or incomplete data for other participants were able to be included and addressed per methods further described in results section.

fMRI Group Analysis

Following individual subject level data processing and data integrity checks, fMRI group analyses were conducted on each participant's data per data analysis plan. Differences in significant voxel activation were masked, identified and thresholded for significant clusters of activation using Gaussian random-field theory and Monte Carlo simulations for family-wise error correction (3dClustSim and 3drefit). Family-wise error correction is a well-recognized approach to improve reliability and correct for multiple comparisons in fMRI (Bennett, Wolford, & Miller, 2009; Nichols & Hayasaka, 2003).

Neuroimaging analyses utilized multivariate modelling methods (3dMVM; (G. Chen, Adleman, Saad, Leibenluft, & Cox, 2014)) to create mixed-model ANOVAs and ANCOVAs for group analyses. These multivariate analysis models represent a strength of this study's statistical methods which leverage statistical efficiency and powerful models in order to determine and incorporate contributions of various factors to differences in brain activation patterns for Specific Aims 1 and 2 as described below. Participants' imaging findings were also correlated with medical history (including demographic information such as biological sex and education) as well as self-report questionnaires, and behavioral task performance measures. These data were entered into the multivariate ANCOVA analysis models as covariates in accordance with each aim. Due to the reduced sample size and modeling constraints, the analysis included fewer demographic covariates than were originally planned. Based on an expected collinearity

between education and rank, education was chosen for inclusion as one of the covariates for the analysis. Age was not selected as one of the covariates for this analysis given the limited amount of variables that could be included in the model. Although initially intended to be a part of the model, given the restricted range of participant ages and expected minimal developmental impacts within this range, age was excluded in favor of capturing the more likely impacts of gender and education in the analyses. Further analyses were conducted according to identified specific aims (described below).

Aim-specific Neuroimaging Analysis Overview

To summarize, the purpose of this project was broadly to: 1) examine differences between mTBI patients and healthy controls on a novel visual attention "Go, No-Go" task; 2) investigate the impact of mTBI history on activation patterns associated with specific attentional efficiency performance metrics. Overall, this project sought to help validate a novel visual attention task expected to be sensitive to differences in attentional efficiency among mTBI patients and controls. A flexible and robust multivariate modeling approach to study data was also implemented. By using the combination of this novel task and modeling approach, while controlling for other previously confounding variables in the mTBI literature (e.g. PTSD symptoms), it was hoped that this research would yield a better understanding of the subtle interactions and differences in brain activation patterns among subgroups of mTBI patients. Significant results for these hypotheses were defined as those which achieved a corrected $p<.05$ (with family-wise error voxel-wise p and cluster size corrections applied). Statistical significance and locations for clusters of activation were analyzed with AFNI (Cox, 1996).

Aim-specific Neuroimaging Group Analyses

To examine attentional efficiency among participants with a history of mTBI, neuroimaging data were processed and whole brain voxel-wise BOLD activation patterns were analyzed using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). Because this study utilized a preliminary pilot task which had not yet been validated in an fMRI environment, a whole-brain voxel-wise analysis was performed to characterize brain activation patterns for responses and to confirm which brain regions and associated networks were activated by the task. Based on previous findings in the literature, demographic factors (e.g., biological sex, education, and mental health conditions) were also examined to determine if these factors made additional significant contributions to these models and whether there were significant correlations among variables included across the study models (see Table 2 for data analysis approach).

Specific Aim 1

To identify the brain regions and factors associated with attentional efficiency, cognitive load (i.e., task conditions), mTBI history, and demographic and symptom information were included into models of attentional efficiency. Due to the limited sample size and large number of covariates included in this analysis, subject data were entered into the model as two groups, an mTBI group and a health control group. The limited sample size prevented the use of three groups as originally planned for this first hypothesis model analysis, although the multivariate modeling approach was utilized to improve statistical power.

Hypothesis 1a)

Multivariate modeling (3dMVM, AFNI) was used to evaluate the association between "Go" task conditions (directional cue, misdirectional cue, and uncued trials) and whole brain voxel-wise BOLD activation patterns in the overall sample. Planned follow-up pairwise comparisons were included in the analyses for task conditions to determine statistically significant differences in clusters of activation.

Hypothesis 1b)

A multivariate modeling approach was also used to evaluate the correlation between groups (mTBI vs. healthy controls) and voxel-wise whole brain BOLD activation patterns across "Go" trials. Planned follow-up pairwise comparisons of mTBI history for statistically significant clusters of activation were included in the analysis.

Hypothesis 1c)

Multivariate modeling (including above analyses 1a and 1b) was used to examine the interaction between task condition (directional cue, misdirectional cue, and uncued trials) and group (mTBI vs. healthy controls) on voxel-wise whole brain BOLD activation patterns. Planned follow-up pairwise comparisons for statistically significant clusters of activation were also performed.

Hypothesis 1d)

Additional analyses within the multivariate model were also conducted to determine additional sources of significant variance in BOLD response activation pattern. Beyond the initial analysis performed, for any significant predictors in the previous hypotheses 1a-c (including task condition, mTBI history and their interaction) PCL and NSI scores and

demographic covariates were analyzed to examine whether these factors provided additional sources of significant variance. .

Specific Aim 2

To examine patterns of neural activation associated with attentional efficiency after mTBI performance accuracy ("inattention" omission errors and "disinhibition" commission errors; for the "Go" and "No-Go" task conditions), performance speed (RT; for "Go" task conditions), and performance consistency (ICV and standard deviation; for the "Go" task conditions) were used as performance measures of attentional efficiency. A multivariate modeling approach was utilized to improve statistical power and minimize chances of statistical error.

Hypothesis 2a)

Multivariate modeling was used to examine associations between patterns of BOLD brain activation and performance accuracy (errors) for the "No-Go" task condition. Due to changes in mentorship personnel and availability of analysis software programming expertise, saccadic performance accuracy data were not able to be analyzed and therefore not included in the analysis. Additionally, due to the low rate of error across all participants, a dichotomous categorical "yes/no" variable was used to represent manual errors within the model.

Hypothesis 2b)

Multivariate modeling analysis was also used to evaluate associations between group (single mTBI vs. multiple mTBI history vs. healthy controls) and voxel-wise whole brain BOLD activation patterns in the "No-Go" condition.

Hypothesis 2c)

Multivariate modeling was used to assess the interaction between group (single mTBI vs. multiple mTBI history vs. healthy controls) and performance accuracy (errors) on voxel-wise BOLD activation patterns in "Go" task trials. Post-hoc pairwise comparisons for statistically significant clusters of activation were also performed.

Hypothesis 2d)

Multiple regression analysis was used to examine the effect of performance speed (RT), accuracy (errors) and consistency (ICV and standard deviation) on whole brain voxel-wise BOLD activation patterns across "Go" task conditions. For performance consistency, two separate analyses were conducted to determine whether ICV or standard deviation might serve as the more efficient performance metric. Due to limited sample size and to minimize potential effects of collinearity, the analyses for speed, accuracy and consistency were performed within separate multivariate model analyses.

Hypothesis 2e)

Multivariate modeling was also used to examine the interaction effects of group (single mTBI vs. multiple mTBI history vs. healthy controls) and performance accuracy (errors) speed (RT) and consistency (ICV or SD) on voxel-wise BOLD activation patterns across "Go" task

trials. Post-hoc pairwise comparisons for statistically significant clusters of activation were also performed.

Secondary Aim

To examine relationships between attentional efficiency variables with demographic and clinical factors, multiple regression analysis and pair-wise t-tests were used to compare several factors including task conditions, performance variables (RT, ICV/SD, errors), demographic variables (including age, education and biological sex), self-report questionnaire scores (PCL-C and NSI), and mTBI history (none vs. single vs. multiple) included in previous analyses.

Table 2. Summary of Data Analyses for Study Hypotheses.

Hypothesis	Independent Variables (IV)	Dependent Variable (DV)	Statistical tests for Group Analyses	Additional follow-up tests and covariates
1a: Go trials	task condition (directional cue, misdirectional cue, and uncued trials)	whole brain voxel-wise BOLD activation patterns	GLTs in multivariate model	pairwise comparisons
1b: Go trials	mTBI history (mTBI combined group vs. controls)	whole brain voxel-wise BOLD activation patterns	GLTs in multivariate model	-
1c: Go trials	b/w Ss: TBI history (combined mTBI vs. controls) w/in Ss: Task condition (directional cue, misdirectional cue, and uncued	whole brain voxel-wise BOLD activation patterns	Multivariate modeling	pairwise comparisons

	trials)			
1d: Go trials	Significant predictors from the previous model analysis (i.e. main effects for task condition, mTBI history, task condition and mTBI history interaction)	whole brain voxel-wise BOLD activation patterns	Hierarchical multivariate modeling (inclusion of covariates to evaluate significant additional variance added to model in 1c)	demographic covariates (e.g. education, biological sex), PCL and NSI scores
2a: No-Go cond	performance accuracy (manual errors)	whole brain voxel-wise BOLD activation patterns	GLTs in multivariate model	If sufficient error variability: saccadic performance (partial and full errors of disinhibition and inattention) follow-up GLTs with DV
2b: No-Go cond	mTBI history (controls vs. single vs. multiple)	whole brain voxel-wise BOLD activation patterns	GLTs in multivariate model	pairwise comparisons
2c: No-Go cond	<u>b/w Ss</u>: mTBI history (controls vs. single vs. multiple) <u>w/in Ss</u>: performance accuracy	whole brain voxel-wise BOLD activation patterns	Multivariate modeling	pairwise comparisons
2d: Go trials	<u>performance measures:</u> speed (RT), accuracy (errors), and consistency (ICV and SD)	whole brain voxel-wise BOLD activation patterns	GLTs *in 4 separate multivariate models (1 for each performance measure)*	pairwise comparisons
2e: Go trials	<u>b/w Ss:</u> mTBI history (controls vs. single vs. multiple) <u>w/in Ss:</u>	whole brain voxel-wise BOLD activation patterns	Multivariate modeling *in 4 separate models (1 for each performance*	pairwise comparisons

	performance measures: speed (RT), accuracy (errors), consistency (ICV and SD)		*measure)*	
Secondary	Performance metrics (ICV and inhibition errors), mTBI history, and self-report questionnaire scores	For each task condition (directional cue, misdirectional cue, uncued, and "No-Go" inhibition trial)	Univariate pairwise comparisons	demographic variables (including age, education, rank and biological sex)

CHAPTER 3: RESULTS

SAMPLE DESCRIPTION

Study participants were Active Duty military DEERS-eligible (DoD beneficiaries enrolled in the Defense Enrollment Eligibility Reporting System) research volunteers at the National Intrepid Center of Excellence (NICoE) who consented to a larger research study of patients with TBI and psychological health issues being conducted within the NICoE Neuroimaging Department. Fourteen mTBI and seven healthy control participants completed this dissertation project sub-study including all study measures. Among the mTBI group, participants were further categorized into subgroups for some of the proposed analyses. Participants with a history of one mTBI with LOC were placed in the "single" subgroup (n=5) and participants with a history of two or more mTBIs with LOC were placed in the "multiple" subgroup (n=9) for indicated analyses investigating the impact of mTBI history. Participants with histories of additional mTBIs without LOC were placed into subgroups based solely on history of mTBI with LOC - regardless of any additional AOC injuries. Participants from the larger neuroimaging research project who only experienced AOCs without any history of LOC were not included in this study (additional details in Inclusion/Exclusion Criteria section). For the purposes of sample demographics, the mTBI group is characterized together consistent with results of Specific Aim 1 and the secondary analysis. Additional results from the secondary analysis indicate any notable differences between the mTBI subgroups are also described, consistent with results of Specific Aim 2.

In the overall study sample analyzed, there was a significant difference in age between the mTBI group and healthy controls (see Table 3 for sample description and statistics). There were no significant differences in mean education level between the mTBI group and healthy

controls. There were significantly more males in the mTBI group compared to the healthy control group. There were no statistically significant differences between groups with respect to race/ethnicity group composition or for military branch or rank. Mean self-reported combat exposure using the Combat Exposure Scale (CES) in the mTBI group was equivalent to moderate-heavy combat exposure, which was significantly higher than the healthy control group (equivalent to light combat exposure). Those in the mTBI group reported significantly more neurobehavioral symptoms compared to controls. Similarly, those in the mTBI group reported significantly more PTSD symptoms on the PCL-C compared to those in the healthy control group.

Specific to certain analyses within the study, various missing data were handled according to procedures detailed as follows. Of note, some participants' data for the PCL (n=3) NSI (n=2) and CES (n=3) was missing. For one control subject, the group average score for NSI and PCL were used in subsequent neuroimaging analyses to maximize available data. For the two participants in the mTBI group, NICoE patient files included scores from these measures at the time of admission (2-3 weeks prior to scan) and these scores were used. Additionally, for one participant in the mTBI group, the uncued (UC) condition of the task was incorrectly completed by the patient in the scanner. To maximize available data, this participant's other "Go" trial speed and variability scores were used and the mTBI group average UC condition-specific error score was used as a proxy in order to retain this participant's data in the analyses. A follow-up reliability QA was conducted to compare results with and without this data, which indicated that this participant's data were not exclusively driving analysis results. While the inclusion of this participant may have added increased variability in the UC condition data, this participant was retained to maximize power in the analysis results for all specific aims. After

exclusion for excessive movement in the scanner (n=1), the final study sample for neuroimaging analyses in specific aims 1 and 2 consisted of mTBI participants (n=13) and healthy controls (n=7) for whom sufficient fMRI task and anatomical image data were available. Participants included in each analysis varied slightly as a result, as indicated in the results for each aim below.

OVERVIEW OF FMRI RESULTS

The multivariate modeling statistical analysis method chosen for this study is a state-of-the-art neuroimaging analysis methodology that confers both advantages and disadvantages (G. Chen et al., 2014; G. Chen, Saad, Adleman, Leibenluft, & Cox, 2015). Specifically, use of an ANCOVA-style model (including interaction effects as well as patient-specific covariates) allows for detection of subtle interaction effects while controlling for the effects of included confounding variables. Because the overall model was specified at the time of execution, however, only a priori comparisons are included in the analysis. Additionally, the number of covariates and general linear tests (GLTs) included in each model is limited by sample size and degrees of freedom. Therefore, post-hoc analysis to determine directionality of results not already pre-specified in the model are unavailable.

Based on the proposed study methods including acknowledged limited power to detect significant results in this smaller sample, all planned interactions and contrasts were still run for any analyses in which main effects were not significant. Additionally, significant activation clusters in some brain areas that indicate trends were included in the results and discussion and marked as not statistically significant. Given the limited sample size and "pilot study" nature of the present dissertation project, such trends may indicate areas for significant findings in larger

sample sizes with appropriate statistical power to detect these effects. Bilaterality, due to a high degree of brain symmetry (Salvador et al., 2005) would suggest a decreased likelihood of Type I error at that specific region. Therefore, including bilateral brain regions which demonstrate non-significant trends in these study results may help clarify other study results and indicate potentially important areas of further investigation for future studies with larger sample sizes.

AIM-SPECIFIC RESULTS

Unless otherwise specified, "*p*" values associated with fMRI analyses represent the specific voxel-wise *p* threshold used, and "α" represents the cluster-wise *p*-value significance, with family-wise error corrections. Given the limited sample size and the pilot nature of the study, activation clusters in some brain areas that indicate trends, but are not statistically significant, are included in the results and discussion. Additionally, all proposed interactions and follow-up tests were performed regardless of whether the main effects were statistically significant. This plan was established in consultation with fMRI statistician and neuroimaging mentors, based on the analysis models used in this study.

Specific Aim 1

Specific Aim 1 examined group differences between the combined mTBI patient group (n=13) and healthy controls (n=7) (between-subjects Independent Variable) on a visual attention task examining "Go" trial task condition cue types (uncued [UC], direct cue [DC], and misdirectional cue [MDC]) as within-subject Independent Variables. The multivariate model ANCOVA analysis comprised two main effects (task condition and group), as well as one 2-way

interaction (task condition*group), with additional main effects and interactions for patient factor covariates included as well, with results specified below.

The F-tests for condition (across both groups, Hypothesis 1a) and group (across conditions, Hypothesis 1b) were not significant. Follow-up t-tests for each condition separately (UC, DC, and MDC vs. baseline) showed no significant differences; however, two of the planned contrasts among these conditions yielded significant results. Significant clusters of activation were found for the UC-DC contrast at L superior medial/frontal (p=.005, α <.01), L angular gyrus/temporoparietal junction (TPJ) (p=.005, α <.01), and L inferior frontal gyrus (IFG)/dorsolateral prefrontal cortex (dlPFC) (p=.005, α<.02; see Figure 3, Table 4 for significant voxel locations/sizes). Significant clusters of deactivation were found for the MDC-UC contrast at L anterior cingulate cortex (ACC)/ventromedial prefrontal cortex (vmPFC) (p=.01, α<.01; see Figure 4, Table 4 for significant voxel locations/sizes). For the interaction between group*condition, (Hypothesis 1c) significant clusters of increased activation were found at R/L vmPFC/middle orbital frontal cortex (OFC) (p=.006, α<.01) and L dlPFC/mid-frontal regions (p=.006, α<.05; see Figure 5, Table 4 for significant voxel locations/sizes). While this F-test was significant, follow-up contrast t-tests for group effects at each condition (UC, DC and MDC) were not significant.

Regarding individual patient characteristics (Hypothesis 1d), the F-test for biological sex was not significant. However, the F and t-tests for education showed a significant main effect with clusters of correlated activation found at R precentral gyrus (p=.02, α<.01), with a bilateral trend at L/R insula (p=.02, *n.s.*; see Figure 6, Table 4 for significant voxel locations/sizes). A group*education t-test revealed a significant positive correlation (mTBI > controls) at R superior medial/frontal gyrus (p=.02, α<.02) and R middle temporal gyrus/medial temporal lobe (MTL)

(p=.02, α<.05; see Figure 7, Table 4 for significant voxel locations/sizes). F-tests for PCL score and NSI score, as well as group interaction with PCL and NSI scores were all not significant. However, a PCL*condition F-test indicated a significant interaction at L/R SMA (p=.002, α<.01) and R dlPFC/middle frontal gyrus (p=.002, α<.01; see Figure 8, Table 4 for significant voxel locations/sizes), and a significant F-test for the interaction between NSI scores and task condition at R/L middle orbital/vmPFC (p=.001, α<.02) (see Figure 9, Table 4 for significant voxel locations/sizes). Post-hoc t-tests PCL and NSI interactions for each task condition, to determine directionality of results, were not run in this analysis.

Specific Aim 2

Specific Aim 2 examined differences in performance measures of attentional efficiency among mTBI patients with single LOC (n=4), patients with a history of multiple LOC mTBI (n=9) and healthy controls (n=7). For these analyses, behavioral performance measures for accuracy (errors) were analyzed separately for "Go" and "No-Go" trials. Behavioral performance measures for speed (RT) and consistency (ICV and SD) for "Go" trials were also analyzed in separate models, to better understand the associations between these measures of attentional efficiency and brain resources utilization in line with the hypotheses. Given the limited sample size, analyses for this Specific Aim were run for each subgroup as planned (healthy controls, single mTBI, and multiple mTBIs) as well as for the combined mTBI group vs. healthy controls. All results indicate which groups were included in the specific analyses being reported.

No-Go task condition results

For the "No-Go" task condition, the F-test for performance accuracy (manual errors, across all groups, Hypothesis 2a) showed significant clusters of activation at L postcentral gyrus (p=.01, α<.01) and L/R SMA/paracentral (p=.01, α<.03; see Figure 10, Table 5 for significant voxel locations/sizes). The F-test for group (mTBI history in three groups, Hypothesis 2b) was not significant. The group*error F-test revealed a significant interaction at R superior/middle temporal lobe (p=.01, α<.01, Hypothesis 2c; see Figure 11, Table 5 for significant voxel locations/sizes), with follow up t-test indicating a significant negative correlation for the interaction between group (combined mTBI vs. controls) and errors identified at R MTL (p=.02, α<.01; see Figure 12, Table 5 for significant voxel locations/sizes). Among the three groups, a follow up t-test for single mTBI vs. controls was not significant. However, follow-up t-tests between those with a history of multiple mTBIs vs. controls yielded significant positive correlations at R superior/middle occipital gyrus (p=.02, α<.05) and between multiple mTBI group vs. single mTBI group yielded significant positive correlations at R middle occipital/precuneus (p=.01, α<.01; see Figures 13 and 14 respectively, Table 5 for significant voxel locations/sizes). The interactions between errors and each of these group contrasts were not significant.

Go task condition results

Behavioral Performance: Speed

For the "Go" task conditions analyses of performance speed, the F-test for RT (across all groups, Hypothesis 2d) demonstrated a significantly negative correlation in follow-up t-test at L insula (p=.004, α<.05; see Figure 15, Table 6 for significant voxel locations/sizes). The F-test

for group (across all "Go" trials) showed significant clusters of activation at L insula/L superior/medial (p=.02, α<.01; see Figure 16, Table 6 for significant voxel locations/sizes). The interaction between group and RT was not significant (Hypothesis 2e). The correlation of RT with activation in the MDC condition indicated a significant negative correlation at L ACC (p=.01, α<.03; see Figure 17, Table 6 for significant voxel locations/sizes), but RT effects for other task conditions was not significant. Across all "go" trials, follow-up t-test between patients with a history of multiple mTBIs and controls demonstrated significant clusters of positive correlation at R cuneus/middle occipital (p=.02, α<.01) and L superior/middle occipital (p=.02, α<.03; see Figure 18, Table 6 for significant voxel locations/sizes). Additionally, follow-up t-test between the multiple mTBI and single mTBI groups yielded a significant cluster of positive correlation at L insula/superior temporal gyrus (p=.01, α<.01; see Figure 19, Table 6 for significant voxel locations/sizes). The interaction between the single mTBI and control group contrast with RT for the UC condition indicated a significant positive correlation at R postcentral gyrus (p=.002, α<.05; see Figure 20, Table 6 for significant voxel locations/sizes), and the interaction between multiple and single mTBI group with RT for the UC condition indicated a significant negative correlation at R postcentral gyrus (p=.003, α<.01; see Figure 21, Table 6 for significant voxel locations/sizes).

Behavioral Performance: Accuracy

For the "Go" task conditions analysis examining performance accuracy, the F-test for errors (across all groups, Hypothesis 2d) was not significant. Significant positive correlation was identified for the interaction (Hypothesis 2e) between mTBI group contrast (single vs. multiple

mTBIs) with errors at L SMA/paracentral gyrus (p=.01, α<.01) and L superior temporal and postcentral gyrus (p=.01, α<.01; see Figure 22, Table 6 for significant voxel locations/sizes).

Behavioral Performance: Variability

For the "Go" task condition examining performance variability this analysis was conducted both for the proposed ICV measure of variability as well as with each participant's reaction time standard deviation (SD) for consideration as a performance measure. For the ICV analysis of performance variability, the F-test for ICV (across all groups and conditions, Hypothesis 2d) was not significant. The interaction between ICV and group (mTBI history in 3 groups, Hypotheses 2e) was not significant, although there was a significant 3-way interaction between mTBI history with ICV and task condition at L/R cerebellum (p=.005, α<.01; see Figure 23, Table 6 for significant voxel locations/sizes). Follow-up analysis indicated that there was a significant effect for ICV in the DC condition (across groups) that was negatively correlated with activation at L/R cerebellum (p=.02, α<.01; see Figure 24, Table 6 for significant voxel locations/sizes), as well as for ICV (across groups) in the MDC condition at L thalamus (p=.01, α<.01) and cerebellar vermis (p=.01, α<.05; see Figure 25, Table 6 for significant voxel locations/sizes). The contrast for multiple mTBI and control groups in the DC condition also showed significant negative correlation with ICV at L medial temporal pole (p=.002, α<.02) and at L parahippocampus (p=.002, α<.05; see Figure 26, Table 6 for significant voxel locations/sizes). The contrast between participants with a history of multiple mTBIs vs. controls also demonstrated a significant interaction with ICV for the MDC task condition, with significant negative correlation at L medial temporal pole (p=.002, α<.01) and L lingual gyrus (p=.002, α<.05; see Figure 27, Table 6 for significant voxel locations/sizes). For the mTBI group contrast

(multiple vs. single mTBIs) a significant negative correlation was found for the interaction with ICV in the MDC condition at L thalamus (p=.02, α<.05), with a trend toward significance at cerebellar vermis (p=.02, *α<.09 (n.s.)*; see Figure 28, Table 6 for significant voxel locations/sizes).

For the "Go" trials analysis using SD as a measure of performance variability in this visual attention task, the F-test for SD (across all groups and conditions, Hypothesis 2d) was not significant. The interaction between mTBI history and SD (Hypothesis 2e) was also not significant. A significant negative correlation effect for SD on activation in the DC condition was observed at L cerebellum (p=.002, α<.02; see Figure 29, Table 6 for significant voxel locations/sizes). The contrast between the multiple LOC mTBI history group and the control group yielded a significant negative correlation with SD in the UC task condition at L ACC/middle cingulate (MCC) (p=.006, α<.03) and L angular gyrus/TPJ (p=.006, α<.04; see Figure 30, Table 6 for significant voxel locations/sizes). This group contrast (multiple mTBI vs. control groups) additionally showed a significant negative correlation effect with SD in the MDC task condition at R OFC/middle orbital cortex (p=.002, α<.04), as well as a bilateral trend toward significance at L/R MCC (p=.002, *α<.07 (n.s.)*; see Figure 31, Table 6 for significant voxel locations/sizes). Finally, the contrast between the multiple and single LOC mTBI groups demonstrated a significant positive correlation with SD in the DC task condition at L cerebellum (p=.002, α<.03; see Figure 32, Table 6 for significant voxel locations/sizes).

Secondary Aim

Secondary analyses for the combined mTBI group (n=14) and healthy controls (n=7) were completed and reported above in the sample description at the beginning of Results (also see Table 3). Additionally, relationships among key attentional efficiency variables were examined using SPSS across the three subgroups; healthy controls (n=7), single LOC mTBI group (n=5) and multiple LOC mTBI group (n=9). No significant differences were found among these three subgroups for age, although a significant difference in education emerged (p=0.029) with controls having significantly more education (**M**=16.8, **SD**=2.2) than either the single mTBI group (**M**=13.3, **SD**=0.5) or the multiple mTBI group (**M**=14.6, **SD**=2.1). Also among the three subgroups, no significant differences were found in performance measures for RT (*p*=.86), errors (*p*=.38), ICV (*p*=.82), or SD (*p*=.81). The significant difference between healthy controls and the combined mTBI group scores on the PCL, NSI and CES were previously reported (also see Table 3). Follow-up t-tests for these tests were not significant between multiple mTBI and single mTBI subgroups (PCL; *p*=.25, NSI; *p*=.50, CES; *p*=.50).

CHAPTER 4: DISCUSSION

Major findings of the study include identification of early visual attention processing region differences between patients with a history of multiple mTBIs, as well as some individual characteristics which may further impact brain activation patterns among mTBI patients and healthy controls. A key methodological feature of this study was the use of a novel multivariate modeling approach to the neuroimaging data which provided a robust framework for identifying these results despite small sample size, as well as the ability to distinguish between the influences of PTSD and mTBI in brain activation patterns – a problem which has confounded much previous mTBI literature.

This study used a novel neuroimaging analysis modeling approach to investigate possible subgroups of chronic mTBI patients and to examine their unique brain activation patterns. Patients with a history of multiple LOC mTBIs demonstrated differences in brain activation patterns with respect to healthy controls as well as with respect to patients with a history of a single LOC mTBI. Differences among these three groups were found at various brain regions in the visual attention processing pathway, at both early and later stages along the visual attention processing pathway. Differences for the multiple mTBI group occurred most prominently at the earliest stages of visual attention processing, as well as some additional differences in ventral stream processing relative to patients with a history of a single LOC mTBI and correlations between behavioral performance measures at different regions along this visual attention pathway. Together these results suggests a pattern of early processing differences for the multiple mTBI subgroup, as well as additional later performance-related processing differences and brain resource utilization patterns. These findings were above and beyond the potential effects of PTSD. Finally, the potential role for education as a moderator suggests that "cognitive

reserve" may safeguard against some of the detrimental effects of mTBI. Previous neuroimaging research has been unable to consistently distinguish significant reliable factors impacting mTBI outcomes (Bigler, 2013; Chapman & Diaz-Arrastia, 2014; Rosenbaum & Lipton, 2012). In particular, prior analytic methods have been unable to distinguish the effects of mTBI from confounding factors such as PTSD, and modeling methods used in most of the field have been unable to successfully and distinguish reliable subgroups among mTBI patients (Chapman & Diaz-Arrastia, 2014; Diwakar et al., 2015; Jeter et al., 2013; Panenka et al., 2015; Rosenbaum & Lipton, 2012; Ruff, 2011). These prior limitations have yielded mixed results, and therefore this study represents an important next step.

Specifically, this research project used a multivariate modeling approach to investigate subtle effects of mTBI history and covariate effects in the I-BEAM neuroimaging task of visual attention. This approach (not previously observed in the fMRI literature for mTBI) enabled increased detection of interaction effects and more precise accounting of individual factor effects in partitioning of model variance. The model also contributed limitations such as interpretation limited to variables and contrasts included *a priori* in the model as well as sample size restrictions on quantity of variables included in models. This novel analytic method and the implications of its use merit additional discussion and will be covered in more depth related both to this specific study, as well as to potential for use in future analyses. Within the proposed attentional efficiency model for this study, each aim sought to relate other aspects of this model to whole-brain voxel-wise BOLD activation patterns. The first study aim was to investigate task-related differences and demographic contributions to brain activation patterns among participants with a history of mTBI relative to healthy controls. Task conditions included uncued (UC), directional cue (DC), misdirectional cue (MDC) and a "No-go" directional cue

(DC-R). Individual participant covariates in this analysis included demographic variables (e.g. education and biological sex) as well as self-reported symptom scores (e.g. PCL and NSI). Aim two of this study focused on behavioral performance measures (e.g. speed, accuracy and consistency), particularly for each of the mTBI history subgroups (controls vs. single LOC mTBI vs. multiple LOC mTBI).

DISCUSSION OF SPECIFIC AIM 1 RESULTS: COGNITIVE LOAD AND INDIVIDUAL CHARACTERISTICS

Task Condition and Groups

Hypothesis 1a predicted that each task condition would produce significantly different patterns of brain activation, related to their differences in difficulty and therefore reflect differential cognitive load. Analysis of the UC, DC and MDC trial types did not demonstrate significant task condition-specific effects compared to baseline. However, contrasts for the UC condition demonstrated higher activation than for the DC condition at L superior medial frontal which is an area implicated in task-switching (Rushworth, Hadland, Paus, & Sipila, 2002). Increased activation for this contrast was observed at L angular gyrus/TPJ suggesting that the uncued task condition may require increased brain resource utilization at areas of the brain known to be associated with visuo-spatial attention orienting (Posner & Rothbart, 2007) and particularly for unattended cues (Kanwisher & Wojciulik, 2000). Additionally, increased activation at L IFG/dlPFC for UC relative to DC, suggests increased demand on the cognitive control network for these condition-related aspects of the visual attention task (Cabeza et al., 2003; Rosen, Stern, Michalka, Devaney, & Somers, 2015). The UC condition also demonstrated increased brain activation compared to the MDC condition at L vmPFC/ACC, which is a region involved in decision-making and adaptive reward learning (Itti & Koch, 2001; Posner &

Rothbart, 2007) and, in particular, for executive functions related to visual attention (Cabeza et al., 2003). These results suggest that while the I-BEAM task may have limited value as a measure of differential cognitive loads, contrasts among the task conditions highlight differences in attentional resource utilization. Specifically, it appears that the uncued task condition requires more attentional resources for orienting and executive decisions than direct cue or misdirectional trials.

Hypothesis 1b predicted a significantly different number and location of activation clusters between groups, which would suggest differences in brain resource utilization. The mTBI and control groups demonstrated no significant differences in overall task-related brain activation patterns. These results are in line with some previous research studies that have indicated that performance on a number of cognitive tasks is not significantly different between mTBI vs. healthy controls (Terry, Adams, Ferrara, & Miller, 2015; Zhang et al., 2010).

Hypothesis 1c predicted significantly different activation cluster sizes and locations between groups by task condition, which would suggest that differences in resource utilization for each task condition is moderated by mTBI history. The interaction between group and task condition yielded significant clusters of activation at bilateral vmPFC/mid-OFC and L dlPFC/mid-frontal brain regions. These regions are likely involved in differential aspects of executive attention and task performance (Bonnelle et al., 2011; Han, Chapman, & Krawczyk, 2016; Mayer et al., 2012; McAllister et al., 2006; McAllister et al., 2001; McDonald et al., 2012). Additional tests were performed to further characterize the observed clusters of activation, but this analysis did not yield significant results. Previous literature has shown prefrontal regions to be influenced by cognitive load (Tomasi et al., 2004) as well as vulnerable to the effects of mTBI (Bigler, 2013). Given that prefrontal regions have also been consistently

implicated as an important compensatory brain region (Rocca et al., 2010; Rocca et al., 2014) including for those with a history of TBI (Kaufman, Keith, & Perlstein, 2016; Maruishi, Miyatani, Nakao, & Muranaka, 2007; Trapp & Bar, 2015), these results may suggest that groups with different mTBI histories may be differentially engaging this region depending upon the perceived cognitive load for the task condition. These results are also consistent with the previous data indicating differential activation patterns among TBI and control participants at various workloads, particularly at executive brain regions (McAllister et al., 2001).

Individual Clinical Factors

Biological Sex

Building on the previously proposed model, hypothesis 1d predicted that individual participant factors would account for additional model variance and further moderate the relationship between mTBI history and task condition on brain activation patterns. Although there was a significant difference in group composition between males and females in each group, there was no significant main effect for biological sex in these analyses. Importantly, this result suggests that biological sex did not significantly impact brain activation patterns and did not impact the interpretation of study results. Although females were only represented in the control group for this study, the finding that biological sex did not impact the results is in line with previous literature (Mathias & Wheaton, 2015). Some literature has suggested that overall outcomes following TBI may be comparable (Mathias & Wheaton, 2015), although given the lack of females in the mTBI group this result should be interpreted with caution.

Education

Education was positively correlated with activation at R precentral and there was a trend of increased activation at the bilateral insulae. Although there are no comparable data on mTBI, these regions of the brain were associated with cognitive reserve in a study of multiple sclerosis (Rocca et al., 2010). Additionally, there was a significant interaction between group and education in this study, suggesting that a higher level of education was associated with larger increases in activation relative to controls at the R superior medial/frontal and R middle temporal brain regions. These findings are also consistent with previous literature findings related to cognitive impairment in multiple sclerosis (Rocca et al., 2010). Previous literature has also found that education correlates with maintenance of fiber tract integrity in compensatory areas including fronto-temporal-parietal regions in other disease states that impair cognition (Rocca et al., 2014; Teipel et al., 2009). Furthermore, recent literature suggests that frontal executive regions may compensate for decreased functional connectivity and early visual processing deficits, and this compensatory ability may be highly associated with cognitive reserve (Gilmore et al., 2016; Oldenburg, Lundin, Edman, Nygren-de Boussard, & Bartfai, 2016). It is possible that education moderates the effects of mTBI on attention modulation and executive attention decisions at these middle temporal and frontal brain regions as compensatory areas involved in cognitive reserve.

Symptom Profiles

With regard to individual symptom profiles, PCL and NSI scores did not demonstrate a significant relation with brain activation patterns across conditions in this visual attention task. Importantly, although significant differences in PCL and NSI symptom scores between the mTBI and control groups were found, neither of these scores explained differences observed between

groups nor revealed unique brain activation pattern results in this study across all task conditions and groups. Due to the novel analysis approach used in this study, this result may represent a unique contribution to the literature. Although a scatter plot between symptoms commonly related to PTSD (i.e., PCL score) and postconcussive neurobehavioral symptoms (i.e., NSI score) for where data are available within this sample (n= 6 CTL, 14 mTBI) suggests a relationship between these variables (see Figure 33), the influence of these symptoms on the group results described in the model for Aim 1 has been statistically controlled. Specifically, the multivariate approach used in the 3dMVM program allowed for inclusion of PCL and NSI as covariates in the model to control for their effects separate from those of mTBI or other task condition and individual characteristics studied (G. Chen et al., 2014; G. Chen et al., 2015). While sample size limitations prevented inclusion of these covariates in Aim 2 models, results from Aim 1 suggest that results for mTBI history may be observed separately from these covariates.

However, a significant interaction between PCL and task condition was found at R/L SMA and R dlPFC/middle frontal brain regions, indicating that PTSD symptoms may have differential impacts on task conditions. While these areas include "alerting" areas within Posner's attention model (Posner & Rothbart, 2007), these areas may also be especially sensitive to effects of PTSD on cognitive reappraisal (MacNamara et al., 2016). Additionally, NSI score demonstrated a significant interaction with task condition at bilateral mid orbital/vmPFC, indicating that neurobehavioral symptoms may also differentially impact task condition brain activation patterns, specifically in regions involved in alerting and executive aspects of attention (Posner & Rothbart, 2007). Determining the exact nature of these interactions would require additional post-hoc tests. Such future analysis is warranted as previous literature has shown that this brain region is particularly vulnerable to the effects of mTBI (Bigler, 2013). Furthermore,

mTBI has been shown to decrease functional connectivity from PFC to other visual attention areas, which may also contribute to additional symptoms and be correlated with processing deficits (Gilmore et al., 2016) in TBI patients (Gilmore et al., 2016; Mayer et al., 2012). The potential presence of brain regions which may be vulnerable to the effects of TBI and contribute to neurobehavioral symptoms represents an important area for future studies. This analysis yielded some significant findings among the additional patient variables (e.g., gender, education and symptom scores) incorporated into this analysis. Findings specific to the effects of mTBI include evidence that these effects are separate from the impacts of PTSD and neurobehavioral symptoms, and also that education demonstrates a differentiable impact on brain activation patterns for this mTBI group relative to controls.

Overall Aim 1 Findings

Within the context of existing literature, results from the analysis model for Aim 1 suggests there may be differences in brain resource utilization between mTBI patients and healthy controls depending upon the specific task being performed. Importantly, these results suggest that the effects of mTBI are independent from the impact of PTSD and other neurobehavioral symptoms. Moreover, education as a type of cognitive reserve may help to moderate the impact of mTBI on visual attention processing.

DISCUSSION OF AIM 2 RESULTS: PERFORMANCE MEASURES OF ATTENTIONAL EFFICIENCY

Specific Aim 2 investigated correlations of various performance measures of attentional efficiency including speed (RT), accuracy (errors) and consistency (ICV and SD) for the I-BEAM task with respect to patterns of brain activation (i.e. resource utilization).

"No-Go" Task Condition Errors

Hypothesis 2a predicted that participants who make more errors would produce significantly different patterns of brain activation compared to those who did not make errors on the "No-Go" task condition. Errors demonstrated a significant effect on brain activation patterns at L postcentral gyrus and L SMA/paracentral gyrus. Because these regions are primarily at motor cortex, it is possible these results reflect activation error movement compared to correct non-movement brain activity. Due to modeling limitations, such regions were not tested *a priori*, and further insight into the precise nature of these activation patterns was unable to be explored. However, prior literature suggests that supplementary sensorimotor areas may be recruited to compensate for increased attentional task demands during a task, and this increased compensatory resource utilization may contribute to cognitive fatigue (L. B. Reid, Boyd, Cunnington, & Rose, 2015). Such a possibility with regard to individuals with mTBI warrants investigation.

"No-Go" Task Inhibition Group Differences

Hypothesis 2b predicted that mTBI history (healthy controls vs. single LOC vs. multiple LOCs mTBI groups) would be significantly associated with different patterns of brain activation. Healthy controls did not differ from patients with a single history of LOC mTBI. Given the

controversy in the literature regarding a lack of consistent fMRI findings associated with mTBI across various cognitive tasks (Zhang et al., 2010)this finding was not surprising. By contrast, patients with a history of multiple LOC mTBIs demonstrated significantly increased activation compared to healthy controls at R superior/middle occipital and compared to patients with a history of single LOC mTBI at R precuneus/middle occipital lobe. Interestingly, prior research with control participants demonstrates fairly consistent middle occipital activation (Mangun, Buonocore, Girelli, & Jha, 1998). In this study, however, differences were observed at this region between multiple mTBI patients compared to both healthy controls and patients with a history of single mTBI. As one of the brain regions involved early in the neural pathway for visual attention, it is therefore possible that these activation differences for patients with a history of multiple mTBIs may contribute to heterogeneity previously reported in the literature regarding patients' performance and outcomes (Kanwisher & Wojciulik, 2000). In particular, given differences in fMRI measures of attentional efficiency found between the mTBI subgroups in this study, patients with a history of multiple mTBIs may represent a unique subgroup meriting further study.

"No-Go" Task Performance Accuracy and Group Differences

Hypothesis 2c predicted differential brain activation patterns between groups (none, single, and multiple LOC mTBIs) with regard to performance accuracy measure of attentional efficiency. Although none of the individual group (healthy controls vs. single mTBI, healthy controls vs. multiple mTBI, and single vs. multiple mTBI history) demonstrated a significant interaction with errors, the contrast for combined mTBI group vs. healthy controls showed a significant effect at R MTL with a higher difference in activation for the mTBI group correlating

with decreased errors. Given the role of MTL in attention modulation (Pessoa, Kastner, & Ungerleider, 2003), it is plausible that differences between healthy control and mTBI groups on this task might reflect an association between behavioral performance (errors) and resource utilization (brain activation pattern) components of the study model of attentional efficiency. Although this hypothesis was partially supported, it is possible that these interaction analyses were underpowered due to small subgroup sample sizes. Future studies with larger sample sizes will be needed to determine the reliability of this effect.

"Go" Trials Behavioral Performance Measures

Hypothesis 2d predicted that for participants with a high degree of behavioral performance inefficiency (e.g. slow RT, large number of errors, and/or high RT variability), significant differences in brain activation patterns would reflect potential differences in underlying neurocircuitry and resource utilization within the study model. For each of the analyses supporting hypotheses 2d and 2e, all three proposed mTBI history subgroups (controls as well as single and multiple LOC mTBI groups) were included and post-hoc analyses were run as indicated. For clarity and comprehension, behavioral performance measure results for each hypothesis will be described separately below.

Reaction Time (RT)

RT demonstrated a significant effect at L insula such that increased activation at this brain region was correlated with decreased (aka faster) reaction time. These results are in line with prior literature supporting the insulae as an important structure in visual attention processing (Gitelman et al., 1999; Menon & Uddin, 2010; Nelson et al., 2010). In particular, the insula has been implicated directly in RT for visual attention (Tomasi et al., 2004),

Specifically, RT was also negatively correlated in the MDC condition with activation at L ACC, suggesting that decreased brain activity at frontal executive attention and decision-making areas is associated with longer reaction times for misdirectional cues. These preliminary findings support existing fMRI literature demonstrating alterations in frontal executive brain activation patterns in response to various task demands (McAllister et al., 2006; Owen, McMillan, Laird, & Bullmore, 2005) and these activation patterns' critical role in proper reaction time and executive control functions (Ansado et al., 2013; Botvinick, Cohen, & Carter, 2004; Matsumoto & Tanaka, 2004). Literature also describes these regions' compensatory role in maintaining adequate behavioral performance. Results of the current study mostly align with literature demonstrating often comparable mTBI patient task performance to that of controls (McAllister et al., 2001; L. B. Reid et al., 2015). It is reasonable to conclude that these regions may already be under strain for certain tasks and thus may be less able to consistently contribute to maintaining compensatory performance for those with a history of mTBI (Fay et al., 2009; Maruishi et al., 2007).

Errors

The "Go" task errors null result indicated that there was no specific significant pattern to brain activation patterns for errors across all tasks and groups. Of note, no significant differences were found between groups in task performance. Given some previously described differences in activation patterns between task conditions and between groups included in this study, it is possible that error processing in the I-BEAM task does not exhibit a single unified pattern.

Intraindividual Coefficient of Variation (ICV)

ICV does not appear to yield a singular activation pattern across the I-BEAM task. However, there was a significant negative correlation for ICV in the DC task condition at bilateral cerebellum, meaning that increased performance variability in this condition correlated with decreased activation at the cerebellum. Prior research has indicated that the cerebellum is also involved in aspects of visual-spatial cognition and attentional processes in addition to integration and coordination of eye and other fine motor movements (Schmahmann, 2004; Schmahmann & Caplan, 2006; Striemer, Chouinard, Goodale, & de Ribaupierre, 2015). Additionally practice effects decrease visual attention network activation at the cerebellum (Tomasi et al., 2004). Therefore insufficient cerebellar activation during the task, and especially while still somewhat novel or unfamiliar, might therefore contribute to inconsistency in this simple RT task measure. A significant positive correlation with brain activation for ICV in the MDC task condition was also found at L thalamus and cerebellar vermis, meaning that increased performance variability in this condition was correlated with higher levels of activation at these brain regions. Because the thalamus plays an important role in regulating arousal and involvement in the "alerting" component of attention (Posner & Rothbart, 2007), altered activation at this brain region might lead to higher response variability. Regulation of both focused and stimulus-driven attention modulation at the thalamus (Clemens et al., 2013) may require increased resource utilization to override the false cue information provided in this task condition in order to generate accurate responses. Interestingly, increased activation at thalamus and cerebellar vermis have also been correlated with task difficulty (Tomasi et al., 2004). It is possible that perceived task difficulty contributes to higher engagement at these brain regions and is correlated with higher within-subject variability. Prior research also suggests that the thalamus may play a role in the generation of anti-saccadic eye movements (Kunimatsu &

Tanaka, 2010). Additionally, the cerebellar vermis has been implicated in the control of eye movements (Striemer et al., 2015; Takagi, Zee, & Tamargo, 2000), which perhaps somewhat differentiates performance of this task condition. Taken together, because the misdirectional task condition requires participants to look in the opposite direction to the cued arrow, the addition of anti-saccadic eye movement and increased demand for eye movement control in this task condition may also fit with prior literature (Kunimatsu & Tanaka, 2010; Striemer et al., 2015; Takagi et al., 2000).

Reaction Time Standard Deviation (SD)

Although RT standard deviation (SD) by itself did not have a statistically significant effect on brain activation patterns, specifically within the DC task condition, SD was significantly correlated with reduced brain activation at L cerebellum. This performance variability correlation with brain activation in the DC task condition suggests that poor engagement of the cerebellum may contribute to response inconsistency, parallel to the results from the analysis for ICV (Schmahmann, 2004; Schmahmann & Caplan, 2006; Striemer et al., 2015; Tomasi et al., 2004).

Group Differences in "Go" Trials Behavioral Performance Measures

Hypothesis 2e predicted that differences in performance metrics (e.g. RT, errors and ICV/SD) would differentially impact brain activation patterns with respect to mTBI history. Significant differences in these measures of attentional efficiency between groups might highlight brain regions that are particularly sensitive to the effects of mTBI.

Reaction Time (RT) Group Differences

RT differences among mTBI history groups (controls, single LOC mTBI, and multiple LOC mTBI groups) across all "Go" trials demonstrated a significant interaction at L insula/superior temporal gyrus. Across all task conditions and regardless of RT, patients with a history of multiple LOC mTBIs demonstrated significantly more activation than controls at R cuneus/middle occipital and L superior/middle occipital regions, primarily overlapping early visual regions correlated with these group differences in the "No-Go" trial analysis. Together these results suggest differences in early visual information processing between these groups may contribute to downstream effects on visual attention and task performance. Patients with a history of multiple LOC TBIs also demonstrated significantly higher brain activation than single LOC mTBI patients at L insula/superior temporal gyrus across "Go" trials. Given similar task performance between these two mTBI subgroups revealed by the secondary aim results, this finding may suggest that increased saliency detection and performance monitoring provided by these brain regions is needed for patients with a history of multiple LOC mTBIs to match comparable visual attention processing to those with a single prior mTBI. Some literature also indicates that the insulae receive projections from the precuneus as part of the visual attention pathway where selective attention and arousal saliency information are integrated with sensorimotor information (Gitelman et al., 1999; Margulies et al., 2009). In particular, it appears that the insulae may assist in error detection and performance monitoring (Nelson et al., 2010) as part of the network for integration of saliency feedback (Menon & Uddin, 2010). Brain activation pattern differences for areas involved in performance monitoring may be unrelated to initial differences in early visual processing. However, these findings suggest that patients with a history of multiple mTBIs may require greater resource utilization than either healthy controls or patients with a history of single LOC mTBI to maintain comparable task performance. While

these specific differences in brain activation patterns between patients with histories of single and multiple mTBI have not been investigated in the neuroimaging literature, previous studies have found altered brain activation patterns for mild and moderate TBI patients relative to controls in a working memory task (McAllister et al., 2001), and for patients with a history of multiple mTBIs relative to controls in a linguistic learning and recall task (Terry et al., 2015).

Significant RT-correlated differences were observed in the UC condition for patients with a history of a single LOC mTBI compared with both healthy controls as well as multiple mTBIs at R postcentral gyrus. These differences suggest that higher RT was correlated with larger activations for single mTBI patients relative to controls, and smaller differences between single mTBI and multiple mTBI patients at this sensorimotor region. Given the inclusion of one patient in the single mTBI group who did not press buttons for the UC condition, it is possible that these specific motor area results are driven by the differences in motor activation from this subject, although a subsequent QA analysis performed without this participant revealed comparable results with reduced power likely due to the relatively small sample size. As suggested in previous literature, the postcentral region may reflect speeded manual responses and eye movements (Corbetta et al., 1998). Together these results suggest that the more single mTBI patients sensorimotor activation patterns are akin to multiple mTBI patients, the slower their responses will tend to be.

Errors and Group Differences

"Go" trial errors significantly interacted with the group contrast between multiple and single LOC mTBI subgroups at L SMA/paracentral and L superior temporal/postcentral brain regions. Given motor area activation found in the RT analysis, it is possible that this result is influenced by a single participant's inaccurate performance in the UC task condition, however, a

comparison analysis without that participant did not significantly change results for this brain region. However, these results also parallel brain regions activated by overall errors in the "No-Go" task condition, which were not compromised UC task response issues for that participant, and results excluding this subject were comparable. Furthermore, these results are highly consistent with models for visual and attention processing (Corbetta & Shulman, 2002; Itti & Koch, 2001; Kanwisher & Wojciulik, 2000; Kastner & Ungerleider, 2000; Margulies et al., 2009), including supplementary sensorimotor and compensatory brain regions in addition to those for ventral visual processing and hand/eye movements (Corbetta et al., 1998; L. B. Reid et al., 2015). Combined with previously identified early visual attention pathway differences between these mTBI groups, differences in error processing at these supplementary vision and motor processing regions may also contribute to downstream effects on behavioral performance. Importantly, these groups all demonstrated comparable task accuracy performance. Therefore, differences in activation at these sensorimotor association and object processing brain areas suggest that they may be recruited as part of a compensatory strategy for patients with multiple mTBIs to maintain adequate comparable behavioral performance to patients with a history of a single mTBI.

Intraindividual Coefficient of Variation (ICV) Group Differences

ICV brain activation patterns did not differ significantly by group. It is possible this analysis was underpowered to detect actual differences between any of the groups. However, it is also possible that RT variability is not a sufficient factor to differentiate between these three groups, suggesting that there may not be a single source of variability in performance, and the process may be more nuanced. Following this premise, a three-way analysis of group ICV and condition yielded a significant interaction effect at bilateral cerebellum. Follow-up analyses

indicated that smaller ICV performance variability in the DC condition correlated with larger differences in activation between the multiple mTBI than controls at L medial temporal pole and L parahippocampus. The correlation between performance variability and temporal pole activation makes sense for its involvement in anticipatory control of visual tracking, and also particularly for its role as a compensatory area for frontal deficits (Diwakar et al., 2015). As peripheral association regions involved in place/object recognition and semantic memory association (Arrington, Carr, Mayer, & Rao, 2000; Cabeza et al., 2003), it is possible that either insufficient deactivation or excessive engagement at these regions for patients with a history of multiple mTBIs contributed to response variability. However, the visual attention literature suggests that medial temporal pole is an important brain region involved in anticipatory control for visual tracking, and may also be involved in compensating for frontal deficits (Diwakar et al., 2015). Therefore, higher engagement of this region among those with a history of multiple mTBI might suggest fewer coordinated compensatory strategies and therefore contribute to more variability in an individual's task performance. The visual attention literature also indicates a role for the parahippocampus in working memory representation of spatial layout for objects (Arrington et al., 2000; Cabeza et al., 2003), which would suggest that higher activation at this region might be necessary to maintain consistent task performance.

Follow-up tests of the group contrast between multiple LOC mTBI patients and controls in the MDC condition indicated that smaller differences in ICV performance variability correlated with larger differences in activation at L medial temporal pole and L lingual gyrus. Similar to previous result, whether insufficient deactivation or excessive brain resource utilization at these regions contributes to performance variability is unclear from the current analysis performed. However, this ambiguity in the results may be better understood within the

context of the visual attention literature. In particular activation at the L medial temporal pole for both the DC and MDC task conditions suggests that for patients with a history of multiple mTBIs higher activation is seen at this location may also contribute to performance variability as a compensatory region (Diwakar et al., 2015). In addition, greater activation at the lingual gyrus makes sense in the context of literature supporting its role in attentional modulation particularly in response to repetitive stimuli (Vuilleumier, Schwartz, Duhoux, Dolan, & Driver, 2005). As a peripheral processing region earlier in the visual attention pathway, it is possible that higher activation at a region tuned to similarity of stimuli might also correlate with inaccurate or inconsistent attentional modulation and therefore contribute to performance variability.

Follow-up tests of the group contrast between multiple and single LOC mTBI patients also indicated that smaller differences in ICV performance variability in the MDC condition correlated with larger differences in activation at L thalamus. While the precise directionality of results is unclear from this analysis, previous literature suggests an important role for the thalamus as an essential component in successful attentional alerting and regulation of arousal (Clemens et al., 2013; Posner & Rothbart, 2007), as well as task differentiation (Tomasi et al., 2004) and anti-saccadic eye-movements (Kunimatsu & Tanaka, 2010) that might be involved particularly for the misdirectional condition. In contrast to the overall effect of ICV in the MDC condition, these results indicate that smaller differences in activation among these two patient groups contributed to higher performance variability. If these smaller differences in activation between groups at this single location contributed to increased variability, it is likely within the context of differential brain activation patterns at other locations as well.

Reaction Time Standard Deviation (SD) Group Differences

Follow-up tests for the contrast between multiple LOC mTBI patients and controls indicated that smaller differences in SD performance variability in the UC condition correlated with larger differences at L ACC/MCC and L angular gyrus/TPJ. Similar to prior analyses, while the precise directionality of these performance variability results cannot be determined from the model that was run, prior literature suggests these areas are typically active in the attention processing pathway for executive attention and visuospatial attention orienting respectively (Posner & Rothbart, 2007). Previous studies indicate an important role for ACC in frontal executive decision making as part of a "top-down" process modulating visuospatial attention (Corbetta & Shulman, 2002; Crottaz-Herbette & Menon, 2006; Pierrot-Deseilligny et al., 2005). The MCC is also an important executive region involved in conflict/error response selection and attentional control, and it has strong connections to other processing and compensatory brain regions (Yu et al., 2011). Regarding activation differences at L angular gyrus/TPJ, prior literature is limited with regard to task performance variability, but suggests this area is an important functional visual association area involved in the ventral processing stream for unexpected stimuli (Vossel, Geng, & Fink, 2014) and is particularly involved in reorienting attention toward unattended locations (Margulies et al., 2009). Multiple mTBI patients demonstrating larger variability in task performance may be associated with less engagement at this area relative to controls (Huettel, Güzeldere, & McCarthy, 2001). These brain regions are also especially vulnerable to the effects of mTBI (Bigler, 2013). As part of the fronto-temporo-parietal network involved in visual attention, the L ACC/MCC and L angular gyrus/TPJ are involved in attention modulation and feedback. Results suggest that for multiple mTBI patients, decreased activation relative to controls at these regions might contribute to greater performance variability.

Follow-up tests for the group contrast between multiple LOC mTBI patients and controls in the MDC condition indicated that smaller differences in SD performance variability correlated with higher activation at R OFC/middle orbital gyrus. While the relative activation levels between groups would require supplementary analysis, this area has been reported to be involved in cognitive decisions and executive attention, particularly with regard to task performance in visual novelty discrimination (Trapp & Bar, 2015), and as a compensatory visual processing area in healthy aging (Kaufman et al., 2016).

This contrast also demonstrated a bilateral trend at the MCC, echoing previously discussed results between multiple mTBI patients and controls for SD in the UC task condition. Frontal executive regions have been demonstrated to have roles in reaction time and executive decisions, and compensatory processing (Ansado et al., 2013; Botvinick et al., 2004; Matsumoto & Tanaka, 2004). Previously discussed results in this study also showed altered activation in this MDC task condition for RT at frontal executive regions. As suggested in the discussion for this RT analysis, if higher engagement is required for both task-related and compensatory responses, these frontal/executive regions might not be able to consistently compensate behavioral performance (Fay et al., 2009; Maruishi et al., 2007). For patients with a history of multiple mTBIs, alterations in brain activation patterns observed relative to the control group at ACC/MCC for the UC and MDC task conditions might suggest difficulties maintaining both these compensatory and task-related demands on attentional resources. Considered together with prior research, the current study results suggest that patients with a history of multiple mTBI may not only expend more brain resources to maintain comparable behavioral performance (McAllister et al., 2001; L. B. Reid et al., 2015) but may also demonstrate subtle deficits indicating a struggle to perform consistently under increased demands.

Follow-up tests for the group contrast between multiple and single LOC mTBI patients in the DC condition indicated that larger differences in SD performance variability correlated with larger differences in activation at L cerebellum. Previous literature suggests that alterations in attentional resources at the cerebellum may be correlated with RT and performance accuracy (Tomasi et al., 2004). Additional follow-up analyses would be needed to determine the precise directionality and size of activation differences for patients in the multiple mTBI group relative to patients with a single mTBI. However, further interpretation of these results is not possible since the analyses were not included in the study model *a priori*. These results are in line with prior studies and visual attention processing models involving the cerebellum (Striemer et al., 2015). Previous literature has also demonstrated the cerebellum's contributions to performance accuracy and sensitivity to cognitive load (Tomasi et al., 2004), as well as its role as a compensatory structure associated with cognitive reserve (Rocca et al., 2010). Thus, future research with a larger mTBI sample should consider these areas for analysis.

Summary Aim 2 Findings

Results of Aim 2 suggest patients with a history of multiple LOC mTBI demonstrate significantly different brain activation patterns at early visual processing areas. These findings are comparable to the effects of a higher cognitive task load compared with single mTBI and healthy controls. Although no significant differences in performance measures for RT, errors and ICV were found, additional differences in brain activation patterns related these attentional efficiency measures were seen among subgroups primarily at middle (dorsal/ventral) and supplementary processing regions. Specifically, more errors and higher variability correlated with decreased engagement of modulatory and compensatory brain regions.

Discussion of Secondary Aim: Clinical Profiles

Although no age differences were found among the three groups, controls had somewhat higher level of education than either of those in the mTBI subgroups. When mTBI subgroups were combined, however (such as in the covariate analysis for Aim 1), no significant differences in education were found between mTBI patients and healthy controls. Therefore, it is likely that the neuroimaging results found to correlate with education were not skewed by disparate groups. Likewise, while there was an expected difference between the healthy controls and combined mTBI patients in PCL scores, no significant differences between the two mTBI subgroups were observed. Additionally, there was an expected difference between the healthy controls and mTBI patients in NSI scores, and a significantly higher NSI-Physical symptoms subscale score was reported for the single mTBI group than for the multiple mTBI group. By contrast, neither NSI-Cognitive score nor NSI-Affective subscale score differed between the mTBI subgroups (single vs. multiple mTBIs). Importantly, the mTBI patients included in this study represent a true clinical sample of Active Duty military chronic mTBI patients who present to NICoE for comprehensive diagnostics and treatment planning. In addition to being expected within the clinical sample, these factors were explicitly controlled for in the Aim 1 analytic model. Otherwise, no significant differences among individual patient factors analyzed were found, or between mTBI subgroups. It is therefore likely that differences seen between these mTBI history groups in brain activation patterns, unless otherwise stated, were not better accounted-for by other individual patient variables. Regarding behavioral performance measures, there were no differences in RT, errors, ICV, or SD among any of the three subgroups. Within the framework of Silver and colleagues' model (Silver et al., 2009), it is likely that biopsychosocial

factors may contribute to sources of performance variability between individuals. However, within the analytic modeling approach applied in the current study, it is unlikely that any of these individual variables confound the results detailed in this discussion.

General Discussion and Implications

Preliminary results suggest an emerging pattern of early visual pathway activation differences for multiple mTBI when compared both to single mTBI patients as well as to controls. While determining the cause of such differences is beyond the scope of this study, these findings suggest that a history of multiple mTBIs may have an effect similar to that of increased cognitive load. Such an interpretation echoes previous literature observing activation differences at these regions correlated with increased cognitive load (Kanwisher & Wojciulik, 2000; Tomasi et al., 2004). Additionally, significant differences were observed at middle (dorsal and ventral processing regions) stages in the visual attention pathway. Differences are particularly evident between mTBIs subgroups for behavioral performance measures and at certain regions previously identified to be involved in compensatory processing (Ansado et al., 2013; Kaufman et al., 2016; Maruishi et al., 2007).

While significant differences were found in comorbid PTSD symptom severity between the mTBI and healthy control groups in this clinical sample, statistical modeling allowed for the representation of individual patient variables included Aim 1 to be separated from the effects of mTBI. Importantly, these mTBI results are not confounded by the effects of PTSD as has often occurred in prior literature (Chapman & Diaz-Arrastia, 2014; Elder, Mitsis, Ahlers, & Cristian, 2010; McDonald et al., 2012). Similar to mTBI, anxiety disorders (such as PTSD) may represent a type of increased cognitive burden (I. Chen & Chang, 2009) in addition to the effects of mTBI.

Diagnostically, use of additional demographic and individual information could help identify meaningful subcategories within the mTBI diagnosis. Clinical availability of such subcategories could assist in treatment planning by identifying therapies that are individually tailored to relieve cognitive burdens for those with a history of one or more prior mTBIs. Education may also act as a moderator for the effects of mTBI as a form of cognitive reserve (Fay et al., 2009; Oldenburg et al., 2016). Therapeutic opportunities for adaptive training or integration of supplementary processing approaches may benefit patients with a history of mTBI (Laatsch, Thulborn, Krisky, Shobat, & Sweeney, 2004; Munivenkatappa, Rajeswaran, Indira Devi, Bennet, & Upadhyay, 2014).

Finally, this study provides support for the use of the MVM analytic modeling approach to neuroimaging studies of this nature as a means to investigate complex and interrelated variables separately within context (G. Chen et al., 2014). Future studies might benefit from additional investigation of relationships among factors included in these models (including directionality) to improve interpretation of these findings in a larger sample.

Limitations in Previous Literature

The TBI outcomes literature remains inconsistent due to TBI classification controversy and lack of clarity about the impacts of pre-injury and post-injury factors. While neuroimaging studies have advanced our knowledge in this field, a number of issues continue to limit our understanding. One area where understanding is limited involves correlations between the pathophysiology of trauma and subsequent effects on the brain networks involved in task performance and neurobehavioral symptoms. Military service members are at elevated risk for incurring multiple mTBIs (Gean, 2014; MacGregor, Dougherty, Morrison, et al., 2011), and a

significant minority report chronic neurobehavioral symptoms that impact operational readiness and long-term quality of life (Chapman & Diaz-Arrastia, 2014; MacGregor et al., 2013). The specific neural correlates of these chronic neurobehavioral symptoms can be conceptualized as individual patient factors that potentially impact behavioral performance measures of attentional efficiency. This conceptual model may provide an explanatory mechanism for the impact of mTBI on clinical outcomes.

Additionally, prior literature has suffered from heterogeneity in diagnostic methods, patient symptom reports and outcomes for mTBI patients. These findings may be partially attributed to the poorly understood and complex pattern of injury and sequelae that can result from mTBI. Significant variability in resource utilization and performance – even among those who have experienced similar injuries – suggests that more sophisticated analyses may be warranted. Specifically, neuroimaging analysis methodology has constrained existing literature due to limitations in detecting interactions and controlling for the effects of covariates (G. Chen et al., 2014).

Study Conceptual Analytic Framework

This research project utilized a novel task and neuroimaging statistical analysis approach to overcome these limitations with detection of effects and confounding covariates found in prior research. In the present study of patients with a history of mTBI and healthy control participants, preliminary evidence suggests that the I-BEAM task of visual attention demonstrated limited utility for measuring differences in cognitive load across conditions. Although brain activation patterns in this visual attention task may not significantly differ between trial types, use of a novel statistical modeling approach to investigate the interaction of differential mTBI history

(i.e. differences between groups with a history of none, single or multiple LOC mTBIs) revealed subtle underlying differences in attentional efficiency likely to be missed without use of such analysis methods. Additionally, this study model was able to account for task effects on brain activation patterns between mTBI and controls separate from the effects of PTSD, which previously has been a confound in much of the literature.

A history of prior mTBIs may also interact with certain task demands captured by behavioral performance metrics and fMRI brain activation resource utilization. To discuss these results further, it will be beneficial to establish a better framework for modeling the brain resource utilization component of attentional efficiency.

Toward an Integrated Visual Attention Network Model

A robust integrated model incorporating relevant visual attention-related models would require significant additional research and is beyond the scope of this study. However, it is hoped that a description of some models in the relevant literature could provide a helpful framework and common language to better present study findings. Establishing such a framework is challenging, in part due to problems in prior literature with respect to accurate and consistent diagnostics for mTBI. Such an undertaking is further complicated by a lack of common descriptive language for brain regions and networks involved in visual attention. The literature related to mTBI and attention spans multiple approaches and methods for investigating similar brain regions and concepts, the lack of a precise alignment between described networks and models further confuses an inherently complex issue. A useful framework will be provided by drawing upon the attentional and visual information processing literature, using general descriptions of structures involved in related tasks and pathologies

Posner and colleagues' description of the alerting, orienting and executive attention networks (Petersen & Posner, 2012; Posner & Rothbart, 2007) described previously, while somewhat varied across papers, generally overlaps task-related visual attention networks described including occipital, thalamus, caudate nucleus, superior and inferior parietal lobes, medial temporal, ACC, PFC, cerebellum, and sensorimotor areas (Cabeza et al., 2004; Cabeza et al., 2003; Kanwisher & Wojciulik, 2000; Striemer et al., 2015).

These models may also be described to have "where/how" and "what" processing streams subserving various aspects of visual and sensory information processing (Kastner & Ungerleider, 2000; Milner & Goodale, 2008; Pierrot-Deseilligny et al., 2005; Vossel et al., 2014). Specifically, information regarding perceived object spatial location and motion may be integrated with motor coordination processes along dorsal regions of the brain, and processes for object recognition and memory-related operations may occur along a ventral pathway within the brain (Pessoa et al., 2003). Additionally, models include elements for both "top down" (frontal/executive) and "bottom up" (saliency-driven) modulation on this system (Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000; Pessoa et al., 2003; Pierrot-Deseilligny et al., 2005).

Although conceptually useful, these models do not integrate as nicely with established network models for more general task-related processing. Specifically, brain regions described above vary by source as to how they are categorized within network models. As previously described, there is no consensus in the literature as to how many networks exist. Together with the above described models there may be some overlap with networks for cognitive control with "executive" areas above at prefrontal cortex (Han et al., 2016; Kanwisher & Wojciulik, 2000; Rosen et al., 2015). Dorsal attention network overlap with these study results also exists at

superior parietal and SMA and frontal eye fields (Han et al., 2016; Kanwisher & Wojciulik, 2000; Rosen et al., 2015). Saliency network overlap integrates with ventral processing stream saliency regulation influences at insula and ACC (Corbetta & Shulman, 2002; Menon & Uddin, 2010). The default mode network often described, however, may be the poorest overlap with above models with some regions of the ventral processing stream as well as "orienting" attention areas and brain regions not otherwise included above (Bonnelle et al., 2012; Corbetta & Shulman, 2002; Han et al., 2016; Raichle et al., 2001; Rosen et al., 2015).

Although this preliminary framework description is based in substantial previous literature from neuroimaging (Bonnelle et al., 2011; Gitelman et al., 1999; Mangun et al., 1998; Rosen et al., 2015), attention and vision (Arrington et al., 2000; Cabeza et al., 2003; Clemens et al., 2013; Corbetta & Shulman, 2002; Corchs & Deco, 2002; Itti & Koch, 2001; Milner & Goodale, 2008; Posner & Rothbart, 2007; Vossel et al., 2014), TBI (Gilmore et al., 2016; Mayer et al., 2012), and other pathologies (Cabeza et al., 2004; Rocca et al., 2010; Rocca et al., 2014), and although this framework may be helpful to discuss results of the current study, the poor integration of these models and lack of common language used to describe them renders preliminary efforts incomplete. The need for a better integrated model of visual attention processing remains an important research endeavor (Cabeza et al., 2003; Itti & Koch, 2001). This study investigated correlations between several task-related and individual-level factors to better investigate differences in brain activation at these areas with respect to mTBI. Particularly, using sophisticated analysis models (G. Chen et al., 2014; G. Chen et al., 2015) there was preliminary evidence for the existence of subgroups within the mTBI population (single LOC vs. multiple LOC). Furthermore, results suggest that aspects of individual

behavioral performance may be differentially affected by brain activation patterns correlating with various processing tasks and networks above.

Study Results in Context

This project further investigated how these specific mTBI subgroup differences impact resource utilization (brain activation patterns) and behavioral performance metrics contained within an "attentional efficiency" conceptual study model. While there appeared to be a differential for task condition among groups, it is unclear what the exact nature or source of significance for this interaction might be. These results might make sense within the context of prior literature regarding frontal executive effects on "top-down" modulation of attention (Kastner & Ungerleider, 2000). Individual factors may also contribute to differences among these groups (Silver et al., 2009) related to brain resource utilization as an element of attentional efficiency. For example, the impact of mTBI history on certain aspects of attentional processing may be moderated by education (Fay et al., 2009; Oldenburg et al., 2016).

Generally, stages may be observed across models for visual attention processing. Specifically, visual perception and initial visual scene processing occurs early at occipital visual regions (Itti & Koch, 2001; Kastner & Ungerleider, 2000; Milner & Goodale, 2008; Vossel et al., 2014). In this study, differences were observed in brain activation patterns at regions early in the visual attention pathway between groups with different mTBI history in both the "No-Go" and "Go" task conditions. Patients with a history of multiple LOC mTBIs demonstrated significantly different patterns of brain activation compared both to controls and to patients with a history of a single LOC mTBI involved in visual attention processing. These differences were observed in

both the "No-Go" task condition as well as across "Go" task conditions primarily in early visual attention processing areas.

In the "middle" phase of processing, dorsal and ventral stream areas may both contribute to "bottom-up" saliency regulation of attention or similarly be modulated by "top down" executive control (Itti & Koch, 2001; Kastner & Ungerleider, 2000; Pessoa et al., 2003). Overall, results from Aim 2 provide preliminary evidence for relationships between some behavioral performance metrics and certain brain regions particularly in regions associated with this middle phase of visual attention processing. In particular, these differential brain activation patterns involved in performance measures for manual reaction time and errors correlated with regions farther along in visual attention processing pathways.

Attentional Efficiency

While PCL and NSI scores were significantly higher among the mTBI group than controls, these scores did not account for differences in measures of attentional efficiency for this study. However, a better understanding of the impact of individual patient variables on attentional efficiency would be advised and their inclusion in future models may be of benefit. Specifically, in line with previous research (Fay et al., 2009; Lingsma et al., 2015; Oldenburg et al., 2016) it appears that education may moderate the impact of mTBI history on measures of attentional efficiency in this study.

Regarding behavior performance metrics of attentional efficiency, it appears that analyses using ICV and SD yielded somewhat different pattern of results. Specifically, ICV correlated with altered activation patterns for alerting, visual encoding and ventral processing stream brain regions. In contrast, SD appeared to engage more frontal executive and visuospatial regions. Interestingly both measures produced differential activation effects at the cerebellum,

particularly in the DC task condition. The differences between ICV and SD results reflect the mathematical removal of mean speed differences between participants for the more standardized ICV measure (Bellgrove et al., 2004). Although SD may provide a more direct interpretation of brain activation results, ICV may provide a more standardized behavioral performance measure for interpretation across participants. While these variables represent similar concepts, it appears that ICV demonstrated greater power than SD to detect effects of study variables on brain activation patterns in this study. While these differences present interesting results, this study was not designed to meaningfully interpret these differences and may merit further research.

These study results also suggest that subtle variations in early visual processing may contribute to alterations in attentional efficiency between groups with differing mTBI histories. Individual patient characteristics, such as severity of PTSD or neurobehavioral symptoms, may create additional burden for some tasks relative to others (I. Chen & Chang, 2009; Silver et al., 2009). Additionally, education may serve as a source of "cognitive reserve" to moderate the impact of mTBI history on attentional efficiency. These variables did not appear to explain the results seen for differences between groups with different mTBI histories. Importantly, patients with a history of multiple LOC mTBIs seem to show differences in early visual attention processing patterns compared to both healthy controls and patients with a history of a single LOC mTBI. Of note, results of this study also support the Silver et al. (Silver et al., 2009) model incorporating additional psychosocial variables into the pre- and post- injury framework for recovery following a TBI, suggesting that education may moderate the impact of mTBI on attentional efficiency (Fay et al., 2009; Oldenburg et al., 2016).

In light of literature regarding "cognitive reserve," (Baker et al., 2016; Fay et al., 2009; Lingsma et al., 2015; Oldenburg et al., 2016) these findings may help elucidate the importance of

certain individual characteristics in mTBI outcomes. Cognitive reserve has been defined as "the brain's capacity to maintain cognitive function in spite of neurologic damage or disease" (Mitchell, Shaughnessy, Shirk, Yang, & Atri, 2012, p. 273; M. Stein & McAllister, 2009). Based in a "brain reserve capacity" theory, the concept of "cognitive reserve" can be conceptualized as a type of buffer which may either protect against initial brain injury damage or promote recovery (Oldenburg et al., 2016). While cognitive reserve does not appear to have a single standardized definition or operationalization in the literature, it is commonly estimated from measures of IQ, education, or current occupation (Oldenburg et al., 2016). Prior literature has used education at least as a partial proxy for cognitive reserve (Fay et al., 2009; Jones et al., 2011; Mitchell et al., 2012), although measuring this concept thought to represent the difference between cognitive function and extent of damage has proven difficult in the past (Jones et al., 2011; M. Stein & McAllister, 2009). While education may commonly be used as a proxy for cognitive reserve (Fay et al., 2009; Mathias & Wheaton, 2015; Teipel et al., 2009), it is unclear precisely what education may be indexing, and also unclear what precise mechanism causes cognitive reserve to affect symptoms and outcomes following mTBI (Oldenburg et al., 2016). The model of attentional efficiency proposed in this study may provide a mechanism through which individual characteristics such as cognitive reserve (e.g. education) may be observed to impact cognitive outcomes.

Additional aspects of visual processing captured by performance metrics may interact with these early processing group differences to create more distinctive patterns of altered activity at later stages in the attention pathway. Previous literature indicates common attentional demands at early stages of visual processing and evidence of some modulation exists across all stages. Which stage of processing attention modulates appears to depend on additional factors

such as task condition and cognitive load (Kanwisher & Wojciulik, 2000). The effects of a history of multiple mTBIs appear comparable to the effects of higher cognitive load at early visual attention processing brain regions. Study findings that support this general conclusion include evidence that selection stage may vary depending on cognitive loading for the task. Specifically, early selection is likely to occur for tasks with higher processing load, while later selection is likely to occur for tasks with lower load (Kanwisher & Wojciulik, 2000). These early differences in resource utilization for the multiple mTBI subgroup may indicate higher processing burden to complete tasks (Kanwisher & Wojciulik, 2000) compared with either single mTBI or controls.

There are additional ventral stream differences in processing between mTBI patients with a history of multiple compared to single LOCs. Interactions between behavioral performance metrics and contrasts for the multiple mTBI group tended to reflect altered brain activation patterns at mid to later processing regions in the visual attention pathway (e.g. errors in the No-Go task condition, and ICV and SD variability particularly in the MDC task condition). Beyond these middle stage ventral and dorsal processing differences correlating with behavioral performance measures, a few additional differences at frontal/executive attention "top-down" and temporal/saliency "bottom-up" regions indicated differences among groups. For the multiple mTBI group, it seems that they demonstrate additional processing differences within this "frontotemporoparietal" network as compared with single mTBI or controls. This difference is evidenced by interactions with task and behavioral performance demands.

In fact, given the brain networks and sequential steps of visual processing, it is likely that any variability in early visual attention processing among the mTBI groups – and specifically for those with a history of multiple LOC mTBIs – impacts later attentional efficiency metrics.

Together these findings suggest that downstream processes are separate, but might be synergistic with early processing differences seen between groups. Overall, results suggest patients with history of multiple LOCs may represent unique subgroup within mTBI. If further research confirms, results may explain some of mTBI group heterogeneity in imaging and outcomes in previous literature.

CLINICAL IMPLICATIONS

In addition to potential improvements in diagnostic classification and targeting of visual attention processing deficits based on mTBI history, clinical improvements are needed to identify additional sources of attentional resource demands and to better target treatment. Factors that may further moderate task performance (perhaps differentially impacting mTBI subgroups) include psychiatric comorbidity, such as PTSD, as a source of additional cognitive load (I. Chen & Chang, 2009). In fact, a recent MEG study of male military veterans with PTSD found increased activation particularly at the prefrontal cortices as part of a fronto-temporal compensatory process thought to underlie study participants' ability to maintain comparable performance on a working memory task (McDermott et al., 2015). Higher PTSD scores were associated with greater cognitive load (McDermott et al., 2015) which appears to be in line with current study results suggesting that PTSD score in particular seems to interact with I-BEAM task condition at prefrontal cortex. Although there is not unanimous agreement in the literature for an exact definition and precise dimensions of "cognitive load" (G. Matthews, Reinerman-Jones, Barber, & Abich, 2015), some prior research indicates this variable comprises a combination of individual and task related characteristics (Galy, Cariou, & Mélan, 2012; Paas, Tuovinen, Tabbers, & Van Gerven, 2003). It appears that factors in addition to task complexity,

such as modality (e.g. visual/spatial or verbal/auditory) and timing demands contribute to the task-related dimension of cognitive load. In addition to psychiatric diagnoses (e.g. anxiety and PTSD), individual variables such as alertness/fatigue and frustration are highly correlated with "mental effort" which, along with task performance, may also play important roles in the individual dimension of cognitive load (Galy et al., 2012; Paas et al., 2003). Given the contributions of these individual factors to cognitive load and subsequently increased resource demands to maintain performance, for patients with mTBI it may be particularly important to mitigate as many of these factors as might be controlled to optimize attentional efficiency. Clinically, these findings lend support for the importance of treating psychiatric comorbidities to reduce overall brain resource burden, particularly among those with a history of multiple mTBI.

Additionally, sources of neural/cognitive reserve were observed to differentially impact behavioral activation patterns between mTBI and controls. While future studies would be needed to confirm results in line with prior literature, study data suggests a possible compensatory process via education for partially mitigating damage in mTBI and allowing comparable task performance. In particular, these education effects were seen at saliency processing and compensatory/integration areas. Interpreting these results in the context of prior literature, these results support the interpretation that brain resource fatigue results from the effort to maintain same level of performance among mTBI patients (McAllister et al., 2006). Additionally, these results suggest that cognitive training may help (Laatsch et al., 2004; Munivenkatappa et al., 2014). While few evidence based cognitive rehabilitation interventions for TBI exist, preliminary research indicates that improvement may be possible following interventions such as "CogSMART," particularly in affective symptoms and quality of life as well as objective measures of cognitive performance (Twamley et al., 2015). Regarding the

mechanism of these improvements, initial pilot neuroimaging studies among patients with a history of brain injury indicate alterations in brain activation patterns may correlate with improvements in neuropsychological testing following cognitive rehabilitation therapy (Laatsch et al., 2004), as well as structural and functional connectivity changes following EEG neurofeedback therapy (Munivenkatappa et al., 2014).

Finally, while the current I-BEAM task conditions did not appear to clearly engage either different attention networks or cognitive load levels, these results support a finding of subtle mTBI history impacts on various aspects of cognitive functioning consistent with prior literature (McAllister et al., 2001). Although minimally detectable differences in fMRI-measured brain functioning between participants and controls would suggest positive clinical outcomes, symptom complaints appear to continue to impact some patients' quality of life (Belanger et al., 2009; Chapman & Diaz-Arrastia, 2014). Some prior literature also indicates that mTBI patients expend higher levels of effort to function at levels of performance comparable to healthy controls (McAllister et al., 2006; McAllister et al., 2001). These results appear to support the study assertion that use of more sophisticated measures could usefully reveal subtle differences in attentional efficiency among patients with varying histories of mTBI. Structures and processes that are vulnerable to attentional impacts of brain injury may serve as potential targets for the development of future interventions and individualized treatment following mTBI. Subsequent differences in attentional efficiency, as demonstrated by brain resource utilization activation patterns, may help explain some of the heterogeneity in mTBI patient behavioral performance and outcomes found in previous literature (Zhang et al., 2010). While relatively few neuroimaging studies have investigated the impacts of multiple mTBIs specifically, a number of

studies have indicated an association with great performance deficits and chronically poorer outcomes (Belanger et al., 2010; Terry et al., 2015). In line with this literature, subtle differences observed in visual attention processing among patients with a history of multiple mTBIs with LOC in this study may reflect more chronic demands for increased brain resource utilization to maintain comparable performance over time. Given research indicating that LOC may uniquely alter white matter integrity relative to AOC (S. Matthews et al., 2012), it is possible that DAI may serve as a potential mechanism for the effects of mTBI on performance variability and attentional efficiency more generally. Supporting this hypothesis, a resting-state fMRI study by Johnson and colleagues found reduced connectivity and increased alterations in DMN activation patterns between dlPFC and parietal cortex as the number of concussions increased (Johnson et al., 2012). Future studies should further investigate the clinical impacts and underlying mechanisms of these initial differences between patients with a history of multiple and single mTBIs. If replicated, study findings which suggest consideration of multiple mTBI patients as a unique subgroup may help to reduce heterogeneity within future mTBI research and improve diagnostic classification.

STRENGTHS AND LIMITATIONS

It was initially hoped that the study would include a larger sample size and saccadic measures, but logistical constraints (e.g., changes in equipment and personnel) interfered with the original study plan. Despite alterations to sample size and timeline, the study results reveal important findings based in models that are statistically reliable, and significant results are expected to replicate. The multivariate modeling approach used in this project contributed both strengths and limitations to the results of the present study. Importantly, this robust statistical

approach provides stronger control over the rate of false positive results than other methods. On the other hand, the rigorous corrections incorporated into this methodology substantially impact detection of significant results. This impact is particularly noticeable with smaller sample sizes effects, such that effects which might be significant in larger samples would not reach significance with this more conservative methodology(G. Chen et al., 2014; G. Chen et al., 2015). It is expected that a study with a larger sample size would provide additional statistical power to detect findings that were not adequately powered in the study sample. Although the sample size of the current study is small and the power is low, results strongly suggest that the method of analysis can serve as a robust model to detect statistically significant results.

It would be expected that differences between multiple and single mTBI subgroups would replicate in future studies with larger samples within a similar military patient population. Future multivariate models including individual patient covariates (e.g. PTSD, NSI and education) would be expected to replicate and add strength to current analysis techniques. Although the difference in composition between mTBI and control groups for biological sex could be seen as a significant limitation to this study, the study analysis modeled likely differences attributable to biological sex and found them not to be significant. Sample size may be too small to conclude with certainty, so balancing the composition of groups for future studies merits further investigation. Additionally, current medication data for each participant was not collected as part of this study and therefore any potential impact medications might have had on performance is not reflected in these results. Future studies should collect medication data for inclusion in analyses. Finally, the selection of patients referred to and accepted to the NICoE may have impacted current study results as well. Specifically, patients eligible for services at NICoE are active duty service members (including DEERS-eligible National Guard and

Reserves) with mild to moderate TBI and comorbid Psychological Health conditions who have failed to respond to standard care delivered at their home duty station healthcare facility (Ayer et al., 2015; NICoE, 2016). As such, patients selected for services at NICoE may represent a unique subpopulation even among active duty military service members who have experienced mTBI. Furthermore, this project's sample of NICoE mTBI patients included 62% special forces personnel per clinical records. Prior studies have indicated altered patterns of neural activation and performance among elite warfighters (Paulus et al., 2010; Simmons et al., 2012; Vythilingam et al., 2009), and the high composition of such service members within this sample of mTBI patients may further impact results. In particular, while fMRI studies of military special forces personnel are relatively limited, some research indicates that such elite warfighters are predisposed toward more efficient processing integration and neural modulation of attention (Simmons et al., 2012). Future studies should investigate the specific impacts of specialized military training and occupational status on cognitive performance and attentional efficiency in visual attention.

FUTURE DIRECTIONS

While these study results utilized a robust analytical model, replication with a larger sample would be warranted to confirm these findings as well as potentially detect additional results insufficiently powered in this study. Given the small sample size, limited interpretation of these results consistent with prior literature may be cautiously considered. However, future research with a larger sample size would be needed to clarify these results. Future studies might also benefit from the inclusion of additional a priori t-tests to determine directionality of results. Particularly within the mTBI group, it appears there is additional benefit to studying these

multiple and single LOC mTBI subgroups. Additionally, more robust analysis of PTSD as covariate, and particularly consideration of other potential psychiatric comorbidities, may help elucidate its potential as a source of additional cognitive load. Future studies might also consider specifically examining the relationship between mTBI and PTSD, and whether additional variables may mediate these effects. For example, future studies should include additional analysis for the specific impacts this variable may contribute, and further investigation as a protective source of cognitive reserve are warranted.

Given the potential for differential temporal effects in visual attention processing, future studies might consider using magnetoencephalography to better the temporal component of processes examined in this project. Multimodal research with visual tracking integrated with neuroimaging might also yield significant contributions. It is also clear that a more integrated and comprehensive brain model of visual attention is needed in this field to better frame results.

It is possible that the variables selected for study in this research proposal do not adequately address significant differences in BOLD activation patterns. Importantly, given the small sample size of this study, it is possible that many analyses were underpowered. Where possible, patterns of results consistent with prior literature have been highlighted for replication in a future study with larger sample size. Based on prior literature (Azouvi, 2000; Bonnelle et al., 2011; Dockree et al., 2006; Eierud et al., 2014; Kanwisher & Wojciulik, 2000; Larson et al., 2012; McAllister et al., 2006; McAllister et al., 2001; Tomasi et al., 2004), findings from the current study and existing models suggest that attentional inefficiency is an important mechanism in neurocognitive deficits and neurobehavioral symptoms following mTBI. Results of this study suggest that more accurate diagnostics and methodology may improve existing knowledge of the specific roles and vulnerabilities of visual attention networks. This study

focused on clinical sample of chronic military mTBI cases, and study results are best understood as pertaining to a military chronic mTBI population. Additional research should be performed to determine if this analysis method might also help better elucidate differences within the military population with a wider range of TBI. In order to extrapolate to a non-military or non-chronic mTBI groups regarding subgroups and correlations with biopsychosocial factors (e.g. education and symptoms) consideration of additional variables might be considered as well. Given the highly specific NICoE population sampled in this study, future research should seek to also include non-military and non-chronic mTBI patients to examine whether these findings generalize to a broader mTBI population.

Study findings suggest that more accurate diagnostics and methodology may improve existing knowledge of the specific roles and vulnerabilities of visual attention networks. This study focused on a population of chronic military mTBI cases, and study results are best understood as pertaining to a military chronic mTBI population. Additional research should be performed to determine whether this analysis method could also help better elucidate differences within the military population with a wider range of TBI. Given the highly specific NICoE population sampled in this study, future research should seek to also include non-military and non-chronic mTBI patients to examine whether these findings generalize to a broader mTBI population. It will also be helpful to expand analyses to this broader population to determine whether the subgroups and correlations with biopsychosocial factors (e.g. education and additional clinical symptoms) found in this study contribute to the larger literature and potential clinical diagnostic applications.

Despite limited sample size, this study was able to provide support for viewing patients with a history of multiple LOC mTBIs as a possible subgroup with uniquely altered attentional

efficiency. This study was also able to demonstrate additional group differences between this multiple mTBI group and patients who had experienced either a single mTBI or no prior mTBIs, and these differences correlated with some behavioral performance measures at intermediate visual attention processing regions as well as at executive and modulatory areas. These results suggest that while a history of multiple mTBIs may serve as a source of increased cognitive load, education may serve as a form of cognitive reserve to help moderate these effects. Finally, these results also support a possible statistical separation between the effects of mTBI and PTSD that can be further investigated using this novel multivariate modeling approach in future neuroimaging studies.

ADDITIONAL FIGURES AND TABLES

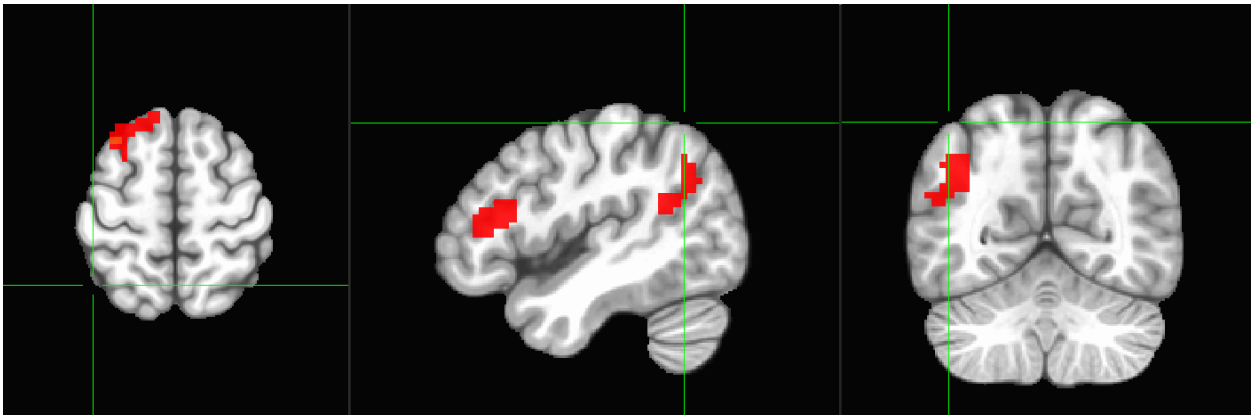


Figure 3. Specific Aim 1: UC-DC t-test

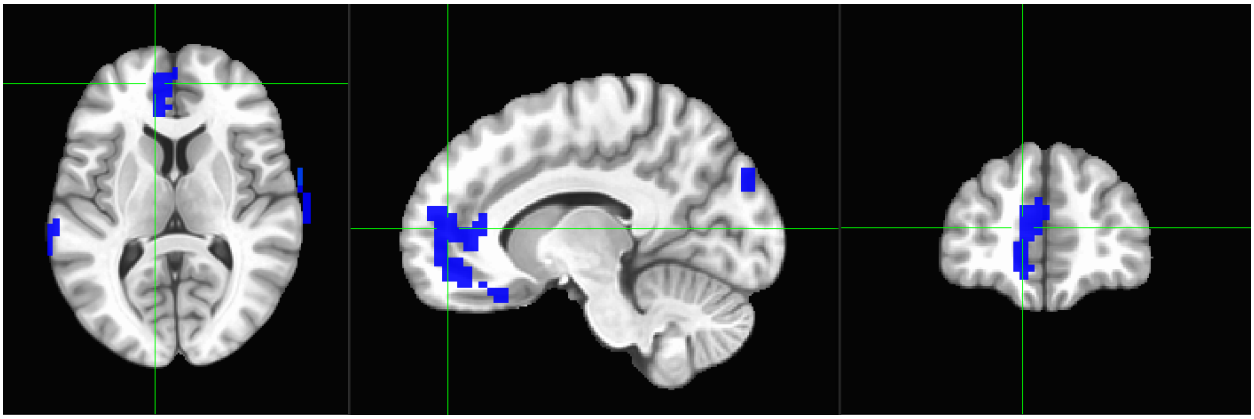


Figure 4. Specific Aim 1: MDC-UC t-test

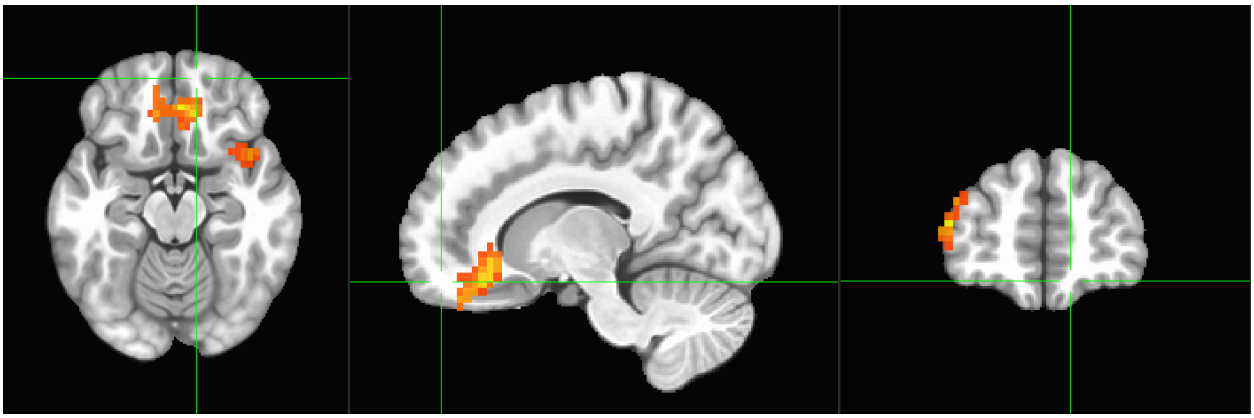


Figure 5. Specific Aim 1: Group*Condition F-test

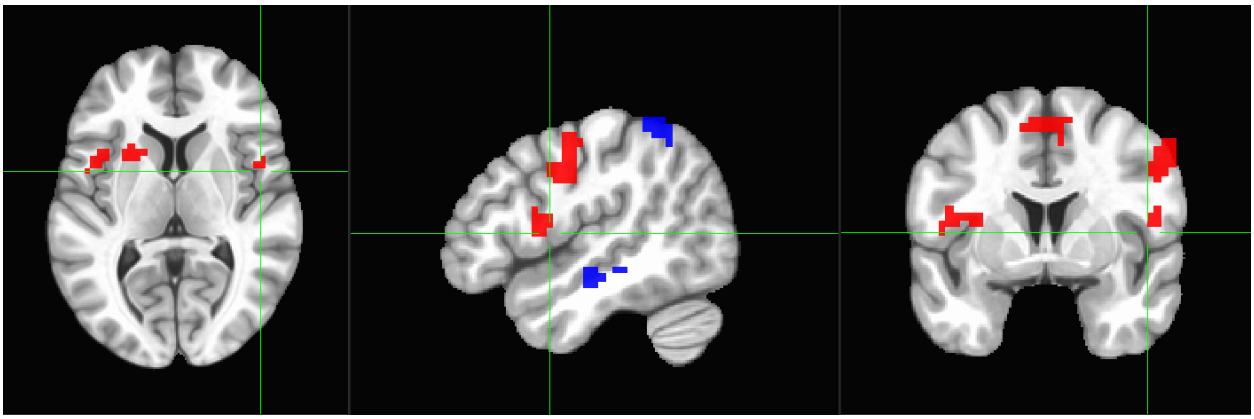


Figure 6. Specific Aim 1: Education t-test

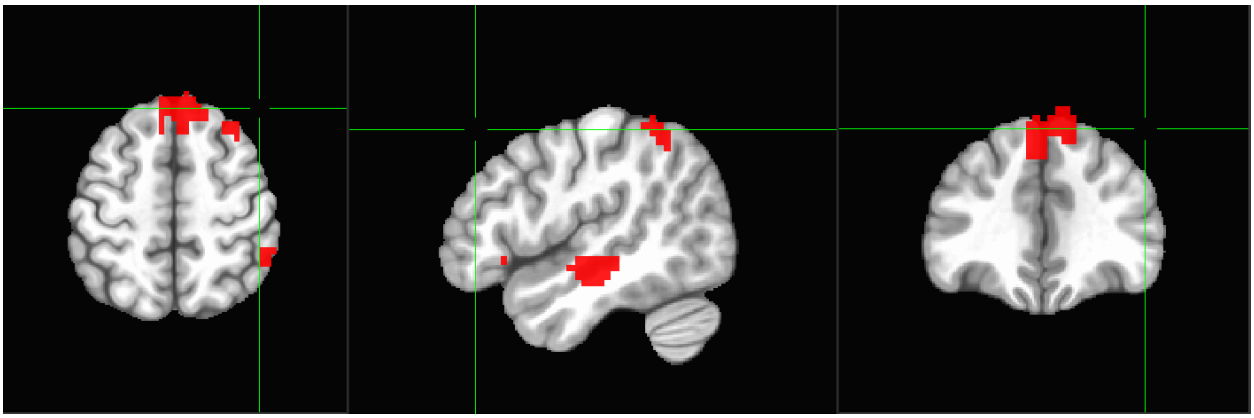


Figure 7. Specific Aim 1: Group*Education t-test

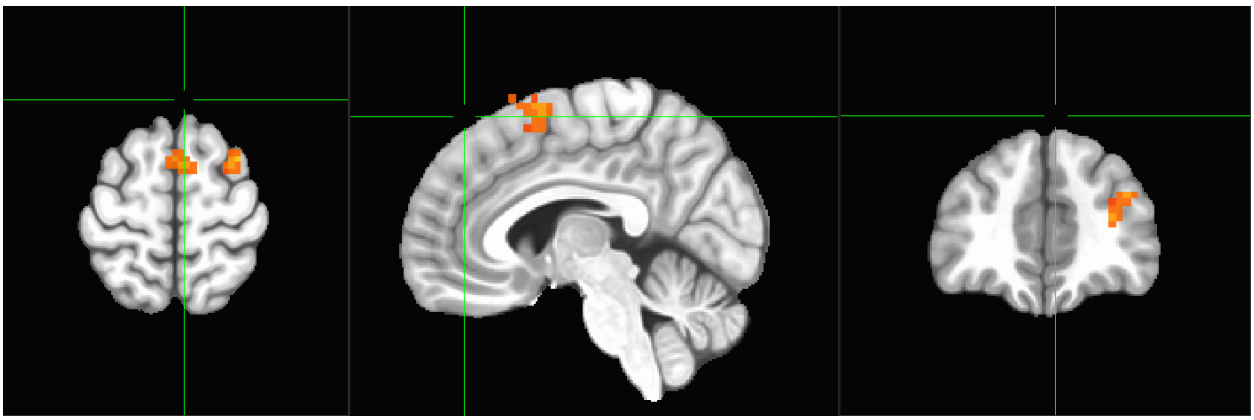


Figure 8. Specific Aim 1: PCL*Condition F-test

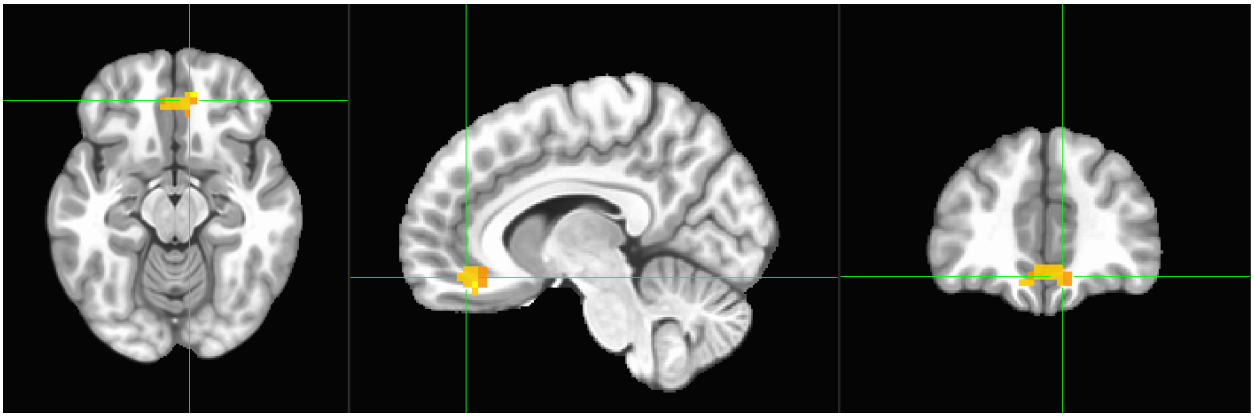


Figure 9. Specific Aim 1: NSI*Condition F-test

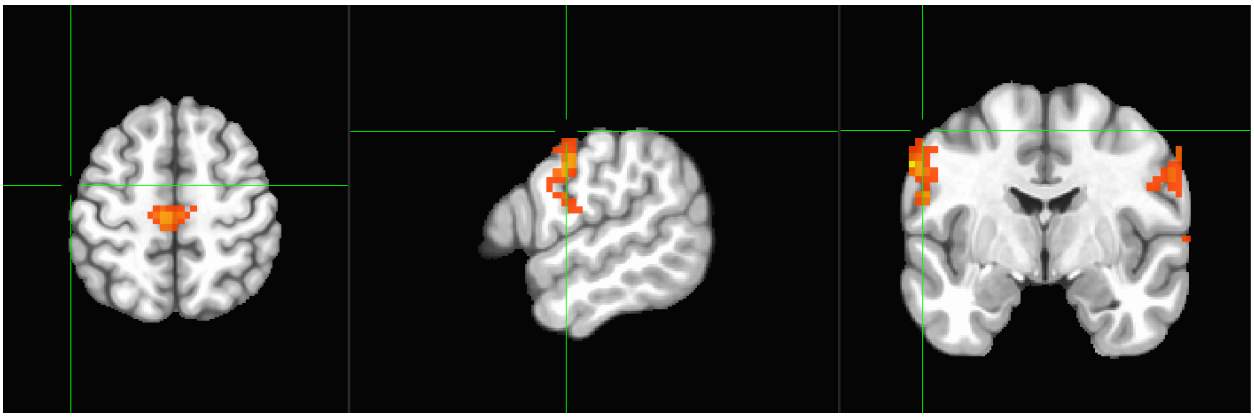


Figure 10. Specific Aim 2 (No-Go): Errors F-test

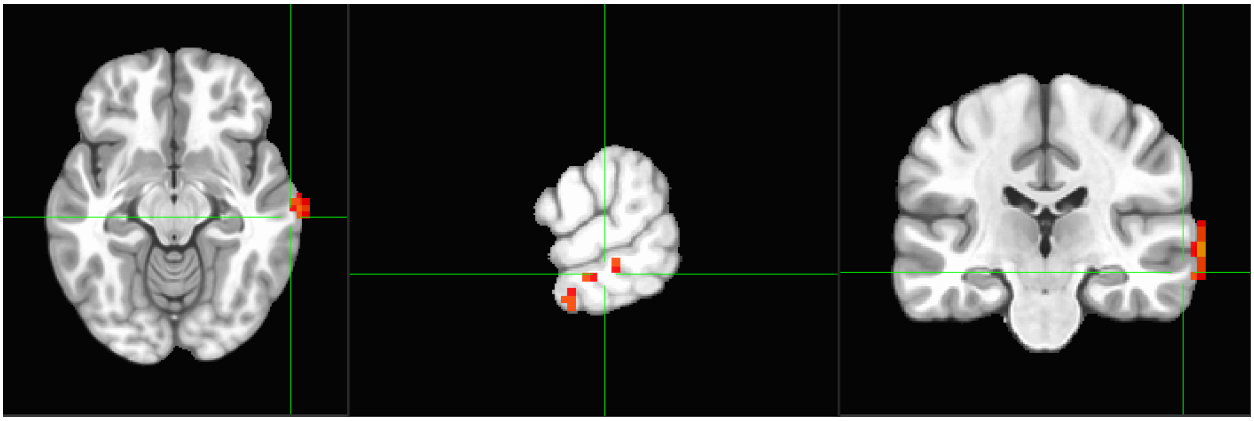


Figure 11. Specific Aim 2 (No-Go): Group*Errors F-test

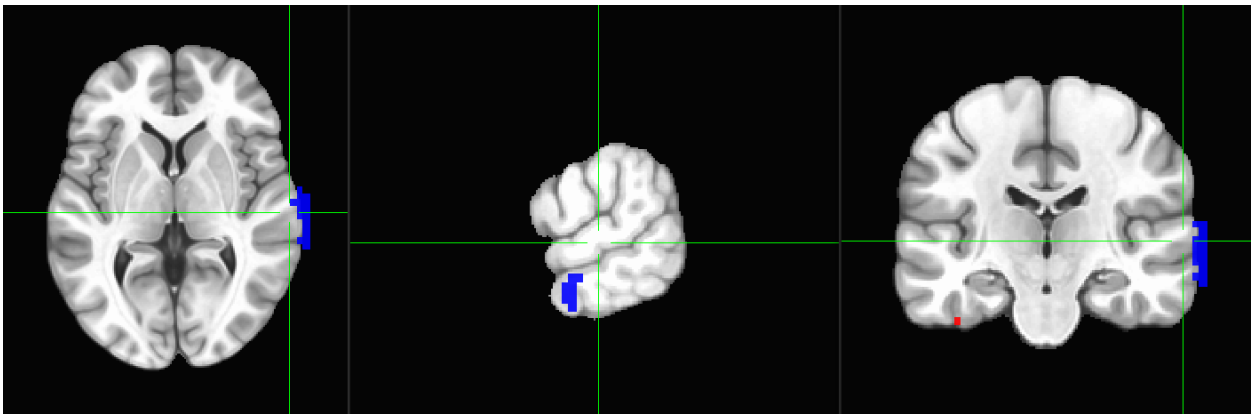


Figure 12. Specific Aim 2 (No-Go): Errors*Group contrast (mTBI vs. controls)

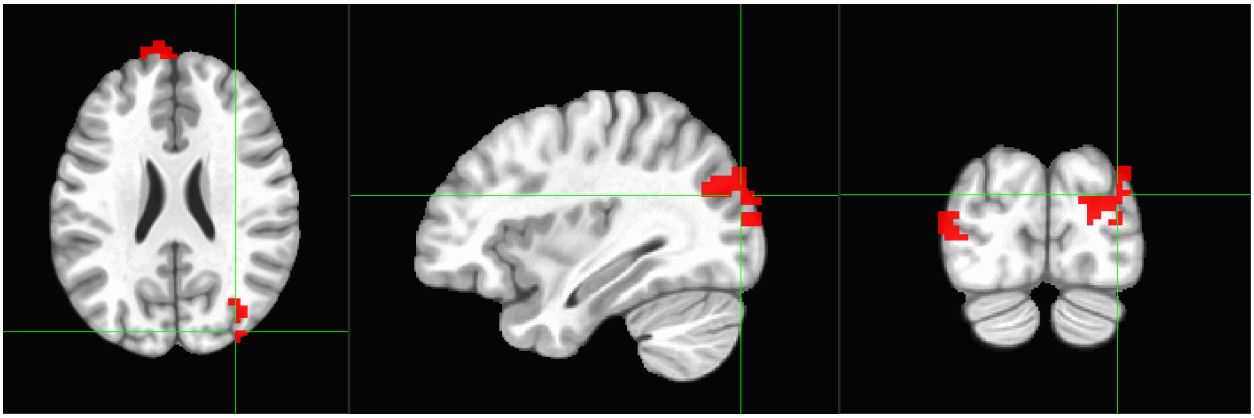


Figure 13. Specific Aim 2 (No-Go): Multiple mTBI vs. Controls groups t-test

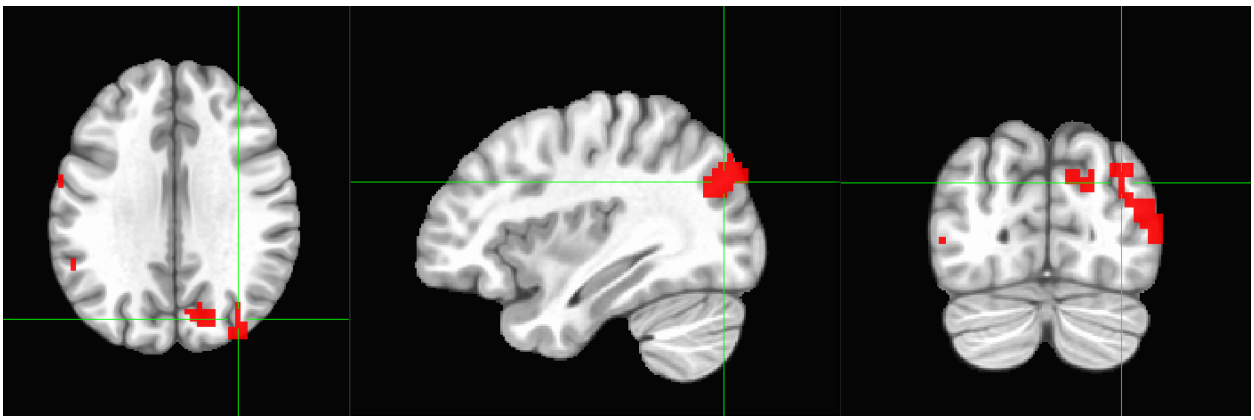


Figure 14. Specific Aim 2 (No-Go): Multiple mTBI vs. Single mTBI groups t-test

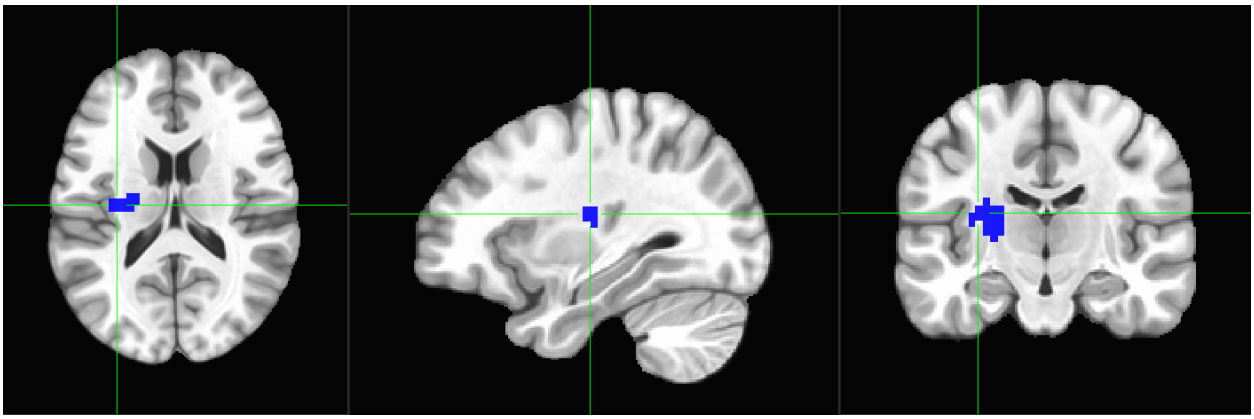


Figure 15. Specific Aim 2 (Go): Reaction Time (RT) t-test

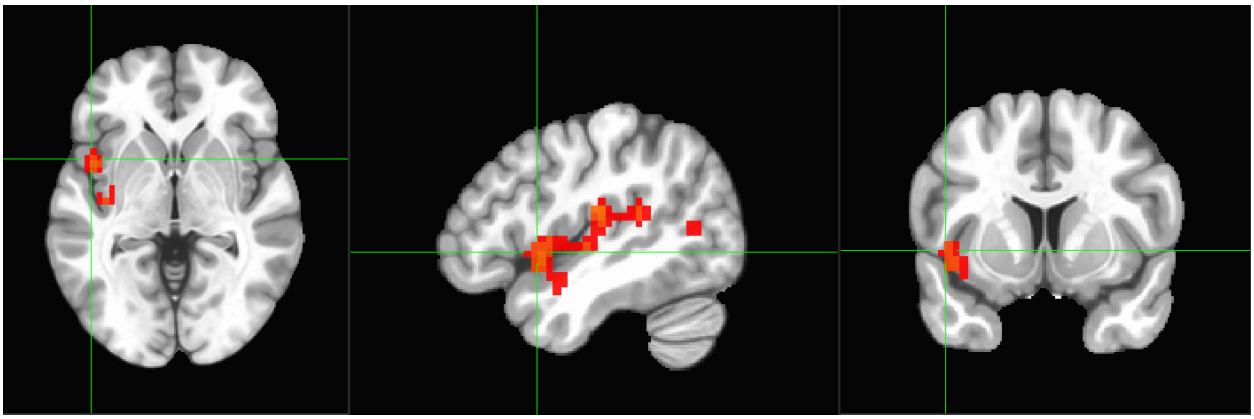


Figure 16. Specific Aim 2 (Go): Group F-test

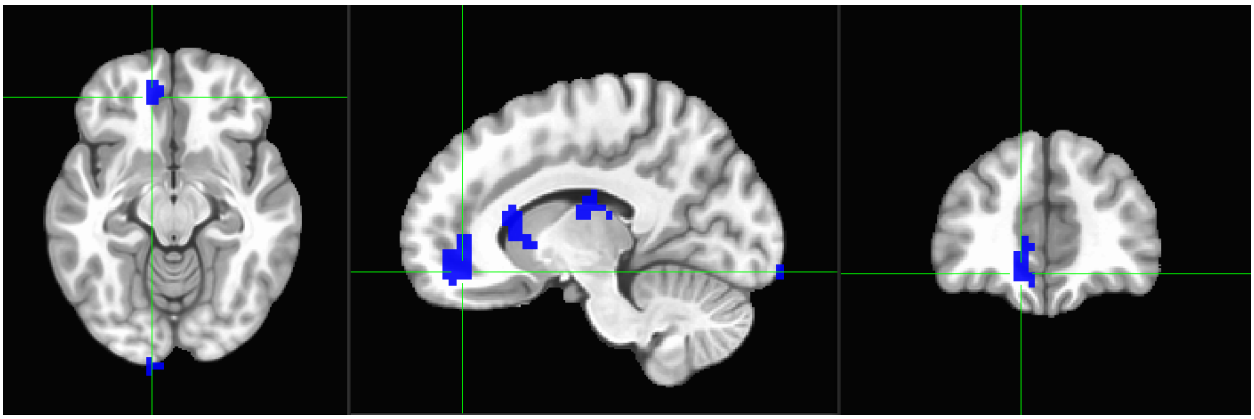


Figure 17. Specific Aim 2 (Go): RT@MDC condition

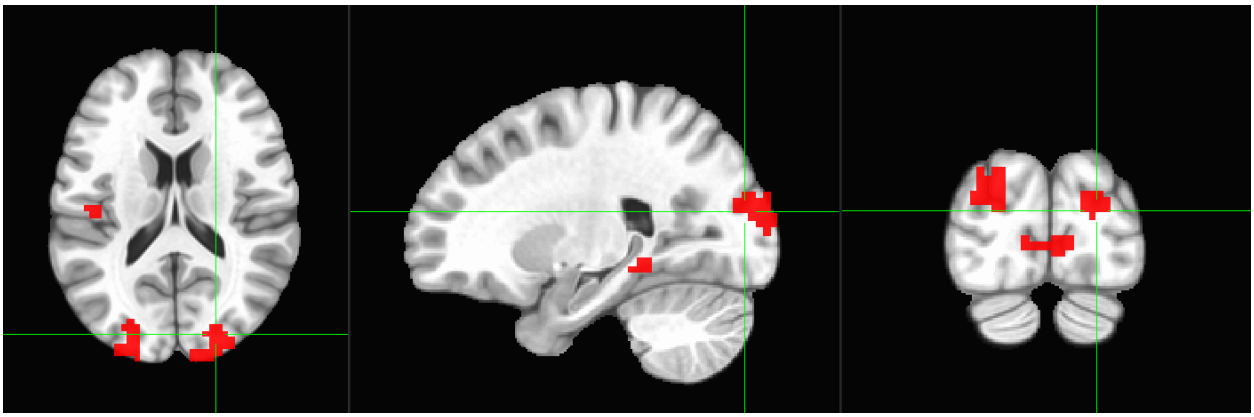


Figure 18. Specific Aim 2 (Go): Multiple mTBI vs. Control groups t-test

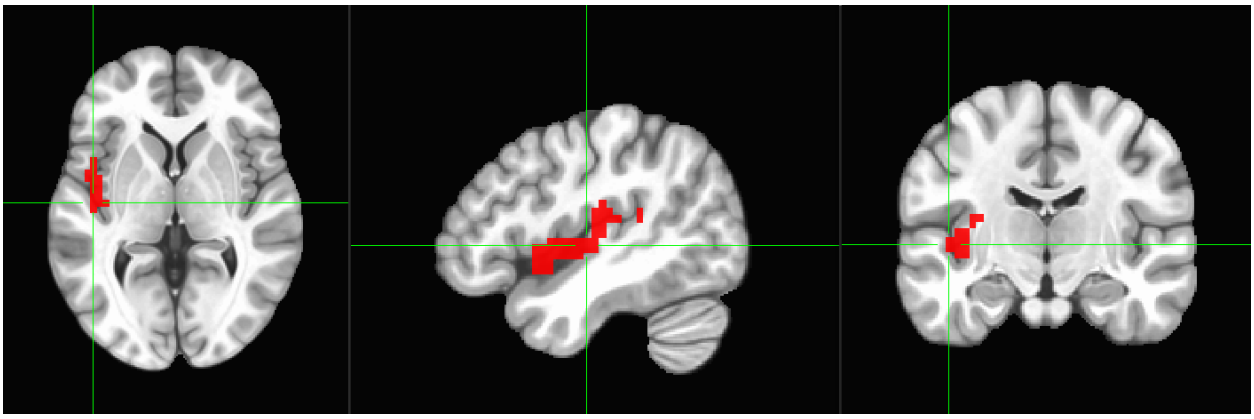


Figure 19. Specific Aim 2 (Go): Multiple vs. Single mTBI groups t-test

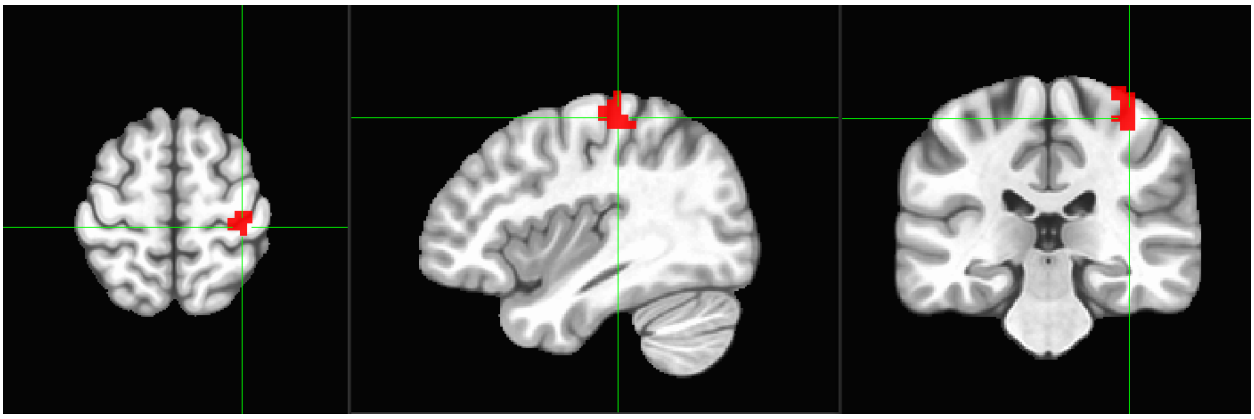


Figure 20. Specific Aim 2 (Go): RT*(Single mTBI vs. Controls) @UC condition

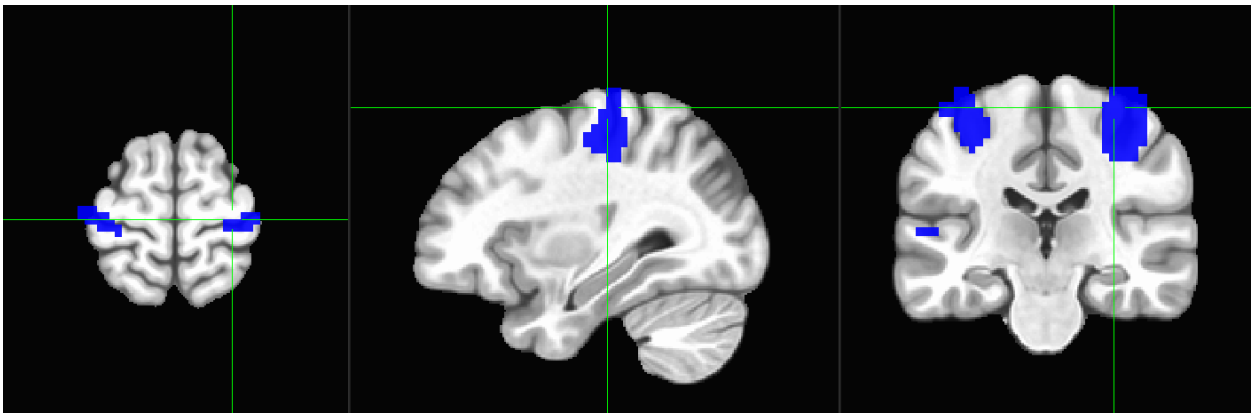


Figure 21. Specific Aim 2 (Go): RT*(Single vs. Multiple mTBI) @UC condition

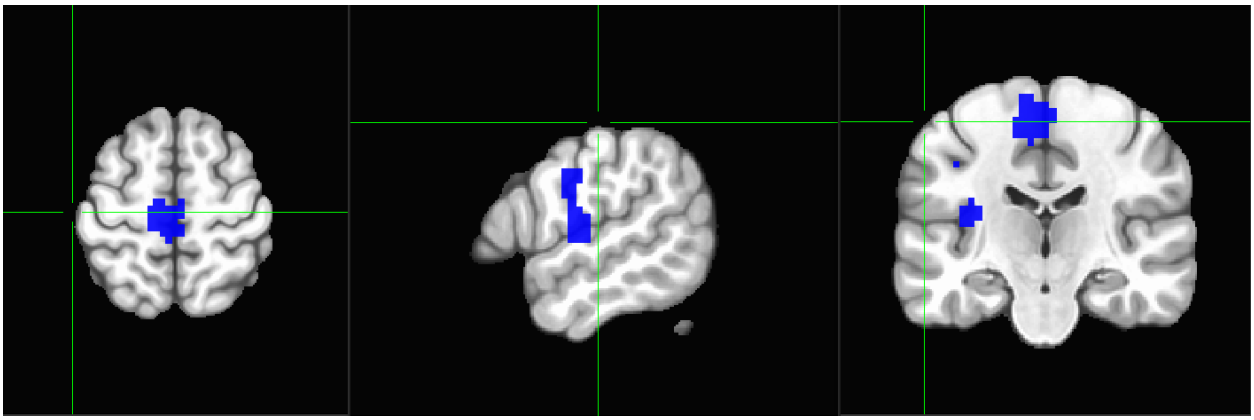


Figure 22. Specific Aim 2 (Go): Errors*(Multiple vs. Single mTBI) t-test

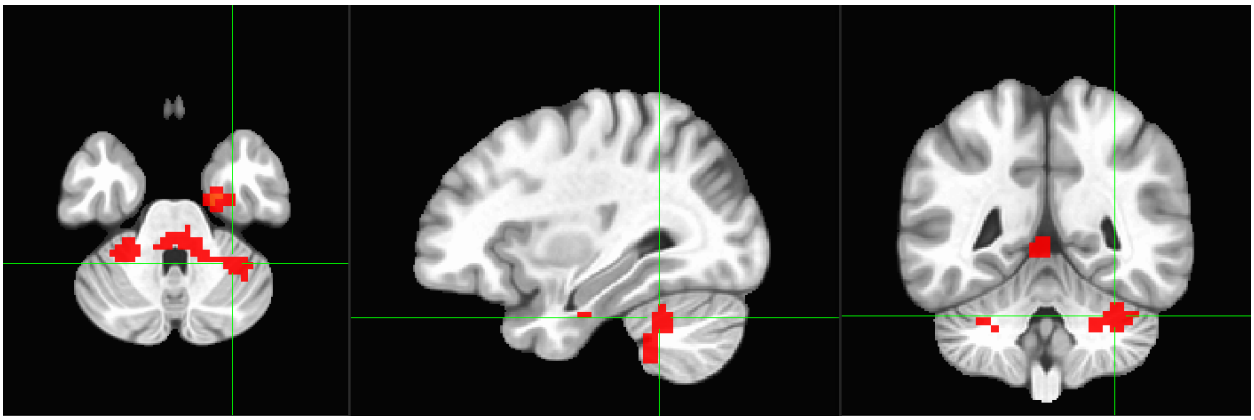


Figure 23. Specific Aim 2 (Go): Group*ICV*Condition F-test

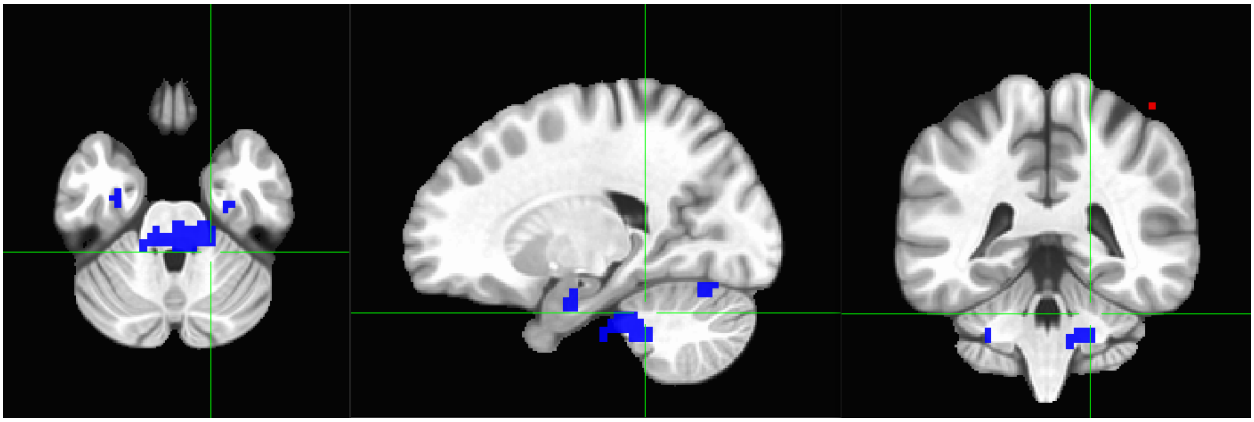


Figure 24. Specific Aim 2 (Go): ICV @DC condition

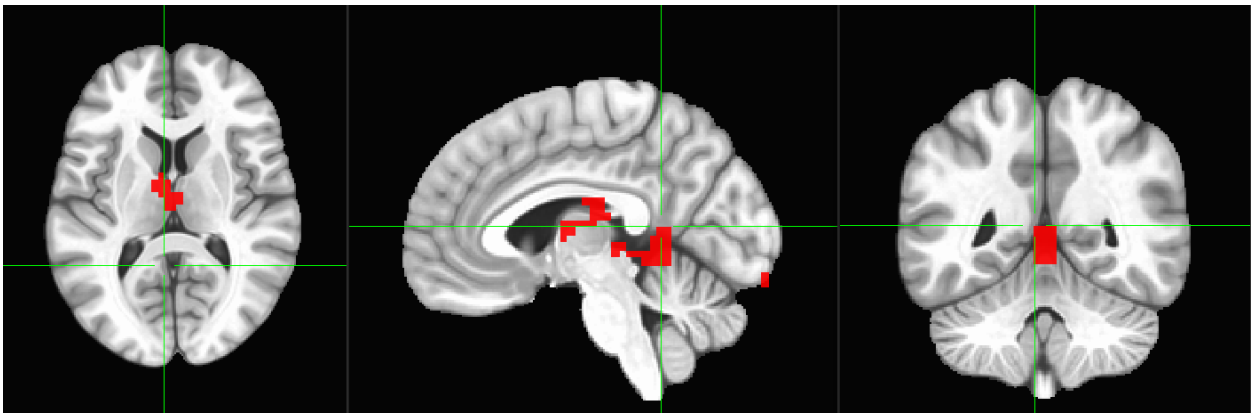


Figure 25. Specific Aim 2 (Go): ICV @MDC condition

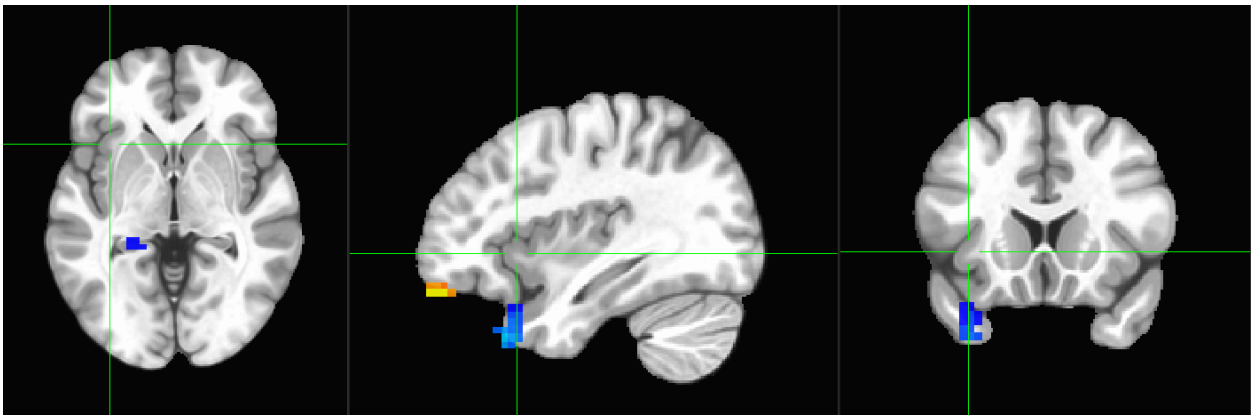


Figure 26. Specific Aim 2 (Go): ICV*(Multiple mTBI vs. Controls) @DC condition

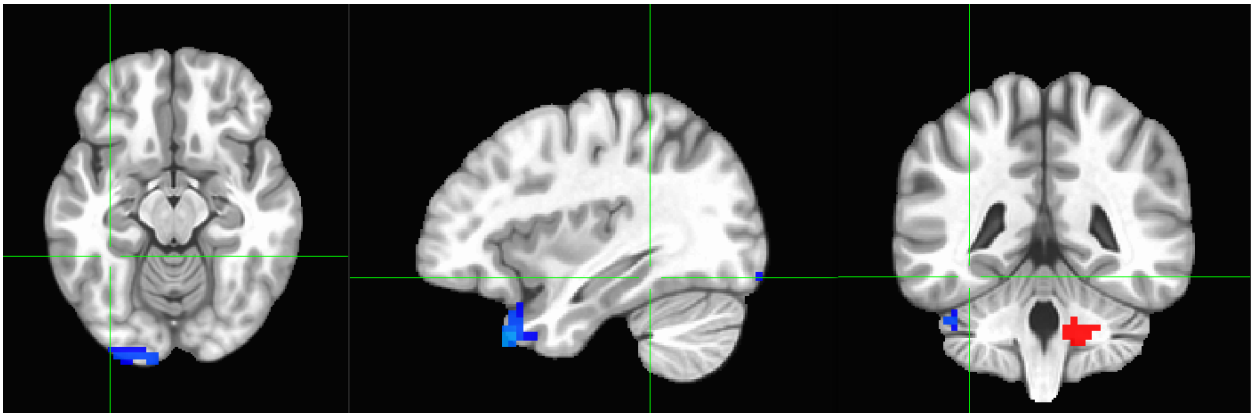


Figure 27. Specific Aim 2 (Go): ICV*(Multiple mTBI vs. Control) @MDC condition

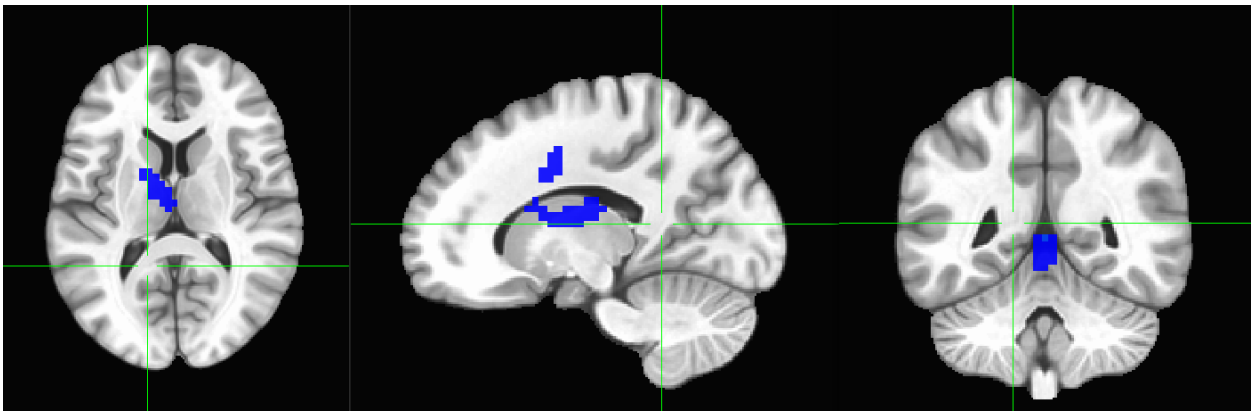


Figure 28. Specific Aim 2 (Go): ICV*(Multiple vs. Single mTBI) @MDC condition

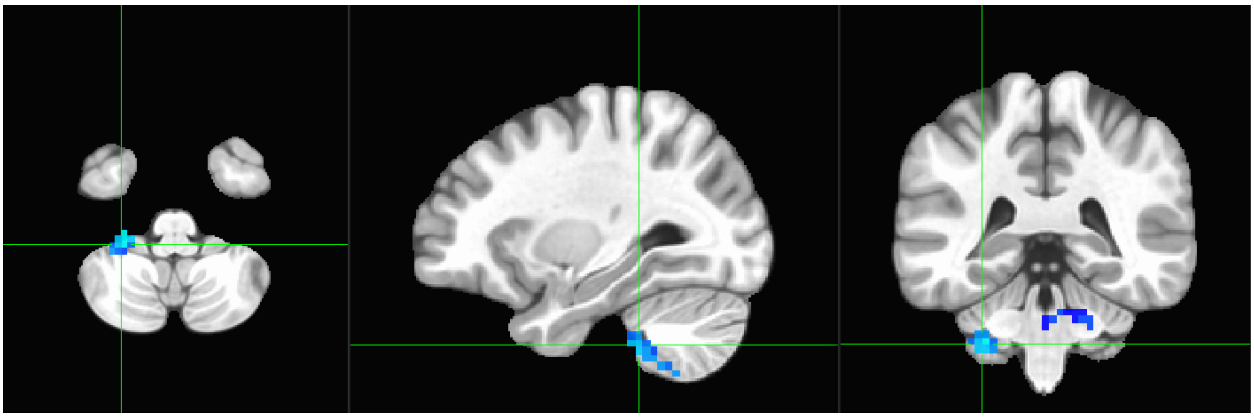


Figure 29. Specific Aim 2 (Go): Standard Deviation (SD) @DC condition

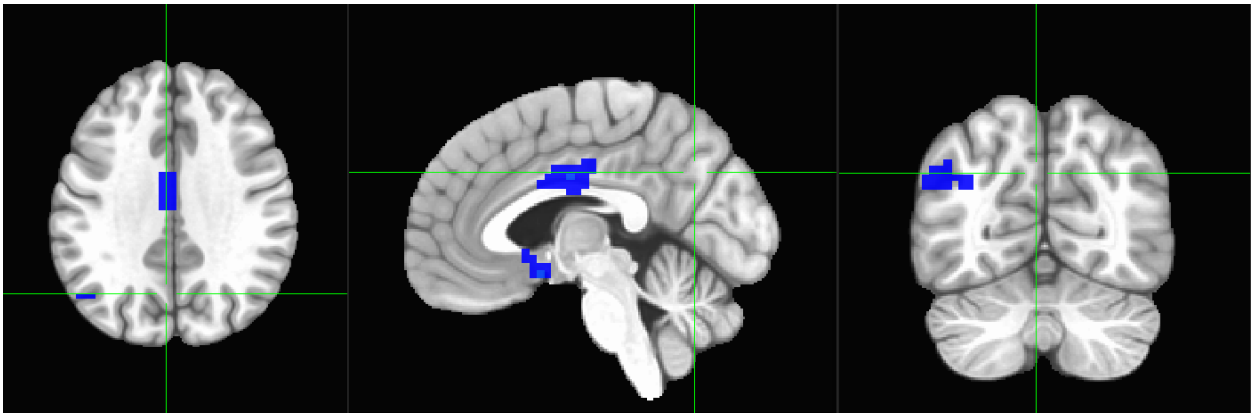


Figure 30. Specific Aim 2 (Go): SD*(Multiple mTBI vs. Controls) @UC condition

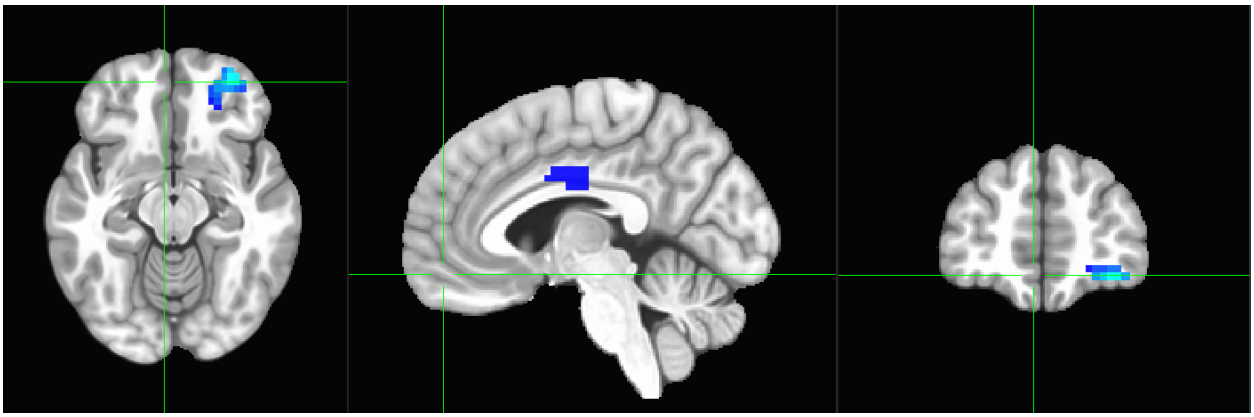


Figure 31. Specific Aim 2 (Go): SD*(Multiple mTBI vs. Controls) @MDC condition

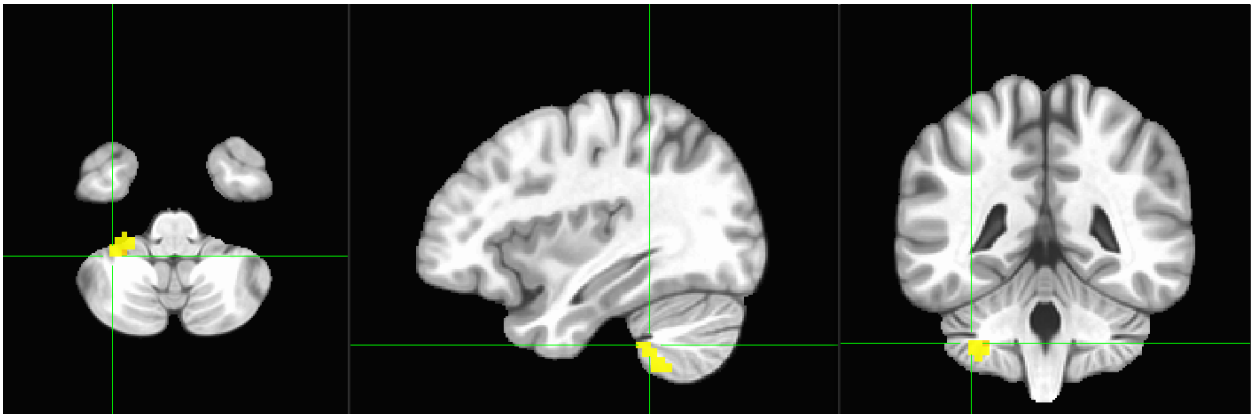


Figure 32. Specific Aim 2 (Go): SD*(Multiple vs. Single mTBI) @DC condition

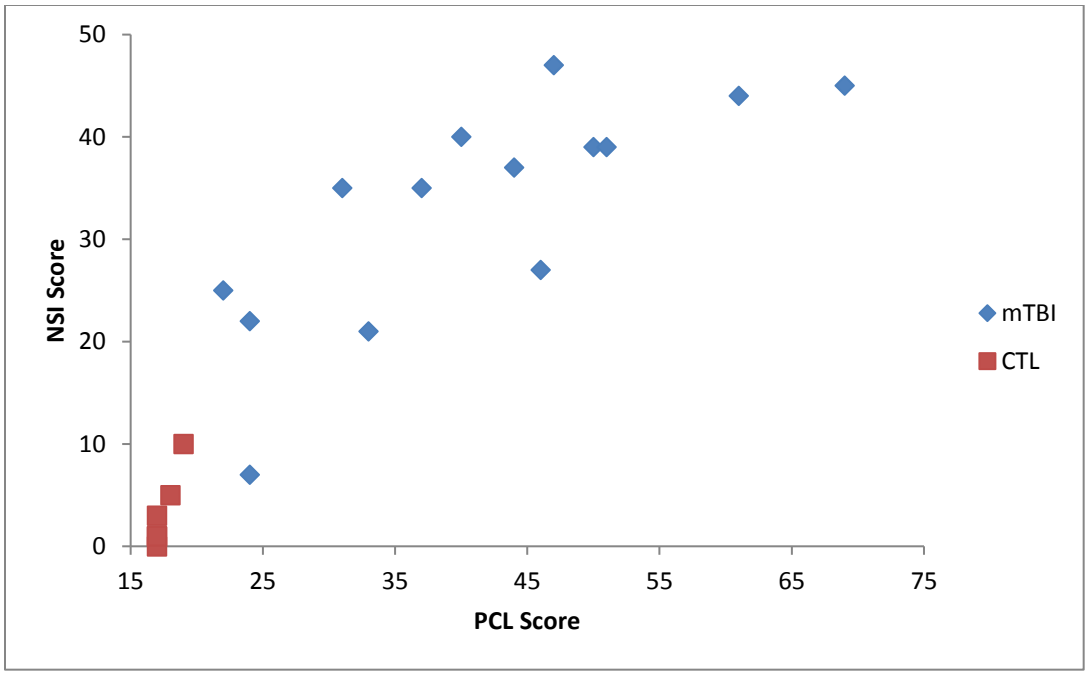


Figure 33. Comparison of PCL and NSI scores by group (n= 14 mTBI, 6 CTL)

Table 3. Sample Description and Demographics.

	mTBI (n=14) **Mean (SD)**	**Controls (n=7)** **Mean (SD)**	**p (t or $\chi 2$)**
Age	39.14 (3.23)	34.14 (5.76)	* p=.02
Education	14.29 (2.05)	16.14 (2.73)	*p=.09*
Biological sex (male)	100%	57.14%	* $\chi 2(1)= 3.94$ p<.05
Race/Ethnicity	White = 8, Hispanic = 2, Unknown/Other = 4	White = 3, Black = 1, Hispanic = 1, Asian = 2	*$\chi 2(4)= 2.86$ p=.58*
PCL-C	41.36 (14.01)	17.50 (0.84)	* p<.001
NSI	33.07 (11.26)	3.33 (3.73)	* p<.001
CES	25 (8.99) *moderate - heavy*	4 (5.32) *light*	* p<.001
Military Branch	USA = 4, USN = 8, USMC = 1, USAF = 1	USA = 4, USN = 2, USCG = 1	*$\chi 2(4)= 1.08$ p=.89*
Military Rank	E1 – E4 = 0 E5-E9 = 10 Officer/WO = 4	E1 – E4 = 1 E5-E9 = 2 Officer/WO = 4	*$\chi 2(2)= 1.36$ p=.51*
mTBI history	1 mTBI w/ LOC: 5 2+ mTBIs w/ LOC: 9	---	---

Table 4. Specific Aim 1: Regions of significant clusters of brain activation/deactivation (mTBI n=13, CTL n=7)

Region/BA	X	Y	Z	Volume (mm3)	voxel-wise p threshold	α
UC-DC						
L superior medial	7	-38	63.5	123	.005	<.01
L angular/TPJ	45.5	60	39	107	.005	<.01
L IFG/dlPFC	52.5	-24	25	62	.005	<.02
MDC-UC						
L ACC/vmPFC	-3.5	-41.5	-20.5	189	.01	<.01
Group*Condition						
R/L mid orbital/vmPFC	-3.5	-38	-17	141	.006	<.01
L mid frontal/dlPFC	42	-62.5	7.5	53	.006	<.05
Education						
R precentral gyrus	-56	4	56.5	139	.02	<.01
R/L insula	*45.5*	*0.5*	*14.5*	*82*	*.02*	*>.10*
Education*Group						
R sup medial/frontal	-3.5	-41.5	60	124	.02	<.02
R middle temporal/MTL	-63	35.5	-17	121	.02	<.05
PCL*Condition						
R SMA	-7	-6.5	67	59	.002	<.01
R middle frontal/dlPFC	-38.5	-45	25	53	.002	<.01
NSI*Condition						
R/L middle orbital/vmPFC	-7	-38	-17	104	.001	<.02

Table 5. Specific Aim 2 (No-Go Trials): Regions of significant clusters of brain activation/deactivation (Multiple mTBI n=9, Single mTBI n=4, CTL n=7)

Region/BA	X	Y	Z	Volume (mm3)	voxel-wise p threshold	α
Errors						
L postcentral g	63	4	39	124	.01	<.01
L/R SMA/paracentral g	7	21.5	56.5	79	.01	<.03
Error*Group						
R sup/mid temporal	-73.5	25	0.5	105	.01	<.01
Error*(MTBI v. Ctl)						
R middle temporal/MTL	-77	25	-3	148	.02	<.01
Multiple mTBI v. Ctl						
R middle occipital	-35	88	28.5	108	.02	<.05
Multiple v. Single mTBI						
R mid occipital/precuneus	-35	88	32	96	.01	<.01

Table 6. Specific Aim 2 (Go Trials): Regions of significant clusters of brain activation/deactivation (Multiple mTBI n=9, Single mTBI n=4, CTL n=7)

Region/BA	X	Y	Z	Volume (mm3)	voxel-wise p threshold	α
RT						
L insula	35	18	11	45	.004	<.05
Group						
L insula/(sup/med temporal)	45.5	-6.5	-3	202	.02	<.01
RT @MDC						
L ACC	7	-45	-17	78	.01	<.03
Multiple mTBI v. Ctl						
R cuneus/mid occipital	-3.5	98.5	7.5	177	.02	<.01
L sup/mid occipital	31.5	102	11	131	.02	<.03
Multiple v. Single mTBI						
L insula/sup temporal	45.5	-10	-3	108	.01	<.01
RT*(Single v. Ctl) @UC						
R postcentral	-35	28.5	74	35	.002	<.05
RT*(Multiple v. Single)@UC						
R postcentral	-38.5	28.5	74	131	.003	<.01
Error*(Multiple v. Single)						
L SMA/paracentral	3.5	18	56.5	118	.01	<.01
L sup temporal/postcentral	59.5	11	11	101	.01	<.01
Group*ICV*Condition						
L/R cerebellum	-3.5	32	-45	350	.005	<.01
ICV @DC						
L/R cerebellum	-21	21.5	-41.5	197	.02	<.01
ICV @MDC						
L thalamus	3.5	18	14.5	155	.01	<.01
cerebellar vermis	0	49.5	4	77	.01	<.05
ICV*(Multiple v. Ctl) @DC						
L medial temporal pole	35	-24	-41.5	43	.002	<.02
L parahippocampus	17.5	39	-3	36	.002	<.05
ICV*(Multiple v. Ctl) @MDC						
L medial temporal pole	35	-2.4	-41.5	45	.002	<.01
L lingual g	14	98.5	-13.5	34	.002	<.05
ICV*(Mult v. Single)@MDC						
L thalamus	0	18	11	118	.02	<.04
cerebellar vermis	*0*	*46*	*0.5*	*100*	*.02*	*<.09*

Region/BA	X	Y	Z	Volume (mm3)	voxel-wise p threshold	α
SD @DC						
L cerebellum	28	35.5	-48.5	42	.002	<.02
SD*(Multiple v. Ctl) @UC						
L ACC/MCC	0	7.5	32	62	.006	<.03
L angular gyrus/TPJ	56	70.5	32	57	.006	<.04
SD*(Multiple v. Ctl) @MDC						
R OFC/middle orbital	-35	-52	-13.5	37	.002	<.04
L/R MCC	*0*	*11*	*32*	*37*	*.002*	*<.07*
SD*(Mult. v. Single) @DC						
L Cerebellum	35	53	-55.5	36	.002	<.03

Table 7. Hypothesis Outcomes: Results with Key Findings

Hypothesis	Independent Variables (IV)	Key Findings	Outcome
1a: Go trials	task condition (directional cue, misdirectional cue, and uncued trials)	UC-DC L sup medial/frontal (+) L angular gyrus/TPJ (+) L IFG/dlPFC (+) MDC-UC L ACC/vmPFC (-)	Partially supported
1b: Go trials	mTBI history (mTBI combined group vs. controls)	--	Not supported
1c: Go trials	b/w Ss: TBI history (combined mTBI vs. controls) w/in Ss: Task condition (directional cue, misdirectional cue, and uncued trials)	Group*condition R/L mid orbital/vmPFC L mid frontal/dlPFC	Supported
1d: Go trials	Significant predictors from the previous model analysis (i.e. main effects for task condition, mTBI history, task condition and mTBI history interaction)	Education R precentral gyrus (+) Education*group R sup medial/frontal (+) R MTL (+) PCL*condition R/L SMA R middle frontal/dlPFC NSI*condition R/L middle orbital/vmPFC	Partially supported
2a: No-Go cond	performance accuracy (manual errors)	Errors L postcentral	Supported
2b: No-Go cond	mTBI history (controls vs. single vs. multiple)	Mult mTBI v. ctl R sup/mid occip Mult v Single mTBI R mid occip/precuneus	Partially supported
2c: No-Go cond	b/w Ss: mTBI history (controls vs. single vs. multiple)	Error*(combined mTBI vs. ctl) R mid temp/MTL (-)	Partially Supported

	w/in Ss: performance accuracy		
2d: Go trials	performance measures: speed (RT), accuracy (errors), and consistency (ICV and SD)	RT L insula (-) RT@MDC L ACC (-) ICV@DC L/R cerebellum (-) ICV@MDC L thalamus (+) Cerebellar vermis (+) SD@DC L cerebellum (-)	Partially supported
2e: Go trials	b/w Ss: mTBI history (controls vs. single vs. multiple) w/in Ss: performance measures: speed (RT), accuracy (errors), consistency (ICV and SD)	Mult mTBI v. Ctl R cuneus/mid occip (+) L sup/mid occip (+) Mult v. Single mTBI L insula/sup temporal (+) RT*(Single v. Ctl) @UC R postcentral RT*(Multiple v. Single mTBI) @UC R postcentral (+) Error*(Multiple vs. Single mTBI) L SMA/paracentral (-) L sup temporal/postcentral (-) Group*ICV*Condition L/R cerebellum ICV*(Multiple mTBI v. Ctl) @DC L medial temporal pole (-) L parahippocampus (-) ICV*(Multiple mTBI v. Ctl) @MDC L medial temporal pole (-) L lingual gyrus (-) ICV*(Multiple v. Single) @MDC L thalamus (-) SD*(Multiple v. Ctl) @UC L ACC/MCC (-) L angular/TPJ (-) SD*(Multiple v. Ctl) @MDC R OFC/middle orbital (-) SD*(Multiple v. Single) @DC L cerebellum (+)	Supported

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