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THE EFFECTS OF SUBCONCUSSIVE HEAD TRAUMA IN ATHLETICS

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Brian Johnson

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The dissertation of Brian D. Johnson was reviewed and approved* by the following:

Semyon Slobounov
Professor of Kinesiology
Dissertation Advisor
Chair of Committee

Karl M. Newell
Professor of Kinesiology and Biobehavioral Health

Wayne Sebastianelli
Professor of Orthopaedics and Rehabilitation

Thomas Neuberger
Director High Field Magnetic Resonance Imaging Facility
Assistant Professor of Bioengineering

David Conroy
Professor of Kinesiology and Human Development & Family Studies
Graduate Program Director

*Signatures are on file in the Graduate School

ABSTRACT

There is a growing concern in clinical practice regarding the immediate and long-lasting effects of multiple and frequent subconcussive blows in athletes participating in full contact sports. The effects of repetitive subconcussive head trauma, occurring in full contact sports, on brain structural, functional and metabolic integrity has not been sufficiently investigated. It is yet to be determined whether these multiple subconcussive blows induce transient alterations in the brain or long-term deficits. Our central hypothesis is that previous concussive episodes lead to chronic cognitive and functional deficits in the brain. Additionally, a history of prior concussion may increase an athletes' vulnerability to repetitive subconcussive blows leading to a compromise in metabolic, structural, and/or functional brain integrity. Thus, specific alteration of brain functional/structural integrity in the acute phase of injury may identify athletes at high risk for recurrent concussion. In order to assess the effect of subconcussive blows advanced neuroimaging techniques (functional magnetic resonance imaging, magnetic resonance spectroscopy, and neuropsychological testing) was completed during two (pregame and postgame) identical testing sessions that occurred within 24 hrs prior to a scheduled full contact game and within 24 hrs of the end of that game. All subjects under study displayed no signs or symptoms of a concussion at either testing session and were also observed during and after the game by a medical professional. Virtual reality assessment of balance, reaction time, and working spatial memory revealed poorer performance in the group with a history of previous concussion compared to those with no prior concussion. Furthermore, there were significant reductions in neurometbolite ratios in the group with a history of concussion as assessed by magnetic resonance spectroscopy. Resting-state functional magnetic resonance imaging revealed reduced connectivity in the group with previous concussion, yet no changes in functional connectivity pre-game to post-game. However, the group with no history of concussion showed a

significant decrease in connectivity in the right lateral parietal and medial pre-frontal cortex following a full contact game. Pre-game to post-game changes did not reveal any significant changes in metabolite ratios or performance on virtual reality modules, although an interesting trend was observed. Consistent across all modalities the group with a previous concussion tended to improve in their post-game evaluations compared to their pre-game assessment. Conversely the group without a history of prior concussion exhibited the opposite trend and consistently performed worse in the post-game evaluation. This unexpected trend brings up the question of whether or not a prior concussion may elicit a neuroprotective effect on the brain when repetitive subconcussive head trauma.

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Chapter 1

Introduction

Recently concussion and subconcussive head trauma have garnered a lot of attention, not only in the scientific and medical communities, but in the public as well. Widespread media coverage and several high profile cases has brought in to question the damaging and long-term effects of sports-related traumatic brain injury (McKee et al., 2009); and the increased risk for developing neurodegenerative diseases associated with these subconcussive and concussive blows (Gavett, Stern, Cantu, Nowinski, & McKee, 2010). Traumatic brain injury (TBI), sometimes referred to as the "silent epidemic" has been identified by the Centers for Disease Control and Prevention (CDC) as a major health concern in the United States (Langlois, Rutland-Brown, & Wald, 2006), and is the leading cause of disability worldwide (Signoretti, Vagnozzi, Tavazzi, & Lazzarino, 2010). Broken down into three grades based upon level of injury and severity, the most common variant of TBI is the mild classification (Bergman & Bay, 2010; Langlois, Rutland-Brown, & Thomas, 2005). Mild traumatic brain injury (mTBI) also known by its more common name concussion (Cantu, 2006), accounts for an annual incidence in the United States of between 1.6 to 3.8 million cases attributed to sports (Langlois et al., 2006). Despite the staggering occurrence of sports-related concussions, these mTBIs can be the result of motor vehicle accidents, falls, and have become the dominant war related injury seen in the military (Zohar et al., 2011).

The mechanical trauma experienced during a single concussive event causes the brain to undergo forceful acceleration and deceleration (Barkhoudarian, Hovda, & Giza, 2011). This

violent shaking of the malleable brain inside the hard confined spaces of the skull is not only expressed in a linear fashion, but rotational forces associated with a concussion apply unnecessary axonal strain leading to diffuse axonal injury (DAI) (Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010). Consequently following a concussive episode there is a destructive pathophysiological response that initiates a complex chain of neurometabolic and neurochemical reactions. Due to the biochemical sequelae that follows a concussion individuals present with a constellation of symptoms that can include physical, cognitive, and emotional manifestations (Bergman & Bay, 2010; Bryant & Harvey, 1999). Some of the most common clinical symptoms include: headache, nausea, visual disturbances, light sensitivity, dizziness, fatigue, poor concentration, short-term memory loss, unsteady gait, and irritability (Bryant & Harvey, 1999). These persistent symptoms from concussion can lead to post-concussive syndrome (PCS) and long-term disabilities (Hughes et al., 2004). For most sport-related concussions there is spontaneous recovery with resolution of symptoms within 10 days post injury (McCrory et al., 2009). However, upwards to 15% of individuals recovering from a concussion report symptoms for more than one year following insult (Ghaffar, McCullagh, Ouchterlony, & Feinstein, 2006). Furthermore, injury to the brain is also associated with an increased susceptibility to a number of psychiatric conditions, as well as certain neuropathologies (Guskiewicz et al., 2005; Kiraly & Kiraly, 2007; McCrory et al., 2009; Reeves & Panguluri, 2011). Compounding the damaging effects from mTBI, there seems to be a higher disposition for subsequent concussions following an initial brain injury (Collins et al., 1999; Gerberich, Priest, Boen, Straub, & Maxwell, 1983; Guskiewicz et al., 2003; Guskiewicz, Weaver, Padua, & Garrett, 2000; Zemper, 2003). Premature return-to-play following a concussion may be a crucial element for the higher risk of recurrent concussions (Guskiewicz et al., 2003) along with neurological and cognitive deficiencies seen in chronic PCS (Cantu, 2006). This increased vulnerability to recurrent head injury is poorly understood and research into this area is needed.

Even with the multitude of signs and symptoms, alterations in the neurochemical environment, and disruption of normal neurometabolic reactions, conventional neuroimaging techniques and neuropsychological tests fail to adequately detect these alterations in the subacute phase of injury (Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011). Additionally, these approaches are unable to differentiate individuals who have suffered a previous concussion from those with no history of prior head injury (Iverson, Brooks, Lovell, & Collins, 2006). Making matters worse is a lack of a universally accepted definition of concussion (Robert C. Cantu, 2007) and diagnostic protocol (Vagnozzi et al., 2007). The lack of sensitivity and specificity of current clinical measures for concussion management is a major concern as is evident by the mounting research demonstrating the damaging effects of cumulative concussions and subconcussive head trauma (De Beaumont, Brisson, Lassonde, & Jolicoeur, 2007; Echemendia & Cantu, 2003; Guskiewicz et al., 2003). Utilizing functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET) advanced neuroimaging techniques have demonstrated cognitive, structural, and metabolic alterations after a single concussion (Gasparovic et al., 2009; Lipton et al., 2008; McAllister et al., 2001; Ptito, Chen, & Johnston, 2007; Slobounov et al., 2011; Zhang et al., 2010). These progressive imaging techniques have highlighted subtle changes and nuances in brain morphology, physiology, and function caused by mTBI (Gasparovic et al., 2009).

There is a growing concern in clinical practice regarding the immediate and long-lasting effects of multiple and frequent subconcussive blows in athletes participating in full contact sports. These effects, in terms of neurocognitive, behavioral, and underlying neural substrates have not been sufficiently studied. Specifically, concern is growing that subconcussive impacts to the head, may adversely affect cerebral functions (Gavett, Stern, & McKee, 2011; Martini et

al., 2011; Witol & Webbe, 2003). Recently Talavage et al. (2010) reported changes in cerebral functions attributed to multiple subconcussive impacts as evidenced by declines in the visual working memory in high school football players in the absence of clinical signs of concussion. Similar neurocognitive vulnerability has been reported by Shuttleworth-Edwards et al. (Shuttleworth-Edwards, Smith, & Radloff, 2008) for rugby players attributed to years of exposure to subconcussive impacts to the brain. Moreover, this increased susceptibility to recurrent concussions suggests that a lower threshold exists for athletes with a history of concussion (Gysland et al., 2012).

To date there have been no advanced brain imaging research reported in the literature that has focused on the immediate effects of subconcussive blows on the human brain from a metabolic, structural, and/or functional brain network approach. Overall, neither the neural mechanisms underlying these alterations, nor other considerations (acute versus chronic phase of injury, history of previous mTBI, immediate and prolonged effects of multiple subconcussive impacts) are understood and have been fully explored. It is our intention to address these issues and potentially to identify neural markers that predict the consequences of multiple subconcussive impacts in athletics.

Hypotheses

The central hypothesis is that history of concussion and exposure to repetitive subconcussive blows will have negative long-term and chronic effects on the cognitive, functional, and metabolic integrity of the brain. Secondary to this, it is also hypothesized that there will be a differential response to subconcussive head trauma in individuals with and without a previous history of concussion. Specifically, the acute effects of subconcussive impacts will be

compounded in individuals with a previous concussion, compared to those with no history of concussion.

Chapter 2

Literature Review

2.1 Sports Related Traumatic Brain Injury

According to the CDC, TBI is a major health concern in the United States (Langlois et al., 2005). TBI is broken down into three classifications, mild, moderate, and severe based upon severity; with mild (mTBI) being the least severe and most prevalent classification consisting of 75-90% of all reported TBI cases. Concussion, synonymous with mTBI, can occur in many ways but has a high incidence in sports, especially full contact sports (Bergman & Bay, 2010; Langlois et al., 2005). In the United States alone between 1.6 to 3.8 million sports-related concussions occur annually (Langlois et al., 2006), and the rate of diagnosed concussions over the past ten years in high school sports has demonstrated an increase of 16.5% annually (Lincoln et al., 2011). However, these numbers may be underestimated as most concussions are under reported by the athlete to their trainers or coaches (Packard, 2008).

There is still a lack of an accepted definition of concussion although attempts by the Congress of Neurological Surgeons, American Academy of Neurology, National Center for Injury Prevention and Control, Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine, Colorado Medical Society and International Symposiums on Concussion in Sport have tried to name a few (Kirkendall, Jordan, & Garrett, 2001; Packard, 2008). Although there are over 18 different grading scales (Terrell, 2004) and despite the many different governing bodies, societies, and conferences most definitions of concussion are based upon recognition of certain signs and symptoms (Kirkendall et al., 2001). To date there is still no

standardized and universally accepted definition of concussion (Robert C. Cantu, 2007). However, the Third International Conference on Concussion in Sport consensus statement (2009) defines it as, “a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces.” To supplement this definition several common clinical, pathological, and biomechanical features were also published in the Third International Conference on Concussion in Sport (2009) consensus statement. These common features stated: (1) that concussion can occur by a direct blow to the head or can also be caused by a blow elsewhere, where the forces have been transmitted to the brain, (2) typically results in short-lived impairment of neurologic function with spontaneous resolution, (3) may also result in neuropathological changes, but symptoms overall reflect functional disturbances, (4) individuals may present with graded symptoms and a concussion does not have to involve loss of consciousness, and (5) presents on structural neuroimaging studies as normal (McCrory et al., 2009).

During the course of a season athletes involved in collision sports may be exposed to thousands of subconcussive impacts (McKee et al., 2009). Specifically, data collected from accelerometers in the football helmets reveals that players are exposed to a large number of subconcussive impacts, with one study reporting individuals with over 1400 subconcussive blows over the course of a season (Khurana & Kaye, 2012). Moreover, during an average game a soccer player heads the ball six to twelve times which is estimated to be over 5,000 headers over a 15 year career (Bauer, Thomas, Cauraugh, Kaminski, & Hass, 2001; Spiotta, Bartsch, & Benzel, 2012). Subconcussive blows are below the threshold to cause a concussion (Shultz, MacFabe, Foley, Taylor, & Cain, 2012) and do not result in a clinically-identifiable concussion, (Gavett et al., 2011; Martini et al., 2011; Witol & Webbe, 2003). Yet despite lacking the necessary forces to induce a concussion, subconcussive impacts can cause brain injury (Bauer et al., 2001). It is becoming ever more apparent that brain injury does not only come from concussive episodes but

that the accumulation of subconcussive blows may be detrimental (Spiotta, Shin, Bartsch, & Benzel, 2011).

Return-to-play guidelines also vary but the most widely accepted are the guidelines proposed by Dr. Robert Cantu (Terrell, 2004). The Congress of Neurological Surgeons recommended that any player who had suffered a grade 1 concussion be removed from competition, but be allowed to return if all symptoms resolved and that participant returned to normal in all neurological realms, where grade 2 concussions were removed and not allowed back until passing neurological and neuropsychological testing (Kirkendall et al., 2001). Return-to-play recommendations include resting athletes for at least seven days, be asymptomatic during and following exercise, and a return to baseline levels on neuropsychological tests (Terrell, 2004). With respect to collegiate athletics a combination of tools are used to evaluate and determine an athlete's ability to return-to-play. These tools include: a subjective self-report symptoms survey (SRSS); a cognitive assessment measure like the SCAT-2 (McCrory et al., 2009) and Balance Error Scoring System (BESS) as outlined by the NCAA: Sports Medicine Handbook (2010-2011). Conversely, it is known that self-reported symptoms are unreliable and subject to falsification by the athlete (Broglio, 2007). The NCAA also recommends further evaluation when returning athletes back to competition by means of neuropsychological assessment. However, the use and implementation of neuropsychological testing is still under debate as they have proven to lack specificity and sensitivity (Mayer et al., 2011; Randolph, McCrea, & Barr, 2005). Neuropsychological evaluation may also not be sensitive enough to detect deficiencies in motor function and, therefore, it is recommended that complex motor tasks be used in return-to-play decisions following a concussion (Parker, Osternig, van Donkelaar, & Chou, 2008).

Following a concussion clinical evaluation includes subjective assessment of self-reported symptoms, and objective measures of the athlete's postural control and cognitive function by means of balance testing and neuropsychological examination (Schmitt, Hertel, Evans, Olmsted, & Putukian, 2004). Neuropsychological testing combined with self-reported symptoms scale allows for quantification of symptoms following concussion, and assessment of postural control assess visual, vestibular, and sensorimotor integration (Schmitt et al., 2004). Furthermore, neuropsychological tests make quantification of cognitive function possible. Return-to-play guidelines do not prevent or manage subconcussive impacts (Johnson, 2012) and unlike concussion, these blows go undiagnosed and are not assessed by medical professionals during the course of a game, resulting in an accumulation of brain injury (Baugh et al., 2012). As seen in boxing many subconcussive hits may have a negative cumulative effect on the brain (Parker et al., 2008). Return-to-play decisions should be taken serious as effects of even a mild concussion may last for extended periods of time well after that person has returned to competition (Kirkendall et al., 2001).

2.2 Biomechanics and Pathophysiology of Sports Related Traumatic Brain Injury

Concussion is caused by the response of the brain to biomechanical forces (Barkhoudarian et al., 2011). These biomechanical forces do not have to come from a direct blow to the head but can be the result from any forces that are translated to the head. After contact that causes translation acceleration of the head, there is a slight lag experienced by the brain which then impacts the skull. This initial contact of the brain to the skull is known as the coup, and these coup injuries often are in the frontal lobe which makes concussion hard to diagnose clinically and test for on the field (Packard, 2008). As the brain is accelerated and then recoils, there are countercoup injuries, that is injuries away from the initial site of impact due to the

jagged and irregular shape of the skull base which can lead to shearing injuries of axons and blood vessels (Kirkendall et al., 2001). In addition to linear accelerations shearing injuries can also be caused by the addition of rotational or angular forces experienced by the brain following a concussive blow especially in the corpus callosum and structures around the third ventricle (Kirkendall et al., 2001). Due to the movement of the brain inside the skull that can cause stress and strain at the cellular level as well as the impact of the brain on the interior of the skull concussion leads to the disruption of neuronal membranes. Stretched and damaged axons swell and then separate, although most axons initially affected gradually recover with time, and for the most part the pathophysiology of concussion is thought to be neurometabolic (Packard, 2008). Following a concussive episode enlargement of the Virchow-Robin spaces can cause damage to the white matter (Packard, 2008). It is speculated that these subconcussive impacts can cause microstructural and biochemical changes in the brain similar full blown concussive episodes just to a lesser extent (Khurana & Kaye, 2012). The report of "footballer's migraine" has been long reported from soccer players due to heading of the soccer ball (Kirkendall et al., 2001). .

Subsequently following a concussive episode there is a destructive biochemical response that initiates a chain of neurometabolic and neurochemical reactions that include activation of inflammatory response, imbalances of ion concentrations, increase in the presence of excitatory amino acids, dysregulation of neurotransmitter synthesis and release, and production of free radicals (Wheaton, Mathias, & Vink, 2011). As outlined by Giza and Hovda (2001), the pathophysiological response to concussion is a complex combination of changes in the brain at a vascular and cellular level. As a result from the trauma the brain undergoes disruptions in neurochemical and neurometabolic homeostasis. This disruption via a physical tearing or shearing of the membrane itself is also compounded by the deregulation of selective ion channels. In order to maintain normal cellular metabolism and homeostasis the neuron relies mainly on the

adenosine triphosphate (ATP) dependent sodium potassium pump to restore proper membrane and equilibrium potentials. In the neuron which undergoes repetitive depolarization and repolarization in response to excitatory and inhibitory action potentials the sodium potassium pump is a key regulator in cellular equilibrium. After a concussive blow there is a large efflux of potassium out of the cell into extracellular space, as well as a large influx of calcium. This large efflux and influx leads to widespread and rapid release of excitatory neurotransmitters, especially glutamate. After this large and diffuse depolarization the brain is believed to experience the phenomenon of spreading depression. Due to the imbalance of normal neuronal ionic concentrations the cell relies mainly on the sodium potassium pumps to restore the imbalances. Since the sodium potassium pumps are not passive and require energy in the form of ATP to be driven the cell starts a period of hypermetabolism where consumption of glucose is increased. The influx of calcium ions, which causes a reversal of what is usually higher concentrations of extracellular calcium, is toxic to the cell. In an attempt to avert this potentially toxic accumulation of calcium ions the mitochondria sequester the calcium. In turn this causes the mitochondria to become less efficient at converting glucose into ATP to drive the sodium potassium pumps. Following the initial period of hypermetabolism, comes a period of hypometabolism, as the cell is incapable/inefficient at converting glucose into ATP to run the sodium potassium pumps to restore the ionic concentrations. This oxidative dysfunction leads to the cell turning to anaerobic respiration to meet its energy needs. This anaerobic respiration leads to the formation of lactate and then to lactic acid. As the lactic acid accumulates in the extracellular space, acidosis occurs which can break down the cellular membrane even further, thus compounding this entire cycle. As you can see this neurometabolic cascade is very damaging at the cellular level, and the main goal to restore equilibrium in the cell which is an energetically expensive, is exacerbated by the cells inability to properly produce the required energy through mitochondrial and oxidative dysfunction. This energy crisis in turn exacerbates the cellular conditions to a state if which it is

not corrected may lead to cell death. So as the name may lead you to believe, there is nothing "mild" about mTBI at the cellular level. As is similar in a full blown concussive episode, repetitive subconcussive head trauma can trigger similar neurochemical and neurometabolic reactions, although often to a lesser extent (Giza & Hovda, 2001) which may lead to long-term or chronic consequences (Jordan, Matser, Zimmerman, & Zazula, 1996).

The acute effects related to sports-related concussion are usually short lived (Mayer et al., 2011) with spontaneous recovery and resolution of symptoms within 10 days post injury (McCrory et al., 2009). However, Rutherford et al. (1977) reported that over 50% of the patients recovering from concussion had symptoms lasting up to six weeks, and 15% of individuals report symptoms lasting over one year (Ghaffar et al., 2006). The most common clinical symptoms include: headache, nausea, visual disturbances, light sensitivity, dizziness, fatigue, poor concentration, short-term memory loss, unsteady gait, and irritability (Bryant & Harvey, 1999). Although not a full blown concussive event, subconcussive impacts may produce signs and symptoms analogous to seeing stars or hearing bells ringing (Terrell, 2004). The most common symptom following a mild head injury is headache although mild head injuries do not always lead to a full blown concussive episode (Packard, 2008). It is common for football players to report headaches following practice and it is not yet known whether this is a posttraumatic phenomenon or caused from subconcussive impacts (Terrell, 2004). These symptoms can be attributed to the damage to neural tissue and the associated biochemical sequelae (Giza & Hovda, 2001) and are reflections of underlying brain trauma induced neuropathology at the cellular level (Bigler & Maxwell, 2012). Subconcussive impacts are implicated in the etiology of several neurologic disorders, and it is believed that the brain may be more vulnerable to these subconcussive blows as they amass over time even though these injuries are not severe enough to elicit a clinically diagnosable concussion (Parker et al., 2008).

Following a concussion it is important to be aware of the effects that a second impact may have. Known as the second impact syndrome, a second head injury to a brain that has impaired vasomotor regulation and cerebral edema may lead to additional cerebral swelling, vascular engorgement, and brain herniation with tragic consequences (Kirkendall et al., 2001). It is hypothesized and repeated studies have identified that there is a temporal window of vulnerability following a concussion where a second insult can lead to much more severe damage if it happens to close to the initial (Vagnozzi, 2008). After a concussive episode chronic and persistent symptoms are referred to as the post-concussion syndrome and can include headache, dizziness, fatigue, memory problems, attention problems, and changes in mood (Kirkendall et al., 2001). These persistent symptoms seen in PCS can lead to long-term disabilities (Hughes et al., 2004). A syndrome is the manifestation of a collection of signs and symptoms that as a whole characterize a disease or disorder, and PCS is one of the most controversial syndromes in psychology and medicine today (Packard, 2008).

Furthermore, research shows that the accumulation of repetitive subconcussive impacts and concussions are linked to certain neurological impairment (Witol & Webbe, 2003) and disorders like early-onset Alzheimer's disease, dementia, depression, and chronic traumatic encephalopathy (CTE) (Guskiewicz et al., 2005; McCrory et al., 2009; McKee et al., 2009). Chronic traumatic brain injury also known by other monikers like dementia pugilistica or CTE is the result of the long-term accumulation of multiple concussions and repetitive subconcussive blows, and can be found in athletes who participated in contact sports (Rabadi & Jordan, 2001). As seen in boxers, punch drunk, has long been associated with repetitive subconcussive blows to the head (McCrory, 2011). CTE which is characterized by ventriculomegaly, delamination of the septum pellucidum, encephalomalacia, and DAI have been found in boxers and the condition is

known to progress even after retirement and mimic Alzheimer's disease (Kirkendall et al., 2001). As troubling as all this is perhaps one of the more troubling problems with concussion is that once someone has received a concussive blow they are three to six times more likely to sustain another concussion (Collins et al., 1999; Gerberich et al., 1983; Guskiewicz et al., 2003; Guskiewicz et al., 2000; Zemper, 2003). It is hypothesized that accumulation of multiple repeated subconcussive blows may leave the brain more vulnerable to these impacts despite not producing clinically-identifiable concussion symptoms (Parker, Osternig, van Donkelaar, & Chou, 2008). This increased susceptibility to recurrent concussions suggests that a lower threshold exists for athletes with a history of concussion (Gysland et al., 2012). Athletes with prior history of brain injury may be more sensitive to subsequent brain injury and more likely to develop PCS (Kirkendall et al., 2001).

2.2.1 Animal Models of Subconcussive Head Trauma

It has been known since the late 19th century that repeated mild blows to the head in animal experiments could be lethal despite any evidence of structural damage to the brain (Tedeschi, 1945). Initial animal models probing the difference between a single versus multiple concussive and subconcussive insults revealed that following a single subconcussive blow there were no behavioral and histologic changes, yet repetitive subconcussive head trauma resulted in permanent injury (Iverson, Gaetz, Lovell, & Collins, 2004). In an early experiment looking at concussion in the rat it was noted that following subconcussive blows the animals showed signs of "posttraumatic amnesia" (Govons, Govons, Heusner, & Vanhuss, 1972). Additionally Govons et al. (1972) reported subconcussive blows produced convulsions in some of the rats, altered activity for 24 hrs, and that the impact caused the animal to be momentarily stunned. Subconcussive head trauma has shown to decrease the polarizability of the cerebrum not to the

extent of a full concussive blow in animals (Spiegel, Henny, Wycis, & Spiegeladolf, 1946). Tedeschi (1945) reported that repetitive subconcussive blows received over a short duration in a rat model elicited a higher incidence of ill effects. Furthermore, post mortem examination of these rats revealed widespread evidence of neuronal injury, myelin loss, and glial proliferation. Other studies of subconcussive head trauma have reported neuropsychological changes and ionic fluctuations, and have been hypothesized to leave the brain more vulnerable to a repeated injury (Barkhoudarian et al., 2011). In a recent animal study investigating the effects of subconcussive head trauma induced by a mild lateral fluid percussion Shultz et al. (2012) found that such an injury caused acute neuroinflammation despite any significant axonal injury, cognitive, emotional, or sensorimotor alterations. Specifically, they documented a short-term increase in microglia, macrophages, and reactive astrogliosis which had returned to normal at a four week follow-up.

Acute neuroinflammation has also been document in other animal and human studies of TBI. Repetitive mTBI, similar to neuroinflammation may have cumulative effects leading to neurodegeneration (Shultz et al., 2012) and linked to behavioral impairments after TBI (Ramlackhansingh et al., 2011). Conversely it has been thought that neuroinflammation may have neuroprotective qualities (Schmidt, Heyde, Ertel, & Stahel, 2005) and the brain may be better protected after an initial TBI (Allen, Gerami, & Esser, 2000). However it has also been reported that by gradually increasing the amount of brain injury, animals could tolerate trauma that would otherwise kill normal animals. This so called "trauma resistance" was due to a stabilization of metabolic processes (Noble & Collip, 1942). This idea of preconditioning has been detailed in cerebral ischemia (Slemmer & Weber, 2005). Fujita et al. (2012) reported that subthreshold head trauma did not cause axonal or vascular changes in the rat, even with repetitive blows. Post-mortem studies have identified that repeated subconcussive head trauma may have

an accumulative effect and lead to neurodegenerative diseases (Shultz et al., 2012). In a study looking at repeated injury to hippocampal cells, Slemmer and Weber (2005) reported that a subthreshold injury, which is an injury that caused no obvious cellular damage, if repeated can lead to damage.

2.3 Cognitive Assessment of Subconcussive Head Trauma

Subconcussive impacts, that are impacts below the threshold of concussion and do not result in any clinically-identifiable signs or symptoms of concussion are a controversial topic as researchers and clinicians are divided on their true effect. These effects, in terms of neurocognitive, behavioral, and underlying neural substrates have not been sufficiently studied. Some research has shown that subconcussive head trauma may have minimal impact on cognitive functions (Miller, Adamson, Pink, & Sweet, 2007) although there is mounting evidence that subconcussive blows have detrimental effects on cognitive and cerebral functions (Gavett et al., 2011; Talavage et al., 2010). It has been hypothesized that exposure to repeated and multiple subconcussive blows throughout an athlete's career may compromise cognitive function (Parker et al., 2008). It is becoming ever more apparent that brain injury does not only come from concussive episodes but that the accumulation of subconcussive blows may be detrimental (Spiotta et al., 2011). A history of multiple concussions and subconcussive blows is known to result in depression, cognitive deficits, and progressive neuropathologies that include neurofibrillary tangles and deposits of amyloid plaques seen in Alzheimer's disease (Packard, 2008).

A majority of the literature that exists on the effects of subconcussive head trauma and cognitive function have been focused on soccer and boxing. Soccer is a contact sport and chronic

traumatic brain injury has been well documented in the literature (Rabadi & Jordan, 2001). There has been no documented case of a concussion in soccer occurring after a player willingly heads the ball, but is due to the players head contacting another player's head, the ground, or the goal post (Schmitt et al., 2004). During an average game a soccer player heads the ball six to twelve times which is estimated to be over 5,000 headers for a 15 year career (Bauer et al., 2001; Spiotta et al., 2012). Despite the correlation between purposeful heading and the incidence of concussion, it has long been know that heading could produce 'footballer's migraine' (Kirkendall et al., 2001). The repeated subconcussive blows that are incurred from heading the soccer ball account for many clinical symptoms that span the spectrum from headache to brain damage and can also lead to alterations in acute and chronic cognitive function (Bauer et al., 2001).

In a preliminary study it was found that out of 77 retired Norwegian professional soccer players that 50% reported symptoms linked to heading, and 75% suffered from disorientation, headache and nausea (Tysvaer & Storli, 1981). Further studies by Tysvaer et al. used electroencephalograph (EEG) to evaluate professional soccer players. They found that 35% of the participants had abnormal EEGs and 70% displayed some form of neurological impairment (Sortland & Tysvaer, 1989; Tysvaer, Storli, & Bachen, 1989). In addition to these findings neuropsychological testing (Wechsler Adult Intelligence Scale) of the same soccer players revealed significant differences compared to controls with one third of participants scores low enough to suggest evidence of organic brain damage (Tysvaer & Lochen, 1991). Matser et al. (1999) reported significant deficits in neuropsychological assessment of amateur soccer players associated with heading. Specifically they reported impaired performance in memory, planning, and visual perception processing that was exacerbated by the number of previous concussions a player had sustained. Downs et al. (2002) reported that subjects with a long history of soccer heading demonstrated slower patterns of motor speed and reaction time. Another study looking

at purposeful heading by Witol and Webbe (2003) revealed that players with the most reported number of headers had the lowest attention, concentration, and IQ scores. Decreased reaction time and reduced speed performing a motor task have been documented when assessing the effects of subconcussive head trauma in soccer (Downs & Abwender, 2002) as well as in athletes following a concussion (Bleiberg et al., 2004) suggesting that reaction time is impaired following repeated subconcussive and concussive head trauma (Parker et al., 2008). Although there is evidence that a long career which accounts to many instances of heading the soccer ball can lead to impaired brain function, it is not clear whether or not this increased likelihood is caused by numerous subconcussive blows or from full blown concussions (Schmitt et al., 2004). Jordan et al. (1996) found that there was a correlation between a history of concussion with increased symptoms in the United Stated national soccer team players and may suggest that full blown concussions as compared to repetitive subconcussive impacts may be the cause of encephalopathic changes. But it seems apparent in the literature that a long soccer career which amounts to a higher frequency of heading and accumulation of subconcussive blows contributes to impairments in cognitive function (Matser, Kessels, Lezak, & Troost, 2001; Schmitt et al., 2004). However not all studies on heading in soccer have observed neuropsychological deficits (Kirkendall et al., 2001).

A majority of the literature that explores the effect of heading in soccer has focused on long-term and chronic effects, with little research looking at the acute effects of purposeful heading. However, Schmitt et al. (2004) tested postural control and recorded subjects' self-reported symptoms immediately and at 24 hrs following a controlled session of intentional soccer ball heading. They found that prior to, immediately following, and at 24 hrs after the 40 min session of heading there were no differences in postural control as assessed by center of pressure (COP) area and velocity between the heading group and a control kicking group. In spite of not

finding any significant difference in postural control after an acute bout of heading, an increase in concussion related symptoms were found immediately following the heading session but not at 24 hours after the heading cohort. The main complaints were headache, dizziness, and feeling lethargic. This reported finding was similar to Tysvaer (1992) who found that ten minutes following a session of purposeful heading all subjects reported suffering from a headache. Consistent with these findings Mangus et al. (2004) also reported no differences in balance following an acute bout of soccer ball heading. Additionally, Broglio et al. (2004) found no significant acute changes in postural control following a study that looked at the effects that purposeful heading in soccer can have on balance.

Biomechanical studies report that the forces like momentum and energy transfer associated with heading the soccer ball are far less than those found in football, boxing, hockey and other full contact sports (Spiotta et al., 2012). Therefore, soccer might not be the ideal sport to assess the acute effects of subconcussive head trauma. In a study by Ravdin et al. (2003) investigating the effects of subconcussive blows, boxers were administered neuropsychological examinations before a fight, after the fight, and at a one month follow-up session. Their results were interesting and questioned the validity of a return-to-baseline as an appropriate criterion for return-to-play decisions. They noted that at one month post fight, neuropsychological performance had increased beyond baseline assessment taken prior to the fight and was believed to be caused by the repeated subconcussive blows the boxers received while training for the fight. Repetitive subconcussive head trauma has been hypothesized to be the main cause of neurocognitive dysfunction in boxers and that accumulation of subconcussive blows may lead to cognitive deterioration of brain function (Jordan et al., 1996).

Shuttleworth-Edwards and Radloff (2008) investigated the differences between rugby players and athletes involved in non-contact sports, and found that rugby players had a poorer performance on visuomotor processing speed. Additionally, they subdivided the rugby player up into two groups, based upon the frequency of the positions to be exposed to subconcussive head trauma. This within group analysis revealed that the group that regularly receives more subconcussive impacts displayed lower scores on the Digit Symbol Substitution visuomotor task. Interestingly enough it has been reported that despite a 5 times greater frequency of head injuries, rugby players out perform soccer players on neuropsychological testing (Rutherford, Stephens, Potter, & Fernie, 2005). Additionally, Parker et al. (2008) found that subjects exposed to repeated subconcussive blows in football, rugby, and lacrosse showed increased medial-lateral sway in their gaits. In a study by Killam et al. (2005) examining athletes with and without a history of concussion and athletes recovering from concussion to a control group without any history of head trauma concluded that subconcussive head trauma seen in contact sports produces subclinical cognitive impairments.

In a recent study by Miller et al. (2007), neuropsychological assessment of collegiate football players in the form of the Standardized Assessment of Concussion (SAC) and the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) were performed at three time intervals, preseason, midseason, and post season. No people under study received a clinically diagnosable concussion yet were exposed to numerous subconcussive blows throughout the season. There were no significant decreases on overall SAC and ImPACT scores reported, yet significant improvements in visual memory and reaction time were noted. Additionally, improvement in verbal memory and processing speed were close to reaching the limits of significance at a *p*-value of 0.06 and 0.05 respectively. Recently Talavage et al. (2010) reported changes in cerebral functions attributed to multiple subconcussive impacts as evidenced by

declines in the visual working memory in high school football players in the absence of clinical signs of concussion.

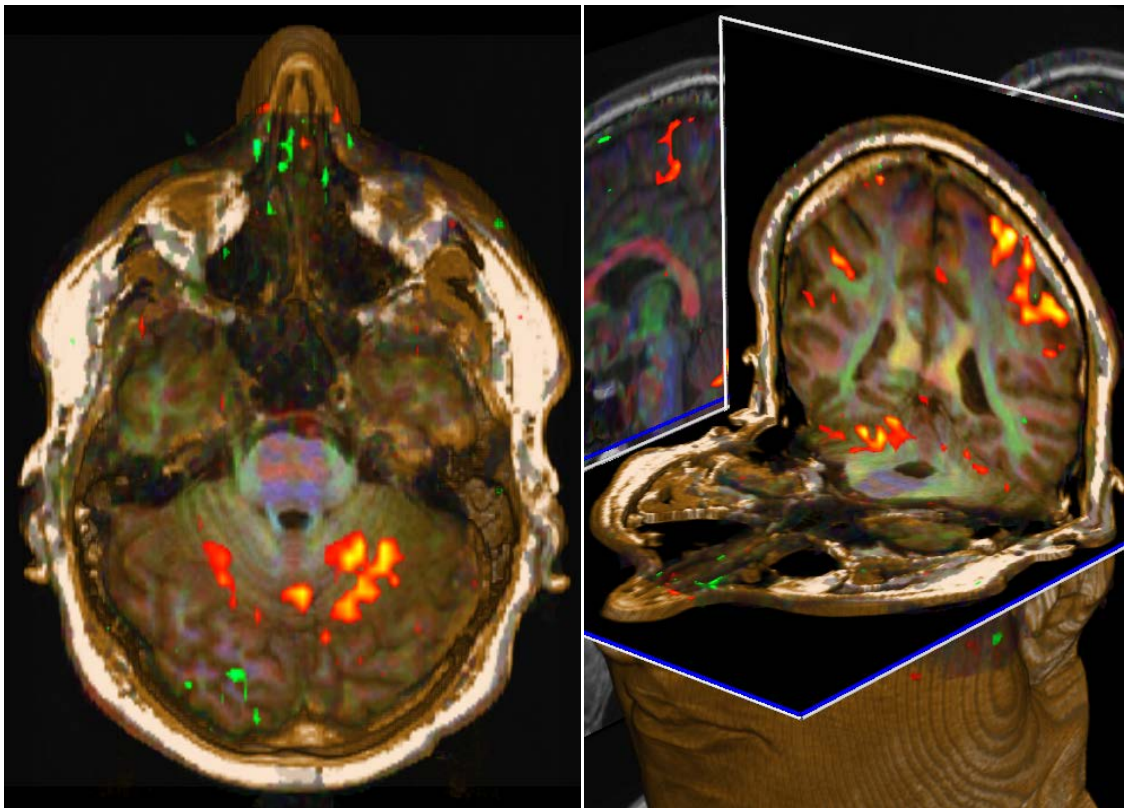
2.4 Neuroimaging of Sports Related Traumatic Brain Injury

Current clinical measures that include conventional neuroimaging techniques fail to be sensitive enough (Mayer et al., 2011) and lack specificity (Iverson et al., 2006) when assessing concussion. Few reports in the literature have found any gross structural differences in the brain following a concussive or subconcussive head trauma as evaluated by computed tomography (CT) and standard magnetic resonance imaging (MRI). CT and MRI for the most part are usually found to be normal following concussion, as it is more of a metabolic reaction to trauma then a structural injury (Lovell, Collins, & Bradley, 2004). Although, there use can be invaluable in ruling out more serious injuries like skull fracture and hemorrhages. However, one study that looked at boxers longitudinally saw evidence in 13% of the boxers of progressive brain injury, as well as several boxers presenting with cortical atrophy and cavum septum pellucidum (McCrory, 2011). Another CT study evaluating soccer players saw an increase in cerebral atrophy and ventriculomegaly in 27% and 18% of the professional soccer players respectively (Sortland & Tysvaer, 1989; Tysvaer et al., 1989). This shortcoming highlights the importance in using more sensitive and specific testing measures in concussion and subconcussive research such as advanced neuroimaging techniques. These newer advanced MRI techniques; like functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) may offer promise in providing some insight on the injured brain due to concussion and subconcussive head trauma (Dashnaw, Petraglia, & Bailes, 2012).

2.4.1 Functional Magnetic Resonance Imaging

As one of the more recent advances in neuroscience and neuroimaging, functional magnetic resonance imaging (fMRI) has grown in popularity and become a common research tool to explore the brain noninvasively (Logothetis, 2008). The principle of fMRI is based upon the differences between oxyhemoglobin and deoxyhemoglobin in the blood and is known as the blood-oxygen-level-dependent (BOLD) contrast. This contrast stems from the fact that deoxyhemoglobin produces a larger local magnetic susceptibility leading to a reduction in signal. The BOLD signal is used as an index of neuronal activity as areas of the brain that require more oxygen due to activation increase their demand for oxyhemoglobin which in turn leads to higher signal intensity and less signal dephasing caused by the local field inhomogeneities associated with deoxyhemoglobin (**Figure 2.4.1**) (Ogawa et al., 1993). The currently accepted notion is that BOLD fMRI most likely detects secondary effects of neuronal firing due to the *hemodynamic response*, allowing *indirect* assessment of the neuronal responses to cognitive and/or sensory-motor task demands (Jueptner & Weiller, 1995).

Figure 2.4.1 Examples of fMRI



Example of fMRI and BOLD contrast overlaid on anatomical MRI images, where warm colors represent activated areas of the brain.

Recent fMRI research has revealed alterations of the BOLD signal in concussed individuals while performing working memory, attention, sensory-motor, and other neurocognitive tasks. However, there is still controversy in the concussion literature regarding fMRI due to mixed experimental findings. For example, McAllister et al. (2001) have shown increased and more widespread BOLD signal response in concussed subjects successfully performing cognitive tasks. Similarly, Jantzen et al. (2010) showed increased BOLD activation specifically in the parietal lobe, lateral frontal lobe, and cerebellar areas in concussed subjects despite no differences in cognitive performances when compared to their pre-injury scans and neuropsychological tests. However, Chen et al. (2004) reported contradictory findings suggesting

a reduction of fMRI BOLD in the mid-dorsolateral prefrontal cortex in symptomatic concussed subjects. Whether these contradictory results are related to the performance differences between normal controls and concussed individuals, working memory and baseline task differences and/or different contrasts used in these studies is still an open question. With regards to concussion most of the fMRI literature has focused on working memory, as working memory deficits are seen in numerous neurological conditions. As stated earlier there have been conflicting results when it comes to an increase or decrease in the BOLD signal, but more studies report an increased BOLD signal in concussed individuals (Jantzen, 2010; McAllister et al., 2001; Slobounov et al., 2010). Consistent throughout the reports that found an increase in BOLD activation was the location with significant increases in the prefrontal and dorsolateral prefrontal cortices (McAllister et al., 2001; Slobounov et al., 2010). In addition to the lateral frontal regions, Jantzen et al. (2010) reported an increase in the BOLD signal in the parietal and cerebellar regions when assessing cognitive performance after concussion when compared to a previous baseline scan.

There have been several hypotheses to explain the functional differences in the form of increased neuronal activation observed via fMRI in concussed individuals when compared to their normal volunteer counterparts. Brain reorganization has been proposed as additional recruitment of the dorsolateral prefrontal cortex shows changes in functional networks and this reorganization is believed to be permanent (Audoin et al., 2003; Chang et al., 2004; Forn et al., 2006; Mainero, Pantano, Caramia, & Pozzilli, 2006; Sanchez-Carrion et al., 2008). Another theory for increased BOLD signal is known as neural compensation. Similar to brain organization, neural compensation is believed to be a transient alteration of brain resources to ensure proper task performance without permanent alterations in functional networks (Maruishi, Miyatani, Nakao, & Muranaka, 2007; McAllister et al., 2001; Scheibel et al., 2009; Turner & Levine, 2008). More recently Hillary et al. (2010) proposed the latent support hypothesis, which

infers that the prefrontal cortex is heavily activated as a support hub to compensate for suboptimal performance. The latent support hypothesis is modeled after the results seen in healthy normal volunteers during task load manipulations (Braver et al., 1997; Landau, Schumacher, Garavan, Druzgal, & D'Esposito, 2004; Rypma & D'Esposito, 1999).

With regrards to fMRI experiments into the effects of subconcussive repetitive head trauma the literature is very scarce. Furthermore, no studies have specifically used advanced neuroimaging to investigate the acute effects of subconcussive blows or whether or not there is a differential effect seen in subjects with a history of concussion. Talavage et al. (2010) took 11 high school football players and performed a fMRI visual working memory paradigm and baseline neuropsychological testing. They found that the number of collisions was significantly correlated to changes in the subject's fMRI activation. Specifically subjects that showed no clinical symptoms of concussion, yet showed poorer neuropsychological tests exhibited a significant reduction of fMRI activation in the dorsolateral prefrontal cortex, middle and superior frontal gyri, and cerebellum. In an extension of this study Breedlove et al. (2012) reported that despite not sustaing a concussion, a large portion of their cohort under study showed significant neuropsychological changes as assesed bt fMRI due to repetitive subconcussive head trauma. Additionally they found a significant relationship between the number of blows and the documented changes in the neuropsychological testing which reinforced their hypothesis that repetative subconcussive head truama may be connected to pathologically altered neurophysiology.

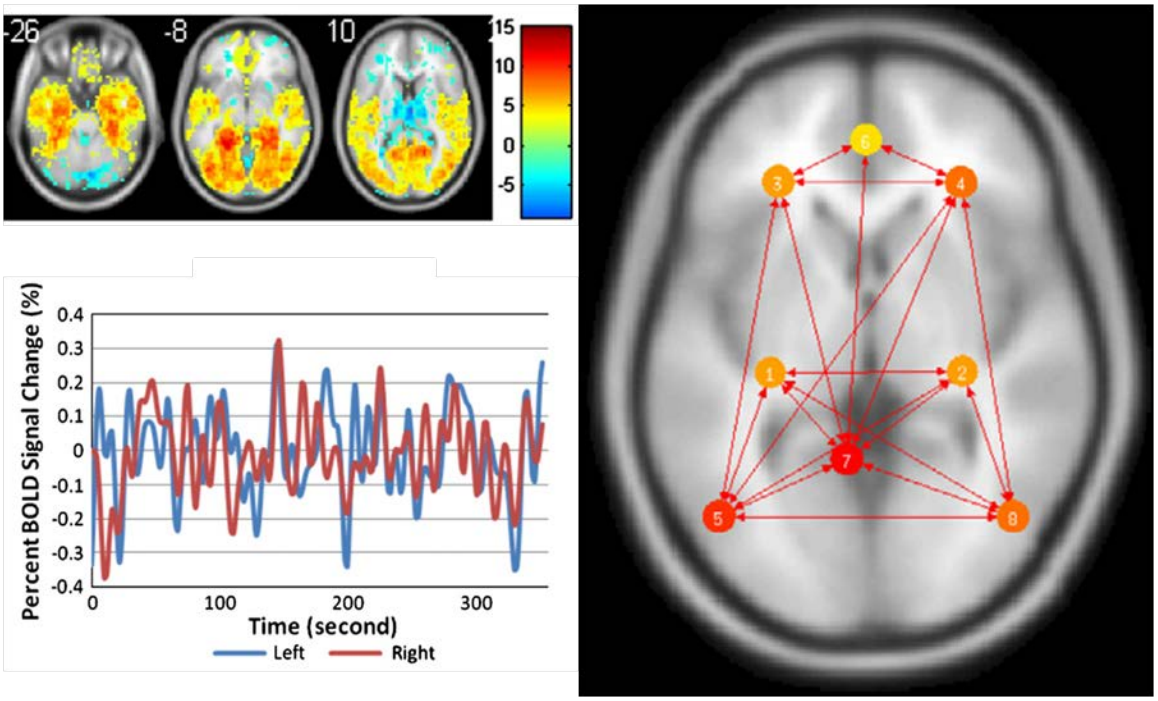
2.4.2 Resting-State Functional Connectivity and Default Mode Network

Recent work with fMRI based functional connectivity and diffusion tensor imaging (DTI) has shown promise in expanding our understanding of human functional networks (M. D. Greicius, Supekar, Menon, & Dougherty, 2008) and given evidence that structural and functional connectivity are closely related (Honey et al., 2009). Although functional connectivity may reflect structural connectivity, it is not a simple one-to-one mapping and cannot distinguish direct and indirect pathways (Greicius et al., 2008). There has been recent focus in studies using fMRI to approximate brain activation patterns by recording temporal oscillations in the BOLD signal. Biswal et al. (1995) were the first to document the spontaneous fluctuations within the motor system and highlight the potential of assessing functional connectivity. Since the discovery of coherent spontaneous fluctuations, many studies have shown that several brain regions engaged during various cognitive tasks also form coherent large-scale brain networks that can be identified using fMRI (Smith et al., 2009). These intrinsic activity correlations lead to the development of resting-state functional magnetic resonance imaging (rs-fMRI) (**Figure 2.4.2)** and offer promise for improving clinical applicability of examining spontaneous modulations in the BOLD signal that occur during resting state (Fox & Raichle, 2007).

Resting state refers to the state in which an individual is awake lying quietly with eyes closed (Raichle et al., 2001) and does not require a specific experimental task or stimulus (Wolf et al., 2011). In contrast to the traditional task-related approach, rs-fMRI has provided unique information about the resting-state networks of the brain. A major benefit that resting-state connectivity provides is the elimination of any bias based upon task performance. Examination of spontaneous activity provides a window into the neural processing that appears to consume the vast majority of the brain resources as there is only a 5% increase associated with task-related

changes compared to the high energy needs of the brain at rest (Raichle & Mintun, 2006). Functional abnormalities of the brain are associated with pathological changes in connectivity and network structures and have been documented in psychiatric populations, including ADHD, autism, depression, PTSD, and schizophrenia (Fox & Greicius, 2010). Specifically, fMRI findings indicated a predominant loss of long-distance functional connections in the resting state in patients suffering from Alzheimer's disease (AD) (Zhou et al., 2008; Rosenbaum et al., 2008).

Figure 2.4.2 Examples of rs-fMRI and Connectivity Analysis



Example of the BOLD activation and temporal BOLD signal change (Left), and representation of functional connectivity analysis showing connections between regions of interest (Right).

Moreover, alterations in resting-state functional connectivity patterns have been reported in TBI. Nakamura et al. (2009) examined neural network properties at separate time points during recovery from TBI and reported that the strength of network connections was reduced, but not the number of connections. Slobounov et al. (2011) using rs-fMRI reported reduced interhemispheric functional connectivity in “asymptomatic” mTBI subjects in the primary visual cortex, hippocampal and dorsolateral prefrontal cortex networks. Furthermore, Marquez de la

Plata (2011) also reported a deficit in the functional connectivity of the hippocampus and frontal lobe circuits six months after traumatic DAI (Marquez de la Plata, 2011).

The existence of a default mode network (DMN) in the brain was originally reported by Raichle et al. (Raichle et al., 2001), and is also known as a task-negative network (TNN). The DMN is comprised of the posterior cingulate cortex/precuneus (PCC), medial prefrontal cortex (MPFC), and medial, lateral, and inferior parietal cortex areas of the brain (Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Krasnow, Reiss, & Menon, 2003). The DMN is deactivated during attention or goal oriented tasks but is active at rest (Raichle et al., 2001). Greicius et al. (2003) was the first to observe the DMN during resting-state fMRI (rs-fMRI) and since then the presence of the DMN has been repeated and validated using rs-fMRI (Beckmann, DeLuca, Devlin, & Smith, 2005; Damoiseaux et al., 2006; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; Greicius, 2002). The DMN is identified in the BOLD signal as low frequency (less than 0.1 Hz) coherent oscillations (Greicius et al., 2003). Along with the advances in neuroimaging and data analysis techniques the DMN has become a focus in the neuroscience and psychological community (Smith et al., 2009) .

Few studies to date (Marquez de la Plata, 2011; Mayer et al., 2011; Slobounov et al., 2011; Sponheim et al., 2011) have investigated the DMN in mTBI. Previous functional connectivity research using fMRI demonstrated altered patterns of the DMN in Alzheimer's disease (AD) (M. D. Greicius, 2004), schizophrenia (Pomarol-Clotet et al., 2008), depression (Greicius et al., 2007), and attention-deficit hyperactivity disorder (ADHD) (Castellanos et al., 2008). A recent study by Mayer et al. (2011) investigated the resting state DMN of subacute mTBI and showed that these subjects displayed decreased BOLD connectivity within the DMN and hyper-connectivity between the right prefrontal and posterior parietal cortices involved in the

fronto-parietal task-related network (TRN). Our recent resting state DMN work revealed that in concussed individuals the resting state DMN showed a reduced number of connections and strength of connections in the posterior cingulate and lateral parietal cortices. An increased number of connections and strength of connections was seen in the medial prefrontal cortex. Connections between the left dorso-lateral prefrontal cortex and left lateral parietal cortex showed a significant reduction in magnitude as the number of concussions increased. Regression analysis also indicated an overall loss of connectivity as the number of mTBI episodes increased (Johnson, Zhang, Gay, Horovitz, et al., 2012). Furthermore, in an extension of that study we found that the functional integrity within the DMN, a main resting-state network remained resilient to a single concussive blow (Zhang et al., 2012). These reports clearly indicate that functional brain alterations in concussion are present and may be overlooked when less sensitive clinical and neuropsychological examinations are used.

2.4.3 Magnetic Resonance Spectroscopy

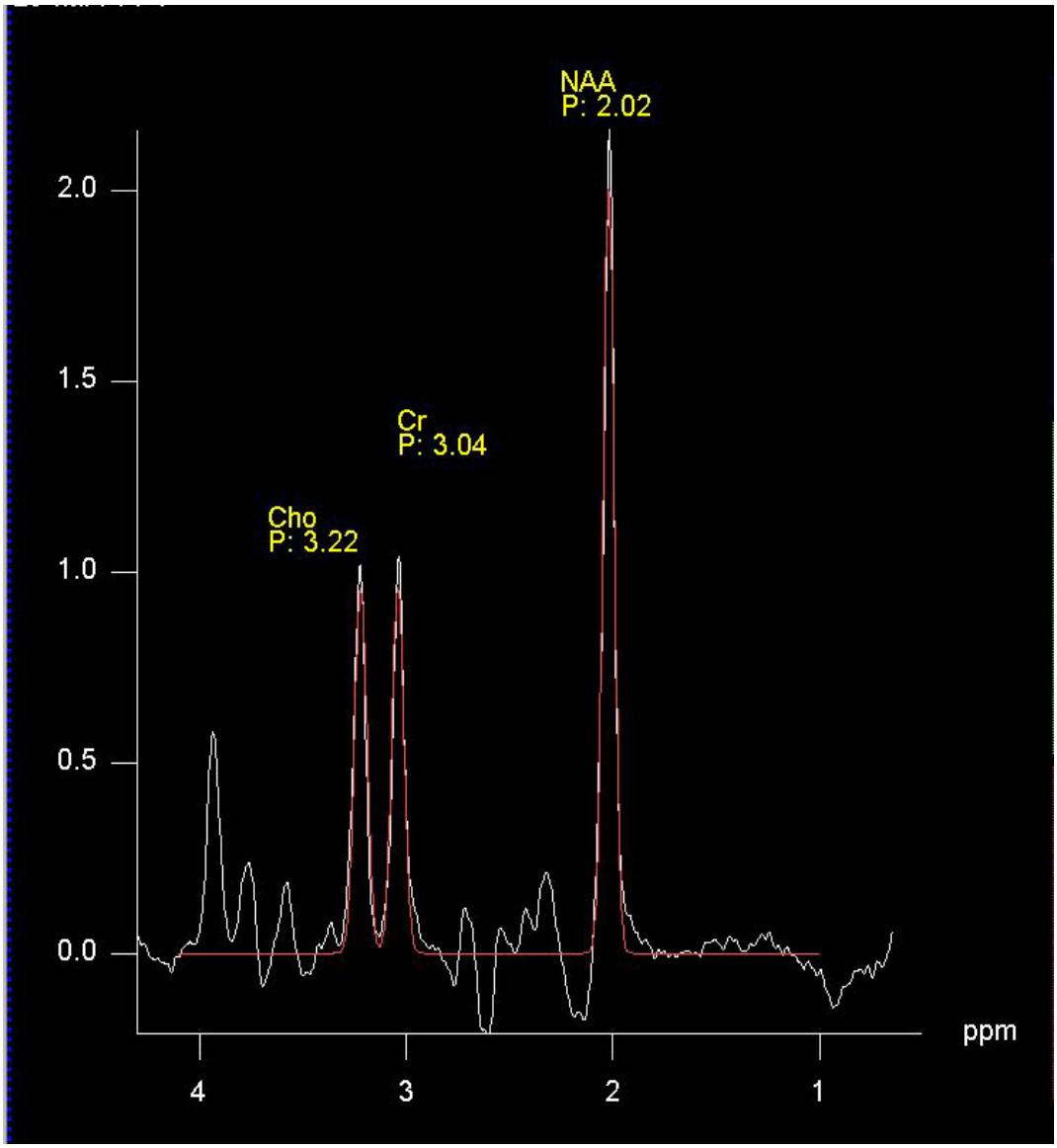
Magnetic resonance spectroscopy (MRS) is a useful and powerful technique that has the ability to probe and examine brain metabolism. MRS allows for identification and quantification of cellular metabolites *in-vivo* (Shekdar & Wang, 2011) and results not in a normal MRI image, but as a spectrum (**Figure 2.4.3**) where peaks are representative of the concentrations of certain chemicals and metabolites at their resonant frequencies (Lin et al., 2012). MRS has been used as a noninvasive tool to help gain better understanding of pathological conditions associated with neurological and psychological disorders (Ross & Sachdev, 2004). Just like other advance MRI acquisition techniques, MRS is suitable for follow-up and longitudinal neurological assessment. Due to its sensitivity to brain metabolism and ability to quantify changes in concentrations of

metabolites, MRS has promise at evaluating the brain following a concussion due to the neurometabolic nature of the injury (Marino, Ciurleo, Bramanti, Federico, & Stefano, 2010).

There are several key metabolites in highest enough concentrations that MRS is sensitive to and to which changes in allow for inferences on the state of the brain to be made. These metabolites include: N-acetylaspartate (NAA), choline (Cho), creatine-phosphocreatine (Cr), lactate (lac), and glutamate and glutamine (Glx) (Belanger, Vanderploeg, Curtiss, & Warden, 2007; Cecil et al., 1998; Govind et al., 2010). Increases or decreases in these metabolites are indicative of certain cellular processes. NAA is an amino acid derivative that is synthesized in the neuron then moved along the axon via anterograde transport (Lin et al., 2012). It is used as an indicator of neuronal and axonal integrity as decreased levels are seen after injury and associated with neuronal loss, metabolic dysfunction, or myelin repair (Gasparovic et al., 2009). Cho is a marker of cell membrane turnover and increases are thought to indicate DAI (Shekdar & Wang, 2011). Decreases in NAA and increases in Cho are the primary and secondary MRS findings associated with brain injury (Ross et al., 1998). The Cr peak, which is a combination of the two creatine-containing compounds (creatine and creatine phosphate), is an accepted indicator of cell energy metabolism (Signoretti et al., 2009), and is used as an internal reference to other metabolites when reporting ratios instead of individual total concentrations. Lac is the end product following anaerobic glycolysis, and an increase in Lac reflects a deficiency in cerebral perfusion seen with hypoxic events (Lin et al., 2012). Glx which is a combination of the excitatory neurotransmitter glutamate and glutamine which are released into the extracellular space following TBI and add to excitotoxicity and neuronal death (Marino et al., 2010). Although MRS is able to detect metabolite changes due to hypoxia, energy dysfunction, neuronal injury, membrane turnover, and inflammation (Marino et al., 2010) it can be an insensitive

method as these metabolites and neurochemicals have to have a sufficient concentration in order to be detected (Ross & Sachdev, 2004).

Figure 2.4.3 Examples of MRS Spectrum



Example of MRS spectrum with NAA peak at 2.02 ppm, Cho at 3.22 ppm, and Cr at 3.04 ppm.

Alterations of metabolite concentrations and metabolic ratios within all lobes of the brain, as well as in the white and gray matter of the brain have been documented following a concussion (Belanger et al., 2007; Govind et al., 2010; Henry et al., 2011). In the literature the acute phase of

injury has revealed the most consistent findings with the majority of the research revealing an initial decrease in NAA (Henry et al., 2011; Vagnozzi et al., 2008). A review of metabolic alterations following mTBI by Lin et al. (2012) also reports that in addition to decreases in NAA, that decreases and increase in Glx within the gray matter and white matter respectively are regularly reported. Govindaraju et al. (2004) showed that there are widespread metabolic disruptions throughout the brain in the subacute phase of mTBI. Specifically NAA/Cho and NAA/Cr ratios were reduced globally. Similarly Cohen et al. (2007) showed that whole brain NAA levels were significantly reduced in mTBI as well as in both the white and gray matter (Belanger et al., 2007; Govind et al., 2010; Henry et al., 2011). Two recent studies of collegiate athletes looked at the genus and splenium of the corpus callosum in the subacute phase of injury as well as any changes therein due to a history of multiple concussions (Johnson, Gay, et al., 2012; Johnson, Zhang, Gay, Neuberger, et al., 2012). Both papers reported that NAA/Cho and NAA/Cr ratios are significantly reduced, yet when the number of previous concussions is taken into account those individuals suffering from an initial concussion show a larger decrease in these ratios when compared to individuals with multiple diagnosed concussions. A 2008 study by Walz et al. (2008) used MRS to look at children ages 3-11 that received a TBI whether it be a mild to severe case. In this study, 3 of the children were classified as having mild TBI but no direct mention or separation of these 3 individuals was done. Overall they found a trend that NAA levels in the medial frontal gray matter were lower and that Glasgow Coma Scale score was significantly correlated in this area to NAA and Cr levels. This MRS research in the acute and subacute phase has shown concussion opens a window of brain metabolite imbalance that is not restored to premorbid levels in subjects recovering from concussion, even though they are clinically “asymptomatic” (Henry et al., 2011; Vagnozzi et al., 2008). However, Maugans et al., (2012) used MRS in assessing children at 3, 14, and 30 days post injury and found no significant differences in the mean NAA and NAA/Cr in the frontal gray matter, left frontal white matter,

and left thalamus between injured and age matched controls, suggesting differential recovery or effects of mTBI in the pediatric population.

Chronic MRS studies have shown that white matter concentrations of NAA are reduced, suggesting that mTBI has long-term and detrimental effects on neuronal and axonal health (Lin et al., 2012). Henry et al. (2010) noted decreases in NAA and Glx in the primary motor cortex in athletes and a reduction of NAA within the prefrontal cortex. Additionally, these chronic studies report increases in Cho levels and decreases in NAA/Cho ratios, consistent with decreases in NAA and increases in Cho (Lin et al., 2012). Vagnozzi et al. have found complimentary results, and in longitudinal studies they have reported an initial reduction in NAA that stabilizes back to normal within 30 days (Vagnozzi, 2008; Vagnozzi et al., 2010). Moreover, they were also able to perform MRS evaluation on three athletes who received a second concussive blow within 15 days of each other. They observed that compared to those exposed to just one concussive event, those doubly concussed athletes had restoration of baseline levels at 45 days following the initial concussion. It is of special interest to note that the slowest rate of recovery was within the first 15 days. Recent studies by Gasporovic et al. (2009) and Yeo et al. (2011) have shown that Cr may not be as stable as once thought and reported elevated levels within the white matter. A MRS pilot study of retired professional athletes with a known exposure to concussions and subconcussive head trauma revealed a significant increase in Cho and Glx concentrations (Lin et al. 2010). In a recent review of the literature on heading in soccer Spiotta et al. (2012) reports that to date there have not been any reports of neurochemical evidence for brain damage due to an acute bout of repeated heading and no research to date in the literature that looks at the acute metabolic effects of repetitive subconcussive blows assessed by MRS.

Chapter 3

Methodology

3.1 Subjects

A total of 24 subjects were recruited for this study (8 males, 16 females, average age of 20.4 years old), please see **Table 3.1** for detailed information on individual demographics. The 24 subjects were split into three groups based upon their history of head trauma, participation in collision or contact sports, and active lifestyle. One group (no mTBI) had no prior history of concussion but currently participate in contact/collision sports. The second group (mTBI) also actively participated in contact/collision sports and has been diagnosed with at least one concussion. The third group (sedentary) was comprised of individuals who have never participated in contact/collision sports and who have not participated in organized sports or exercise regularly. Specifically, 16 individuals from the Penn State men's and women's rugby team made up the no mTBI and mTBI groups. The sedentary group was age-matched and also comprised of Penn State students. Please refer to **Table 3.2** for a breakdown of group demographic information.

Table 3.1. Individual Demographic Information

	Group	Sex	Age	# mTBI
1	No mTBI	M	22	0
2	No mTBI	F	18	0
3	No mTBI	F	19	0
4	No mTBI	M	19	0
5	No mTBI	F	21	0
6	No mTBI	M	20	0
7	No mTBI	F	21	0
8	No mTBI	F	19	0
9	mTBI	F	21	1
10	mTBI	M	19	2
11	mTBI	F	20	1
12	mTBI	M	19	2
13	mTBI	F	21	1
14	mTBI	M	20	2
15	mTBI	M	22	2
16	mTBI	M	23	2
17	Sedentary	F	20	0
18	Sedentary	F	22	0
19	Sedentary	F	19	0
20	Sedentary	F	21	0
21	Sedentary	F	21	0
22	Sedentary	F	21	0
23	Sedentary	F	22	0
24	Sedentary	F	22	0

Individual demographic information

Table 3.2. Group Demographic Information

Group	Subdivision	n =	Males	Females	Avg Age	Avg #mTBI
Subconcussive		16	8	8	20.2	0.8
	no mTBI	8	3	5	19.9	0
	mTBI	8	4	4	20.4	1.6
No Subconcussive						
	Sedentary	8	0	8	20.8	0

Demographic information for each of the three groups, with those individuals experiencing subconcussive head trauma split into two groups based on history of concussion (mTBI), or no previous history of concussion (no mTBI).

Rugby players were targeted as rugby is a collision sport and players do not wear a lot of protective equipment (Marshall & Spencer, 2001). Furthermore, as is the nature of the sport, rugby players are exposed to numerous violent collisions and physical confrontations throughout the course of a game and are largely unshielded from these forces. The tackle is a prominent part of the game and can lead to many dangerous situations that can cause whiplash or head to head contact. Concussion is a major concern in rugby and Stephensen et al. (1996) reported that injury rates in rugby are higher than in other contact sports and the head and the neck the highest number of injuries. There is high risk for repeated concussions in rugby as well as exposure to numerous subconcussive impacts, which are similar to concussion but are associated with smaller mechanical forces and do not elicit clinical signs or symptoms of concussion (Shuttleworth-Edwards & Radloff, 2008).

Initially quantification of subconcussive impacts was planned to be done, yet a number of hurdles made it an unrealistic goal. The full contact nature of rugby is apparent to anyone who has watched a match and there is a high incidence of collisions/impacts per game with one study reporting this number to be upwards of 40 if not more (Marshall & Spencer, 2001). The rugby matches were recorded, but due to limited resources and access to high speed cameras positioned in different angles, the standard one position video camera failed to be adequate enough to accurately quantify the number of subconcussive impacts. Compounding the difficulty to quantify the number of subconcussive impacts in rugby are certain prominent elements of the game including the tackle and scrum (Marshall & Spencer, 2001). These events often results in a massive pileup of players and jeopardizes the accuracy of quantifying the number of subconcussive hits as players under the pile can experience anything from kicks, elbows, or any other type of blow to the head not visible to the outsider. Furthermore, biomechanical studies have went to great lengths to quantify and identify a threshold for concussive hits to no avail

(Duma & Rowson, 2011), as this is difficult because each concussion is different (Cantu, 2007). However, we did perform a single observer study of a rugby match in order to try and see if the number of impacts was similar to what was reported in the literature. Specifically we had three rugby players familiar with both the game and their teammates focus on one different player each. They used specialized observational charts to tally the number of impacts each player under observation received during a match. Results from the single observers put the number of impacts at between 30 and 45. This is in agreement with what was reported by Marshall and Spencer (2001), and most impacts were categorized as torso to torso collisions.

3.2 Overall Design

Both groups, mTBI and no mTBI, underwent identical initial testing sessions. These sessions included acquisition of rs-fMRI and MRS via the 3T Siemens whole body MRI scanner. In addition to brain imaging, virtual reality (VR) assessment was also performed at that time. Only the Subconcussive group went through a follow-up testing session, with the same brain imaging and VR protocol. These two testing sessions were scheduled 24 hrs prior to a scheduled full contact game and a follow-up session was performed within 24 hrs after the end of that game. The mTBI and no mTBI groups' participants had their initial and follow-up scans scheduled and performed at the same time of the day to reduce any effects that may have been caused by circadian rhythms. No participants reported concussive symptoms at the either time of testing and additionally no players were diagnosed with a concussion on the field by certified athletic trainers as a part of the routine protocol of the Sport Concussion Program at the Pennsylvania State University.

3.3 Virtual Reality Assessment

3.3.1 Rationale

To quantify the subtle alterations in cerebral functions following repeated subconcussive blows experienced in a game, a portable Virtual Reality (VR) System with three different testing modules was used. VR is an interactive, computer generated 3D environment that simulates the real world and provokes a sensation of immersion in the subjects. Continuing advances in VR technologies along with cost reductions have stimulated both research and development of VR systems aimed at psychological, physical/behavioral and emotional assessment/rehabilitation of brain injured individuals. VR has the potential to overcome some of the shortcomings of conventional neuropsychological tests that are not designed for repeated measures and also lack sensitivity in certain key areas of concussion assessment (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010). In fact, the Zurich Consensus Statement on concussion in sport (McCrory et al., 2009) identified VR among the key areas of future research and possible clinical application.

The three distinct modules are aimed at assessing the most common cerebral dysfunctions seen in concussion, including working memory, balance, and speed of information processing (Notebaert & Guskiewicz, 2005). There is consent among clinical practitioners dealing with sports-related concussions that neurocognitive, motor and executive functions are the most prominent deficits that concussed athletes experience at least within the acute phase of injury (Eckner, Kutcher, & Richardson, 2011). In agreement the Zurich Consensus Statement (2009) recommend that working memory, attention/vigilance, visual learning and memory, reasoning/problem solving and speed of information processing are the most important

neurocognitive functions that need to be accurately assessed to define the degree of brain damage induced by a concussive blow.

3.3.2 Procedures and Data Acquisition

All three testing modules paradigms were created by the Penn State Center for Concussion Research and Service and software implementation was provided by HeadRehab, (HeadRehab, LLC, USA, www.HeadRehab.com) and generated by a VTC Open GL developing kit. The three dimension VR environment was presented via a head mounted display (Rockwell-Collins, USA, www.rockwellcollins.com) capable of providing high resolution three dimension stereo display to the participant. All modules created by HeadRehab, LLC automatically generated score reports for each module in addition to a comprehensive score that accounted for all three modules. Scores were on a scale from 0 to 10, with 10 being the maximum score and indicative of better performance.

The assessment of spatial working memory which includes the underlying constructs for encoding, retention, and retrieval was implemented via a three dimensional presentation of a virtual corridor. The paradigm consisted of the subject being shown a specific navigation route in a virtual corridor to remember and encode, and then asked to replicate the path correctly from start to finish (retrieval). The subjects navigated around using their right thumb to freely move forward, backward, and side-to-side directions. They were also given a practice session before the start of the test to get comfortable and familiar with the controls and setup. Performance of the spatial navigation task was scored combining three variables that included: if the participant correctly found the desired end point by using the path shown to them, the number of attempts need to successfully complete the task (note a maximum of three attempts was allowed), and

finally the time needed to successfully navigate the desired route from start to finish (note a maximum of 30s were allowed for each attempt).

The second VR task module was used to assess balance, as balance abnormalities are the most common symptom following sports-related mTBI, and can be exacerbated by employing a visual-kinesthetic task (Guskiewicz, 2001). The same head mounted display used in the spatial navigation task was used in the balance task to present a moving room perturbation. Preprogrammed manipulations of the VR moving room included the following: (1) viewing stationary VR room; (2) VR room forward-backward oscillatory translation within 18 cm displacement at .2 Hz; (3) VR room "Roll" around heading *y*-axis between 10-30 degrees at .2 Hz; (4) VR room "Pitch" around *x*-axis between 10-30 degrees at .2 Hz; (5) VR room "Yaw" around vertical *z*-axis between 10-30 degrees at .2Hz; (6) VR room translation along x-axis within 18 cm displacement at .2 Hz. The subjects were instructed: a) to acquire the Romberg stance and stand as still as possible on the force platform while viewing the computer generated "moving room" visual scenes for 30 s trial duration. The area of the center of pressure (COP) was calculated from accelerometer attached to the head mounted display was computed by the HeadRehab LLC, software and used to produce a score ranging from 0, loss of balance, to 10.

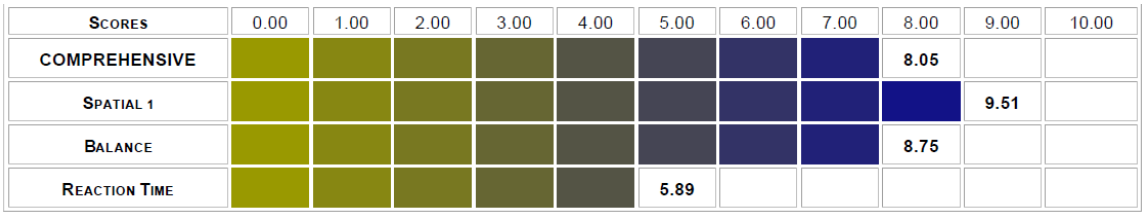
The third VR module for reaction time used was developed by HeadRehab, LLC and allows for assessment of reaction time of the whole body response to unpredictable manipulation of optic flow. The subject was requested to oscillate forward and backward to follow the anterior-posterior (A-P) translation of the "moving room" at .2 Hz for 30s trial duration. Unpredictable change of moving room from A-P to medial-lateral (M-L) directions was randomized requiring the subject to respond via whole body motion and follow the motion of the "moving room". The measured reaction time (with the best time being set at a minimum of 200 ms) and errors of anticipation (wrong direction of response) was calculated, interpolated and

converted into scoring system from 10 (best score, 200 ms) to 0 (more than 800 ms) and included in the comprehensive reports.

3.3.3 Data Analysis

Scores for each module were automatically computed and exported for each module by the HeadRehab, LLC software, with scores ranging from 0 to 10 (**Figure 3.3.1**). The maximum score is 10 and poorer performance was indicated by lower scores. Minitab 16 Statistical Software was used to perform statistical analysis. A factorial multivariate analysis of variance (MANOVA) was performed on comprehensive, balance, working spatial memory, and reaction time modules between the groups and testing sessions. Significant values were set at a *p*-value < 0.05.

Figure 3.3.1 Example of Exported Results for VR Module



Comprehensive score report generated by HeadRehab, LLC module.

3.5 Magnetic Resonance Spectroscopy

3.4.1 Rationale

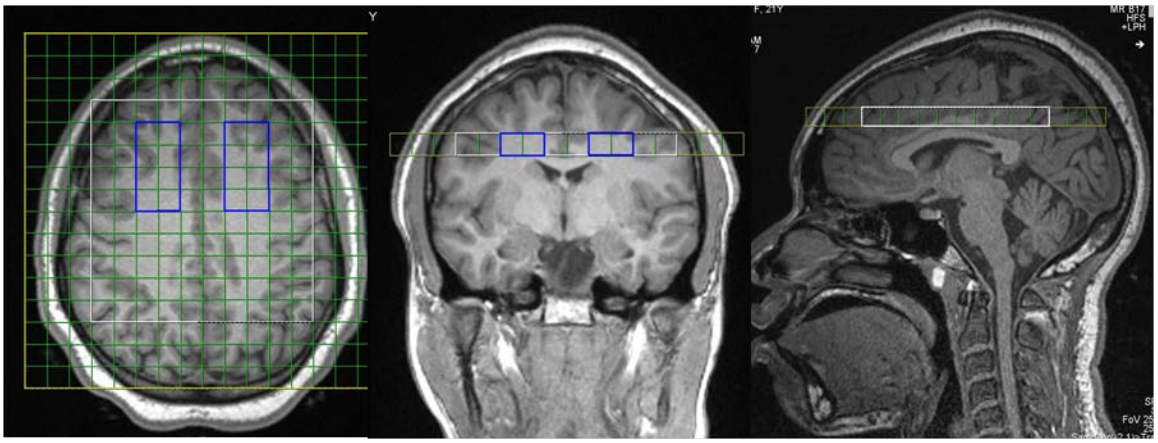
MRS is a useful tool that allows for identification and quantification of cellular metabolites *in-vivo* (Shekdar & Wang, 2011). The metabolites in the brain that are most often

studied are N-acetylaspartate (NAA), choline (Cho), and creatine-phosphocreatine (Cr) (Belanger et al., 2007; Cecil et al., 1998; Govind et al., 2010). As these metabolites are used as indicators of neuronal and axonal integrity (Gasparovic et al., 2009) , cell membrane turnover (Shekdar & Wang, 2011), and cell energy metabolism (Signoretti et al., 2009). As mTBI is seen more as a neurometabolic injury compared to strictly a structural injury and to date there have been no acute evaluations of the effects of acute subconcussive head trauma MRS evaluation was implemented. Specifically, we focused on the frontal lobe of the brain as it the most common site of injury following a moving head impact (Cantu, 1997).

3.4.2 Procedures and Data Acquisition

Two-dimensional multivoxel Chemical Shift Imaging (CSI) MRS was acquired in the axial plane just above the corpus callosum to avoid the lateral ventricles and the partial volume effect from CSF (**Figure 3.4.1**) with parameters optimized for evaluation of *in-vivo* NAA, Cho, and Cr metabolites (100 x 100 x 100mm Field of View, 10.0mm x 10.0mm x 10mm voxel size, TR=1510 ms, TE=135ms, iPAT= none, NSA= 3, acquisition time = 6:53). Siemens auto-align software was implemented in the placement of the CSI slice. The auto-align software is a FDA cleared alignment algorithm that allows for accurate and repeatable slice placement on the same subject over different scans. Placement of the voxels in single voxel spectroscopy or the slice in CSI in the same position for the same subject over repeated scans is important and one of the causes for error and lack of longitudinal MRS studies.

Figure 3.4.1 CSI Slice Selection and ROI

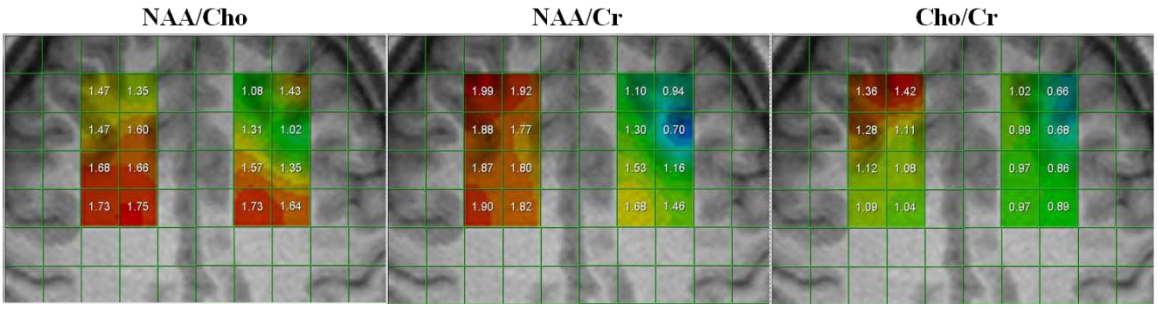


Placement of CSI slice for MRS acquisition, blue outline represents ROI selected for analysis.

3.4.3 Data Analysis

The MRS CSI data were processed off-line using standard scanner software (spectroscopy Card, Siemens) and included zero filling, eddy current correction, water suppression, Fourier transform, baseline and phase correction post processing steps. Spectra and metabolite maps (with peaks for NAA= 2.02 ppm, Cho at 3.22 ppm, and Cr at 3.04 ppm) were automatically calculated for each voxel within the CSI slice (**Figure 3.4.2**). Within the CSI slice two ROIs were selected, one ROI from each hemisphere. Each ROI consisted of six voxels that were individually selected to be within the frontal lobe based upon anatomical T1 images overlaid with the corresponding acquired CSI slice (**Figure 3.4.1**). Spectra from each ROI was added together and overall NAA/Cho, NAA/Cr, and Cho/Cr ratios were computed for each ROI (Nakabayashi, 2007; Vagnozzi et al., 2010).

Figure 3.4.2 Metabolite Maps



Example of metabolite maps generated by Siemens Spectroscopy card.

Minitab 16 Statistical Software was used to perform statistical analysis. In order to test the multiple dependent variables and potential correlations, factorial MANOVA was performed on NAA/Cho, NAA/Cr, and Cho/Cr ratios between the groups and scans. Again significant values were set at a p-value < 0.05.

3.5 Resting-State Default Mode Network

3.5.1 Rationale

Recent fMRI reports have indicated alterations of resting state functional connectivity in neurological populations, including mTBI, and have brought new insight into better understanding the pathophysiology of these disorders. Functional abnormalities of the brain are found to be associated with the pathological changes in the connectivity of the structures that make up the default mode network (DMN) (Raichle et al., 2001). The examination of spontaneous BOLD oscillations reflects the enduring and intrinsic properties of the brain (Greicius et al., 2008) and allows us to obtain a characterization of possible brain dysfunction as a result of multiple subconcussive blows. By eliminating the task associated with fMRI, rs-fMRI

eliminates bias based upon performance which is important in certain psychiatric and neurologic conditions (Wolf et al., 2011).

3.5.2 Procedures and Data Acquisition

While in the MRI scanner subjects were asked to lay quietly with their eyes open and not fall asleep during collection of the rs-fMRI sequence. The two-dimensional BOLD echo planar rs-fMRI sequence were acquired in the axial plane parallel to the anterior and posterior commissure axis covering the entire brain (3.0 x 3.0 x 3.0mm resolution, TR=2490ms, TE=24ms, iPAT=None, EPI factor=74, Echo spacing=0.48ms, NSA=1, acquisition time=5:04). Three-dimensional isotropic T1 weighted magnetization prepared rapid gradient echo (MP-RAGE) anatomical images were acquired in the sagittal plane parallel with the longitudinal fissure covering the entire brain (1mm x 1mm x 1mm resolution, TE= 3.46ms, TR= 2300ms, TI= 900ms, flip angle= 9°, 160 slices, iPAT= none, NSA= 1).

3.5.3 Data Analysis

For data analysis Statistical Parametric Mapping (SPM) version 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), in addition to Functional Connectivity (CONN) toolbox (http://web.mit.edu/swg/software.htm), software was used. Images were first preprocessed which included realignment, co-registration, segmentation, normalization and band filtering. During preprocessing, images were motion-corrected, registered with structural images, and normalized to the standard brain template from the Montreal Neurological Institute (MNI). White matter, cerebrospinal fluid (CSF), and physiological noise source reduction were taken as confounds, following the implemented CompCor strategy (Behzadi, Restom, Liau, & Liu, 2007).

Whole brain BOLD signal was excluded as a regressor to eliminate erroneous anti-correlations (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). The CONN toolbox performs seed-based correlation analysis based on the temporal low-frequency fluctuations of BOLD signals. Region of interest (ROI) evaluations include those structures identified by Raichle et al. (2001) to make up the DMN. Specifically, four ROIs were evaluated including: right lateral parietal (RLP), Precuneus (PCC), medial pre-frontal cortex (MPFC), and left lateral parietal (LLP). Bi-variate correlations were then calculated between each pair of ROIs as reflections of connections. Fisher transformed Z-scores are introduced to validate multiple comparisons and SPM functions are called by the CONN toolbox for spatial statistical tests. ROI based analysis was then performed for all subjects' data with a general linear model (GLM) test to determine significant resting state DMN connections. An unpaired t-test with a threshold set at p-value <0.05 was used to determine significant DMN connections.

Chapter 4

Results

4.1 Virtual Reality Assessment

All subjects under study reported no signs or symptoms of concussion at the time of pre-game testing. Likewise, all subjects again reported no signs or symptoms of concussion when reporting for post-game evaluation, and were not diagnosed or held for observation during or after the game by medical professionals as part of the routine protocol of the Sport Concussion Program at the Pennsylvania State University.

Pre-game VR assessment revealed consistent findings. The no mTBI group performed the best and scored highest in all three VR modules as well as in the comprehensive score report which is computed from all three of the modules. In a similar fashion the sedentary group performed second best in three out of the four score reports, only falling lower than the mTBI group in the working spatial memory module. As predicted the mTBI group scores were at the bottom in a majority of all modules including on the comprehensive score report.

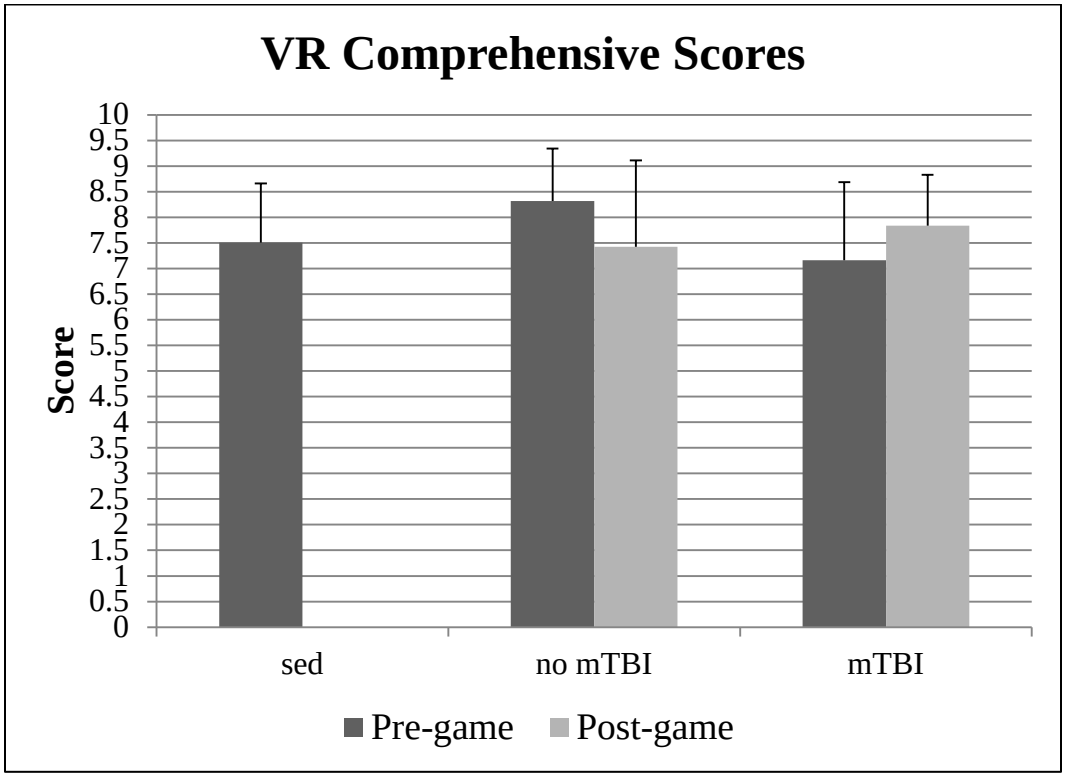
Specifically the comprehensive report (**Figure 4.1.1**) average group scores are as followed; the sedentary group scored 7.5 out of 10, the no mTBI group scored 8.32 out of 10, and the mTBI group score was the lowest at 7.16 out of 10. Group averages and standard deviations for each of the modules can be found in **Table 4.1.1**. Averages of the raw data used to compute scores for each VR module is presented in **Table 4.1.2**. Despite the mTBI group routinely performing the worst, there were no statistically significant differences between groups when it

came to the comprehensive score. Although the pre-game difference between the no mTBI group and mTBI group was approaching significance at p=0.09. Scores for the balance module (**Figure 4.1.2**) resulted in 9.11 out of 10 for the sedentary group, 9.4 out of 10 for the no mTBI group, and 7.77 out of 10 for the mTBI group. Again statistical analysis revealed no significant differences between groups, with the difference between the no mTBI group and mTBI group getting the closest to a significant value p=0.13. In the reaction time module (**Figure 4.1.3**), the mTBI group showed the poorest performance with a score of 4.28 out of 10, and scores for the no mTBI and sedentary group were 6.11 and 6.01 out of 10 respectively. No significance was found between groups. The working spatial memory module (**Figure 4.1.4**) revealed scores for the no mTBI group, mTBI group, and sedentary group of 9.43, 9.41, and 7.34 out of a possible 10. No statistical significance was revealed between groups.

As was evident in the pre-game testing session, the mTBI group performed the worse overall. However, this was not the case in the post-game testing session, as roles were reversed and the mTBI group out performed both the no mTBI group and sedentary group in the comprehensive, working spatial memory, and balance portions of the VR assessment (**Table 4.1.1**). Comprehensive scores for the mTBI, no mTBI, and sedentary group were 7.83, 7.43, and 7.5 out of 10 respectively. Balance scores were rather close with 9.18 out of 10 for the mTBI group, followed by the no mTBI group with 9.15 out of 10 and the sedentary group average of 9.11 out of 10. Reaction time module revealed scores of 5.33 out of 10 for the mTBI group, 5.69 out of 10 for the no mTBI group, and 6.01 out of 10 for the sedentary group. The last module to report on is the working spatial memory test, with scores of 8.98, 7.44, and 7.38 out of 10 corresponding to the mTBI, no mTBI, and sedentary groups. Similar to the pre-game testing session, no statistically significant differences were seen between groups for any of the four score reports.

Investigation into any changes between the pre-game and post-game testing sessions did not reveal any significant changes. However, it is important to note that although no within group differences were seen, a trend for the mTBI group to perform better on the post-game testing session was observed coupled with a tendency for the no mTBI group to perform worse on their post-game session (**Figures 4.1.5**). This trend was consistent in the score reports for comprehensive, balance, and reaction time. Of the three modules, working spatial memory did not show this paradoxical tend, and both the mTBI and no mTBI group scores decreased pre-game to post-game. None the less the mTBI group showed less of a drop in performance compared to the no mTBI group.

Figure 4.1.1 VR Comprehensive Scores



Graph of scores for the comprehensive VR module for both pre-game and post-game sessions, error bars represent standard deviation. Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

Table 4.1.1 Average Group Scores and Standard Deviations

	Pre-game		**Post-game**	
	Comprehensive	std dev	**Comprehensive**	std dev
sed	7.504	1.154	-------	-------
no mTBI	8.316	1.026	7.426	1.682
mTBI	7.164	1.521	7.834	0.993
	Spatial		**Spatial**	
sed	7.383	3.361	-------	-------
no mTBI	9.43	0.156	7.436	3.394
mTBI	9.407	0.227	8.984	1.138
	Balance		**Balance**	
sed	**9.114**	0.947	-------	-------
no mTBI	9.401	0.263	9.1525	0.9714
mTBI	7.774	2.291	9.1825	0.583
	Reaction Time		**Reaction Time**	
sed	6.013	2.019	-------	-------
no mTBI	6.11	2.918	5.691	3.053
mTBI	4.277	2.029	5.333	2.583

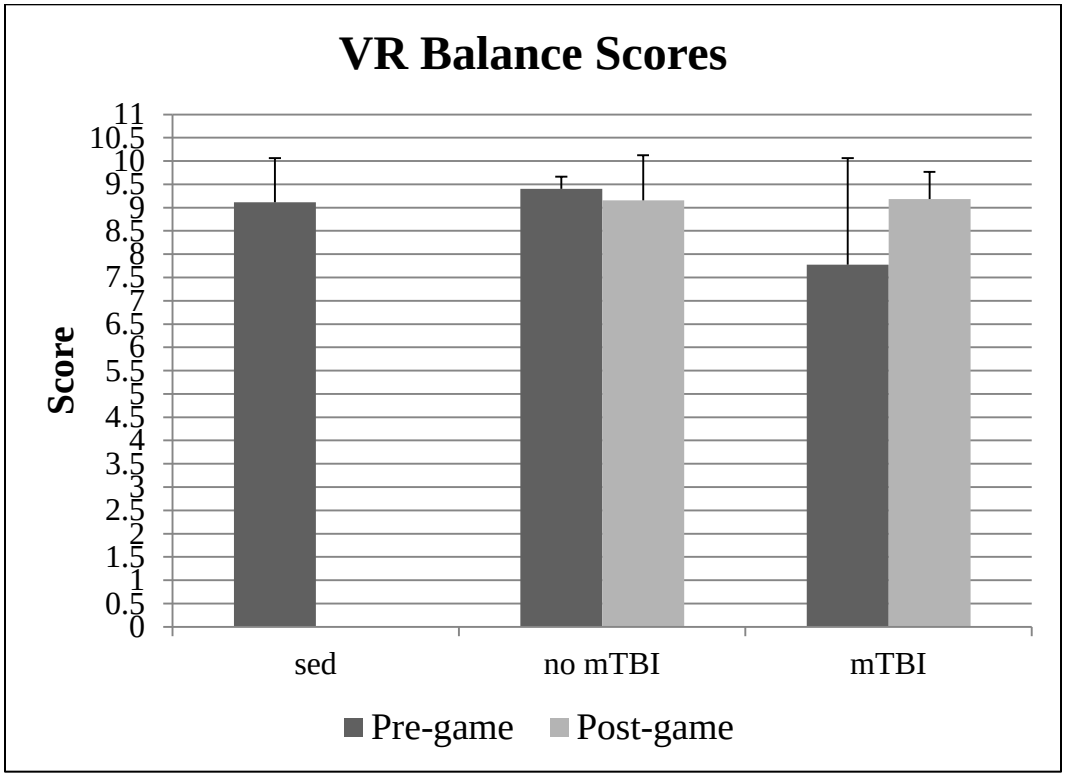
Chart showing average and standard deviations for each group's performance on all VR modules including the comprehensive score report.

Table 4.1.2 Average Group Raw Data and Standard Deviations

	Pre-game		**Post-game**	
	Spatial	Std dev	**Spatial**	Std dev
sed	43.3	19.46	-------	-------
no mTBI	33.99	9.64	44.00	25.61
mTBI	35.51	13.5	39.67	14.79
	Balance		**Balance**	
sed	22.42	12.77	-------	-------
no mTBI	17.37	7.52	17.68	10.55
mTBI	23.34	17.32	19.4	11.27
	Reaction Time		**Reaction Time**	
sed	0.66	0.599	-------	-------
no mTBI	0.528	0.583	0.856	0.656
mTBI	0.958	0.748	0.734	0.627

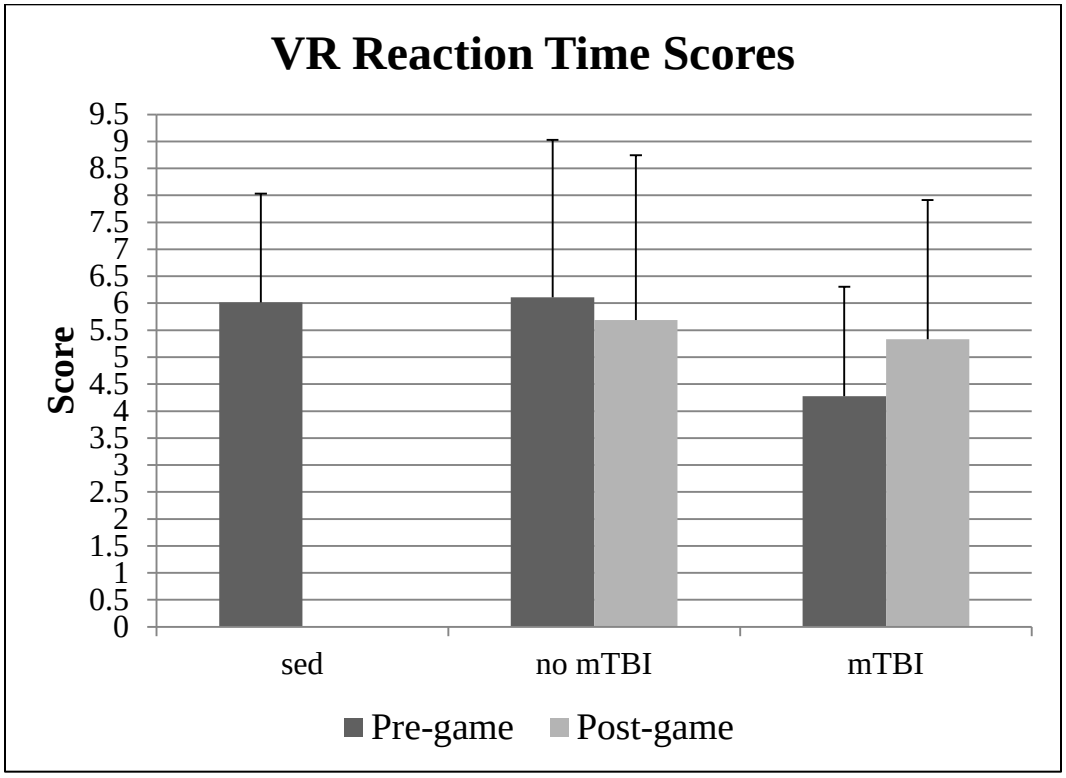
Raw data averages and standard deviations (std dev) for each group. Sed = sedentary group, no mTBI = group with no history of mTBI, mTBI= group with a previous history of mTBI. Spatial data is in seconds and is the total time needed to complete the spatial navigation task. Balance represents the center of pressure in cm^2, and reaction time is in seconds.

Figure 4.1.2 VR Balance Scores



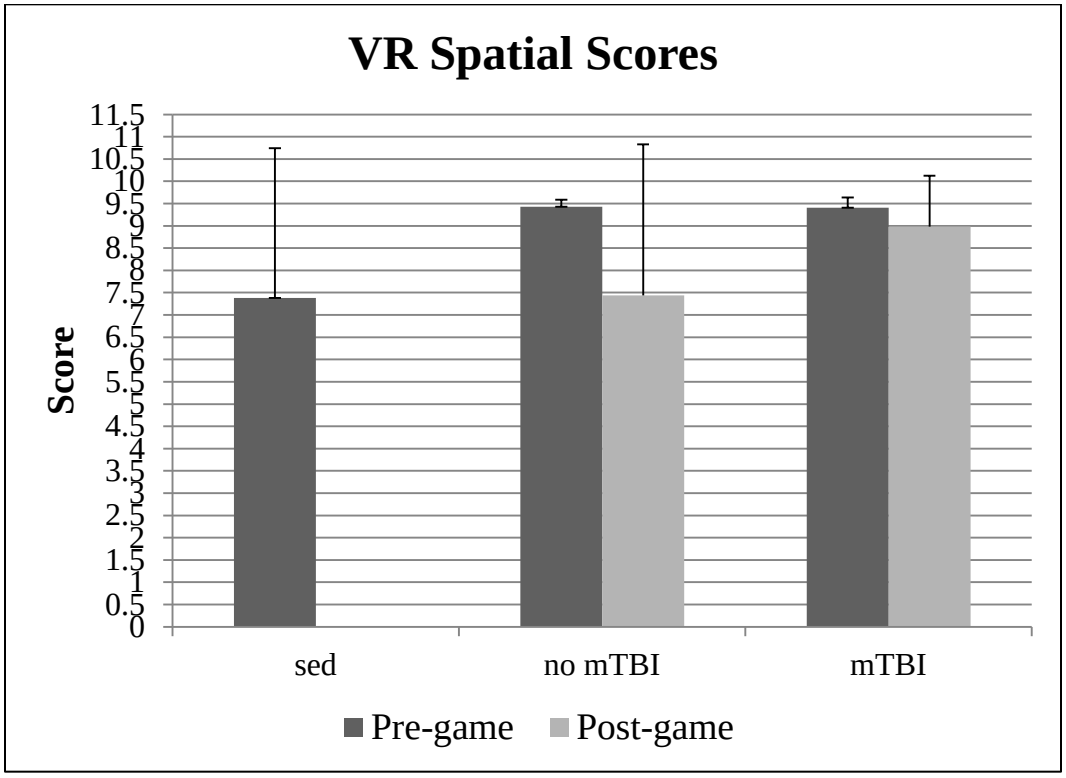
Graph of scores for the balance VR module for both pre-game and post-game sessions, error bars represent standard deviation. Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

Figure 4.1.3 VR Reaction Time Scores



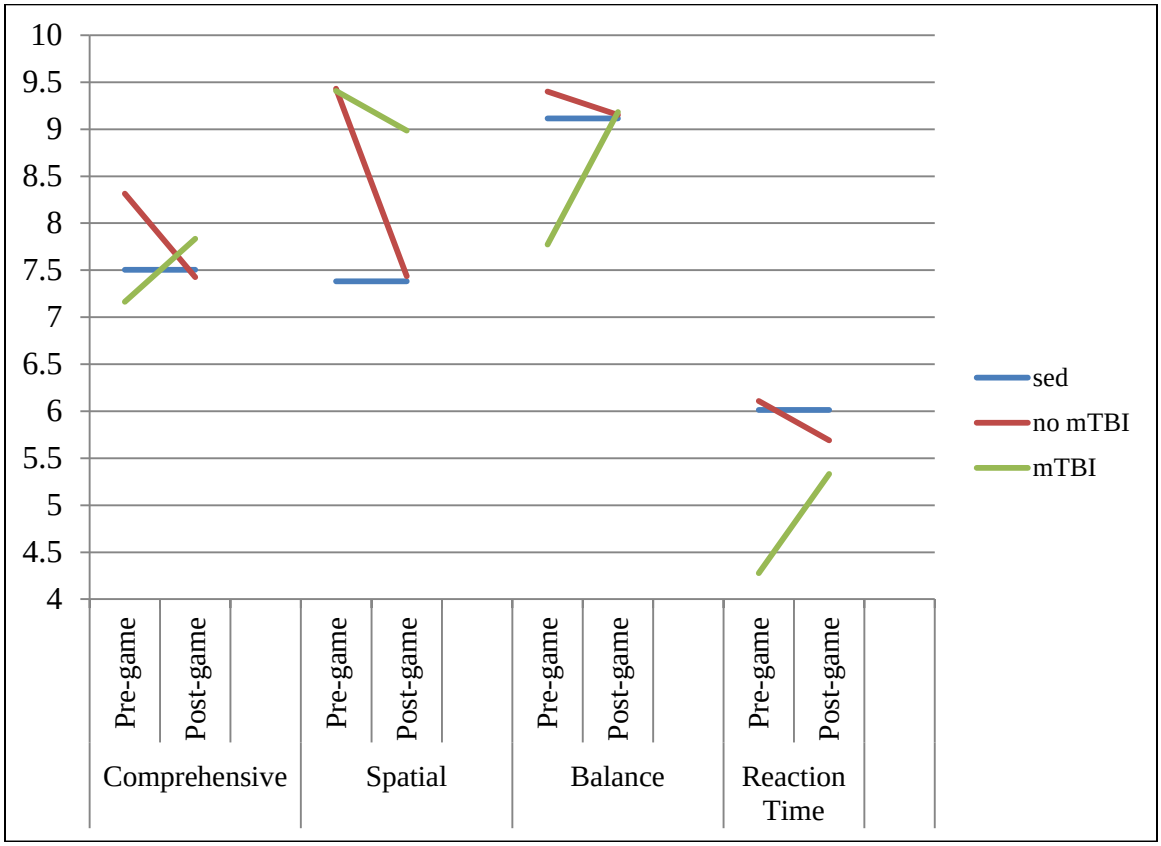
Graph of scores for the reaction time VR module for both pre-game and post-game sessions, error bars represent standard deviation. Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

Figure 4.1.4 VR Working Spatial Memory Scores



Graph of scores for the working spatial memory VR module for both pre-game and post-game sessions, error bars represent standard deviation. Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

Figure 4.1.5 VR Pre-game to Post-game Trends



Graph shows the trend of changes in VR module scores from pre-game to post-game evaluation. Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

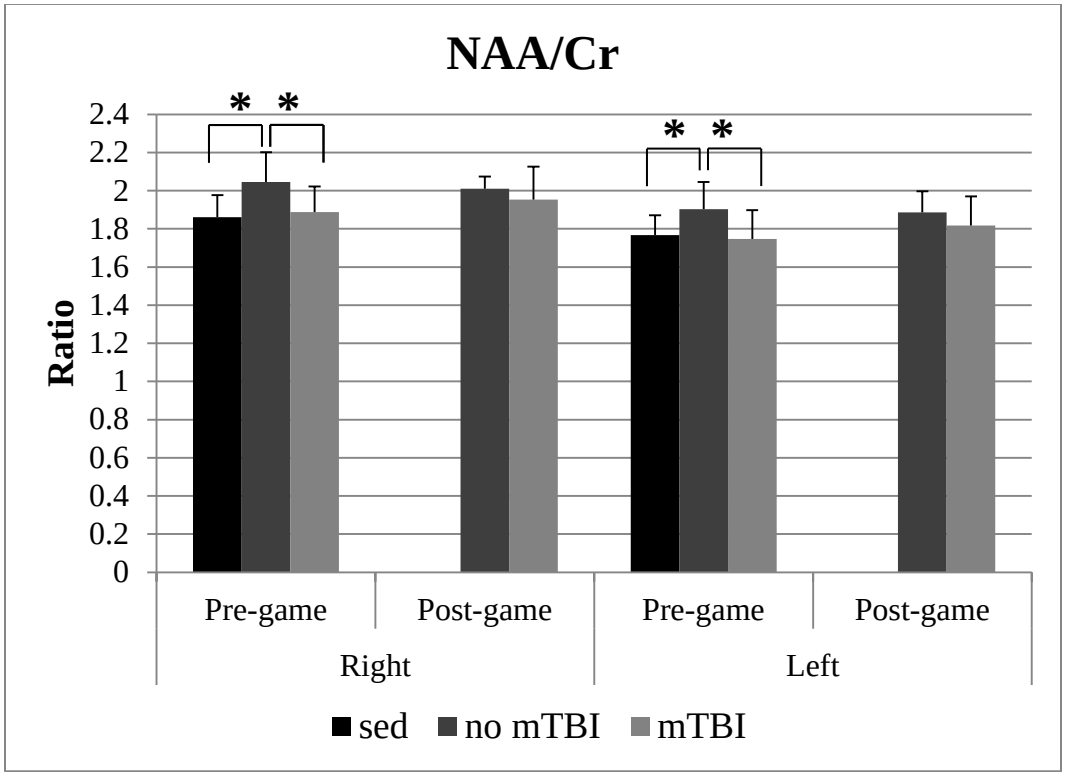
4.2 Magnetic Resonance Spectroscopy

Similar to the pre-game VR results, the mTBI group showed lower pre-game metabolite ratios for NAA/Cr (**Figure 4.2.1**) and Cho/Cr (**Figure 4.2.2**), yet a slight increase in NAA/Cho (**Figure 4.2.3**) when compared to the no mTBI group. Specifically, pre-game NAA/Cr ratios for the mTBI group were significantly lower in both the left (p=0.047) and right (p=0.05) hemispheres in than in the no mTBI group. Additionally, significant reductions were seen in both hemispheres (right p=0.045, left p=0.039) for the pre-game Cho/Cr ratio between the mTBI and no mTBI groups. No significant differences were noted between the pre-game NAA/Cho ratios for these two groups, as well as no differences compared to the sedentary group's pre-game NAA/Cho ratio. In parallel, significant reductions in both pre-game NAA/Cr and Cho/Cr ratios were seen in the sedentary group compared to the no mTBI group. Particularly, the sedentary group displayed lower NAA/Cr ratios in both the left (p=0.018) and right (p=0.046) hemispheres, and nearly significant reductions in pregame Cho/Cr ratios (right hemisphere p=0.06, left hemisphere p=0.09). However, the NAA/Cho ratio did not show any significant difference between the groups. Post-game metabolite ratios did not show any differences between any of the groups or for any of the metabolite ratios (**Table 4.2.1**).

As was seen in the VR results, the MRS results did not show any statistically significant changes from the pre-game MRS metabolite ratios to the post-game ratios. Despite no significant changes, a similar trend was observed as was seen in the VR module trends (**Figure 4.2.4**). Where NAA/Cr dropped in the no mTBI group pre-game to post-game, it rose in the mTBI group, and Cho/Cr decreased albeit minimally in the no mTBI group it again rose in the mTBI group. The NAA/Cho ratio was the only metabolite ratio where both groups showed the same trend, and as in the VR working spatial memory module the no mTBI group showed the biggest change from pre-game to post-game.

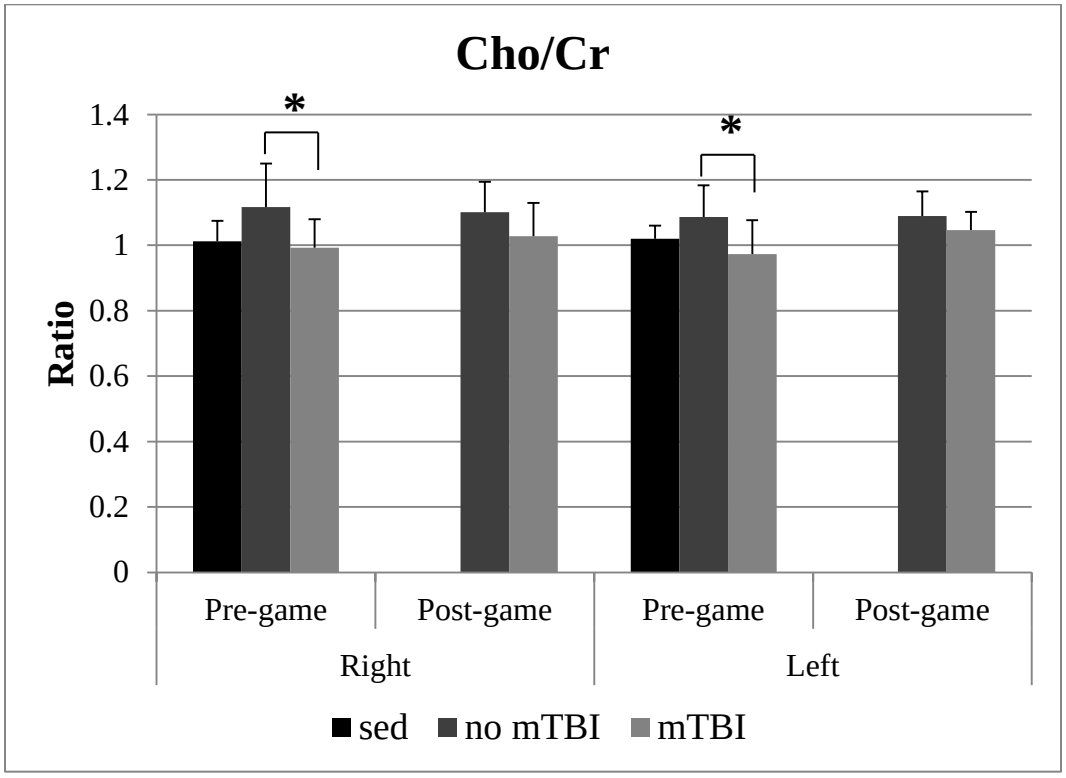
To further explore if there was any relationship between NAA/Cho, which have been linked in several papers to be able to predict neuropsychological and recovery outcomes following mTBI (Govind et al., 2010), correlation analysis was performed. The NAA/Cho ratios were tested against the comprehensive score, as it is an overall measure of the three VR modules combined (**Figure 4.2.5** and **Figure 4.2.6**). Pre-game comprehensive scores were significantly correlated with NAA/Cho (r=0.69, p=0.05) in the no mTBI group, but no significant correlations were seen in the mTBI group. Post-game correlation analysis revealed the opposite results, with the mTBI group showing a strong correlation (r=0.76, p=0.029) of the NAA/Cho with the comprehensive score, and no significant correlations with metabolite ratios and VR comprehensive score report in the no mTBI group.

Figure 4.2.1 NAA/Cr Ratio



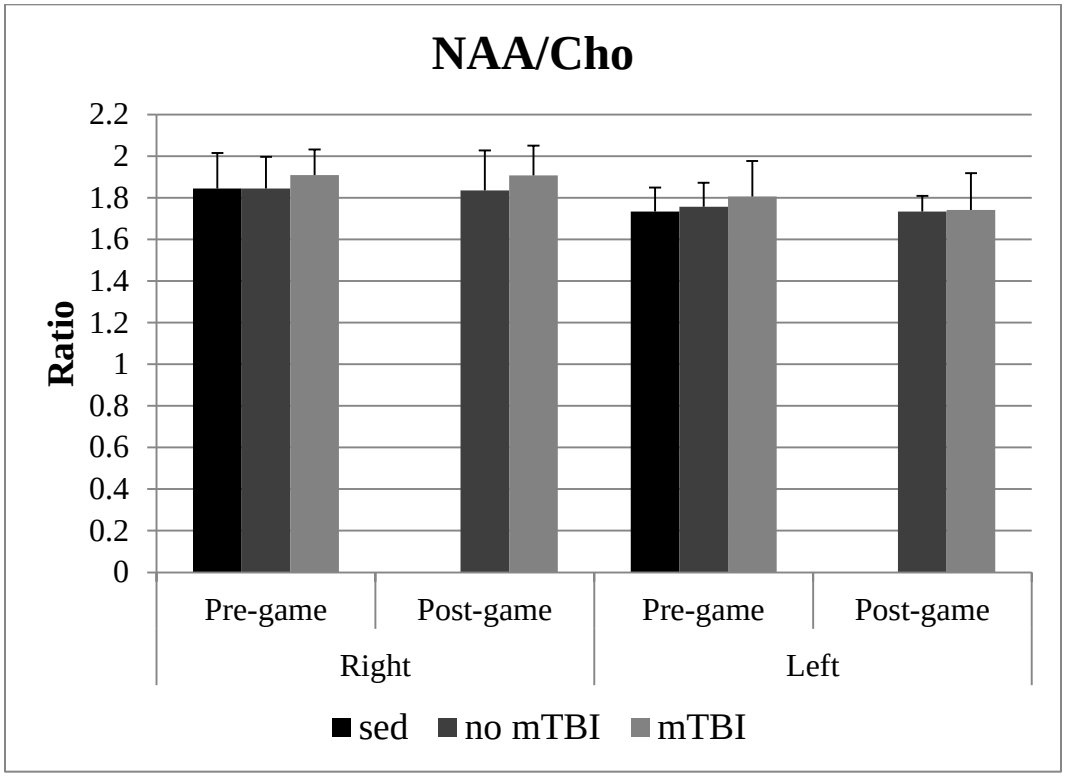
NAA/Cr ratios for right and left hemisphere as well as pre-game and post-game sessions, error bars represent standard deviation. * represent significant differences, p<0.05. Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

Figure 4.2.2 Cho/Cr Ratio



Cho/Cr ratios for right and left hemisphere as well as pre-game and post-game sessions, error bars represent standard deviation. * represent significant differences, $p<0.05$.
Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

Figure 4.2.3 NAA/Cho Ratio



NAA/Cho ratios for right and left hemisphere as well as pre-game and post-game sessions, error bars represent standard deviation. Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

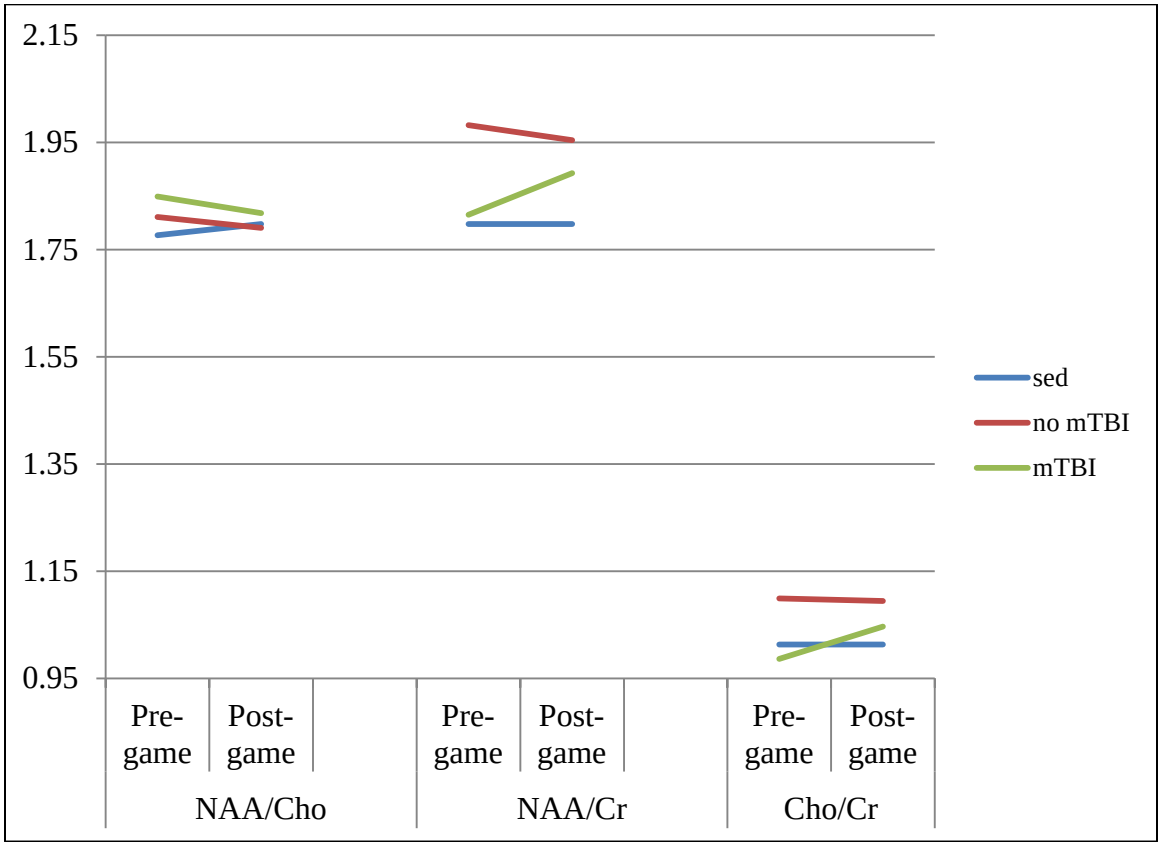
Table 4.2.1 Average Metabolite Ratios and Standard Deviations

	Right Pre-game		**Right Post-game**	
	NAA/Cho	std dev	**NAA/Cho**	std dev
sed	1.84	0.16	-----	-----
no mTBI	1.84	0.15	1.83	0.193
mTBI	1.91	0.12	1.90	0.1433
	NAA/Cr	std dev	**NAA/Cr**	std dev
sed	1.86*	0.11	-----	-----
no mTBI	2.05	0.15	2.00*	0.0643
mTBI	1.88**	0.13	1.95**	0.1734
	Cho/Cr	std dev	**Cho/Cr**	std dev
sed	1.01	0.06	-----	-----
no mTBI	1.11	0.13	1.10	0.0924
mTBI	0.99**	0.08	1.02	0.1018

	Left Pre-game		**Left Post-game**	
	NAA/Cho	std dev	**NAA/Cho**	std dev
sed	1.73	0.11	-----	-----
no mTBI	1.75	0.11	1.73	0.07
mTBI	1.80	0.16	1.74	0.17
	NAA/Cr	std dev	**NAA/Cr**	std dev
sed	1.76*	0.10	-----	-----
no mTBI	1.90	0.14	1.88	0.1106
mTBI	1.74**	0.15	1.81	0.1524
	Cho/Cr	std dev	**Cho/Cr**	std dev
sed	1.01	0.04	-----	-----
no mTBI	1.08	0.09	1.08	0.07
mTBI	0.97**	0.10	1.04	0.05

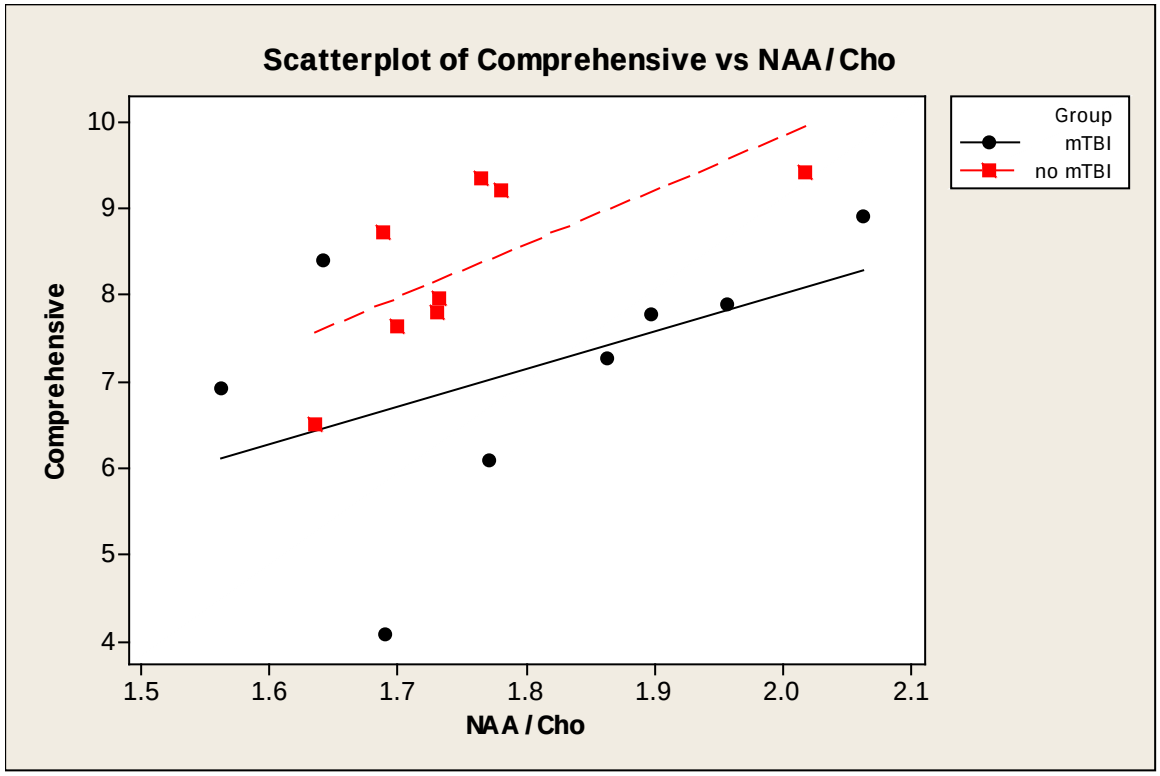
Table showing average metabolite ratios and standard deviations for each testing session and each hemisphere. * represents significant difference between no mTBI group and sedentary group, where ** represents significant difference between no mTBI group and mTBI group. Significance level set at $p<0.05$.

Figure 4.2.4 Magnetic Resonance Spectroscopy Trends



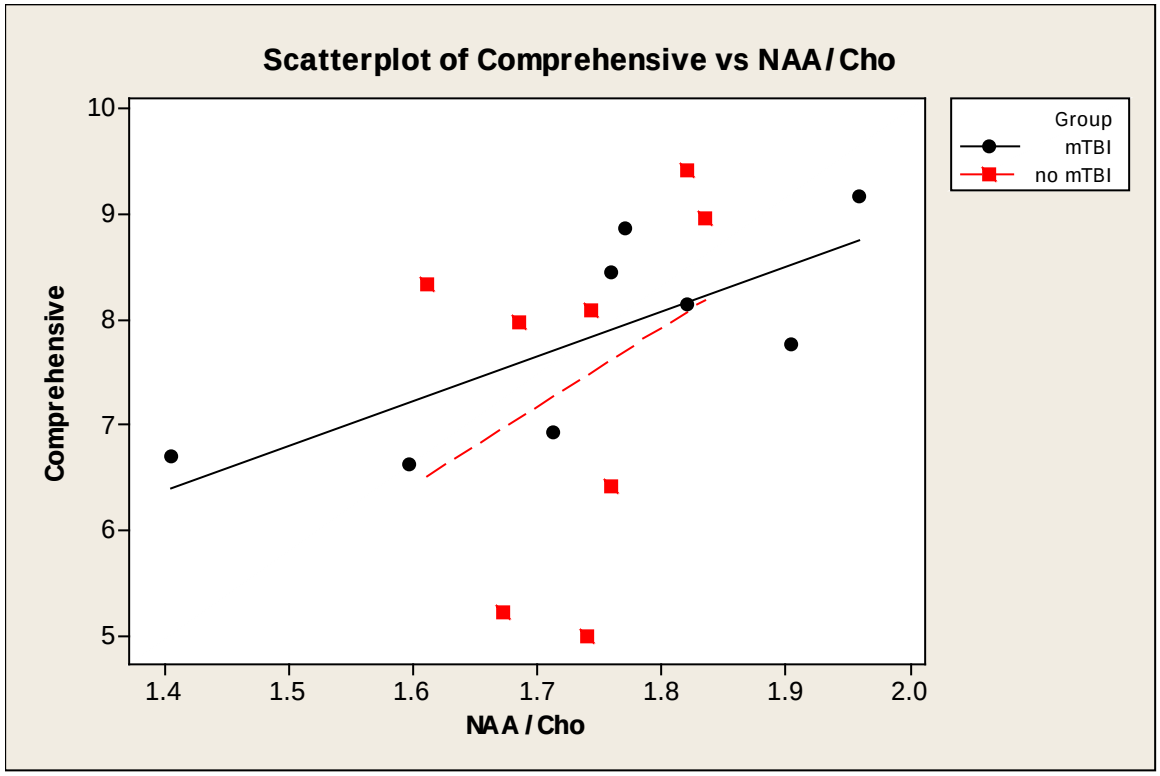
Graph shows the trend of changes in metabolite ratios from pre-game to post-game evaluation. Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

Figure 4.2.5 Pre-game Correlation NAA/Cho to Comprehensive VR Score



Correlation analysis of NAA/Cho and comprehensive VR scores for the pre-game session. red= no mTBI group and black= mTBI group.

Figure 4.2.6 Post-game Correlation NAA/Cho to Comprehensive VR Score



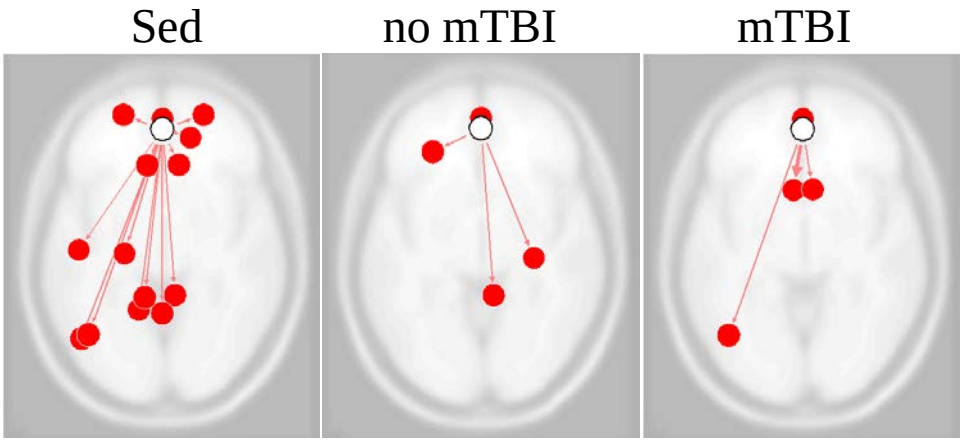
Correlation analysis of NAA/Cho and comprehensive VR scores for the post-game session. red= no mTBI group and black= mTBI group.

4.3 Resting-State Default Mode Network

Staying consistent with the pre-game results seen in every modality, the resting-state fMRI results showed that the mTBI group showed the lowest number of connections as well as the weakest strength of these connections for all four ROIs under study. Continuing in an increasing order, the no mTBI group showed an intermediate number and strength of functional connections compared to the sedentary group that had the highest number of connections. Although visually different (**Figure 4.3.1**) there was no significant differences between the three groups at the pre-game scan. Furthermore, no significant differences between groups were revealed at the post-game scan as well.

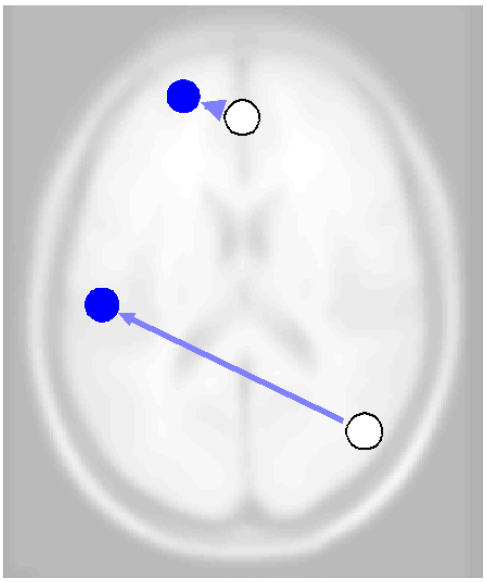
Unlike the VR and MRS results, the no mTBI group did display a significant change from the pre-game to post-game scan. This change was in the form of decreased connectivity with the RLP to left primary somatosensory cortex ($p=0.035$) along with a decreased connectivity from the MPFC to the left anterior prefrontal cortex ($p=0.004$) (**Figure 4.3.2**). The mTBI group showed no significant changes from pre-game to post-game scanning. Interestingly the mTBI group post-game scans increased in the number and strength of connections which closely reflected the no mTBI group's pre-game scan for each of the ROIs under investigation (**Figure 4.3.3**). For more detailed connectivity results please refer to **Table 4.3.1**.

Figure 4.3.1 Sample Connections From the MPFC



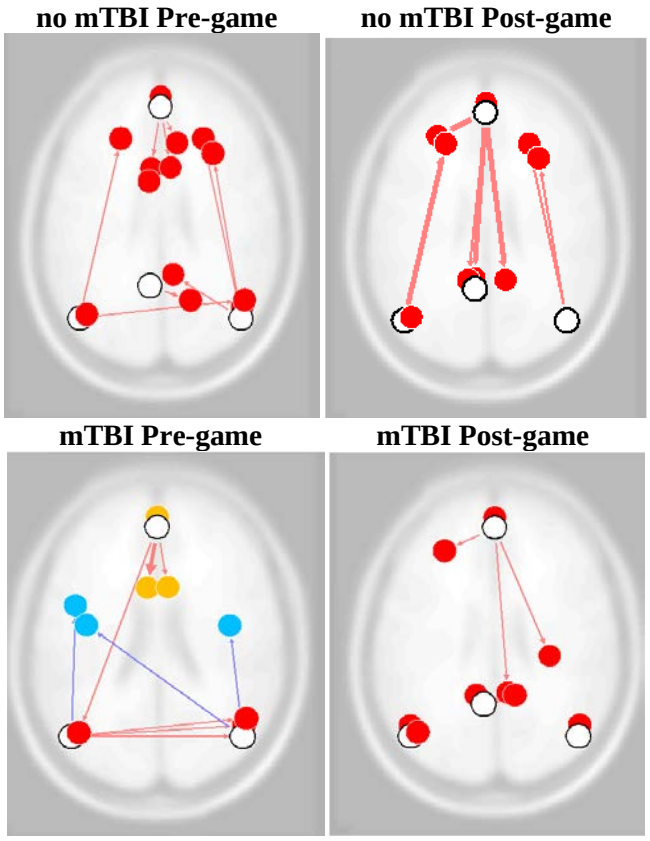
Connections from pre-game session from the MPFC source in all three groups. Sed = sedentary group, no mTBI = group without any history of concussion, and mTBI = group with a previous history of concussion.

Figure 4.3.2 Pre-game to Post-game Differences in the no mTBI Group



Significant decreases as indicated by the cool color, seen functional connectivity in the no mTBI group from pre-game to post-game evaluation in the right lateral parietal and medial prefrontal cortex.

Figure 4.3.3 No mTBI and mTBI Pre-game and Post-game Connections



DMN connections for no mTBI (top) and mTBI (bottom) groups in each session. White circles represent seed points for right and left lateral parietal, precuneus, and medial prefrontal cortex. Warm colors represent positive connections and cool colors represent negative significant connections.

Table 4.3.1 mTBI and no mTBI Pre-game and mTBI Post-game Connections

ROI	no mTBI Pre		mTBI Pre		mTBI Post	
	BA	*p*(FDR)	BA	*p*(FDR)	BA	*p*(FDR)
Right Lateral Parietal						
	39(R)	0.003	13(L)	-0.03	39(R)	0.017
			39(R)	-0.3	8(R)	0.03
			13(R)	-0.03	29(R)	0.04
					23(R)	0.04
					1 (R)	-0.04
					31(R)	0.04
					29(L)	0.05
Precuneus						
	31(L)	0.021	23(L)	0.01	33(R)	0.037
	31(R)	0.047	23(R)	0.04	31(R)	0.039
	29(R)	0.019	31(R)	0.04	31(L)	0.039
	30(L)	0.022			7(R)	0.02
Medial Pre-frontal Cortex						
	36(R)	0.02	25(R)	0.001	25(L)	0.015
	29(R)	0.02	25(L)	0.04	24(L)	0.016
	9(L)	0.02			32(R)	0.02
					25(R)	0.023
					33(R)	0.038
					34(L)	0.039
					32(L)	0.045
					36(R)	0.045
Left Lateral Parietal						
	39(L)	0.02	39(R)	0.04	8(L)	0.039
					31(R)	0.04
					39(R)	0.04

Table showing the pre-game significant connections for the no mTBI group and the pre-game and post-game connections for the mTBI group. BA represents Brodmann areas, and p(FDR) are corrected p values.

Chapter 5

Discussion

In this current research project a multi-modal approach was used to explore whether or not a history of concussive and repetitive subconcussive episodes leads to chronic deficits in metabolic, functional, and cognitive integrity of the brain; and whether or not a history of previous concussion leads to a differential response to subconcussive head trauma. Specifically, implementation of VR was used to assess working spatial memory, balance, and reaction time. This combined with MRS and resting-state fMRI advanced neuroimaging techniques allowed assessment of both the metabolic and functional effects of previous concussion and subconcussive head trauma. The results herein support our major hypothesis that prior history of concussion leads to decline in the brain's metabolic, functional, and cognitive integrity. This was evident by the mTBI group lowered VR scores, decreased neurometabolite ratios, and decreased functional connectivity in the pre-game evaluation. Paradoxically, our ancillary hypothesis that a prior history of concussion would result in further deterioration of the integrity of the brain was not supported, and the results point to an underlying preconditioning effect of a previous concussions.

Despite the limited presence of overwhelming alterations in metabolic, connectivity, and cognitive function from pre-game to post-game, it actually serves as a good internal standard for this experiment. As widely reported in the literature; cerebral deficits and impairments documented by neuropsychological testing, alterations in fMRI BOLD activity and functional

connectivity, and significant changes in brain metabolites have all been observed in the acute and subacute setting of mTBI. All participants under study reported no concussion signs or symptoms at both the pre-game and post-games testing sessions, as well as none being diagnosed with a concussion during or after the game. This lack of significant changes between sessions, fits under the definition of what subconcussive impacts are, below the threshold to cause a concussion (Shultz et al., 2012) and do not result in a clinically-identifiable concussion (Gavett et al., 2011; Martini et al., 2011; Witol & Webbe, 2003). The pathophysiology of concussion is thought to be mostly neurometabolic (Packard, 2008), and presumably if there were significant changes in the MRS ratios from pre-game to post-game participants would have reported concussion like signs and symptoms. That being said this study is not without its own limitations. This study has a small sample size and the subjects were predominately female, with females making up the entire sedentary group. Additionally the number of previous concussions was not taken into account and this may have explained some of the high variability seen in the mTBI group and the number of subconcussive blows experienced was not quantified.

There is still widespread controversy surrounding concussion in the literature as well as in the medical field. There is no standard definition of concussion clinically (Cantu, 2007) and contrasting research reports put the recovery timeline from spontaneous resolution within 10 days (McCrory et al., 2009) and can range up to one year post injury with documented symptoms, cognitive, and emotional deficits (Ghaffar et al., 2006). Current clinical measures lack sensitivity and specificity for concussion management (Iverson et al., 2006; Mayer et al., 2011) although more advance techniques have highlighted subtle changes and nuances in brain morphology, physiology, and function caused by mTBI (Gasparovic et al., 2009). Recent attention has been focused on the cumulative effects of both concussive and subconcussive head trauma that athletes experience over there career, and there is speculation that the accumulation of these hits puts

athletes at a higher risk for long-term and chronic neurological deficits and pathologies including CTE (McKee et al., 2009), although no concrete link has been found. Adding to the confusion and what seems to be two differing frames of thinking on the severity and recovery of a concussive injury; whether or not there is a neuroprotective or detrimental effect of a concussion on the brain. There is no doubt that both the medical and research fields are divided on the subject of concussion, and uncertainty in the definition, assessment, recovery, and what are the best methodological approaches or techniques may help to add to the confusion.

The Zurich Consensus Statement (2009) recommend that working memory, attention, visual learning and memory, problem solving and speed of information processing are the most important neurocognitive functions that need to be accurately assessed to define the degree of brain damage induced by a concussion. In support of these recommendations research studies have documented that postural control, reaction time, and executive functions are the most prominent deficits seen in individuals recovering from a mTBI (Broglio, 2007; Eckner et al., 2011). Several studies have documented deficits in postural stability (Guskiewicz, 2001) as well as alterations in brain function while performing working spatial memory (Slobounov et al., 2010). Similar to these reports the mTBI group here showed the poorest performance most often in the corresponding VR modules. It has long been hypothesized that repeated head trauma leads to compromised cognitive function and research utilizing neuropsychological tests aimed at investigating the effects of subconcussive hits have demonstrated mixed results. Additionally, these studies have been relegated and centered on only a couple of specific sports. Furthermore, there are even less studies that have been directly focused on the acute effects of subconcussive head trauma, with a majority of studies looking at the chronic effects of repetitive subconcussive blows. These long-term neuropsychological studies have shown impaired performance in memory, planning, visual perception processing (Matser et al., 1999), slower patterns of motor

speed and reaction time (Downs & Abwender, 2002). In addition to these cognitive deficits, a long history of subconcussive head trauma can produce symptoms of disorientation, headache and nausea (Tysvaer & Storli, 1981).

Most of the studies looking at the acute effects of subconcussive head trauma have been done in soccer (Broglio et al., 2004; Mangus et al., 2004; Tysvaer, 1992). Our VR assessment of balance revealed no significant differences between the pre-game and post-game testing sessions. This finding is in agreement with Schmitt et al. (2004) who looked at what effects purposeful heading had on postural control. They found that prior to, immediately following, and at 24 hours after the heading session there were no differences in postural control as assessed by center of pressure (COP) area and velocity. They also reported that there were no changes in the subjects' self-reported symptoms immediately before and 24 hours after. These findings were in parallel with those reported by Broglio et al. (2004), that there were no acute changes in postural control following a bout of purposeful soccer heading. In our tests of reaction time and working spatial memory no differences were seen between testing sessions. There are limited studies in the literature that have implemented neuropsychological testing to study the acute effects of subconcussive impacts. Although, one study by Miller et al. (2007) looked at collegiate football players and performed neuropsychological testing at three times throughout the season. They found that there were no significant differences on SAC and ImPACT scores at preseason, midseason, and post season evaluations.

Although we saw no differences between testing sessions, the no mTBI and mTBI group showed opposite trends in two out of the three VR modules as well as in the comprehensive scores. Initial scores from the mTBI group were on average lower and consistent with the school of thought showing that a history of concussions may induce chronic effects. A tendency for the

no mTBI group to perform worse in post-game testing is comparable to the current postural control and neuropsychological testing in the acute phase of concussion results in the current literature. A growing body of research has demonstrated postural stability deficits, as measured by the Balance Error Scoring System (BESS) 1 day post injury (Guskiewicz, 2001; Riemann & Guskiewicz, 2000). This deficit in balance seems to extend from one to three days post injury, with the second day has been identified as particularly problematic (Peterson, Ferrara, Mrazik, Piland, & Elliott, 2003). Conversely this decline seen during the post-game session for the no mTBI group was not mirrored by the mTBI group. In fact in the comprehensive, balance, and reaction times scores the mTBI group received higher post-game scores. In the same study by Miller et al. (2007) that used SAC and ImPACT neuropsychological tests to evaluate collegiate football players over the course of the season, they specified that no athlete under study received a diagnosable concussion over the season, but did not specify if athletes with a history of concussion were excluded from the study. They also found that over the course of the season that subjects showed significant improvements in reaction time, as well as improvements in verbal memory and processing speed that almost reached levels of significance. Whether or not this increased performance can be attributed to a practice effect or to a preconditioning effect was not elaborated on.

To date there have been no MRS studies or neurochemical evidence for brain damage due to an acute exposure to subconcussive head trauma (Spiotta et al., 2012). Much of the pathophysiology we know about concussion has come from animal models and it is well documented that concussion causes a complex biochemical cascade and disruptions in metabolic processes (Giza & Hovda, 2001). MRS studies of concussion in humans have revealed consistent findings. An initial drop of NAA coupled with an increase in Cho concentrations has been widely documented (Belanger et al., 2007; Henry, 2010; Ross et al., 1998). This also has led to

constant reports of decreases in the NAA/Cho ratios following mTBI (Lin et al., 2012) as the most reported finding. Longitudinal MRS studies have shown that even though NAA concentrations drop, with time they do restore back to baseline levels in about 30 days post injury. This recovery is marked by a faster recovery phase that exhibits exponential characteristics from days 15 to 30 post injury (Vagnozzi et al., 2010). Whether or not this exponential rebound in NAA stops once it returns to baseline or there is an overshoot that remains elevated and then eventually returns to normal has not been studied. This may explain why we saw slightly elevate NAA/Cho in the mTBI group compared to the no mTBI group at the pre-game scan even though they had a reduced NAA/Cr ratio, which has also been commonly reported in the MRS literature following a concussion. Commonly used as an internal reference, the Cr peak is thought to be stable although the stability for the Cr peak has been brought into question as of late (Gasparovic et al., 2009; Yeo et al., 2011). The no mTBI group post-game scan demonstrated the classic response reported in the literature following a concussion, albeit to a lesser extent. Both NAA/Cho and NAA/Cr ratios were reduced and there was little if any change in the Cho/Cr ratio. Contrasting this typical response, the mTBI group showed a negligible drop in NAA/Cho, and increases in NAA/Cr and Cho/Cr ratios. A recent study by Vagnozzi et al. (2012), reported that when Cr concentration do not remain stable as indicated by the Cho/Cr ratio, and in fact they reported an increase in the Cho/Cr ratio there also an acute increase in the NAA/Cr ratio which then dropped below baseline levels by 15 days post injury. NAA/Cho and NAA/Cr ratios have been correlated to be predictors of cognitive function and severity of injury in TBI (Govind et al., 2010). Specifically higher NAA/Cho and NAA/Cr metabolite ratios are indicative of better cognitive function and less severe extent of injury. Here we also found that there was a positive correlation of NAA/Cho and comprehensive VR scores. Other studies of mTBI utilizing radiotracers to assess alterations in metabolic processes have yielded mixed results even within the mTBI cohorts under investigation. For example, Gross et

al. (1996) reported hyper and hypometabolism in a positron emission tomography study of 20 subjects recovering from a concussion.

In our previous studies investigating the resting-state DMN connectivity in athletes recovering from concussion we have found that in concussed individuals the resting state DMN showed a reduced number of connections and strength of connections in the PCC, RLP and LLP cortices, in addition we saw an increased number of connections and strength of connections in the MPFC (Johnson, Zhang, Gay, Horovitz, et al., 2012) . This was consistent with the findings we saw in the connectivity analysis of the mTBI group when compared to the two other groups. Concordantly, a recent study by Mayer et al. (2011) showed mTBI subjects displayed decreased DMN connectivity. Again the no mTBI group's response to subconcussive head trauma more closely mirrored the typical response seen in a full blown concussive episode, while the mTBI group's response more closely resemble those seen in the no mTBI pre-game session. This trend for the no mTBI group to show similar characteristics to those consistently found in the concussion literature following an acute bout of subconcussive head trauma over all three modalities highlights the possible damaging long-term and chronic effects that repeated head trauma may pose on the integrity of the brain, as well as making its case for some of the long-term impairments seen in sports related traumatic brain injury. Contradictory to this are the same consistencies seen in the mTBI group in response to subconcussive impacts, where it seems that a history of prior concussion has neuroprotective effects.

Beyond the speculation of the preconditioning effects that a concussion may have on the brain, it is also important to note a major difference between the groups under investigation. Both the mTBI and no mTBI groups actively workout and exercise whereas the sedentary group does not. This difference is important as exercise is known to be beneficial for the human body, the

brain included. Exercise has been shown to increase brain volume, specifically hippocampal volume, as well as influence cognitive function (Ahlskog, 2011; Chaddock et al., 2010; Ploughman, 2008). Chaddock et al. (2010) reported that an exercise regimen improve cognitive scores in adolescents and increased hippocampal volume , while also decreasing the decline of cognitive function seen in the elderly (Ahlskog, 2011). Additionally a study looking at exercise and Alzheimer's disease found that an exercise intervention increased cognitive scores (Ahlskog, 2011). The association between exercise and the biochemistry of the brain as assessed by MRS is barely nonexistent. The limited number of studies that do are focused on the acute effects of exercise on brain metabolites, and not any long-term benefits, but they do report observing alterations in brain metabolites (Maddock, Casazza, Buonocore, & Tanase, 2011). We have also shown that that functional connectivity is increased immediately following physical stress in the form of exercise in both normal controls and athletes who have suffered a concussion (Slobounov et al., 2011). The benefits of exercise are not disputed and may explain why the sedentary group was not the top performer in cognitive assessment or why they did not have the highest metabolite ratios. This being said, exercise cannot fully explain the trends we observed in the mTBI and no mTBI groups.

In a recent animal study by Shultz et al. (2012) investigating the effects of subconcussive head trauma found that there was no significant axonal injury, cognitive, emotional, or sensorimotor alterations documented, even though there was acute neuroimflammation. The presence of acute neuroimflammation was confirmed by short-term increase in microglia, macrophages, and reactive astrogliosis, which return to baseline levels four weeks post injury. Repetitive mTBI, similar to neuroinflammation may have cumulative effects leading to neurodegeneration (Shultz et al., 2012) and linked to behavioral impairments (Ramlackhansingh et al., 2011). On the other hand neuroinflammation may also have neuroprotective qualities

(Schmidt et al., 2005) and the brain may be better protected after an initial TBI (Allen et al., 2000). Reports of a gradual increase in the amount of brain injury, coined "trauma resistance," has been attributed to stabilization of metabolic processes (Noble & Collip, 1942) and the ability of an animal to withstand a blow that would otherwise kill a normal animal. This phenomenon of preconditioning has been well described and documented in cerebral ischemia (Slemmer & Weber, 2005). This idea of a neuroprotective effect due to preconditioning by a previous concussion is one explanation to as to why there were contrasting pre-game to post-game changes seen throughout all three modalities.

As for the increase in VR performance seen in the mTBI group one could simply attribute the improvements seen in the mTBI group solely to a practice effect, but presumably if there was a practice effect it would also have been apparent in the no mTBI group as well. We saw that there was a positive correlation with NAA/Cho and cognitive function, and previous studies have also shown a significant correlation with NAA/Cho to initial Glasgow Coma Scale and clinical outcome in TBI (Du, Li, & Lan, 2011). The mTBI group showed less of a drop in NAA/Cho following the game compared to the no mTBI group. Although the exact function of NAA is not known, it has been widely used as an indicator of axonal integrity (Ross et al., 1998). However, more recent research has implicated NAA in protecting neurons from osmotic stress as well as playing a part in the citric acid cycle to help meet the demands of continuous energy production (Stork & Renshaw, 2005). It is also well know that reduced NAA levels following full blown concussive events are eventually restored (Vagnozzi et al., 2010) and there seems to be more evidence mounting that alterations in NAA concentrations are a better representation of mitochondrial function as compared to axonal death (Stork & Renshaw, 2005). Yin et al. (2008) reported that injury to the brain increases the biogenesis of neuronal mitochondria, suggesting a previous mTBI up regulates the production of mitochondria and therefore can more adequately

meet the energy demands following subconcussive head trauma and maybe one reason we observed increased NAA/Cr ratios and less attenuated NAA/Cho ratios in the mTBI group following the game. Furthermore, the NAA/Cr ratio has also shown similar correlations as well as being positively correlated to performance on neuropsychological tests (Govind et al., 2010). Slemmer and Weber (2005) used a mechanical stretch to simulate a mTBI in hippocampal cell cultures and found that when the tissue was preconditioned they observed a significant decreases in S-100β indicating a positive effect of glial preconditioning. Moreover, Allen et al. (2000) reported in a rat model of repetitive mTBI that preconditioning served to preserve motor function following a severe TBI and also elicited activation of secondary sites in the brain that may aide in recovery. This same neuroprotective argument can also be made for the results in the no mTBI group, as a recent study using a stretch injury device to simulate mTBI in hippocampal slice cultures hypothesize that following a mTBI certain genes modulations cause the brain to enter a hypometabolic state in order to attenuate oxidative/nitrosative stress and apoptosis during a time of mitochondrial dysfunction (Pietro et al., 2013).

However, further studies are needed to refute or strengthen these findings, especially longitudinal studies that investigate whether or not this “neuroprotective” response remains constant over time or is just an acute transient activation of the anti-inflammatory response then followed by a switch to a pro-flammatory action that can lead to secondary injuries (Schmidt et al., 2005). Furthermore, studies that also quantify the subconcussive impacts may show that the number and severity of these insults plays a major factor in alterations of brain metabolism or function. Here we used a multi-modal approach, but use of other advanced imaging techniques like diffusion tensor imaging (DTI) or susceptibility weighted imaging (SWI) may add valuable information on white matter integrity and vascular changes following sports related head trauma.

Chapter 6

Conclusions

In conclusion, concussion leads to long-term and chronic deficits seen in the form of cognitive, functional, and metabolic processes in the brain. Whether these alterations are purely caused by strictly full blown concussive events, or if repeated subconcussive head traumas, especially those seen in full contact sports, are indicated in these impairments has yet to be determined. All subjects under study were by current clinical standards asymptomatic at both pre-game and post-game evaluations despite showing subtle differences between groups and across all three modalities. These subtleties bring into question the efficacy of current clinical guidelines on concussion management and return-to-play criteria and highlight the need for reevaluation of these measures to include more specific and sensitive methods. In addition to the long-term deficiencies we consistently saw in the group with a history of concussion, our results may suggest that there is a differential effect of subconcussive blows on the concussed and non-concussed brain, although further research is needed. Whether this increase in VR performance, elevated metabolite ratios, and intact functional connectivity seen in the mTBI group post-game is evidence for the precondition effects of a concussion or just an acute transient alteration needs to be determined. Futures studies need to take into consideration this evolution and perform follow-up testing. Additionally, future studies need to account for some of the shortcomings of this present study by quantifying subconcussive blows and looking at individuals with a history of one or multiple concussions separately to help better understand the characteristics of the trend we have observed here.

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Brian Johnson M.S., R.T. (N)(MR), CNMT
bdj5039@psu.edu
215-989-1421

EDUCATIONAL BACKGROUND:

The Pennsylvania State University, University Park, PA
Ph.D., Kinesiology, May, 2013 (*expected*)
M.S., Bioengineering, May, 2013 (*expected*)
M.S., Kinesiology, August, 2011

Thomas Jefferson University, Philadelphia, PA
Bachelor of Science, Radiologic Science *magna cum laude*, August, 2006

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American Society of Radiologic Technologists Education and Research Foundation Professional Research Grant
Differential Effect of Repetitive Subconcussive Head Trauma in Concussion $9,722

PEER-REVIEWED PUBLICATIONS:

1. **Johnson B**, Zhang K, Gay M, Neuberger T, Hallett M, Horovitz S, Sebastianelli W, Slobounov S (2012) The Use of Magnetic Resonance Spectroscopy (^{1}H-MRS) in the Sub-Acute Evaluation of Athletes Recovering from Single and Multiple MTBI. Journal of Neurotrauma doi:10.1089/neu.2011.2294.
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6. Slobounov S, Gay M, Zhang K, **Johnson B**, Pennell D, Sebastianelli W, Horovitz S, Hallett M (2011) Alteration of brain functional network at rest and in response to YMCA physical stress test in concussed athletes: RsFMRI study. NeuroImage 55:1716-1727.
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