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The Relationship Between Blast-Related Mild Traumatic Brain Injury and Executive Function is Associated with White Matter Integrity

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Abstract

This project details the outcomes of mild traumatic brain injury (mTBI) including injury mechanism, immunological response, and cognitive performance. The study investigates if the integrity of certain brain regions influences the association between remote mTBI and executive function. Based on data from 182 veterans from the Minneapolis VA Medical Center, an association between blast injury severity and executive function was found to be moderated by white matter integrity of the right hippocampal cingulum in veterans with blast exposure history, such that those with higher blast severity showed a greater effect of the association between lower integrity and worse performance.

Keywords: executive function, white matter integrity, blast, mTBI, hippocampal cingulum

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Introduction

Traumatic brain injury has been considered a public health issue for decades, and in the last fifteen years, the incidence has only increased, especially in military populations. Most amplified is the rate of mild traumatic brain injury (mTBI), in part due to heightened awareness, better screening procedures, and the wars in the Middle East. Because of the greater technological improvement in body armor than head protection, veterans are now surviving once-fatal bodily injuries, but coming away with significant head damage. In particular, improvised explosive devices have caused a steep increase in the occurrence of blast mTBIs. However, the heterogeneity and complexity of veterans' deployments and experiences during their service can lead to TBIs ranging from mild to severe that are caused by any number of events. Along with blasts, impact and extreme rotation and acceleration can cause mTBIs (such as in motor vehicle accidents). This variety of mechanisms and severity of injury means analysis, diagnosis and treatment of mTBI can be incredibly difficult (Nelson et al., 2011). Blast mTBIs are currently the main focus of research due to the increase in explosive warfare (Belanger et al., 2011), and while blast and non-blast are known to have different mechanisms that can result in distinct outcomes, the specific ways in which experiencing and recovering from each type does differ has not been fully fleshed out (Davenport et al., 2012).

Because of this uptick in prevalence and diagnosis of traumatic brain injury, research has needed to play catch-up. Ongoing work in mTBI studies focuses on areas such as diagnosis, treatment and long-term outcomes in hopes of developing more preventative measures and assisting with acute and chronic symptoms. Often, when a veteran returns from their deployment, a battery of neuropsychological evaluations and

self-reports lead to a slew of consultations with medical professionals that may or may not be helpful for an individual (Lamberty et al., 2013). These treatments tend to focus on deficits and impairments seen well after the mTBI. However, acute management of the injury may be the most effective in preventing later-stage symptoms. This is unfortunately difficult to achieve, as most often, a mild head injury is not cause enough to send a soldier home, and when they do return, treatment may not be sought immediately, especially if they do not remember experiencing the mTBI or think the injury is not cause for serious concern. Furthermore, the treatments offered are unlikely to work for all patients, and without detailed knowledge of the injury's nature and potential sequelae, the mTBI's effects may never be fully resolved (Lamberty et al., 2013). Furthermore, mTBI is of particular importance, as the remote sequelae are often subtle and similar to those of other conditions like post-traumatic stress disorder, depression or anxiety.

As such, understanding the details of mTBI from the original incidence to remote cognitive outcome will hopefully lead to improved care for patients. Currently, active treatments cannot be implemented until the veteran returns home and undergoes a medical consult. Even then, patients rarely go to follow up appointments or stick with their treatment plans, which can include a long list of therapies from cognitive behavioral and speech pathology to physical and occupational therapy. If the physiological response the brain endures after a traumatic incident can be elucidated, individual biology-based medicine may become more useful, and in-theatre treatments for mTBI could be developed. If the immune response can be halted or slowed down to prevent potential chronic outcomes, many people may be relieved of having life-long cognitive impairments. Knowing if there are separate courses of recovery depending on

circumstances of the mTBI and how they progress could help create these specialized treatments.

The mechanism of injury, the immune response of the brain, and the cognitive outcomes, as well as potential confounding variables are all important to understand the puzzle of mTBI (Blennow et al., 2012). Currently, the aftermath of moderate and severe injuries is better understood because they cause more obvious detriments, but mild injuries are the most common, for civilians and military personnel. MTBI tends to affect people more subtly, with chronic deficits that can go unnoticed, but can seriously diminish quality of life (Lamberty et al., 2013). Understanding how those chronic effects come about is key, and defining the immune system's initial response may be one way to achieve this. While current evidence has not pointed to a large difference in immune response to blast and non-blast mTBI, even slight divergences could potentially result in global effects. The immune system helps hold the brain in such a delicate homeostasis, and a serious insult to the environment causes many physiological repercussions that can permeate.

Certain skills and cognitive abilities seem to be particularly affected by mTBI. Due to the combination of rotational, acceleration, and impact forces present in non-blast injury, and the additional pressure waves in blast injury, the brain is often affected in somewhat predictable ways that are specific, significant, and irreversible (Kinnunen et al., 2011; Zohar et al., 2003). Acutely after mTBI, working memory, recall, and executive functions were shown to be worse than in controls (de Freitas Cardoso et al., 2019). However, there is less understanding of exactly which functions are affected by blast compared to non-blast mTBIs. Cognitive decline after experiencing an mTBI is treated

broadly, but identifying specific detriments connected to these types of injuries could lead to an increase in the efficacy of treatments, as they could be appropriately specialized. Based on these concepts, any significant difference in the acute post-injury sequelae of blast and non-blast mTBI is worthwhile to pursue.

In this thesis, I will discuss two broad mechanism of mild traumatic brain injuries: blast and non-blast, and the potential differences in immune response the brain has to each of these. Then, I will outline the study I conducted, which explores the connection between mechanism of injury and remote cognitive performance and consider wider implications of my findings for mTBI research.

Injury Mechanisms

Head injuries can have a multitude of sources, often simultaneously (or very close in time), which is just one of the many causes of the heterogeneity of mTBI. These can be broadly divided into blast and non-blast injuries. Blast injuries are mostly found in combat situations, whereas non-blast injuries are present in both civilian and military circumstances.

Determining if there are distinguishing factors between blast and non-blast is crucial to understanding mTBI. These two differing mechanisms of injury likely impact the brain in distinct ways (Belanger et al., 2011). One distinction is that blast injuries tend to be diffuse, while non-blast are generally more focal, though can have diffuse effects (Bandak et al., 2015). Diffuse injuries tend to spread throughout the brain as low energy waves, affecting a larger volume of the brain and mainly damaging microstructures (Bandak et al., 2015). Diffuse injuries can come from forces like blasts, or experiences such as motor vehicle accidents, which complicates the division between blast and non-

blast mTBI, particularly in mild cases (Andriessen et al., 2010). Non-blast injuries are significantly more concentrated and direct higher energy to a more localized area, often from collision forces and compression (Andriessen et al., 2010). Usually in mTBI, the dura and skull are unharmed, though if seen, non-blast injuries more commonly display these injuries than blast injuries (Bandak et al., 2015)

Macro-Damage

Blast Injury

Blast injuries are frequent in military combat and tend to be complex. They are usually incurred by the overpressure wave that occurs just after detonation of a bomb, most often an improvised explosive device encountered in the field. The resulting shock wave travels faster than sound and is followed by a blast wind (Elder et al., 2010). Then, the air pressure rapidly decreases, creating a reverse blast wind. Before returning to equilibrium, a second, smaller positive blast wave also passes through the air (Elder et al., 2010). The body reflects some of the energy and some can be deflected by the surroundings, but most of the pressure waves pass into the body (Leung et al., 2008; Miller et al., 2015). Depending on the orientation of the body compared to the blast, incident, dynamic, and effective pressure waves can impact the person and may contribute to consequent brain pathology (Leung et al., 2008; Miller et al., 2015). The blast causes high-frequency stress waves, which cause smaller-scale injuries to tissue and create a pressure differential; as well as low-frequency, long-duration shear waves that compress the body (Elder et al., 2010; Leung et al., 2008). Some of these waves are absorbed by the torso, but they still often reverberate up to the brain and reflect within the skull (Bandak et al., 2015). This sequential and multi-dimensional attack on the brain

results in strain, shearing, spallation, micro-cavitation, embolisms, and implosion of neural tissues (Elder et al., 2010; Rosenfeld et al., 2013).

Furthermore, primary blast injury tends to be rare. Usually, secondary through quaternary injuries that result from the initial explosions complicate matters. Explosions can hurl debris and shrapnel, and throw people against surfaces or onto the ground, which can further injure the brain. Due to this, blast injuries are often compounded with one or more non-blast injuries, making diagnosis and research difficult.

Non-Blast Injury

Non-blast mTBI is associated with neural and neurovascular tissue damage through skull deformation, rotation of the brain and increased intercranial pressure (Young et al., 2015). Even though the anatomy of the head is designed to withstand natural course-of-life injuries, concussions are obviously still detrimental. While blunt force trauma is similar to blast in some respects, the focal nature of the injury separates the two phenomena (Aravind et al., 2020; Macciocchi et al., 1996). For focal injuries, at points of skull contact the brain damage is likely to be more intense: one theory posits that the degree of damage is relative to the intensity of the injury in how deeply the brain is affected (Young et al., 2015). With rotational force, deeper structures of the brain, even reaching into the diencephalon, are disrupted (Young et al., 2015). Thus, these two types of mechanisms are different enough on a global scale to be deemed separate, and their sequelae may be similarly distinctive.

Micro-Damage

Looking deeper at the damage done to the brain by an mTBI, there are two particularly common phenomena that trigger physiological responses: traumatic axonal

injury and blood-brain-barrier breakdown, which lead to neuronal death (McKee & Lukens, 2016). They tend to occur in the order listed, but there is not a large temporal separation, and the consequential biological responses are intertwined as well (McKee & Lukens, 2016). An important note: these main initial processes occur in both blast and non-blast mTBI, and while much of the aftermath is very similar, there are thought to be a few slight temporal and proportional differences that are worth exploring as they may have later consequences (Cernak & Noble-Haeusslein, 2010).

Traumatic Axonal Injury

Traumatic axonal injury (TAI) is one of the most significant immediate injuries that occurs after mTBI (Adams et al., 1989). It is defined as small, scattered lesions and brain swelling in white matter regions of the brain, that often results in impaired axoplasmic transport, axonal swelling, and disconnection (Adams et al., 1989; Bruggeman et al., 2020; Salmond et al., 2005). It is considered a progressive event, where local axonal alterations become more widespread over time (Adams et al., 1989; Salmond et al., 2005; Yoganandan et al., 2008). Also known as diffuse axonal injury and shear injury, it is present in some capacity in the majority of brain injuries, from mild to severe, though is often at the microscopic level (Adams et al., 1989). It is caused by rapid acceleration and deceleration of the brain tissue, as well as blunt-force trauma (Adams et al., 1989; Bruggeman et al., 2020; Büki & Povlishock, 2006; Yoganandan et al., 2008). In scenarios where the brain's intercranial pressure is raised Adams et al. (1989) found that 70% of the population showed evidence of TAI. In a model of non-human primates, directional forces were shown to matter in the case of TAI, where coronal (front-to-back) acceleration is worse than rotational (around the axis of the neck) acceleration, which is

yet worse than sagittal (side-to-side) acceleration (Adams et al. 1989; Blennow et al., 2012; Leung et al. 2008). While both blast and non-blast injury can cause all types of these forces, the widespread nature of pressure waves coursing through the brain may cause a different combination than non-blast injuries, which have a focal point of impact (Yoganandan et al., 2008). Because of this potential variance in the tracts damaged, different mental faculties may be affected between the two types of injuries.

TAI most notably affects white matter tracts along the brain's midline such as the corpus callosum and internal capsule (Adams et al., 1989, Bruggeman et al., 2020). Some studies have found evidence that suggests blast injury affects the frontal and temporal lobe in a way not seen in non-blast (Ryu et al., 2014), though the midline long fiber tracts tend to most affected in all types of mTBI (Li et al., 2012; Ryu et al., 2014).

The primary axotomy of TAI is the physical damage to the axons by overstretching that leads to shear injuries and immediate disconnection of axons (Andriessen et al., 2010). Secondary axotomy from the smaller-scale aspects of TAI, however, is where the real damage seems to lie, and occurs in a larger proportion of neurons (Dixon et al., 2017; Wolf et al., 2001). TAI results in excitotoxicity and mitochondrial dysfunction that can lead to serious, irreversible damage to axons, including cell death (Singh, 2017; Yonutas et al., 2016). Evidence suggests two forms of neuron atrophy from TAI (Andriessen et al., 2010; Dixon et al., 2017; Farkas & Povlishock, 2007; Ryu et al., 2014). One is characterized by increased axon permeability, cytoskeleton breakdown, and mitochondrial swelling leading to primarily necrosis, while the other is more so characterized by disrupted axonal transport and local spheroidal

swelling resulting in mostly apoptosis (Andriessen et al., 2010; Dixon et al., 2017; Farkas & Povlishock, 2007; Singh, 2017).

This first type of damage is incurred mostly by calcium, which has a multifaceted role throughout TAI processes, and is certainly not wholly isolated to one version of secondary axotomy (Singh, 2017). The initial tensile shearing force causes damage as well as disrupting intracellular organelles, allowing calcium to flow into the cytoplasm from a variety of locations (Büki & Povlishock, 2005; Kelley et al., 2005; Wolf et al., 2001; Yonutas et al., 2016). Extracellular calcium enters the injured axon by way of two main mechanisms: the increased permeability of the axolemma, and the dysfunction of the sodium channels that trigger voltage-gated calcium channels (Büki & Povlishock, 2005; Siedler et al., 2014). Sodium channels, especially those of the sodium-calcium exchanger, allow for depolarization to occur that can affect other voltage-gated channels along the membrane (Wolf et al., 2001). The steep increase in concentration from both intra- and extracellular calcium influx also leads to a number of proteolytic cascades that slowly damage proteins within the axons (Büki & Povlishock, 2005). Some examples of such a calcium-modulated process are the release of calpain, which over time causes microtubular loss, mitochondrial swelling and neurofilament compaction, and calcineurin, which leads to neurofilament side-arm modification and disassembly (Büki & Povlishock, 2005). Neurofilaments are crucial to maintaining somatic and axonal morphology and function, and thus destruction of the intricate system can threaten the cell (Ray et al., 2002; Siedler et al., 2014). The breakdown of the cytoskeleton often results in thin axons and weakened soma, which are then susceptible to further damage from the environment (Büki & Povlishock, 2005; Siedler et al., 2014).

The most noticeable effect of the second type of TAI is swollen retraction bulbs along the axon (Andriessen et al., 2010; Farkas & Povlishock, 2007). Damage usually occurs at multiple locations along the axon shaft, at the nodes of Ranvier and at the terminal, causing varicosities, mechanoporation and dysregulation (Greer et al., 2013; Tang-Schomer et al., 2011). They can be seen early on post-injury, continuing to increase in size over time (Bruggeman et al., 2020; Chen et al., 2019; Greer et al., 2013; Povlishock & Christman, 1995; Siedler et al., 2014). The axon can even become completely severed, significantly shorten, and lose synaptic connections (Povlishock & Christman, 1995).

These two types of damage do not generally occur in the same cell but can be found around the same injury site (Dixon et al., 2017; Farkas & Povlishock, 2007; Singh, 2017). There is evidence that injuries from events such as motor vehicle accidents and injuries from blast display slightly different morphologies (Ryu et al., 2014). Damaged axons after motor vehicle accidents are more sparse but more sizable than those from blast, which are smaller, more circular, and greater in number (Ryu et al., 2014). Though this difference may be modulated by other factors, it is interesting to posit if the different forms of axonal injury are at play. Could the difference in bulb size and density correlate with the type of response the axon is exhibiting? More multi-focal, localized damage causing mitochondrial dysfunction and increased axonal permeability has been shown to be present after non-blast mTBI and matches up with the first type of axon injury response (Andriessen et al., 2010; Farkas & Povlishock, 2007; McAllister, 2011). In blast injury, axonal damage tends to be more widespread throughout the brain due to the pressure waves that pervade the brain and blood (Bandak et al., 2015; Bass et al., 2011).

The terminated axonal transport and the more subtle permeability changes due to diffuse disruption of the entire axon as seen in the second type of axon damage match this mechanism of injury as well (Farkas & Povlishock, 2007).

Connecting this to the axonal bulbs themselves; more focal injuries such as a non-blast mTBI tend to damage the neuron in one place along the axon, and thus the cell can often accommodate for the damage (Andriessen et al., 2010; Farkas & Povlishock, 2007; McAllister, 2011). In blast injury, the axon is disrupted in multiple places, and therefore cannot remedy the injury fast enough to ensure axon transport remains possible, causing a multitude of issues (Farkas & Povlishock, 2007). While in many non-blast injuries, both focal and diffuse damage is present, the uniformity of a blast pressure wave as it moves throughout the brain as compared to the more localized damage – even if seen throughout the brain – of a non-blast injury may affect neurons differently (Hayes et al., 2015; McAllister, 2011).

Blood Brain Barrier Disruption

The blood-brain-barrier (BBB) is vital to the health of the brain, as it serves as a protective filter to keep the brain in homeostasis (Alluri et al., 2015). It is composed of cerebral microvascular endothelial cells connected through tight junctions, capillary base membranes, astrocytes and pericytes, all of which form a physical transport and metabolic barrier (Alluri et al., 2015; Shetty et al., 2014). Disruption of this protective layer leads to a number of issues, including the allowance of peripheral cells and molecules into the environment and tearing of the endothelial cells themselves (Chodobski et al., 2011). While many injuries and diseases can affect the BBB, mTBI – and especially blast-derived brain injury – is particularly damaging (Alluri et al., 2015;

Uzunalli et al., 2021). Usually in a physical mTBI, the brain collides with the skull and is compressed, which stresses the BBB and disrupts the cellular makeup of the barrier and neurovascular units, leading to breakdown (Alluri et al., 2015; Shlosberg et al., 2013). The response is biphasic, with the initial assault rapid and lasting only a few hours, and the follow-up a direct response to the injury; though both result in increased permeability (Shlosberg et al., 2013). Evidence has shown that microvascular disruption occurs across the mTBI severity scale, both acutely and chronically (Wu et al., 2020).

After a focal injury, endothelial cells of the blood vessels in the area are often sheared, which can cause a localized ischemia (Shlosberg et al., 2013). This type of contusion is short of a hematoma or hemorrhage and can be relatively sequestered to the area where the injury occurred, though can also permeate out further (Kuriakose et al., 2018; Shlosberg et al., 2013). The pathophysiology of BBB disruption has been heavily researched in recent years as it is a particular signature of blast injury (Kabu et al., 2015; Toklu & Tümer, 2015). As the shockwave from a blast propagates through the brain, it rapidly damages blood vessels, causing deformation and leakages (de Lanerolle et al., 2015; Kabu et al., 2015). The amount of acute damage is proportional to both the pressure wave intensity, and to the relative density and vascularization of the brain areas (Kuriakose et al., 2018). Blasts at 35 kiloPascals showed no significant BBB damage like that of 70 kPa and above did (Kuriakose et al., 2018). Increases in pressure and a higher degree of vascularization both lead to more damage to the BBB that continues to aggravate the cerebral environment, potentially including phenotypic changes in blood vessel wall cells (Elder et al., 2015; de Lanerolle et al., 2015; Kabu et al., 2015;

Kuriakose et al., 2018). This may indicate a possible difference in BBB permeability following blast versus non-blast mTBI (de Lanerolle et al., 2015).

Due to the variation in vessel organization, BBB disruption does not always uniformly affect the brain. In one study conducted in rats, the neocortex was more affected than junctions of gray and white matter after blast injury (Kuriakose et al., 2018). In another of blast injury, small lesions of disrupted blood vessels were found in focal areas symmetrically throughout the brain (Yeoh et al., 2013). In both of these experiments, the authors do note that acceleration and deceleration forces are not a significant factor, as the animals were held in place to experience the blast (Kuriakose et al., 2018; Yeoh et al., 2013). Evidence also suggests that blast-affected brains tend to show axonal damage nearby to vasculature within the brain, indicating the role that the BBB and blood vessels have in this secondary pathology (Elder et al., 2015; Kobeissey et al., 2013; Ryu, et al., 2014).

To allow for a robust immune response, the BBB must permit passage for the immune cells. If this is not properly regulated, it can lead to just as serious effects as direct disruption of the barrier does, namely through edema (Sholsberg et al., 2013). Edema can raise intercranial pressure, impair cerebral perfusion and disrupt oxygenation and the balance of hydrostatic-osmotic forces, affecting axon stability and structure (Shlosberg et al., 2013; Toklu & Tümer, 2015). The secondary effects of BBB affect the brain long-term in many ways (Alluri et al., 2015). Hypoxia, vasospasm, coagulopathy, glutamate excitotoxicity, clearance deficiency, increase in reactive oxygen species, endothelial transport malfunction, damage to astrocyte end-feet and inflammatory pathway activation are some known down-stream outcomes of BBB disruption from

primary mTBI that lead to white matter damage, acutely and over time (Alluri et al., 2015; Chodobski et al., 2011; Shlosberg et al., 2013; Wu et al., 2020).

Many of these processes can also perpetuate the damage already done by TAI (Alluri et al., 2015; Kabu et al., 2015). Recent research has focused on blast injury aftermath, as the damage seems to be more widespread than in non-blast, even if the processes triggered are similar. After blast mTBI, BBB disruption is a more acute problem, rather than a delayed response or collateral of other types of damage, as is seen in non-blast mTBI (Toklu & Tümer, 2015). For example, the large release of calcium and glutamate that follows TAI can lead to BBB disruption even if the barrier was not originally severely damaged (Shlosberg et al., 2013; Toklu & Tümer, 2015; Wu et al., 2020). This provides evidence for a temporal difference between blast and non-blast mTBI regarding the BBB, even if the end result is similar. If the control the BBB maintains over the brain's environment is disrupted, neurons suffer damage through imbalances and infiltrations of ions and cells. Thus, the axons that comprise white matter are not only partially prevented from repairing, but further harmed as well.

Mitochondria

Mitochondria are another major player in the aftermath of mTBI. They are not only negatively affected by the inundation of calcium from TAI, as the membrane permeability transition pore is opened both directly by the ion and by calpain, but also release calcium themselves, further contributing to the heightened concentration (Büki & Povlishock, 2005; Wolf et al., 2001). This results in a collapse of energy production as adenosine triphosphate (ATP) production is interrupted, and a loss of ionic homeostasis from malfunctioning sodium-potassium pumps that rely on ATP (Büki & Povlishock,

2005; Wolf et al., 2001). Mitochondrial failure also leads to the release of cytochrome-c and caspases that begin the cell death cascade in the soma and/or the axon (Büki et al., 2000). Mitochondria also lose their ability to regulate oxygen free radicals and reactive oxygen species flourish (Kabu et al., 2015; Ray et al., 2002; Yonutas et al., 2016). Without the delicate balance between production and destruction of reactive oxygen species maintained, the mitochondria, proteins, nucleic acids, cell membranes and vasculature can be damaged (Hiebert et al., 2015; Ray et al., 2002; Toklu & Tümer, 2015).

Gross disruption of mitochondria has not been found to be consistently present in blast models, though increases in oxidative stress have been observed (Kabu et al., 2015; Yonutas et al., 2016). Similarly, in diffuse injuries, mitochondria damage was present, but not as significantly as in more focal injuries (Yonutas et al., 2016). That focal injury tends to leave mitochondria struggling to remain effective lends support to the notion that mitochondrial swellings are more so a factor of non-blast injury, and that necrosis is the type of cell death suffered.

Excitotoxicity

After mTBI, amino acids, most notably glutamate, flood into the cerebrospinal fluid and extracellular space causing a variety of disruptions (Andriessen et al., 2010; Ray et al., 2002). Glutamate is released from the synapses, leaks through damaged axolemma, and enters via the disrupted BBB (Yi & Hazell, 2005). The amino acid binds a number of places: to NMDA receptors allowing sodium and calcium influx, to AMPA receptors allowing sodium in and potassium out, and metabotropic receptors that signal intracellular second messengers, as well as glutamate-regulating receptors on astrocytes

(Ray et al., 2002; Yi & Hazell, 2005). Lack of feedback loops involving these receptors (potentially from other mTBI-triggered pathologies) leads to further unwanted excitation (Yi & Hazell, 2005). Astrocytic swelling can also cause a further release of glutamate, worsening the over-activation of the surviving receptors (Yi & Hazell, 2005). This pattern of binding creates a dangerous environment of excitotoxicity in affected brain regions, which can increase oxidative stress, prolonged depolarization of neurons, ionic imbalance, and depletion of ATP within the cell and further damage to the already compromised blood-brain-barrier (Chodobski et al., 2010; Ray et al., 2002; Werner & Engelhard, 2007; Yi & Hazell, 2005).

The overall increase in cellular stress from glutamate has been shown to be linked to both necrosis and apoptosis, as well as interacting with calcium-modulated cell death processes (Ankarcrona et al., 1995). Glutamate excitotoxicity tends to affect the immediate area most negatively, but does diffuse outwards, and there is a difference in temporal patterns of glutamate reuptake between an immediate lesion and the area around the lesion (Ankarcrona et al., 1995; Guerriero et al., 2016). Connecting this to non-blast versus blast injuries, there may be a distinction in how glutamate excitotoxicity is handled by the brain after an injury that has more of a localized impact point compared to a broader scope of assault, even if the original over-release of glutamate is somewhat ubiquitous.

Clearly, it is not always the initial impact that causes the worst damage (Büki & Povlishock, 2006; Povlishock & Christman, 1995). Secondary axotomy, which can be considered separate or as a continuation of primary axotomy, involves a complex molecular response to partial axon damage that is both inflammatory and apoptotic

(Bruggeman et al., 2020). Homeostatic disruption can cause imbalances that last, preventing the brain from returning to baseline (Büki & Povlishock, 2006; Toklu & Tümer, 2015). Pathology in relation to axon damage has been shown to be significantly present up to 18 years post-injury, emphasizing just how long-term the effects of a mTBI can be (Johnson et al., 2013).

Cell Death

The ultimate consequence of mTBI is cell death. The many cascades and processes that TAI and BBB trigger lead to both apoptosis and necrosis of neurons and glia, both soon after the injury and after time (Colicos et al., 1996; Hausmann et al., 2004; Leung et al., 2008). Physical damage and excitotoxicity can cause calpain cascades, caspase activity, and energy production disruption, which have all been shown to lead to cell death (Colicos et al., 1996; Nicotera et al., 1999; Raghupathi, 2004; Stoica & Faden, 2010). In a rat model, both blast and non-blast injury groups were found to have fewer neurons than sham groups in the hilar region of the hippocampus, with the blast injured animals having even fewer than the non-blast-injured (Aravind et al., 2020). Furthermore, evidence from the same study suggested a potential difference in the pathway to cell death, as only the non-blast mTBI rats showed evidence of neurodegeneration, but neuronal loss still occurred in the blast group (Aravind et al., 2020). The lasting loss of neurons in the hippocampus after blast mTBI suggests a difference in the secondary mechanisms that propagate cell death after blast and non-blast mTBI (Aravind et al., 2020). These separate patterns of cell death could lead to distinct consequences for the brain down the line, as the death of neurons in the brain is generally irreparable (Shlosberg et al., 2013).

In focal injury, most cell death occurs within the direct vicinity of the contusion, or in the corresponding contralateral region, whereas in diffuse injury, dying neurons are often spread much further and in less predictable arrangements (Farkas & Povlishock, 2007). This suggests separate phenomenon. Furthermore, some have theorized that neurons are at higher risk of cellular death following focal injury, while diffuse injury affects glia more (Raghupathi, 2004). There is also discussion of the differences and similarities between necrosis and apoptosis following insult to the brain. Both necrosis and apoptosis are types of cell death but may be triggered and develop in the cell in separate ways (Raghupathi, 2004). In a study comparing excitotoxic cell death – which is related to necrosis – with physiological cell death (also known as apoptosis), these two post-trauma processes were shown to differ ultrastructurally (Ankarcrona et al., 1995; Dikranian et al., 2001). Furthermore, excitotoxic cell death was found to occur rapidly and more locally at the site of head injury, whereas physiological cell death was disseminated throughout the brain and occurred more slowly (Dikranian et al., 2001).

Some research has shown a temporal difference in post-blast and post-non-blast injury, where neuronal loss is a more elongated process after blast, suggesting apoptosis (Aravind et al., 2020; Toklu & Tümer, 2015). In non-blast, cell death seems to occur quite rapidly, as the cells are so damaged, they cannot even undergo programmed cell death, suggesting necrosis (Stoica & Faden, 2010). Furthermore, necrosis is associated with loss of ionic homeostasis, membrane integrity breakdown and swelling of the organelles, which mirrors the first type of TAI defined by swollen axonal bulbs (Andriessen et al., 2010; Dikranian et al., 2001; Stoica & Faden, 2010). And, apoptosis is characterized more so by nuclear condensation, fragmentation along the axon and a

subsequent decrease in cell volume, as seen in the second type of TAI hallmarked by a slower demise (Dikranian et al., 2001; Stoica & Faden, 2010). There are suggestions that there is a continuum from necrosis to apoptosis, that the two processes are intertwined, or that there is some combination process, (Nicotera et al., 1999; Raghupathi, 2004; Stoica & Faden, 2010). And, necrosis and apoptosis may be able to be triggered and mediated by similar processes, so allocating all blast-related cell death to apoptosis and non-blast to necrosis would be irresponsible (Singh, 2017). Proportionally, however, knowing the prominent cell death type in each mechanism could certainly be informative.

There are many overlaps of the effects traumatic axonal injury and blood-brain-barrier disruption have on the brain: both begin complicated cascades of inflammatory response that range from the molecular to the cellular to the systematic, and lead to cell death throughout the brain. Understanding the details of the immune response to these head injuries will help elucidate the potential differences between blast and non-blast mTBI and inform treatments.

The Immune Response

As beneficial as the immune response is intended to be within the body and brain, it is well established that overactivity, backfiring, or irreversibility of once-beneficial immune processes can actually cause harm or slow the repairing of physiological trauma (McKee & Lukens, 2016; Milman et al., 2005; Ray et al., 2002). For example, some posit that secondary response can be more clinically significant than the initial injury, and in the case of mTBI this can be subtle enough to escape detection via neuroimaging (Bruggeman et al., 2020; Corps et al., 2014; Ray et al., 2017; Verboon et al., 2021). Therefore, distinguishing the immunological response to blast and non-blast mTBIs will

not only be informative, but assist in creating potential treatments, as the window of secondary axotomy is significantly wider than the initial insult and could potentially be intervened. Broadly, the four outcomes of the response are: 1) blood-brain-barrier breakdown and edema, 2) neuronal cell death, 3) gliosis and immune cell infiltration, and 4) upregulation of inflammatory factors (Dixon, 2017; McKee & Lukens, 2016). The first three of these tend to spike relatively quickly after injury, but the fourth can be longer lasting. To repair itself, the brain initiates a host of immunological processes ranging from micro to macroscopic scales. These can compound upon one another to create an intricate response in the brain (Povlishock & Christman, 1995). Previously the brain was thought to be immune-privileged and separate from the peripheral immune system. Recently, this has been shown to be untrue, and following trauma to the brain, peripheral immune cells will move to the brain to assist in repairing the damage (Simon et al., 2018). Degree and mechanism of injury both influence the relationships between the central and peripheral immune system (Simon et al., 2018).

The brain has a highly complex reaction to injury, and thus a highly complex immune response (Ray et al., 2017). Many of the processes overlap or occur in tandem, comprehensively trying to address the damage. Therefore, when considering how the brain goes about repairing itself, it is crucial to note that no one process is responsible, nor does it exist in a vacuum. Feedback loops, cellular cross talk, and self-amplification are just a few examples of how the complexity of the response plays out (Ray et al., 2017). There is an inundation of communicative factors in the brain after injury, and nothing works individually. After an injury, the immune system is responsible for sequestration of tissue, engulfment of cellular debris, healing of the original wound, and

returning the environment to homeostasis (McKee & Lukens, 2016). Signaling molecules, inflammasomes, microglia and astrocytes, neutrophils and leukocytes, and components such as tumor necrosis factors all respond to the injury, ideally leading to regeneration of salvageable neurons and protection of the brain, but all too often end up causing further neurodegeneration (Simon et al., 2017).

Cytokines and Chemokines

Immediately after an mTBI, a host of inflammatory molecules are released to trigger the recruitment of immune cells and begin protective processes (McKee & Lukens, 2016; Morganti-Kossmann et al., 2019). Chemokines and cytokines are the main inflammatory mediators that begin this cascade of events, usually starting by upregulating the production of more mediators (Morganti-Kossmann et al., 2019). They are triggered by larger-scale phenomenon such as mechanical stretching and damage, and breakdown of the BBB, as well as smaller-scale environmental changes like expulsion of ATP from harmed cells, glutamate excitotoxicity and increased oxidative stress (McKee & Lukens, 2016; Verboon et al., 2021). Chemokines are responsible for signaling to neutrophils, lymphocytes, monocytes and T-cells, while cytokines such as interleukins assist in cellular communication, neuronal protection and suppression of microglia and astrocytes (Ziebell & Morganti-Kossmann, 2010). TNF-alpha has been shown to be particularly involved in repair of the BBB and production of other cytokines, as well as trigger both necrosis and apoptosis (Lenzlinger et al., 2001). Both neurons and glia synthesize and release various subgroups of chemokines and cytokines, creating a highly complex system of amplification and suppression that can lead to both beneficial and harmful

outcomes, acutely or chronically (Lenzlinger et al., 2001; Ziebell & Morganti-Kossmann, 2010).

There is little research directly regarding potential differences in blast mTBI and non-blast mTBI cytokine and chemokine levels (Rusiecki et al., 2020). However, because of the potential slight differences in damage profiles – such as vasculature being more affected in blast mTBI – the interleukins subsequently released may differ in proportion or type (Rusiecki et al., 2020). Due to the feedback loop-heavy nature of signaling during such an immune response, this could result in a significant effect on the brain that may be reflected later. For example, a different proportion in chemokines that attract monocytes compared to neutrophils could perhaps lead to a distinction in the type of repair processes employed. Furthermore, the diffusion of the injury may determine how widespread the release of mediators is, changing how much of the brain is then affected by the recruited immune cells.

Microglia and Astrocytes

Glia in the brain are paramount to survival. Microglia are constantly patrolling the brain managing the microenvironment, regulating cell death, synapse elimination, and neurogenesis (Loane & Kumar, 2017). Astrocytes are responsible for maintaining homeostasis, supporting neuronal function and glial transmission, and provide integrity to the BBB (Karve et al., 2016). After an insult such as an mTBI, glia take on a wide variety of forms and roles that assist in isolation and repair of the damage and reforming of neural circuitry (Burda et al., 2017). Astrocytes and microglia that were not damaged in the original insult secrete cytokines and chemokines to draw more immune cells to the site (Loane & Kumar, 2017; Shi et al., 2019; Simon et al., 2017). While these peripheral

cells migrate to the injured axons, microglia and astrocytes proliferate and transform into their reactive states to begin the repair process (Clark et al., 2019; Loane & Kumar, 2017). Isolating the area and creating a scar using an inhibiting extracellular matrix, astrocytes attempt to contain the damage and inflammation to allow for neuron repair (Loane & Kumar, 2017; Shi et al., 2019). Evidence shows that astrocytes take on a few forms during this process, with some being more helpful than others, especially in the long-term (Clark et al., 2019). For management and repair of the BBB, astrocyte end-feet help to hold tight junctions in place (Clark et al., 2019; Karve et al., 2016). They act to close the gaps in the BBB that allow unregulated molecules through (Clark et al., 2019; Karve et al., 2016). Furthermore, astrocytes respond to glutamate excitotoxicity, working to take up the excess amino acid and prevent damage (Karve et al., 2016).

Responding to danger signals from neurons and astrocytes, microglia activate and shift their morphology and genetic expression to their hypertrophic state which is like that of a macrophage in many ways (Corps et al., 2015; Loane & Kumar, 2017). There are multiple forms that microglia can take, similar to the spectrum along which macrophages are seen, where some phenotypes favor promoting pro-inflammatory cytokines, chemokines, TNF, and reactive oxygen species and are associated with phagocytosis (Cao et al., 2016; Loane & Kumar, 2017). While this state is intended to be neuroprotective, it is often considered neurotoxic, especially if regulation of its presence goes awry (Loane & Kumar, 2017; Hu et al., 2014). Other microglia associated with immune cell memory will shift into anti-inflammatory forms (Loane & Kumar, 2017). While the neuroprotective microglial phenotype tends to subside relatively quickly, the neurotoxic form has been shown to persist for months and years after the mTBI,

potentially causing chronic issues and neurodegeneration (Loane & Kumar, 2017; Karve et al., 2016). It is important to note that there are many subsets of these forms, and research has shown that the neurotoxic/neuroprotective dichotomy is an oversimplification of the phenomenon, though general patterns are still worthwhile to consider (Clark et al., 2019).

As the environment of the brain dictates which morphology the glia take on and how long they remain in their activated state, any potential differences between blast and non-blast mTBI could affect this (Burda et al., 2017; Cao et al., 2016; Karve et al., 2016). For example, microglia found near the site of ischemic injury are distinct from those in the surrounding area, and a more rapid transition from their inactive to active state has been demonstrated in white matter as compared to gray matter (Loane & Kumar, 2017). Astrocytes have also been found to have a proportional relationship to injury based on distance (Burda et al., 2017). Perhaps similar distinctions of location and form of glia exist between BBB disruption and traumatic axonal injury. Just for the BBB, the nature of injury seems to affect how quick the glial response is (Huber et al., 2017). The damage to penetrating arteries and cortical vessels common after blast injury allows for increased influx of microglia, which then become activated (Huber et al., 2017). Despite a robust involvement of microglia in focal injuries as well, this widespread pattern of activation is not seen, as a denser accumulation of microglia is observed near the injury site (Huber et al., 2017). Astrocytes have also been shown to be involved in more focal injury – particularly controlled cortical impact models – as the nature of the insult leads to creation of a large and defined glial scar (de Lanerolle et al., 2015).

Also, duration of overpressure wave experienced during a blast may influence the activation patterns of these cells, with higher pressure leading to more significant immune function gene upregulation for microglia, and an increase in number for astrocytes (Kane et al., 2016; Miller et al., 2015). Interestingly, evidence suggests that this genetic modification is more common after blast, and that outright destruction of microglia is seen more in localized injury (Kane et al., 2013; Miller et al., 2015). As microglia are generally primarily active next to damaged white matter, the spread of injury may influence how widespread the glial inflammatory response is and how many cells are present (de Lanerolle et al., 2015; Wofford et al., 2018). There is evidence suggesting preferential localization of microglia to neurons with damaged plasmalemma, so when considering the difference in types of secondary axotomy after traumatic axonal injury this may mean that blast and non-blast injury show different distributions or proportions of microglia and astrocytes (Wofford et al., 2018).

Peripheral Immune Cells

Responding to the signal from the brain for assistance, neutrophils, macrophages and other lymphocytes migrate to the injury site (Shi et al., 2019). These cells cross the BBB and choroid plexus to enter the brain and cerebrospinal fluid (Chodobski et al., 2012). Partially due to their abundance in the periphery, neutrophils often arrive first to the site, reacting to signaling from chemokines, cytokines, microglia, and astrocytes (Corps et al., 2015; Shi et al., 2019). Within minutes in some cases, neutrophils can be seen in the brain beginning phagocytosis of dead cells, clearing debris and assisting in blood vessel support (Alam et al., 2020; Liu et al., 2018). Neutrophils localize to the meninges to perform these processes, displaying a protective role (Liu et al., 2018). They

also interact with microglia, astrocytes, and oligodendrocytes through cytokine signaling to increase the inflammatory response and prevent infection (Liu et al., 2018).

Evidence also shows an abundance of circulating monocytes-turned macrophages in the brain after mTBI (Alam et al., 2020; Jassam et al., 2017). Chemical signaling recruits the cells and triggers their expression of reparative genes and begins phagocytosis (Alam et al., 2020; Hsieh et al., 2013). Much of their behavior is similar to that of the activated resident microglia, especially in the forms they take (Alam et al., 2020). Like microglia and astrocytes, these have a variety of slightly differing roles, and will morph over time to fit the needs of the brain (Hsieh et al., 2013).

Because their activation period is so short, a significant difference in neutrophil response to blast and non-blast has not been demonstrated. However, similar to microglia and astrocytes, localization of activation changes the response neutrophils have to injury sites (Corps et al., 2015). Therefore, between injury types there may be a broader distinction seen at a larger scale than individual neutrophils acting on damaged cells. In some cases of diffuse injury, a smaller contribution of circulating macrophages has been found (Loane & Kumar, 2017). Furthermore, as microglia are essentially the monocytes and macrophages of the central nervous system, and all three of these cell types look similar in the inflamed brain, it can be difficult to decipher which are present (Chodobski et al., 2012; Hsieh et al., 2013). But subtle differences in the cells' morphological profile may be important in the grander scheme, as an unequal distribution or activation of various cells could result in longer-term changes that are more specialized to injury type.

Long-Term Effects

Evidence has shown that chronic inflammatory activity – even low grade – in the brain is connected to physical and mental deficits (Collins-Praino et al., 2018; Loane & Kumar, 2017; Smid et al., 2015). The response of peripheral immune cells is heterogenous and complex, and often can be more harmful than helpful. While some inflammatory response is certainly necessary – and evidence shows severe damage in the absence of it – too much can cause global effects that start acutely after injury and sometimes become chronic for the brain and body (Corps et al., 2015; Lenzlinger et al., 2001; Loane & Kumar, 2017; Shi et al., 2019). This is also, unfortunately, all too easy. There is a deep intertwining of these processes that can allow for the delicate balance to fall apart and inflammation to persist.

There are a number of ways the immune response can turn dangerous for the brain, the most notable being continuous activation of glia, called gliosis (Corps et al., 2015). Both cytokine and chemokine pathways have been shown to be upregulated for some time after mTBI as the inflammatory processes address the injury sites (Redell et al., 2013). As the mediating cells are also often damaged, suppression of these processes can take a while, allowing further damage to occur to the brain. Consistent release of cytokines allows for the continuous propagation of immune cell cascades, including activation of microglia and astrocytes and recruitment of peripheral cells, even if the original injury has been mostly addressed (Block et al., 2007; Clark et al., 2019; Corps et al., 2015; Elder et al., 2015; Johnson et al., 2013; Lenzlinger et al., 2001; Morganti-Kossmann et al., 2019; Wofford et al., 2018). One way this plays out is in a phenomenon known as reactive microgliosis (Block et al., 2007). Microglia respond to injury, causing

damage to neighboring neurons, which then signal for the presence of more microglia, continuing the detrimental cycle (Block et al., 2007). Epigenetic changes can also lead to microglia and astrocytes remaining in their semi-activated or primed states, constantly expressing pro-inflammatory or highly sensitive receptors (Clark et al., 2019; Collins-Praino et al., 2018; Huber et al., 2017; Kane et al., 2013; Redell et al., 2013). They will also release nitric oxide, causing oxidative stress and affecting the permeability of the BBB (Block et al., 2007; Chodobski et al., 2012). Evidence has been found for active microglia remaining years past injury, continuing to facilitate white matter degeneration, inflammation, and disruption of the homeostasis of the brain (Johnson et al., 2013; Wofford et al., 2018).

Astrogliosis is one of the most common detrimental effects of astrocytes seen after mTBI. The precise regulation of proliferating astrocytes is crucial to avoiding excessive scar formation and inhibition of axonal repair (Clark et al., 2019). Astrocytes that remain active can lead to BBB damage, which allows for continued infiltration of immune cells and further perturbation of the barrier (Perez-Polo et al., 2013). Due to the importance of the BBB in protecting and maintaining the brain's environment, this increased permeability can lead to a host of problems that can affect behavior and cognition (Perez-Polo et al., 2013). The cells involved in scar creation are quite different from inactivated astrocytes in their morphology and genetic expression and can stifle neuronal regeneration if too many proliferate (Clark et al., 2019). This is another example of an intended beneficial process that if dysregulated, can hinder recovery. Completely blocking proliferation of astrocytes leads to a slowdown in repair time and cell death, but reducing the number shows a decrease in severity of glial scarring and negative outcomes

(Karve et al., 2016). The swelling of astrocytes from glutamate excitotoxicity can also lead to cytotoxic edema within the brain, perpetuating the inflammatory environment another way (Burda et al., 2017; Chodobski et al., 2012).

The infiltration of peripheral immune cells such as neutrophils and monocytes has been connected to the extent of post-injury damage in the brain (Chodobski et al., 2012). These cells produce inflammatory cytokines, generate reactive oxygen species, and release destructive enzymes, all of which are neurotoxic (Chodobski et al., 2012). The proteases seem to most notably affect BBB permeability (Chodobski et al., 2012; Liu et al., 2018). Neutrophils also promote coagulopathy and hypoperfusion after mTBI, as they aim to bind and repair the endothelium, but end up causing blockages (Liu et al., 2018). Through cascade amplification, neutrophils increase microglia and astrocyte activity, partially contributing to the formation of cytokine storms (Liu et al., 2018). Neutrophils are known to be highly damaging to neurons beyond the acute phase, and reduction of their numbers in the brain proves neuroprotective (Liu et al., 2018; Roth et al., 2014).

There is some evidence, however, that suggests the potential for a general shift toward an anti-inflammatory state after mTBI (Schwulst et al., 2013). A depletion of circulating monocytes and a prominent population of the anti-inflammatory microglial form has been found months following the mTBI, which contradicts the findings of increased immune cell presence (Schwulst et al., 2013). Perhaps this shift is seen as the brain and body try to prevent over-inflammation, though exact reasoning is yet unknown.

Glial crosstalk, cytokine signaling, and cascade amplification are likely all highly dependent on both micro and macro-environments, and thus there is a potential for a difference in presentation after blast and non-blast injury (Block et al., 2007; Clark et al.,

2019). Some research suggests that the pro-inflammatory processes seen after blast particularly contribute to susceptibility of brain to neuronal damage, especially regarding epigenetic changes (Aravind et al., 2020; Kane et al., 2013). Microglia have been shown to be genetically affected by blast overpressure waves, increasing production of pro-inflammatory forms (Kane et al., 2013). Comparing focal and diffuse injury, and the spread of initial damage and immune response throughout the brain, it can be assumed the more chronic damage from overactivated immune cells follows a similar pattern. And, as the impact of the inflammation tends to spread out beyond the initial injury site, there may be a noticeable distribution of immune cell-mediated neurotoxicity toward neurons and glia, which could differ in blast and non-blast injury (Miller et al., 2015). More research is needed to elucidate the exact pattern of gliosis and inflammation in these types of scenarios.

Systemic inflammation affects areas such as circumventricular organs and the brain endothelium, leading to a downstream disruption in white matter and synaptic plasticity that can impact cognitive performance (Sun et al., 2019). This can then aggravate existing problems like post-concussive syndrome and neuronal disconnection, or prevent repair and rehabilitation, which can lead to a variety of issues (Sun et al., 2019). Cytokine cascades have been implicated in the likelihood of developing post-traumatic stress disorder for soldiers exposed to combat, and glial hypersensitivity to depression, impaired plasticity and increased neuronal degeneration (Loane & Kumar, 2017; Smid et al., 2015). Rats who have greater populations of pro-inflammatory microglia demonstrate worse memory consolidation and more depressive behavior (Collins-Praino et al., 2018). In human studies, higher cytokine expression was associated

with memory issues as well (Bai et al., 2020; Sun et al., 2019). These highly detrimental effects on functioning and performance warrant deeper exploration of the cause and outcome. Knowing exactly what kind of deficits are likely to come about after mTBI is important for specialization of treatment and understanding of the brain.

The Present Study

At the cellular level, there appear to be differences in the damage incurred and the immune response to the brain between blast and non-blast injuries. While evidence has not conclusively defined such distinctions, findings do point in that direction. These likely cause detriments to function at a much higher level – namely cognition.

One way to explore these potential larger-scale differences is through the use of diffusion tensor imaging (DTI) to measure fractional anisotropy (FA). DTI is one of a variety of magnetic resonance (MRI) processes used to measure brain activity, function, and structure through analysis of microstructural properties (Salat et al., 2017). DTI works by measuring diffusion of water molecules throughout brain tissue, detecting heterogeneity and direction (Salat et al., 2017). The specific measure FA determines the integrity of white matter through the fractional diffusion of water within axons, which can range from isotropic to anisotropic. Isotropy is equal movement of water in all directions, while anisotropy is diffusion in a more focused and singular direction (O'Donnell & Westin, 2012). In axons, cellular membranes maintain the anisotropy, which means that DTI can be used to establish anatomy by visualizing the direction of tracts (O'Donnell & Westin, 2012). Higher FA indicates a distinct directionality to water diffusion, implying the structure of an axon being intact, and lower FA indicates an isotropic diffusion, where the membranes of the axons are perforated and allowing

diffusion outward in all directions. Specifically after an mTBI, DTI can be used to assess demyelination and degeneration of white matter tracts, including the presence of a glial response surrounding the axons (Donat et al., 2021; McClelland et al., 2018; Salat et al., 2017; Stone et al., 2020). Stress, strain and shearing are all partially quantifiable by FA using DTI, as evidence shows that higher strain rates correlate with decreases in FA (Donat et al., 2021). The lack of restricted directional movement is correlated to dysfunction in the pathways the tracts support and can even be connected to worsened PTSD and chronic injuries (Davenport et al., 2015; Petrie et al., 2014; Salat et al., 2017). Even though the technique is not sensitive to cause of damage, FA is a generally good measure for assessing consequences of mTBIs in white matter in the brain.

Begonia et al. (2014) studied if blast and non-blast injury affected the progression of an mTBI, aiming to not only determine if there is a difference, but how the brain responds to each. In their experimental model, rats were exposed to either a blast or non-blast injury, and DTI analysis data was gathered on the corpus callosum as the rats recovered (Begonia et al., 2014). Both injury types showed a greater level of disorganization in white matter tracts than controls, indicating changes in axonal microstructure post-injury, where the effect was slightly greater after blast than non-blast mTBI. The authors suggest that there may be varying damage based on injury due to the temporal and spatial patterns they discovered, such as the presence of edema (Begonia et al., 2014). They also posit that non-blast injury may have more significant primary injury effects due to deformation during trauma that causes extensive tearing and shearing, but that blast injury results in more damage from secondary injury (Begonia et al., 2014).

In humans, due to the heterogeneity of the condition and inability to control for outside factors, using DTI is significantly more complicated. Petrie et al. (2014), measuring metabolism as well as FA, evaluated veterans with blast mTBI. Veterans with blast mTBI were shown to have reduced FA, indicating chronic alterations in their white matter as compared to veterans with non-blast or no mTBIs, suggesting that blast mTBIs have a greater impact on white matter integrity than non-blast mTBIs (Petrie et al., 2014).

Another study suggests that differences in white matter integrity after blast compared to non-blast are more subtle. Davenport et al. (2012) studied the association between blast injury and white matter disruptions in a military population. The participants were all veterans, and those with current PTSD symptoms or diagnosis were excluded, though presence of mild symptomology and previous diagnoses of PTSD were not deemed excluding criteria. Using DTI and comparing those who had experienced blast injuries to those who had not, the authors calculated average FA across 20 white matter tracts of interest (Davenport et al., 2012). Critically, there was not an overall difference in average FA between blast and non-blast groups. However, there was a higher number of low-FA voxels in 10 of the 20 regions in blast compared to non-blast groups, indicating that only individual voxels showed differences, but not the whole tract between blast-exposed and non-blast exposed veterans (Davenport et al., 2012). This study suggests that blast mTBI results in widespread but specified damage to the brain (Davenport et al., 2012). The changes in integrity may have been subtle in these 10 tracts, but they are notable.

In contrast, other researchers have not observed a difference in white matter integrity between blast and non-blast mTBI. McClelland et al. (2018) compared blast-

exposed veterans to controls who had no history of blast mTBI and looked at biological and structural elements of the brain and found few differences. In terms of FA, results revealed mixed directionality of alterations in white matter structure, with some areas showing increased FA after blast compared to non-blast mTBI and some showing decreased FA after blast compared to non-blast mTBI (McClelland et al., 2018). Thus, DTI research comparing white matter integrity after blast and non-blast mTBI is mixed, with some observing greater widespread impairment after blast than non-blast (Petrie et al., 2014), some observing subtle and localized impairment (Davenport et al., 2012), and some observing no differences (McClelland et al., 2018).

Another way to examine larger-scale aftereffects of mTBI is through cognitive tests. Diffuse injury has been associated with longer processing times on certain speed tests (such as the Stroop Test), while focal contusion has been connected to deficits in spatial reasoning rather than interference tests (Wallesch et al., 2001; Zohar et al., 2003). Executive function, control of attention and planning, information processing speed, acquisition, consolidation, retention, and recollection of episodic memory, and working memory are frequently disrupted and are often the foremost areas of complaint in mTBI (Bogdanova & Verfaellie, 2015; Himanen et al., 2005; Konrad et al., 2015; Macciocchi et al., 1996; Mendez et al., 2013; Rabinowitz & Levin, 2013).

Acutely after injury, much research has shown no significant difference in cognitive and psychological performance between blast and non-blast injury, while other research has indicated a distinction (Luethcke et al., 2010; Mendez et al., 2013; Milman et al., 2005; Zohar et al., 2003). In a rodent study that limited blast effects to only the overpressure wave, deficits in memory, learning and cognition were found, as well as

increased anxiety (Budde et al., 2013). When looking at mTBI in athletes, self-reported deficits in neurocognition were found within a week after injury, but mostly resolved within 10 days (Macciocchi et al., 1996). Episodic and incidental memory have been associated with non-blast mTBI, along with visual and verbal memory (de Freitas Cardoso et al., 2019). Cognitive reserve and cognitive speed have been theorized to be most consistently affected by mTBI, though this is likely also due to how many faculties can fall in these categories (Luethcke et al., 2010). Resolution of post-concussive symptoms has been reported, but often, it is not a full return to pre-injury baseline (Macciocchi et al., 1996; Milman et al., 2005; Scheid et al., 2006). Six months after the baseline evaluation, one study found subjects still exhibited memory, attention, and general ability deficits, indicating the chronicity of the effects (de Freitas Cardoso et al., 2019). Importantly, the variability present in cognitive sequelae is certainly greatly due to individual variance between people and the general heterogeneity of mTBI (Sorg et al., 2021; Spitz et al., 2012). Clearly, the scope of cognitive ailments connected to experiencing a mTBI is quite wide. However, like DTI research, results are mixed regarding the extent to which blast and non-blast mTBI might affect executive function differently (Budde et al., 2013).

Martindale et al. (2021) evaluated the effect of deployment on executive function in veterans. Although they did not measure blast specifically, deployment-related mTBIs are much more likely to be due to blast than are non-deployment mTBIs, and therefore deployment vs. non-deployment may be used as a proxy for blast vs. non-blast mTBIs. They administered a cognitive battery that included the Trail-Making Test (TMT). This is a common test used to evaluate executive function and informational processing, as well

as visual searching, scanning abilities, and mental flexibility (Bai et al., 2020; Jia et al., 2020; Tombaugh, 2003). Generally, executive function has been seen to suffer after mTBI, based on self-reports and performance on the TMT (Bai et al., 2020, Jia et al., 2020). The TMT has two forms: A and B. TMT-A consists of a page with number arranged randomly, and the participant is asked to draw lines between them in numerical order. TMT-B is the same, except that letters are also included, and participants are asked to connect the circles in numerical and alphabetical order, such that the pattern 1-A-2-B-3-C…. L-13 is followed (Tombaugh, 2003; Spreen & Strauss, 1998). The time taken to complete this is measured in seconds, and the Heaton Manual can be used to standardize scores based on age, race and education level.

A correlation between scores on the TMT and deployment mTBI was found, such that performance was worse for those who had deployment-related injuries (Martindale et al., 2021). No such correlation existed for PTSD or non-deployment mTBI, suggesting a specific relationship between deployment-related mTBIs and executive function (Martindale et al., 2021). In contrast to these findings, however, when blast and non-blast categories were used, there were no significant differences found between groups on the TMT (Belanger et al., 2009). This suggests that blast does not impair executive function to a greater extent than non-blast. These incongruent results highlight the heterogeneity and difficulty in studying outcomes of mTBI. Definite connections between damage to white matter and executive function abilities after experiencing blast and non-blast mTBIs have not been established.

Bai et al. (2020) examined white matter integrity and longitudinal changes in information processing after mTBI and found that the extent of white matter damage

could predict the severity of cognitive deficits. This was found for tracts throughout the brain, though the direction of the altered diffusion (more compared to less diffusion) was inconsistent (Bai et al., 2020). However, they did not include information on the type of mTBI their participants experienced, and thus their data only describes general trends across all mTBI (Bai et al., 2020).

This study will examine the relationship between white matter integrity, as measured through fractional anisotropy, and executive function, as measured through the Trail Making Test B, in blast and non-blast mild traumatic brain injury. This will evaluate the hypothesis that the critical difference between blast-related and non-blast related mild TBI is due to the relationship between white matter integrity and executive function, rather than either independently.

The investigation focused on 6 out of the 10 tracts taken from Davenport et al. (2012), as they were found to be particularly affected after blast injury in not only Davenport et al.'s study, but in Bai et al. (2020) and de Souza et al. (2021) as well. Bai et al. (2020) determined a connection with information processing speed after mTBI in general, and de Souza et al. (2021) found correlations with these tracts in sports-related mTBIs, where lower FA was found to be associated with worse performance on the TMT.

These six regions are the cingulum, the hippocampal cingulum, the corticospinal tract, the inferior fronto-occipital fasciculus, the superior longitudinal fasciculus, and the uncinate. The cingulum, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus are some of the most prominent association bundles in the brain (Vanderah & Gould, 2021). The cingulum projects through the cingulate gyrus and parahippocampal gyrus, almost completing a circle, and facilitates communication between components of

the limbic system (Bubb et al., 2018; Vanderah & Gould, 2021). The superior longitudinal fasciculus is a complex bundle that arches above the insula and extends into the parietal, occipital and temporal lobes (Nakajima et al., 2019; Vanderah & Gould, 2021). It is involved in a variety of functions, from visuospatial attention to language processing (Nakajima et al., 2019). These two tracts are adjacent and have such a close relationship that portions of the superior longitudinal fasciculus have been considered part of the cingulum (Wang et al., 2015). The inferior fronto-occipital fasciculus similarly runs below the insula, connecting the occipital and parietal lobes with the frontal lobes, along the temporal lobe, and projects widely at either end (Conner et al., 2018). This fasciculus is involved in semantic processing, executive control, and goal-oriented behavior (Conner et al., 2018). Its projections are adjacent to the uncinate, which connects the orbital cortex with the anterior temporal cortex by way of the lateral sulcus and plays a role in episodic memory, language and social-emotional processing (Conner et al., 2018; Von der Heide et al., 2013). The corticospinal tract, responsible for movement of the body, arises from the premotor, motor, and supplementary motor cortex and extends through the brain stem and down the spinal cord (Vanderah & Gould, 2021).

One crucial element of studying TBIs, especially mild TBIs, is controlling for post-traumatic stress disorder (PTSD). Brain injuries are generally traumatic, and there is an extremely high comorbidity rate between mTBI and PTSD (Dolan et al., 2012). Most blast injuries are inherently tied to a threat on the person's life (Loignon et al., 2020). With explosions so commonplace in warfare now, and not always happening on the battlefield, an unexpected attack on a base where soldiers are unarmored can lead to many serious injuries, physical and psychological. With the advent of missiles and

mortars, combat is not limited to active battle. While non-blast injuries can certainly be emotionally traumatic as well (domestic abuse, devastating motor vehicle accidents) (Loignon et al., 2020), it is not as ubiquitous. Furthermore, military personnel are exposed to a variety of deeply traumatic experiences beyond being blown up. Therefore, it is important to consider the role of PTSD in conjunction with mTBI, as it is considerably more common for those with blast exposure and is likely to be a confound.

Research has shown that the symptoms, comorbidities and cognitive deficits after mTBI and from PTSD are quite similar (Hickling et al., 1998). Irritability, sleep disorders, somatic disorders, substance abuse disorders and memory, concentration, attention, processing speed, decision-making, executive function and overall intellectual ability are all particularly affected by PTSD, though it is unclear if the effect is due to physiology or psychology (Dolan et al., 2012; Mattson et al., 2019; Tanev et al., 2014). For those with both PTSD and mTBI diagnoses, verbal processing and executive function have shown particular deficits (Dolan et al., 2012). DTI research has determined overlap in the brain regions affected by PTSD and mTBI in veterans as well as indicated that development of PTSD correlates with lower fractional anisotropy (Raji et al., 2015; Spadoni et al., 2018).

Davenport et al. (2016) conducted a study to investigate the interactions between PTSD and white matter in mTBI, as well as determine if deployment status or mechanism of injury is more pertinent in predicting cognitive outcomes. The participants in this study had all screened positively for mTBI, and current and lifetime PTSD data and deployment history were collected. Looking first at civilian mTBI, they found that presence of current PTSD diminished the relationship with white matter integrity but did not disappear (Davenport et al., 2016). For deployment mTBI, the interaction between

lifetime PTSD and mTBI was found to be significant, such that in the absence of PTSD, deployment history predicted lower FA (Davenport et al., 2016). They also note that this finding somewhat contradicts the hypothesis that blast mTBI causes additional damage beyond that of impact, as in this study, the differences are accounted for by situation rather than mechanism (Davenport et al., 2016). However, Davenport et al. (2016) claim that their methodology of conducting multiple analyses with variations of their variables allowed them to account for PTSD, mechanism and context without making erroneous conclusions based on classification method. Thus, the authors conclude that the relationship between mTBI and context of injury is relatively straightforward for civilian mTBI and more complex for deployment-related mTBI due mainly to the factor of PTSD (Davenport et al., 2016).

No matter the etiology of PTSD and mTBI, the symptoms are similar enough and co-occur often enough that they must be considered in tandem and controlled for to appropriately analyze their individual and joint sequelae. Thus, the present study controlled for PTSD in hopes of circumventing some of these pitfalls.

Methods

Participants

Participants were from two studies at the Minneapolis VA. “The Effects of Explosive Blast as Compared to Post-traumatic stress disorder on Brain Function and Structure” ran from April 2008 to March 2012, was funded by the Department of Defense and is abbreviated to SATURN. “Essential Features of Neural Damage in Mild Traumatic Brain Injury,” is known as DEFEND and funded by the VA Rehabilitation Research and

Development Service and took place from July 2012 to June 2016. Dr. Scott Sponheim was the principal investigator for both.

SATURN studied 133 Operation Iraqi Freedom and Operation Enduring Freedom (OIF/OEF, Iraq and Afghanistan) veterans who had experienced blast injuries and/or PTSD. DEFEND evaluated 124 OIF/OEF veterans who had screened positively for possible mTBI. Exposure to pressure waves as primary injury, or in conjunction with secondary and tertiary injuries were all coded as blast injuries, and injuries without pressure waves were coded as impact (non-blast) mTBI. Of the combined SATURN and DEFEND dataset, only 182 participants were included in this analysis after data cleaning. Female participants (n = 13) were excluded due to their low numbers, as well as those with missing data.

Procedure

In both studies, participants underwent a clinical interview, answered self-reports, and were neuropsychologically evaluated. They also performed tasks while electroencephalographic (EEG) data was collected and gave blood for analysis. In a magnetic resonance imaging (MRI) machine, diffusion tensor imaging (DTI) was taken. Appendix A contains details on the exact tests and tasks done. Regarding DTI, using a 3T MRI scanner and 12-channel birdcage head coil, mean diffusivity (MD) and fractional anisotropy (FA) data was gathered for each voxel, and generalized fractional anisotropy (GFA) was calculated for SATURN. DEFEND ran the same evaluations, using a 3T MRI scanner and 32-channel birdcage head coil instead.

Measures

Trail Making Test B

As described above, the TMT-B consists of a page with numbers and letters arranged out of order, and the participant is asked to draw lines between them following the order of number-letter, such that the pattern 1-A-2-B-3-C…. L-13 is followed (Tombaugh, 2003). The time taken to complete this is measured in seconds.

Minnesota Blast Exposure Screening Tool

The Minnesota Blast Exposure Screening Tool (MN-BEST) was developed to numerically score concussions (Nelson et al., 2011). The veteran is asked to provide information about their potential blast-related concussions including the date and location, and the three most significant events are then rated on severity from Type 0 to Type III. Type 0 is defined as events where no loss of consciousness (LOC) or post-traumatic amnesia (PTA) occurred, but neurologic symptoms are present and receive a score of 1. Type I events include those with alteration or transient loss of consciousness, PTA under 60 seconds, and at least one neurologic symptom, receiving a score of 2. Type II concussions are those with an LOC up to 5 minutes, PTA ranging from 1 minute to 12 hours, and at least one neurologic symptom, and are given a score of 3. Type III concussions have an LOC of 5 to 30 minutes, PTA over 12 hours, and at least one neurologic symptom, receiving a score of 4. Because blast and non-blast mTBIs were counted and scored separately, each participant had up to 6 injuries coded in total. Therefore, the possible score ranged from 0 (no injuries) to 24 (three Type III blast concussions and three Type III non-blast concussions) (Nelson et al., 2011).

Clinician Administered PTSD Scale

The Clinician Administered Post-Traumatic Stress Disorder Scale (CAPS-IV) was used in both SATURN and DEFEND to evaluate PTSD severity. The fourth version of the assessment aligns with the DSM-IV criteria. It is a structured interview given by a clinician to a patient to diagnose and measure symptom severity (*Clinician Administered PTSD Scale*). Questions address each category of criteria as listed in the DSM-IV to measure frequency and intensity of each symptom. Frequency is rated on a scale from 0 – 4 ("none" to "most of the time") and intensity from 0 – 4 ("none" to "extreme"). The individual symptom severity score is the sum of the frequency and intensity score for each symptom, and all 17 symptoms are summed together to create the final overall severity score, which results in the range of possible scores: (0, 136). Diagnosis is made using the DSM-IV criteria and scoring system. Inter-rater reliability, test-retest reliability, internal consistency and convergent validity are all considered good, supporting the use of this measure (*Clinician Administered PTSD Scale*).

Results

To understand the potential relationships between injury type, white matter damage, and cognitive outcomes, a number of statistical analyses were run. The program R was used for all analyses.

First, two cohorts were created to allow exploration of the potential difference between blast and non-blast exposed individuals. Based on self-report of blast exposure, individuals were sorted into blast and non-blast. Blast, non-blast and total mTBI severity were calculated using the MN-BEST. Then, basic numerical summaries were calculated for these two groups. Averages of age, current PTSD symptoms, total mTBI severity

score, performance on the TMT-B, and FA were all calculated, and Student's *t*-test was performed to compare the cohorts. Of the 182 participants (100% male), 86 (47%) reported exposure to blast. The average age was significantly lower for the blast group. Regarding PTSD, those exposed to blast reported more current PTSD symptoms and more lifetime PTSD symptoms, though only the former was significantly different between the cohorts. Total mTBI severity showed a significant difference, with the blast exposed group rating higher. There was no difference in overall TMT-B performance between the blast and non-blast cohort, and average FA (across all tracts) was found to have no significant difference (see Table 1). Analysis of these same variables for four cohorts: blast only, non-blast only, combined type, and no mTBI, were also run, and are presented in Appendix B.

Table 1

Characteristics of Blast and Non-Blast Cohorts

	Non-Blast Mean	**Blast Mean**	***p***	**t(df)**
n	96	86		
Age (years)	35.68 (9.25)	32.44 (7.86)	**0.012**	2.55(180)
Current PTSD	34.99 (24.41)	44.62 (27.60)	**0.014**	-2.48(171)
Total mTBI Severity	2.16 (2.51)	5.24 (2.78)	**< 0.001**	-7.83(172)
TMT-B Raw Score	59.90 (18.46)	58.37 (20.86)	0.60	0.52(171)
Average FA	0.44 (0.018)	0.45 (0.019)	0.07	-1.79(174)

Only total mTBI severity and age are significantly different between the two cohorts.

The six tracts taken from Davenport et al. (2012) were first investigated in preliminary analysis where a regression model predicting TMT-B performance was run to identify which tracts to further probe. Only two: the hippocampal portion of the right cingulum (CGHR), and the right superior longitudinal fasciculus (SLFR), were found to be significant for FA score and current PTSD (see Table 2).

Table 2

Preliminary Model Exploring TBI Type, mTBI Severity, FA Score and PTSD

	Bilateral CGC			**Left CGC**			**Right CGC**		
	B	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***
No TBI	55.47	24.13	0.02	59.32	22.27	<0.01	50.19	24.17	0.04
Blast TBI	4.95	4.94	0.32	4.88	4.94	0.32	4.99	4.93	0.31
Non-Blast TBI	6.05	4.61	0.19	6.01	4.6	0.19	6.11	4.61	0.19
Combined TBI	3.71	5.84	0.53	3.68	5.83	0.53	3.78	5.84	0.52
Total mTBI Severity	-1.19	0.67	0.08	-1.19	0.67	0.08	-1.2	0.67	0.08
FA Score	-0.68	39.71	0.99	-6.86	35.43	0.85	8.41	41.21	0.84
Current PTSD Dx	-2.72	4.3	0.53	-2.72	4.3	0.53	-2.67	4.3	0.54
Current PTSD Sx	0.15	0.08	0.07	0.15	0.08	0.07	0.15	0.08	0.07
	Bilateral CGH			**Left CGH**			**Right CGH**		
	B	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***
No TBI	71.33	13.03	<0.001	60.83	13.06	<0.001	76.55	11.71	<0.001
Blast TBI	5.27	4.91	0.29	5.03	4.93	0.31	5.51	4.89	0.26
Non-Blast TBI	6.19	4.58	0.18	6.11	4.6	0.19	6.2	4.55	0.18
Combined TBI	4.19	5.82	0.47	3.78	5.83	0.52	4.7	5.79	0.42
Total TBI Severity	-1.14	0.67	0.09	-1.16	0.67	0.09	-1.16	0.66	0.08
FA Score	-34.49	26.52	0.2	-12.38	26.92	0.65	-44.99	23.31	**0.05**
Current PTSD Dx	-2.44	4.28	0.57	-2.54	4.31	0.56	-2.62	4.25	0.54
Current PTSD Sx	0.16	0.08	0.06	0.15	0.08	0.07	0.17	0.08	**0.04**
	Bilateral CST			**Left CST**			**Right CST**		
	B	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***
No TBI	65.77	19.3	<0.001	68.24	18.04	<0.001	59.93	18.25	0
Blast TBI	4.65	4.95	0.35	4.58	4.95	0.36	4.82	4.95	0.33
Non-Blast TBI	5.79	4.62	0.21	5.76	4.61	0.21	5.92	4.63	0.2
Combined TBI	3.42	5.85	0.56	3.28	5.85	0.58	3.61	5.84	0.54
Total TBI Severity	-1.14	0.68	0.09	-1.12	0.68	0.1	-1.17	0.68	0.08
FA Score	-20.18	35.72	0.57	-24.69	33.09	0.46	-9.24	33.98	0.79
Current PTSD Dx	-2.22	4.38	0.61	-2.04	4.39	0.64	-2.53	4.35	0.56
Current PTSD Sx	0.15	0.08	0.08	0.14	0.08	0.08	0.15	0.08	0.07
	Bilateral IFO			**Left IFO**			**Right IFO**		
	B	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***
No TBI	58.92	20.64	0.01	49.45	18.73	0.01	64.82	18.43	<0.001
Blast TBI	4.98	4.93	0.31	4.82	4.95	0.33	4.88	4.93	0.32
Non-Blast TBI	6.03	4.6	0.19	6.03	4.6	0.19	5.91	4.6	0.2
Combined TBI	3.72	5.83	0.52	3.67	5.83	0.53	3.7	5.83	0.53
Total TBI Severity	-1.2	0.67	0.08	-1.17	0.67	0.08	-1.19	0.67	0.08
FA Score	-7.29	38.37	0.85	10.94	35.76	0.76	-17.98	33.29	0.59
Current PTSD Dx	-2.74	4.3	0.52	-2.64	4.3	0.54	-2.74	4.3	0.52
Current PTSD Sx	0.15	0.08	0.07	0.15	0.08	0.07	0.15	0.08	0.07

	Bilateral SLF			Left SLF			Right SLF		
	B	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***
No TBI	95.68	29.01	0	73.26	29.71	0.01	105.21	25.8	<0.001
Blast TBI	5.03	4.9	0.31	4.9	4.93	0.32	5.28	4.88	0.28
Non-Blast TBI	5.38	4.6	0.24	5.73	4.62	0.22	5.27	4.57	0.25
Combined TBI	3.71	5.8	0.52	3.46	5.84	0.55	4.38	5.78	0.45
Total mTBI Severity	-1.16	0.67	0.08	-1.16	0.67	0.09	-1.2	0.66	0.07
FA Score	-81.05	57.42	0.16	-36.54	59.21	0.54	-99.41	50.64	**0.05**
Current PTSD Dx	-2.67	4.27	0.53	-2.74	4.29	0.52	-2.56	4.25	0.55
Current PTSD Sx	0.16	0.08	0.05	0.15	0.08	0.06	0.17	0.08	**0.04**
	Bilateral UNC			**Left UNC**			**Right UNC**		
	B	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***
No TBI	39.5	17.38	0.02	46.54	14.61	0	37.55	17.3	0.03
Blast TBI	4.91	4.92	0.32	5.03	4.93	0.31	4.78	4.92	0.33
Non-Blast TBI	6	4.59	0.19	6	4.6	0.19	6.02	4.59	0.19
Combined TBI	3.72	5.82	0.52	3.8	5.83	0.52	3.6	5.81	0.54
Total TBI Severity	-1.19	0.67	0.08	-1.18	0.67	0.08	-1.19	0.67	0.08
FA Score	28.8	31.46	0.36	16.27	26.99	0.55	31.77	30.67	0.3
Current PTSD Dx	-2.71	4.29	0.53	-2.73	4.29	0.53	-2.68	4.29	0.53
Current PTSD Sx	0.15	0.08	0.06	0.15	0.08	0.07	0.15	0.08	0.07

Values of the first multiple regression model, run for each of the six *a priori* tracts, for the right and left hemisphere individually and as a whole. Only the FA score and Current PTSD symptoms of the CGHR and SLFR were found to be significant for predicting raw TMT-B score (shown highlighted in gray). CGC = cingulum; CGH = hippocampal cingulum; CST = corticospinal tract; IFO = inferior fronto-occipital fasciculus; SLF = superior longitudinal fasciculus; UNC = uncinate; L/R at the end of tract abbreviation = left/right hemisphere; Sx = symptoms; Dx = diagnosis. To evaluate the variables included in the regression model, hierarchical analyses were run, which can be found in Appendix C.

Next, a multiple regression analysis was run to probe the potential effect of FA, PTSD and mTBI severity on TMT-B performance, as well as any meaningful interactions between these variables. The independent variables were 1) FA score of the CGHR, 2) FA score of the SLFR, 3) current PTSD symptom severity, 4) blast mTBI severity scores,

5) non-blast mTBI severity score, 6) blast exposure (yes = 1, no = 0), 7) study membership (SATURN/DEFEND), and the interactions between the FA scores of each tract and mTBI severity as well as the interaction between PTSD and blast severity; resulting in 5 interaction terms. The dependent variable was TMT-B performance. The interaction between FA and blast mTBI severity was found to be significant, but only for the CGHR (see Table 3).

Table 3

Exploration of the SLFR, CGHR, mTBI Severity and Blast Exposure as Main Effects and in Interaction Terms

	B	SE	p	η2
Age	0.29	0.168	0.09	0.015
FA of CGHR	1.79	44.07	0.97	0.009
FA of SLFR	-128.97	102.183	0.21	0.004
Current PTSD Sx	0.06	0.079	0.45	0.024
Blast Severity	4.73	13.365	0.72	< 0.001
Non-Blast Severity	-10.36	10.703	0.33	0.013
Study	4.56	4.285	0.29	0.006
Blast Exposure	0.17	4.648	0.97	< 0.001
FA of CGHR: Blast Sev	-56.79	16.702	**0.001**	0.058
FA of CGHR: Non-Blast Sev	13.57	12.379	0.28	0.006
FA of SLFR: Blast Sev	42.01	31.315	0.18	0.009
FA of SLFR: Non-Blast Sev	4.89	26.202	0.85	< 0.001
Current PTSD Sx: Blast Sev	0.05	0.032	0.14	0.011

Values from the second multiple regression analysis to investigate the CGHR and SLFR as well as interactions between variables. Only the interaction between the FA of the CGHR and the blast mTBI severity score was found to be significant in predicting raw TMT-B score (shown highlighted in gray). CGHR = right hippocampal cingulum; SLFR = right superior longitudinal fasciculus; Sx = symptoms; Sev = mTBI severity score

In a second model that isolated the interaction between the CGHR and blast severity, the interaction was found to be significant (see Table 4). This interaction

suggests that at higher levels of blast mTBI severity, there is an association between lower FA of the CGHR and worse TMT-B performance (see Figure 1). The interaction reaches significance in individuals with blast mTBI severity above 1.68, such that for those whose mTBI severity score exceeds 1.68, the FA score of the CGHR has a meaningful association with TMT-B performance (see Figure 2). The spread of points below and above this threshold as they predict TMT-B performance are shown in Appendix D. After completing these analyses, presence of outliers, the fit and accuracy of the model was evaluated, which can be found in Appendix E.

Table 4

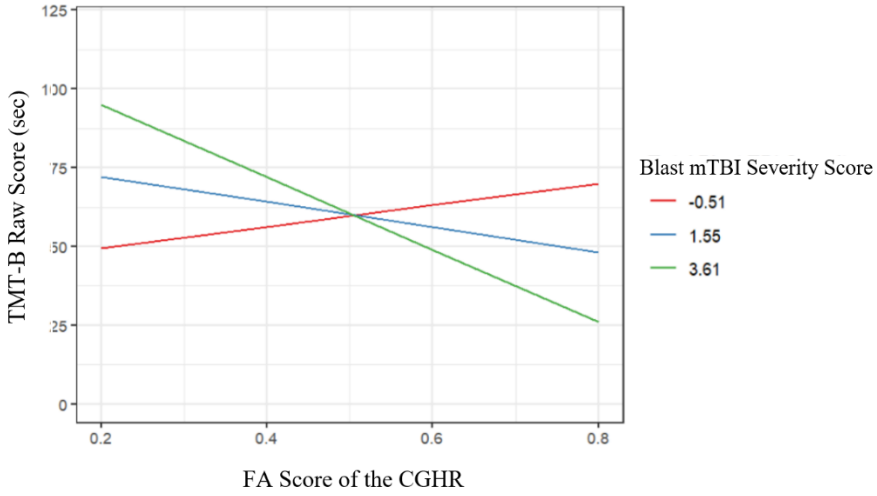
Interaction Between CGHR and Blast mTBI Severity Model Output

	B	**SE**	***p***	**η^2**
FA Score	15.99	30.03	0.56	0.015
Blast Severity	18.35	6.84	**0.008**	0.0005
FA Score: Blast Severity	-36.29	13.31	**0.007**	0.039

Exploration of main effect and interaction of CGHR FA exploring interaction term between the FA of the CGHR and blast mTBI severity score as they predict TMT-B score for blast-exposed veterans. Both the main effect of blast mTBI severity and the interaction term were found to be significant (shown highlighted in gray). CGHR = right hippocampal cingulum.

Figure 1

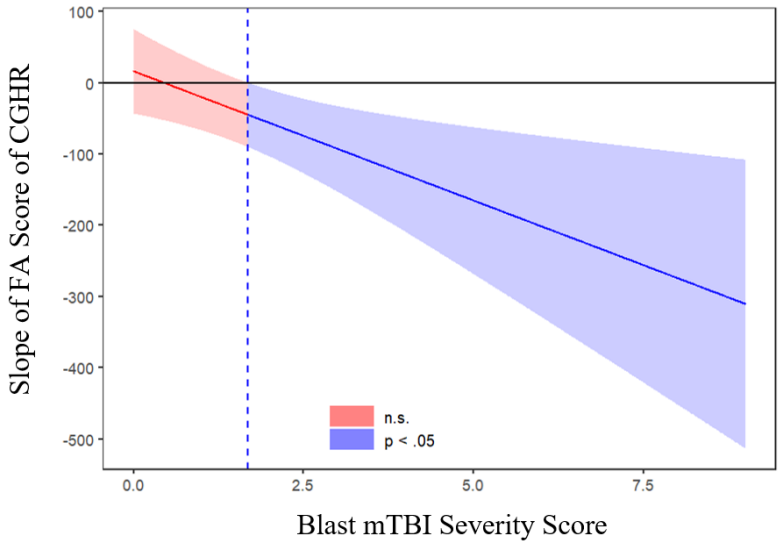
Plotted Interaction Model of the FA Score of the CGHR and TMT-B Score



This plot visualizes Table 4, where performance on the TMT-B is predicted by FA of the CGHR, with a significant interaction with blast mTBI severity for blast-exposed veterans. The steepest line (green, negative slope) shows the relationship for those with a blast mTBI severity score of 3.61 (mean score + 1 standard deviation [SD]), such that as FA score increases, the number of seconds taken to complete the TMT-B decreases, indicating better performance. The middle line (blue, moderately negative slope) shows the relationship for those with a mean blast mTBI severity score, such that as FA score increases, seconds taken to complete the TMT-B decreases, but not to the same degree as the mean + 1 SD group. The line with a positive slope (red) shows the relationship for those with a blast mTBI severity of mean – 1 SD of -0.51. This score is not possible, as the minimum is 0, but the line still displays that at lower mTBI severity scores, the relationship between FA and TMT-B performance is not particularly significant and may even be the reverse of that at higher mTBI severity scores.

Figure 2

Johnson-Neyman Plot of the Slope of the FA of the CGHR and the Moderating Variable: Blast mTBI Severity Score



This plot shows the threshold of significance for the slope of the FA score of the CGHR as it changes with the moderator: blast mTBI severity score. The dashed line is at a blast severity score of 1.68. Thus, the slope of the FA score is significant for any blast-exposed veterans whose blast severity score is greater than 1.68 (shaded blue, right side of the dashed line), and is not significant for those below that threshold (shaded red, left of the dashed line).

Discussion

The present study was designed to investigate the potential effect of mechanism of mTBI on white matter integrity and the consequential cognitive outcomes. Analyzing a sample of 182 OIF/OEF American veterans collected via the SATURN and DEFEND studies, no difference was found between blast-exposed and non-blast exposed veterans

in average fractional anisotropy (FA) or performance on the Trail Making Test B (TMT-B). However, probing deeper and evaluating individual white matter tracts in blast-exposed individuals revealed a significant difference in FA of the right hippocampal portion of the cingulum (CGHR), as well as a meaningful interaction between the FA of this tract and severity of the blast injury in predicting TMT-B performance. These results suggest that the FA of the CGHR has a significant relationship with cognitive outcomes for those with a blast injury, where the effect is significant for those with a blast mTBI severity score over 1.68. While current PTSD symptom severity was found to be significantly higher in the blast cohort compared to the non-blast, neither the individual effect nor the interaction between PTSD and blast mTBI severity score was significant. This suggests that the found effect between the CGHR and TMT-B was independent of PTSD. This data contributes to the evidence on physical changes in the brain after mTBI as well as the evidence on cognition, especially executive function and informational processing, being significantly affected by blast-related mTBI.

Regarding white matter damage, this study revealed highly specific differences in the tracts affected after blast and non-blast mTBI. Davenport et al. (2012) determined that there were subtle and widespread effects throughout the brain after blast mTBI but did not find evidence for any specific tracts that were consistently affected. However, the present study indicates that looking at specific tracts may reveal novel relationships, as the CGHR was the only tract that showed a correlation with blast mTBI. The lack of significant findings in the corpus callosum is somewhat incongruous with other findings in the field, however. The corpus callosum is frequently identified as an area significantly affected after blast mTBI (Johnson et al., 2013; Kinnunen et al., 2011; Lancaster et al.,

2016; Mendez et al., 2013; Niogi et al., 2008, Wallesch et al., 2001). However, a number of studies have also identified the CGHR as a particular region of interest after head injury (Bai et al., 2020; Davenport et al., 2012; de Souza et al., 2021). Davenport et al. (2016) used multiple categorization systems (civilian vs. deployment; blast vs. non-blast) to analyze mTBI and white matter damage. By comparing these multiple approaches, they claim it allowed them to circumvent the conclusion that there was no relationship between mTBI and white matter beyond that found between non-blast mTBI and the CGHR. But a different finding was revealed in the present study: that blast mTBI severity and CGHR are associated with cognition.

Turning to the connection the CGHR may have with cognitive performance, looking at sports-related concussion de Souza et al. (2021) found an association between lower FA in the CGHR and performance on TMT-B in populations with and without an mTBI. This suggests that executive function may not be as significantly affected by non-blast mTBI compared to controls, a result that agrees with those from the present study. Therefore, executive function may be a more specific deficit after blast mTBI. Furthermore, another study, whose population was only those with non-blast mTBIs, found variable differences in FA in the CGHR and that overall, abnormal diffusion measures correlated with worse information processing speed in the future (Bai et al. 2020). In the present study, no relationship between cognitive performance and non-blast injuries was found. One possible explanation for this discrepancy in results is that Bai et al. (2020) conducted a longitudinal study and were thus able to track individuals' progress or decline over time.

The present study's results do agree with Martindale et al. (2020)'s findings, though. They found that deployment-related mTBI is significantly correlated with worse performance on cognitive measures, including the TMT-B (Martindale et al., 2020). While the present study used blast and non-blast as categories instead of deployment and non-deployment-related, blast injuries almost entirely occur while deployed, and thus the results are still applicable. This is especially true seeing as one of the major differences in deployed and non-deployed environments is the frequency of traumatic events, and PTSD was not found to interact with the type of mTBI (Martindale et al., 2020). Thus, in agreement with Martindale et al. (2020), the long-term outcomes of differing types of mTBIs appear to have different trajectories.

Crucially, severity of blast mTBI was shown to moderate the relationship between FA of the CGHR and TMT-B performance in the present study. Belanger et al. (2009) found similar results that indicated severity of an injury was more predictive of performance on cognitive assessments than the mechanism of injury. The TMT-B, however, demonstrated no significant association with severity of the mTBI. Belanger et al. (2009) measured severity using mild, moderate and severe categorizations, though, while the present study focused only on mTBI and severity rankings within that category. Thus, similarly to white matter damage, investigating at a finer level may reveal new relationships previously obscured by other larger trends.

That the blast group in the present study did not show an effect of PTSD is surprising, as previous findings suggest that PTSD may indirectly affect white matter integrity and alter the remote effects of an mTBI (Davenport et al., 2016). Davenport et al. (2016) found that PTSD was only a significant factor in predicting white matter damage

for deployment-related mTBI. The relationships for blast and non-blast mTBI were similar, but weaker. This finding is especially interesting as some of the data for the present study overlapped with that used in the Davenport et al. (2016) study. Perhaps when looking at the individual tract level, PTSD does not have as strong an effect as on global FA or other brain-wide measures.

Clearly, the mTBI-affected brain is complex and heterogenous, but there a few possible avenues worth investigating as reasoning behind findings such as those from the present study. Firstly, the structure and orientation of the CGHR may leave it particularly susceptible to damage. The cingulum runs anterior to posterior through the center of the brain and extends throughout the majority of the dorsal brain, curving down toward the hippocampus. Because of the length and orientation, angular and rotational acceleration could lead to particular damage to the cingulum due to twisting motions that might lead to specific interruptions in cognition (Blennow et al., 2012). While this type of motion is present in both blast and non-blast injury situations, it may be a partial mechanistic explanation of the damage seen.

Secondly, the function of the cingulum may play a role in the severity of the physiological and psychological damage. Perhaps the emotionally traumatizing nature of an mTBI and the function of the tract account for PTSD, hence why it was not a significant predictor. The cingulum is part of the limbic system, responsible for visceral and more primal emotions, motivations and behaviors (Bubb et al., 2018). Cingulotomy has revealed that emotion, apathy, executive function, anxiety, depression, and response to chronic pain are all associated with anterior cingulum function (Bubb et al., 2018). The posterior cingulum has not frequently been the target of lesioning surgery, and thus little

is known about its role in particular. However, imaging analysis has supported the connection between the parahippocampal cingulum learning and episodic memory (Bubb et al., 2018; Salmond et al., 2005). The bundle as a whole has also been implicated in cognitive diseases such as Alzheimer's and Parkinson's as well as psychiatric disorders, including obsessive-compulsive disorder and depression. The role of the cingulum is clearly vast and disruption to it could cause an array of issues.

The results from this analysis draw a connection between the biological damage after blast mTBI and the psychological aftermath of the injury. That there was a measurable difference between the injury types that was not accounted for by PTSD suggests the potential for a difference in response to the insult within the brain, even at the level of an individual tract. In this data, damage to only one tract – the hippocampal portion of the right cingulum – emerged as significantly different between the injury types and significant for predicting TMT-B outcome, but further research could search out other areas in the brain that play a similar role, for TMT-B or other cognitive evaluations. When looking more specifically at individual regions within the brain and at particular tasks, differences between mechanisms of brain injury seem to become salient. Examining the traumatically injured brain on a global level may not be enough to truly understand the processes that lead to dysfunction in the brain.

Limitations

There are a number of limitations to this study. Firstly, one common issue with studies on military veterans is the use of retrospective self-report. Because veterans often return home long after experiencing an injury, and then seek treatment even later, the exact sequelae of an mTBI can be hard to identify. Many veterans experience countless

potential concussive events and remembering all of them well is unlikely. Memory of details of the event are especially likely to suffer due to the possibility of altered mental status, post-traumatic amnesia and loss of consciousness. Furthermore, cognitive deficits and psychological disorders can interfere with the accuracy of reports. However, unless the patient can be evaluated in theatre, self-reports must be relied upon to try and ascertain the circumstance of the injury, the aftermath, any treatment or assessment they may have received, and symptomology. Measures of standardization and detailed leading questions are in place to assist in the extraction of the memory and accurate recording of the event, but self-report is inherently unfaithful.

Furthermore, the highly heterogenous nature of mTBI and the situation in which veterans experience them mean that it is difficult to isolate symptoms and effects that are distinctly due to the brain injury. The many comorbidities that are common complicate things. Depression, anxiety and of course, PTSD, are often seen in tandem with mTBI, and not only show similar symptomology but can stem from the same event as well. Also, humans are inherently complex, and symptomology will present differently in every patient. Considering all of these factors, determining sequelae from only mTBI is near impossible in a human population.

Throughout this thesis, the possible immunological differences between blast and non-blast mTBIs have been discussed. However, no data was collected on the participants to evaluate the reality of immunology in the brain. Therefore, the immunological aspects of blast and non-blast mTBIs are based solely on previous literature and are theorized to be occurring. Even if blood and cerebrospinal fluid could have been collected from this population, the time since the injury would mean that any findings would solely be

regarding chronic immunological effects. While this is equally necessary, investigating acute changes in the brain after mTBI would be crucial to confirming the theories discussed

Conclusion

This study investigated the relationship between mechanism of traumatic brain injury and cognition, specifically if those who experienced blast-related and non-blast related mild TBIs showed a difference in performance on the executive functioning task Trail Making Test B. For blast-exposed participants, a relationship between the right hippocampal cingulum and performance moderated by severity of the blast injury was found. This indicates that when the mTBI-affected brain is investigated at the level of the individual tracts, more specific relationships between white matter damage and cognition may be revealed.

Future Directions

The field of remote sequelae mTBI is still relatively new, though significant progress is constantly being made. From this study, there are a few directions that would be worthwhile to pursue. Firstly, examining the actual immunological differences in the brain and body between blast and non-blast mTBIs. Bai et al. (2020) conducted a longitudinal study to look at the presence of immune cells over time for those with non-blast TBIs, and a similar study could be done using a blast-exposed population or comparing the two. Identifying precise differences might allow for the development of treatments that can address acute responses, which would be extremely useful in theatre. Being able to administer a treatment such as a pill directly after experiencing an mTBI might help prevent chronic ailments from developing. Secondly, identifying other tracts

that may have relationships with cognitive functions would allow for a more robust understanding of the biological and psychological connections in mTBI. There are so many areas of cognition beyond executive function that are affected by mTBI, and if specific tracts are shown to be associated with them, an even more detailed picture of the brain could be constructed. Studies that target questions like these would allow for the aftermath of mild traumatic brain injury to be further elucidated, and a significant population of people, veterans and not, to be helped.

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Appendix A

List of examinations, assessments and tasks conducted in SATURN and DEFEND studies. Many are shared, but not all. Those highlighted in gray are those pertinent to the present study.

Element	**SATURN**	**DEFEND**
Clinical Interview	**CAPS-IV** SCID **MN-BEST**	**CAPS-IV** SCID **MN-BEST**
Self-Report	PCL-M BDI MPQ-BF SAS-SR MMPI-2 (?) DMQ	PCL-M BDI MPQ-BF SAS-SR MMPI-2 CES DRRI
Neuropsych	WTAR CVLT-II WAIS (Coding, Digit Span, Information, Block Design) **Trails** A/**B** Rey COWAT Stroop	WTAR CVLT-II WAIS (Coding, Digit Span, Information) **Trails** A/**B** VSVT
MRI	T1-MPRAGE **DTI** Resting fMRI Auditory Oddball fMRI FLAIR	T1-MPRAGE **DTI** Resting fMRI Emotional N-Back fMRI
EEG	Resting (Eyes Open & Closed) DS-CPT Startle Task Decision Task (Gehring) Verbal Memory Task Balance Board Task	Resting (Eyes Open & Closed) DS-CPT Flanker N-Back Dichotic
Blood	Serum Plasma PAX	Serum Plasma PAX

Full List of Tracts Studied in SATURN/DEFEND:

The full tract name is listed, and any subdivisions are nested below. (L/R) after the tract indicates that the tract was considered as a whole, and within each hemisphere. Those highlighted in gray are the 6 that are overlap with the 10 tracts studied in Davenport et al. (2012).

Corpus callosum
- Body
- Genu
- Splenium

Cingulum/cingulate gyrus (L/R)
- Hippocampal portion(L/R)

Corona radiata (L/R)
- Anterior (L/R)
- Posterior (L/R)
- Superior (L/R)

Corticospinal tract (L/R)
External capsule (L/R)
Fornix
- Stria terminalis (L/R)

Internal capsule (L/R)
- Anterior limb (L/R)
- Posterior limb (L/R)
- Retrolenticular (L/R)

Inferior fronto-occipital fasciculus (L/R)
Posterior thalamic radiation (L/R)
Superior fronto-occipital fasciculus (L/R)
Superior longitudinal fasciculus (L/R)
Sagittal striatum (L/R)
Uncinate fasciculus (L/R)

Appendix B

To understand the potential relationships between injury type, white matter damage, and cognitive outcomes, a number of analyses were run prior to those discussed in the *Results* section. The program R was used for all analysis. Of the combined SATURN and DEFEND dataset, only 182 participants were included in this analysis after data cleaning. Female participants were excluded due to their low numbers, as well as those with missing data.

Firstly, the sample was divided into four cohorts: blast injury only, non-blast injury only, both types of injury (combined), and no head injuries (controls). Student's t-test was performed comparing each cohort on current PTSD symptoms and diagnosis, lifetime PTSD symptoms and diagnosis, and raw, t-scored, and z-scored scores on the Trail-Making Test B (TMT-B). Next, the average fractional anisotropy (FA), mean diffusivity (MD), and axial diffusivity (AD) were calculated for each cohort and compared. FA was chosen as the main measure of white matter integrity based on previous research indicating it performs well as a measure (Davenport et al., 2012). Then, t-tests were calculated to compare the average FA of tracts between cohorts. No significant differences were found between them on age, total mTBI severity, average current PTSD symptoms (Sx), average lifetime PTSD symptoms, and average TMT-B raw, t-score, and z-scored scores (see Table 1). No significant differences in average FA, MD, or AD were found between the cohorts (see Table 2).

Table 1

Participant Characteristics by Cohort

	n	Mean Age	Total mTBI Severity Mean	Current PTSD Sx Severity Mean	Lifetime PTSD Sx Severity Mean	Raw TMT-B Score Mean	TMT-B T Score Mean	TMT-B Z Score Mean
blast	40	32.53	3.875	47.55	64.83	60.9	49	-0.10
non-blast	53	36.81	3.66	32.58	56.74	60.57	49.02	-0.10
combined	46	34.28	6.434	42.07	61.89	56.17	50.3	0.03
none	43	32.36	0.302	37.95	62.19	59.07	49.91	-0.01

Table 2

Average scores of FA, MD and AD, all measure of diffusivity and white matter integrity in the brain.

	DTI Measure Mean		
	FA	**MD**	**AD**
blast	0.44	0.00072	0.0011
impact	0.45	0.00073	0.0011
both	0.44	0.00071	0.0011
none	0.44	0.00072	0.0011

No significant difference between the cohorts on any measure. DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity

The original dataset contained 23 tracts, 18 of which also had right and left portions, while the remaining five were midline tracts (see Appendix A for full list). However, only six of these were considered, based on previous evidence suggesting their relationship with blast mTBI: the cingulum, hippocampal portion of the cingulum, corticospinal tract, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate, bilaterally and for each hemisphere (Davenport et al., 2012) (see Table 3).

When comparing average FA scores for each of these, only the whole tract was evaluated, but for each of these six tracts individually.

Table 3

Student T-test Comparisons Between Cohorts of the Average FA Score for Each of the Six a priori Tracts.

	CGC	CGH	CST	IFO	SLF	UNC
blast x control	0.61	0.13	0.66	0.81	0.41	0.95
impact x control	0.63	0.46	0.47	0.49	0.12	0.82
blast x impact	0.99	0.42	0.79	0.34	0.03	0.80

No significant differences were found. CGC = cingulum; CGH = hippocampal cingulum; CST = corticospinal tract; IFO = inferior fronto-occipital fasciculus; SLF = superior longitudinal fasciculus; UNC = uncinate.

Appendix C

Hierarchical models were created to determine if the FA scores of the CGHR and SLFR were significantly predicting TMT-B, even in the presence of other variables. These were separated by cohort. Based on the model created that predicted TMT-B performance by TBI type, total TBI severity, current PTSD diagnosis and symptoms, and FA score, the right hippocampal cingulum (CGHR) and right superior longitudinal fasciculus (SLFR) were the only two tracts that showed significant associations between FA and TMT-B performance. See the Results section for detailed description of these findings. Thus, the CGHR and SLFR were each probed individually to determine the relationship between the FA of the tract, PTSD, TBI severity and TMT-B score. Separated by cohort, two models were created: one where TMT-B was predicted by FA score of the individual tract, and another where TMT-B was predicted by current PTSD symptoms and TBI severity, without the involvement of FA. These two models investigated the individual effects these variables were potentially having on TMT-B. The first, which predicted TMT-B based on the FA of the tract in each cohort, found that only for those in the blast-only cohort did FA score have a significant effect on TMT-B performance, for both the CGHR and the SLFR (see Table 1). The second, which predicted TMT-B only on PTSD symptom and TBI severity, showed that the involvement of current PTSD symptoms was only significant for the combined cohort (see Table 2).

Table 1

Model predicting TMT-B performance by FA score of each tract, divided by cohort.

CGHR				**SLFR**			
All	**B**	**SE**	***p***	**All**	**B**	**SE**	***p***
FA of CGHR	-38.63	22.79	0.09	FA of SLFR	-79.61	48.92	0.11
Blast				**Blast**			
FA of CGHR	-194.63	52.34	**<0.001**	FA of SLFR	-277.33	125.43	**0.03**
Impact				**Impact**			
FA of CGHR	10.08	34.31	0.77	FA of SLFR	-7.16	68.87	0.92
Combined				**Combined**			
FA of CGHR	-35.38	40.85	0.39	FA of SLFR	-24.2	91.1	0.79
Controls				**Controls**			
FA of CGHR	74.79	60.12	0.22	FA of SLFR	-50.34	152.18	0.74

Only for the blast cohort were the values significant (shown highlighted in gray). CGHR = right hippocampal cingulum; SLFR = right superior longitudinal fasciculus; FA = fractional anisotropy

Table 2

Values of Hierarchical Models Predicting TMT-B Performance On Only TBI Severity and PTSD Symptoms.

All				**Blast**				**Non-Blast**			
TBI	**B**	**SE**	***p***	**TBI**	**B**	**SE**	***p***	**TBI**	**B**	**SE**	***p***
Total TBI Severity	-0.91	1.31	0.49	Total TBI Severity	-3.00	1.86	0.11	Total TBI Severity	-1.02	1.30	0.44
PTSD				**PTSD**				**PTSD**			
Current PTSD Sx	0.10	0.05	**0.06**	Current PTSD Sx	-0.06	0.15	0.70	Current PTSD Sx	-0.09	0.10	0.36
TBI + PTSD				**TBI + PTSD**				**TBI + PTSD**			
Total TBI Severity	-1.21	1.31	0.36	Total TBI Severity	-3.06	1.98	0.13	Total TBI Severity	-0.95	1.31	0.47
Current PTSD Sx	0.11	0.06	**0.05**	Current PTSD Sx	0.01	0.15	0.93	Current PTSD Sx	-0.09	0.10	0.38

Combined				**Controls**			
TBI	**B**	**SE**	***p***	**TBI**	**B**	**SE**	***p***
Total TBI Severity	-0.19	0.96	0.85	Total TBI Severity	-1.66	1.6	0.31
PTSD				**PTSD**			
Current PTSD Sx	0.29	0.08	**0.001**	Current PTSD Sx	0.24	0.12	**0.05**
TBI + PTSD				**TBI + PTSD**			
Total TBI Severity	0.01	0.86	0.99	Total TBI Severity	-1.13	1.58	0.48
Current PTSD Sx	0.29	0.08	**0.002**	Current PTSD Sx	0.22	0.12	0.07

Current PTSD was the only significant variable (shown highlighted in gray).

Another two models were created to examine the two tracts individually and together, along with TBI severity and current PTSD, in hierarchical analyses. For the first model (see Table 3) the independent variables were: 1) the FA score of the tract, 2) total TBI severity, and 3) current PTSD symptoms, with TMT-B performance the dependent variable, and this was run using the FA score of the CGHR and SLFR separately, and for each subsequent cohort. For the first model, the blast cohort had the most variables that significantly predict TMT-B performance.

Table 3

By-Cohort Hierarchical Model Separated by CGHR and SLFR.

CGHR				**SLFR**			
All	**B**	**SE**	***p***	**All**	**B**	**SE**	***p***
FA + TBI				**FA + TBI**			
FA of CGHR	-34.27	22.92	0.14	FA of SLFR	-75.67	48.77	0.12
Total TBI Severity	-0.70	0.48	0.15	Total TBI Severity	-0.75	0.47	0.11
FA + PTSD				**FA + PTSD**			
FA of CGHR	-49.03	22.99	**0.03**	FA of SLFR	-106.94	49.69	**0.03**
Current PTSD Sx	0.13	0.06	**0.02**	Current PTSD Sx	0.13	0.06	**0.02**
FA + TBI + PTSD				**FA + TBI + PTSD**			
FA of CGHR	-44.67	23.08	**0.05**	FA of SLFR	-103.55	49.47	**0.04**
Total TBI Severity	-0.72	0.47	0.13	Total TBI Severity	-0.80	0.47	0.09
Current PTSD Sx	0.13	0.06	**0.02**	Current PTSD Sx	0.14	0.06	**0.02**

Blast	**B**	**SE**	***p***	**Blast**	**B**	**SE**	***p***
FA + TBI				**FA + TBI**			
FA of CGHR	-182.52	53.54	**0.002**	FA of SLFR	-284.22	122.06	**0.03**
Total TBI Severity	-1.76	1.68	0.30	Total TBI Severity	-3.13	1.76	**0.08**
FA + PTSD				**FA + PTSD**			
FA of CGHR	-200.51	54.5	**<0.001**	FA of SLFR	-299.51	136.58	**0.03**
Current PTSD Sx	0.06	0.13	0.66	Current PTSD Sx	0.07	0.15	0.66
FA + TBI + PTSD				**FA + TBI + PTSD**			
FA of CGHR	-190.3	54.83	**0.001**	FA of SLFR	-344.46	132.72	**0.01**
Total TBI Severity	-2.12	1.76	0.24	Total TBI Severity	-3.85	1.87	**0.05**
Current PTSD Sx	0.10	0.14	0.45	Current PTSD Sx	0.17	0.15	0.26
Non-Blast	**B**	**SE**	***p***	**Non-Blast**	**B**	**SE**	***p***
FA + TBI				**FA + TBI**			
FA of CGHR	10.12	34.44	0.77	FA of SLFR	-17.75	70.34	0.80
Total TBI Severity	-1.02	1.31	0.44	Total TBI Severity	-1.08	1.34	0.42
FA + PTSD				**FA + PTSD**			
FA of CGHR	14.58	34.64	0.68	FA of SLFR	1.03	69.56	0.99
Current PTSD Sx	-0.10	0.10	0.34	Current PTSD Sx	-0.09	0.10	0.37
FA + TBI + PTSD				**FA + TBI + PTSD**			
FA of CGHR	14.43	34.81	0.68	FA of SLFR	-9.19	71.26	0.90
Total TBI Severity	-0.95	1.32	0.47	Total TBI Severity	-0.99	1.35	0.47
Current PTSD Sx	-0.09	0.10	0.36	Current PTSD Sx	-0.09	0.10	0.40
Combined	**B**	**SE**	***p***	**Combined**	**B**	**SE**	***p***
FA + TBI				**FA + TBI**			
FA of CGHR	-35.63	41.31	0.39	FA of SLFR	-22.58	92.66	0.81
Total TBI Severity	-0.21	0.96	0.83	Total TBI Severity	-0.16	0.97	0.87
FA + PTSD				**FA + PTSD**			
FA of CGHR	-59.21	36.49	0.11	FA of SLFR	-84.09	82.65	0.31
Current PTSD Sx	0.31	0.08	**<0.001**	Current PTSD Sx	0.30	0.09	**<0.001**
FA + TBI + PTSD				**FA + TBI + PTSD**			
FA of CGHR	-59.21	36.92	0.12	FA of SLFR	-85.54	84.26	0.32
Total TBI Severity	-0.01	0.85	0.99	Total TBI Severity	0.12	0.87	0.89
Current PTSD Sx	0.31	0.08	**<0.001**	Current PTSD Sx	0.31	0.09	**0.001**
Controls	**B**	**SE**	***p***	**Controls**	**B**	**SE**	***p***
FA + TBI				**FA + TBI**			
FA of CGHR	72.76	60.15	0.23	FA of SLFR	-35.31	152.93	0.82
Total TBI Severity	-1.59	1.59	0.32	Total TBI Severity	-1.62	1.63	0.33
FA + PTSD				**FA + PTSD**			
FA of CGHR	55.15	59.52	0.36	FA of SLFR	-91.16	147.8	0.54
Current PTSD Sx	0.22	0.12	0.08	Current PTSD Sx	0.25	0.12	**0.05**
FA + TBI + PTSD				**FA + TBI + PTSD**			
FA of CGHR	55.12	59.89	0.36	FA of SLFR	-79.12	150.12	0.60
Total TBI Severity	-1.13	1.59	0.48	Total TBI Severity	-1.02	1.61	0.53
Current PTSD Sx	0.20	0.12	0.11	Current PTSD Sx	0.23	0.12	0.07

Only for all participants and the blast cohort were the FA scores significant (shown highlighted in gray), and for all participants, the blast cohort and the combined cohort was Current PTSD Sx significant (shown highlighted in gray).

Following the same pattern, where both tracts were included, but cohorts were still separated, only the blast cohort showed a relationship between FA score and TMT-B performance across all iterations of the model, and only for the CGHR, suggesting that this latter tract has a stronger relationship with performance on the TMT-B (see Table 4).

Table 4

Hierarchical Analysis of the Model Predicting TMT-B Performance from FA Score of the CGHR and SLFR, TBI Severity and Current PTSD Symptoms, Separated by Cohorts

All	**B**	**SE**	***p***	**Blast**	**B**	**SE**	***p***
FA of CGHR + FA of SLFR				**FA of CGHR + FA of SLFR**			
FA of CGHR	-25.5	28.7	0.38	FA of CGHR	-194.9	70.18	**0.01**
FA of SLFR	-46.44	61.56	0.45	FA of SLFR	0.89	153	0.90
FA of CGHR + FA of SLFR + TBI Sev				**FA of CGHR + FA of SLFR + TBI Sev**			
FA of CGHR	-20.12	28.83	0.49	FA of CGHR	-170.34	73.79	0.03
FA of SLFR	-49.72	61.39	0.42	FA of SLFR	-38.26	157.14	0.81
Total TBI Severity	-0.71	0.48	0.14	Total TBI Severity	-1.86	1.75	0.30
FA of CGHR + FA of SLFR + PTSD Sx				**FA of CGHR + FA of SLFR + PTSD Sx**			
FA of CGHR	-30.5	28.39	0.28	FA of CGHR	-194.75	70.94	**0.01**
FA of SLFR	-68.18	61.39	0.27	FA of SLFR	-20.93	161.71	0.90
Current PTSD Sx	0.14	0.06	**0.02**	Current PTSD Sx	0.06	0.14	0.65
FA of CGHR + FA of SLFR + TBI Sev + PTSD Sx				**FA of CGHR + FA of SLFR + TBI Sev + PTSD Sx**			
FA of CGHR	-24.95	28.49	0.38	FA of CGHR	-161.87	74.55	**0.04**
FA of SLFR	-72.06	61.19	0.24	FA of SLFR	-96.89	170.2	0.57
Total TBI Severity	-0.75	0.47	0.12	Total TBI Severity	-2.48	1.89	0.20
Current PTSD Sx	0.14	0.06	**0.01**	Current PTSD Sx	0.13	0.15	0.37

Table 4 Continued

Non-Blast	B	SE	*p*
FA of CGHR + FA of SLFR			
FA of CGHR	27.66	51.02	0.59
FA of SLFR	-47.96	102.34	0.64
FA of CGHR + FA of SLFR + TBI Sev			
FA of CGHR	37.87	52.23	0.47
FA of SLFR	-75.65	106.64	0.48
Total TBI Severity	-1.29	1.37	0.35
FA of CGHR + FA of SLFR + PTSD Sx			
FA of CGHR	30.48	51.17	0.55
FA of SLFR	-43.62	102.56	0.67
Current PTSD Sx	-0.10	0.10	0.35
FA of CGHR + FA of SLFR + TBI Sev + PTSD Sx			
FA of CGHR	39.83	52.41	0.45
FA of SLFR	-69.75	107.11	0.52
Total TBI Severity	-1.20	1.38	0.39
Current PTSD Sx	-0.09	0.10	0.39

Combined	B	SE	*p*
FA of CGHR + FA of SLFR			
FA of CGHR	-42.69	49.89	0.40
FA of SLFR	28.84	110.41	0.80
FA of CGHR + FA of SLFR + TBI Sev			
FA of CGHR	-44.08	50.73	0.39
FA of SLFR	33.12	112.88	0.77
Total TBI Severity	-0.25	0.98	0.80
FA of CGHR + FA of SLFR + PTSD Sx			
FA of CGHR	-54.94	44.03	0.22
FA of SLFR	-17.42	97.97	0.86
Current PTSD Sx	0.31	0.08	**<0.001**
FA of CGHR + FA of SLFR + TBI Sev + PTSD Sx			
FA of CGHR	-54.87	44.79	0.23
FA of SLFR	-17.67	100.43	0.86
Total TBI Severity	0.01	0.87	0.99
Current PTSD Sx	0.31	0.09	**<0.001**

Controls	B	SE	*p*
FA of CGHR + FA of SLFR			
FA of CGHR	84.99	62.48	0.18
FA of SLFR	-102.6	155.45	0.51
FA of CGHR + FA of SLFR + TBI Sev			
FA of CGHR	81.49	62.7	0.20
FA of SLFR	-86.62	156.69	0.58
Total TBI Severity	-1.50	1.62	0.36
FA of CGHR + FA of SLFR + PTSD Sx			
FA of CGHR	67.10	61.35	0.28
FA of SLFR	-129.0	151.46	0.40
Current PTSD Sx	0.23	0.12	0.07
FA of CGHR + FA of SLFR + TBI Sev + PTSD Sx			
FA of CGHR	65.96	61.89	0.29
FA of SLFR	-116.9	154.01	0.45
Total TBI Severity	-0.97	1.61	0.55
Current PTSD Sx	0.21	0.13	0.10

Only in the blast cohort did the FA of the CGHR show significance, and current PTSD symptoms were significant in the whole population (“all” cohort) and the combined cohort.

Then, a model was created to explore the potential relationship between FA score and these two white matter tracts using another grouping approach for TBI type that did not include cohorts. Here, the independent variables were: 1) FA of the CGHR; 2) FA of the SLFR; 3) current PTSD symptoms; 4) blast TBI severity; and 5) impact TBI severity, all predicting TMT-B score. Using this method, the type of TBI was accounted for along a continuous severity scale instead of by category. Running a hierarchical analysis of this model, only current PTSD symptoms showed a significant relationship with predicting TMT-B performance (see Table 5).

Table 5

Hierarchical Models Predicting TMT-B Performance on FA Scores of Both the CGHR and SLFR, Blast and Non-Blast TBI Severity Scores, and Current PTSD Symptoms

FA				**FA + PTSD + Blast Sev**			
	B	**SE**	***p***		**B**	**SE**	***p***
FA CGHR	-25.50	28.70	0.38	FA of CGHR	-30.03	28.43	0.29
FA SLFR	-46.44	61.56	0.45	FA of SLFR	-63.70	61.72	0.30
FA + PTSD				Current PTSD Sx	0.15	0.058	**0.02**
	B	**SE**	***p***	Blast Severity	-0.58	0.73	0.43
FA of CGHR	-30.50	28.39	0.28	**FA + Blast Sev + Non-Blast Sev**			
FA of SLFR	-68.18	61.39	0.27		**B**	**SE**	***p***
Current PTSD Sx	0.14	0.06	**0.01**	FA CGHR	-18.81	28.89	0.52
FA + Blast Sev				FA SLFR	-60.00	62.47	0.34
	B	**SE**	***p***	Blast Severity	-0.23	0.72	0.75
FA of CGHR	-25.29	28.80	0.38	Non-Blast Severity	-1.04	0.61	0.09
FA of SLFR	-44.92	62.20	0.47	**FA + PTSD + Blast Sev + Non-Blast Sev**			
Blast Severity	-0.14	0.72	0.84		**B**	***SE***	***p***
FA + Non-Blast Sev				FA CGHR	-24.45	28.64	0.39
	B	**SE**	***p***	FA SLFR	-74.25	62.03	0.23
FA of CGHR	-19.22	28.78	0.51	Blast Severity	-0.61	0.73	0.40
FA of SLFR	-62.23	61.92	0.32	Non-Blast Severity	-0.84	0.60	0.17
Non-Blast Severity	-1.03	0.602	0.09	Current PTSD Sx	0.13	0.058	**0.02**

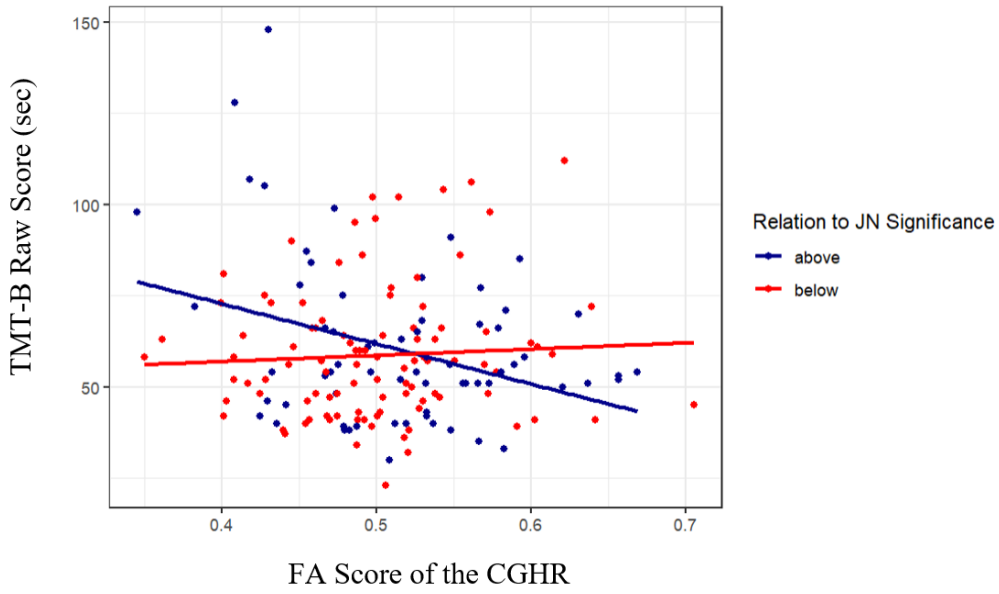
Only the PTSD Sx was found to be significant (shown highlighted in gray).

Based on these analysis, TBI severity was chosen to be measured using blast and non-blast severity, and TBI type was not included in the final model. Also, the CGHR was determined as the only tract to be included in the models, due to the lack of significance found for the SLFR in predicting TMT-B performance.

Appendix D

Figure 1

Distribution of the Data Points Showing Relation to Johnson-Neyman Thresholds



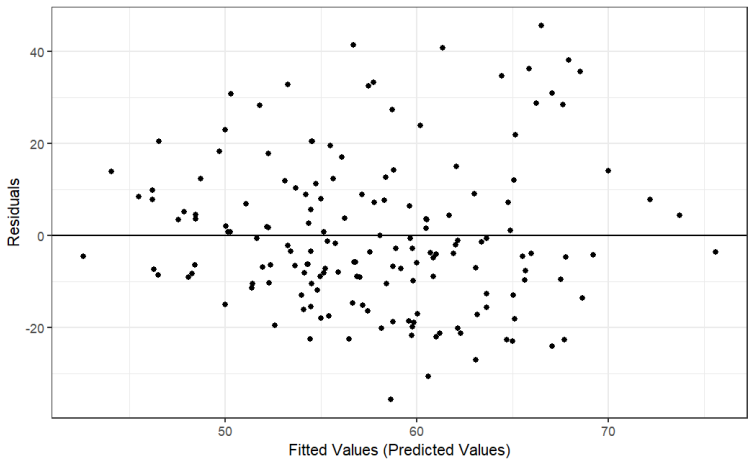
This plot shows the distribution of points, distinguished by the Johnson-Neyman interval. The points are plotted by FA score of the CGHR as they predict TMT-B performance, and the colors indicate whether the point falls above the J-N significance threshold of 1.68, or below (Blue, steeper sloped line = above; red, flatter line = below). The spread of points in these two groups supports that for those with higher blast severity scores, the relationship between the FA score and TMT-B is stronger, such that higher FA is associated with better TMT-B performance.

Appendix E

The final model that explored the potential interactions between the tracts' FA scores, blast severity and PTSD symptoms was evaluated by plotting the residuals of the model. The interaction model specific to the CGHR and blast severity was evaluated using Cook's Distance Plot, as well as by plotting the residuals. Based on these analyses the models were deemed to be sufficient.

Figure 1

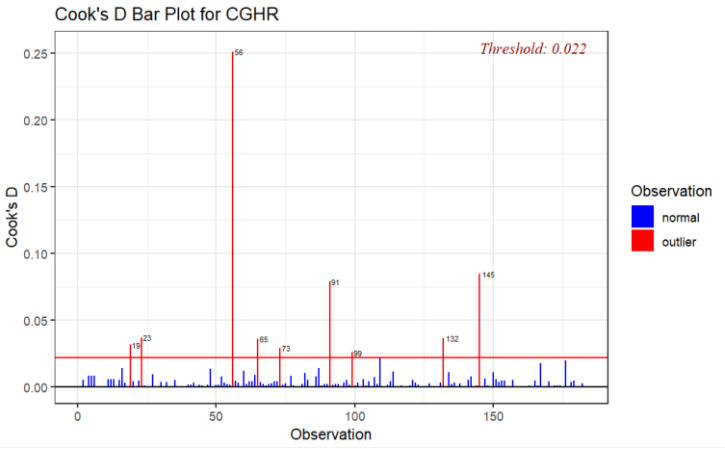
Residual Plot for Large Multi-Tract Interaction Model



This shows a relatively wide spread of points, no distinct trends or clusters, and no extreme outliers, indicating a decent model fit.

Figure 2

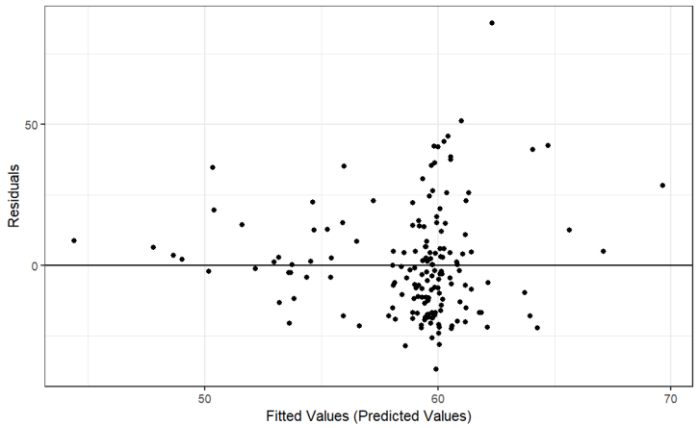
Cook's Distance Plot for the Model of the Interaction Between the FA of CGHR and Blast Severity



This plot revealed no statistical outliers. Data point #56 appears to be an outlier but does not exceed the predetermined threshold (>1), and when it was removed from the dataset, there was no significant change in the interaction between the FA of the CGHR and the blast severity.

Figure 3

Residual Plot for the CGHR-Interaction Specific Model



This shows a relatively even spread below and above 0, but there is a distinct cluster of points at 60 (predicted TMT-B score). Looking at the spread of the points in Appendix D (Figure 1), however, this cluster reflects the majority of the scores on the TMT-B. There are no strong indications that a transformation would improve the fit.