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EXPLORING BRAIN ACTIVATION PATTERNS IN ASYMPTOMATIC ATHLETES WITH AND WITHOUT A HISTORY OF TWO OR MORE CONCUSSIONS

By

Robert J. Elbin III

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ABSTRACT

EXPLORING BRAIN ACTIVATION PATTERNS IN ASYMPTOMATIC ATHLETES WITH AND WITHOUT A HISTORY OF TWO OR MORE CONCUSSIONS

By

Robert J. Elbin III

The long-term effects of multiple concussions in athletes are unclear. Functional magnetic resonance imaging (fMRI) studies have previously reported compensatory brain activation patterns and brain activation (i.e., engagement) differences in symptomatic athletes with a history of multiple concussions. These fMRI findings are in absence of any neurocognitive impairment. No fMRI study has examined brain activation patterns in athletes with a history of concussion who are asymptomatic. **OBJECTIVE:** The current study evaluated neurocognitive performance and brain activation patterns in asymptomatic athletes with and without a history of two or more concussions. **DESIGN:** Paired case-control **SUBJECTS:** Fourteen athletes with a history of two or more concussions were matched (age, sex) to 14 athletes with no history of concussion. **MEASUREMENTS:** A neurocognitive test battery (Trail-Making Test Form A and B, Symbol Digit Modalities Test, and ImPACT); N-back Working Memory Task; Functional MRI. **RESULTS:** Similar performance on the Trail Making Test Form A and B, Symbol Digit Modalities Test, and ImPACT were observed in both groups. The history of concussion group was less accurate than controls on the low (p =.01), moderate (p =.04), and high (p =.02) working memory load. No compensatory brain activation patterns were observed between groups and these common brain regions used to perform the task were used to the same degree during low, moderate, and high working memory demands. **CONCLUSIONS:** Following the resolution of symptoms, a history of two or

more concussions is not associated with reduced neurocognitive performance or compensatory brain activation patterns.

DEDICATION

To my family:

Mom, Dad, Kyle, Kurt, Danae, Grandma, and Pap

"I can do all things through Christ which strengthens me"
Philippians 4:13

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"Nothing in the world can take the place of persistence. Talent will not; nothing is more common than unsuccessful men with talent. Genius will not; unrewarded genius is almost a proverb. Education alone will not; the world is full of educated derelicts. Persistence and determination alone are omnipotent" – John Calvin Coolidge

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CHAPTER I

INTRODUCTION

A recent story published in the New York Times reports that 12 former professional athletes with a history of multiple concussions plan to donate their brains for research after they die (Schwarz, 2008). These athletes currently live with chronic cognitive impairments (e.g., memory problems) and post-concussive symptoms (e.g., recurrent headaches). News of athletes donating their brains comes in the wake of recent scientific findings that propose a link between a history of multiple concussions and the earlier onset of Alzheimer's Disease (Guskiewicz et al., 2005) and depression (Guskiewicz et al., 2007). Moreover, autopsy results from six deceased professional football players (ages 36 to 50 years) with a history of multiple concussions, have revealed clinical pathology (i.e., chronic traumatic encephalopathy: CTE) similar to retired boxers in their 70's and 80's with dementia pugilistica (Casson, Pellman, & Viano, 2006; Omalu et al., 2006; Omalu et al., 2005). Chronic traumatic encephalopathy is associated with loss of neurons, scarring of cortical tissue, and the presence of neurofibrillary tangles which are linked to dementia-like symptoms (Casson et al., 2006). These alarming findings are driving current research efforts with the purpose of providing greater transparency of the long-term consequences that may be associated with multiple concussions.

The potential long-term effects of concussion in professional athletes brought to light in the popular press raises important questions about the possible consequences of concussion in younger populations. For example, based on the aforementioned reports on professional athletes, one can postulate that high school and collegiate athletes with a

history of multiple concussions may experience similar effects that could influence future academic, social, and occupational functioning. In fact, early signs of CTE have been recently found in a deceased 18-year-old football player with a history of multiple concussions (Hohler, 2009). Currently this is the only reported case of CTE in any football player under the age of 36. While this is an important finding, the long-term effects of multiple concussions in high school and collegiate athletes are still unknown.

Overview of the Problem

Approximately 1.6 to 3.0 million concussions occur every year in the United States (Center for Disease Control, 2006). As athletic participation rates continue to rise and concussion surveillance improves, the incidence of sport-related concussion is also expected to increase (Lovell, 2009). Current estimates show that 8.9% of all high school (Gessel, Fields, Collins, Dick, & Comstock, 2007) and 7.9% of all collegiate (Hootman, Dick, & Agel, 2007) athletic injuries are concussions. In addition, recent studies have found female athletes to be at a greater risk for concussion than males at both high school (Gessel et al., 2007) and collegiate levels (Covassin, Swanik, & Sachs, 2003b). The published epidemiological data for sport-related concussion is most likely a conservative estimate, as many concussions go unreported (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). As a result, it has become a priority to educate athletes, coaches, parents, and the overall general public about the signs and symptoms of sport-related concussion. Complementing these educational efforts are recent advances in the fields of neuropsychology, neurology, and sports medicine which have led to improved clinical practices for detecting, diagnosing, and managing this injury.

Sport-related concussion is defined as a "complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" (Aubry et al., 2002, p. 56). This injury occurs from direct impact to the head, face, neck or elsewhere on the body (i.e., whiplash) that accelerates/decelerates the head in a linear or rotational manner (Holbourn, 1945). This abrupt movement causes the brain to make contact with the bony protuberances on the inside of the skull. The impact between the brain and skull causes shearing and stretching injuries to axons that impair neuronal function and also damage blood vessels and capillaries in the brain (Giza & Hovda, 2000). Underlying these events is an unregulated release of excitatory neurotransmitters (e.g., glutamate) which creates an ionic imbalance involving accumulation of extracellular potassium (K^+) and intracellular calcium (Ca^{2+}) (Giza & Hovda, 2001). The brain responds to this imbalance by activating sodium (Na) and K^+ pumps which require large amounts of energy (e.g., glucose). However, an energy crisis develops such that the need for glucose is not sufficiently met due to the dysfunction of the autoregulatory properties of the cerebrovascular system (Giza & Hovda, 2000). Thus, the concussed brain enters into a depressed state of function that can last for days following injury (Yoshino, Hovda, Kawamata, Katayama, & Becker, 1991). Cognitive changes and symptom sequelae of concussion typically occur in the next 5 to 10 days following injury (Field, Collins, Lovell, & Maroon, 2003; Lovell et al., 2003).

An athlete who sustains a concussion can experience a variety of cognitive, behavioral, and somatic signs and symptoms. These commonly include post-traumatic amnesia (PTA), confusion, dizziness, headache, disorientation, and loss of consciousness (LOC). Traditionally, grading scales and return-to-play guidelines have been used to

assess the severity of concussion (e.g., Grade I, II, or III) and to also determine when an injured athlete may safely return to competition. There are over 19 grading scales and 14 return-to-play guidelines available for use by sports medicine professionals (Collins, Grindel et al., 1999). These management guidelines have been criticized for their lack of empirical support and over-reliance on LOC as a primary marker for assessing severity. However, studies have shown that LOC does not occur as often as once thought, which questions the utility of these management practices (Guskiewicz, Weaver, Padua, & Garrett, 2000). Studies also suggest that these guidelines may be too liberal. For example, researchers have found that mildly concussed athletes (i.e., Grade I severity classification) who were returned to the same game after their sideline symptoms had resolved showed memory impairments 36 hours later (Lovell, Collins, Iverson, Johnston, & Bradley, 2004). In light of these findings and others (e.g., Collins et al., 2003; Guskiewicz et al., 2005; Guskiewicz et al., 2000; McCrea et al., 2004), recent consensus statements and position papers have recommended that the current grading scales be abolished (Aubry et al., 2002).

The increasing popularity of neurocognitive testing has added much needed objectivity to the management of sport-related concussion (Van Kampen, Lovell, Pardini, Collins, & Fu, 2006). The implementation of baseline neurocognitive testing offers a more individualized approach to assessing the cognitive sequelae and symptom presentation following concussive injury. This tool has also afforded researchers the opportunity to identify factors that may influence the neurocognitive recovery from sport-related concussion such as age (Field et al., 2003), sex (Covassin, Schatz, & Swanik, 2007), and history of concussion (Covassin, Stearne, & Elbin, 2008). For example, high

school athletes have been found to demonstrate a longer neurocognitive recovery (e.g., 7-14 days) following concussion than college athletes (e.g., 3-5 days) (Field et al., 2003). Other research has shown that females are at a higher risk for concussion and demonstrate longer recovery times than males (Covassin et al., 2007). In addition to age and sex differences, concussion history has also been suggested to influence the risk and recovery from concussion (Covassin et al., 2008).

Studies have found that athletes with a history of concussion are at a higher risk for future concussive injury. Guskiewicz and colleagues (2003) reported that college athletes with a history of three or more concussions had a higher risk (3.4 times) for sustaining subsequent concussion than those with one (1.5 times) or two (2.8 times) previous incidents. Moreover, athletes with a history of three or more concussions may be predisposed to sustaining more severe concussions in the future. Collins, Lovell, Iverson, Cantu, and Maroon et al. (2002) reported that concussed athletes with a history of three or more concussions were 9.3 times more likely to present three to four abnormal on-field markers (e.g., LOC, PTA, confusion, disorientation) of concussion severity. These studies reveal that a dose-response relationship exists between the actual number of previously sustained concussions and the risk for incident concussion (Guskiewicz et al., 2003).

In addition to this increased risk, studies also suggest that a dose-response relationship exists between the number of previously sustained concussions and recovery time from future concussion. Macciocchi et al. (2001) did not report any differences in attention or processing speed between athletes sustaining their first or second concussion. However, college athletes with a history of two or more concussions have shown memory

impairment and slowed reaction time at 5 days post-concussion compared to athletes without a history of concussion (Covassin et al., 2008). Other researchers reported that athletes with a history of three or more concussions demonstrated worse neurocognitive performance at two days post-concussion than athletes without a history of three or more concussions (Iverson, Gaetz, Lovell, & Collins, 2004). In addition, athletes with three or more previous concussions were also 7.7 times more likely to demonstrate a major decrease in memory performance at 2 days post-injury than athletes with no previous concussion (Iverson, Gaetz et al., 2004).

There is little debate in the extant literature that the risk for future concussion and prolonged recovery from incident concussion may be a function of the number of previously sustained concussive injuries (i.e., dose-response). It seems that although one concussion poses few consequences, the risk and recovery time significantly increases following two previous concussions (Covassin et al., 2008) and may be even more exacerbated following three concussions (Iverson, Gaetz et al., 2004). These studies raise question to the long-term effects of multiple concussions.

Significance of the Problem

The management of a single, uncomplicated concussion often follows a straightforward approach such that athletes can be returned to play once their symptoms and cognitive impairments have resolved. However, this management practice can become complicated when concussed athletes have a prior history of multiple concussions. In these instances sports medicine professionals are often required to make difficult decisions regarding the immediate and long-term participation in sport for that athlete. These decisions can range from prolonged removal from participation to medical

disqualification for the season or even career. These decisions are made with the long-term health and well-being of the athlete in mind. Therefore the question relevant to high school and college athletes is, "How many concussions are too many?"

Studies investigating the potential long-term effects associated with a history of multiple concussions have produced mixed results. Collins and colleagues (1999) found that college football players with a history of two or more concussions performed worse on baseline (i.e., pre-injury) measures of executive function,processing speed, and reported more symptoms than football players with zero or one previous concussion. A related study by Moser, Schatz, and Jordan (2005) found similar performance on measures of attention, concentration, and processing speed between recently concussed high school athletes (within two weeks of study) and high school athletes with a history of two or more concussions (asymptomatic for six months). The results of Moser et al. demonstrate that athletes with multiple concussions who have been asymptomatic for over 6 months, exhibit similar cognitive performance to those athletes who have incurred a recent concussion and are still symptomatic. There seems to be initial support for the notion that multiple concussions are associated with long-term decreases in neurocognitive function in both high school and collegiate athletes. However, the previously mentioned studies that support this premise have all used formal paper-and-pencil neurocognitive test batteries.

Contrary to these findings, the majority of studies using computerized forms of neurocognitive tests have not found any neurocognitive performance differences between athletes with and without a history of multiple concussions (Broglio, Ferrara, Piland, Anderson, & Collie, 2006; Bruce & Echemendia, 2009). Iverson et al. (2006)

found no differences between groups of athletes with zero, one, or two previous concussions on verbal memory, visual memory, reaction time, and processing speed as measured by a computerized neurocognitive test battery (Immediate Post-concussion Assessment and Cognitive Test: ImPACT). Collie, McCrory, and Makdissi (2006) used a different computerized neurocognitive test battery (Concussion Resolution Index: CRI) and also failed to find differences between athletes with and without a history of four or more concussions. At first glance, formal paper-and-pencil neurocognitive tests may be better suited for detecting the potential long-term changes in neurocognitive function than computerized versions. However, Bruce and Echemendia (2009) did not find differences on computerized or paper-and-pencil neurocognitive test batteries between athletes with and without a history of multiple concussions. Researchers have concluded that if long-term effects from multiple concussions do in fact exist, then neurocognitive testing may not be sensitive enough to detect the long-term subtle changes in neurocognitive function (Broglio et al., 2006).

The recent use of Functional Magnetic Resonance Imaging (fMRI) has been found to be sensitive to the effects of concussion (Chen et al., 2004; Jantzen, Anderson, Steinberg, & Kelso, 2004; Lovell et al., 2007). More importantly, this tool has detected differences in brain activation patterns between concussed athletes and non-injured controls in the absence of neurocognitive impairment (Chen et al., 2004; Jantzen et al., 2004; Lovell et al., 2007; McAllister et al., 1999; McAllister et al., 2001). Functional MRI has afforded researchers the opportunity to investigate specific neurological functions of the brain and may be useful in the investigation of potential long-term or cumulative effects associated with multiple concussions.

Of the few fMRI studies that have examined sports-related concussion, all have used some variant of a working memory paradigm. The brain regions involved in working memory are well-documented as this cognitive process is localized to frontal, parietal, and hippocampal areas (E. E. Smith & Jonides, 1998). Furthermore, working memory has been suggested to support higher executive cognitive processes (Chen et al., 2004; Ptito, Chen, & Johnston, 2007), which are commonly affected following sport-related concussion (Field et al., 2003; Lovell, Collins, & Bradley, 2004; Lovell et al., 2003; Lovell, Collins, Iverson et al., 2004). Therefore, working memory paradigms have been a popular choice for observing functional changes in the brains of concussed athletes (Chen, Johnston, Collie, McCrory, & Ptito, 2007; Chen, Johnston, Petrides, & Ptito, 2008; Chen et al., 2004; Lovell et al., 2007; McAllister et al., 1999; McAllister et al., 2001).

The results from fMRI studies exploring brain activation patterns in concussed athletes and mild traumatic brain injury (MTBI) patients have found two distinct patterns of activation between these injured populations and controls. First, concussed athletes appear to demonstrate brain activations outside regions of interest not observed in non-injured controls, which may indicate an effect of neural compensation following concussion (Chen et al., 2004; Jantzen et al., 2004). Second, studies using MTBI patients reported varying degrees of activation, or "engagement," within the same brain regions in MTBI patients and controls. While these studies have had similar purposes (i.e., to study functional changes in brain activity associated with concussion and MTBI), the sample selection criteria was different in regards to the time since last concussion, symptomology, and previous concussion history. As a result, these differences in sample

demographics, not only address a wide variety of research questions, but also reveal new questions that warrant attention.

Jantzen and colleagues (2004) conducted the only prospective fMRI study to-date using eight concussed athletes and non-injured controls. Using fMRI to study brain activity before and approximately one-week following concussion, Jantzen and colleagues found marked increases in the amplitude and extent of blood oxygen level dependent (BOLD) activity in concussed athletes compared to controls. These increases in activity were found in frontal and parietal areas in concussed athletes, which were more than twice the area activated by controls. Moreover, these activation differences were observed in the absence of any declines in behavioral performance for memory, processing, and coordination. Jantzen et al. (2004) concluded that increases in functional activity observed in concussed athletes may reflect recruitment of additional (i.e., compensatory) neural resources following concussive injury.

Other researchers have also found compensatory brain activation patterns in symptomatic concussed athletes with a history of concussion (e.g., one, two , three, four, and five or more previous concussions) studied approximately five months since their last concussion (Chen et al., 2004). Chen et al. used a working memory task during fMRI and found that symptomatic concussed athletes exhibited greater activation in temporal and parietal regions and less activation in frontal areas compared to non-injured controls. There were no behavioral differences on the working memory task between these groups. In a follow-up analysis to these initial findings, Chen and colleagues (2004) retested several concussed athletes approximately three months later when all symptoms had resolved. Again no differences were found on working memory performance; however

brain activation patterns were more localized to frontal areas formerly observed in controls. These results not only underscore the importance of symptomology during the recovery time following concussion, but tentatively support the concept for a neurophysiological recovery as well. Nonetheless, these studies provide support for a compensatory mechanism following concussion observed in athletes who are symptomatic and have a history of multiple concussions.

McAllister and colleagues (McAllister et al., 1999; McAllister et al., 2001) also reported brain activation differences between an older sample (i.e., 30 years old) of symptomatic MTBI patients and controls on an auditory task of working memory (e.g., N-back). At approximately one month post-injury, both MTBI patients and controls performed similarly on the N-back task and demonstrated task-induced activation in the same brain regions in response to increases in working memory load. Within these commonly used brain regions, McAllister and colleagues found varying magnitudes of activation between the MTBI patients and controls. These researchers concluded that this finding best represents an "engagement" difference with respect to increases in working memory load. This may be indicative of a limited working memory capacity or the inability to appropriately allocate resources to meet increased working memory demands (McAllister et al., 2001). The latter explanation could be due to the dysfunction of the central executive component of working memory located in the frontal regions of the brain.

The potential for fMRI in evaluating long-term effects from multiple concussions is promising (Lovell et al., 2007). Researchers who have found a pattern of neural compensation (Chen et al., 2004; Jantzen et al., 2004) and other varying degrees of brain

activation (i.e., engagement differences) (McAllister et al., 1999; McAllister et al., 2001) in concussed athletes and MTBI patients have uncovered many questions that deserve attention. In particular, is there evidence of neural compensation in athletes who are asymptomatic with a history of two or more concussions? Additionally, the neural compensation observed in the concussed brain has not been assessed past five months since injury, which leaves question to the permanence of these brain activation patterns (i.e., brain reorganization). Finally, do the engagement differences found by McAllister et al. (2001) exist in asymptomatic athletes with a history of two or more concussions? No study to date has examined the nature of these brain activation patterns and neurocognitive performance in asymptomatic athletes with a history of two or more concussions.

Purpose of the Study

The main purpose of this study was to explore brain activation patterns relevant to a working memory task in asymptomatic athletes with and without a history of two or more concussions. More specifically, the current study investigated the "compensatory" and the "engagement" mechanisms found in previous fMRI studies using a sample of asymptomatic athletes with a history of two or more concussions. A secondary purpose was to examine differences in behavioral performance on a computerized and paper-and-pencil neurocognitive test battery between asymptomatic athletes with and without a history of two or more concussions. Finally, brain regions that deactivate during working memory will also be explored between asymptomatic athletes with and without a history of two or more concussions.

Hypotheses

H1: There will be no differences on ImPACT verbal memory performance between asymptomatic athletes with and without a history of two or more concussions.

H2: There will be no differences on ImPACT visual memory performance between asymptomatic athletes with and without a history of two or more concussions.

H3: There will be no differences on ImPACT motor processing speed between asymptomatic athletes with and without a history of two or more concussions.

H4: There will be no differences on ImPACT reaction time between asymptomatic athletes with and without a history of two or more concussions.

H5: There will be no performance differences on the Trail-Making Test Form A between asymptomatic athletes with and without a history of two or more concussions.

H6: There will be no performance differences on the Trail-Making Test Form B between asymptomatic athletes with and without a history of two or more concussions.

H7: There will be no performance differences on the Symbol Digit Modalities Test between asymptomatic athletes with and without a history of two or more concussions.

H8: There will be no differences in reaction time on the N-back working memory task between asymptomatic athletes with and without a history of two or more concussions.

H9: There will be no differences in accuracy on the N-back working memory task between asymptomatic athletes with and without a history of two or more concussions.

H10: There will be differences in whole-brain regional patterns of activation relevant to the N-back working memory task, indicative of brain "compensation," between asymptomatic athletes with and without a history of two or more concussions.

H11: There will be differences in the amount of "engagement" in brain regions used when performing the N-back working memory task between asymptomatic athletes with and without a history of two or more concussions.

Exploratory Questions

EQ1: Are there brain deactivation differences between asymptomatic athletes with and without a history of two or more concussions?

Limitations

This study will be limited by: 1) the ability of athletes to accurately self-report history of concussion; 2) the accurate diagnosis of concussion by sports medicine professionals; 3) a selection bias (i.e., convenience sample), as this study will not use a random sample; 4) including only asymptomatic athletes with and without a previous history of two or more concussions; 5) examining brain activation patterns only relevant to working memory task; 6) including only high school and collegiate athletes located in the mid-Michigan area; 7) the listed exclusionary factors; 8) a small sample size and concomitant low power for behavioral hypotheses (i.e., H1- H9)

Assumptions

This study will make the following assumptions: 1) athletes will perform to the best of their ability on neurocognitive testing batteries and N-back working memory paradigm for fMRI; 2) the N-back working memory task used in this study will elicit

brain activation patterns relevant to working memory; 3) subjects will honestly and accurately report concussion history and all other data.

CHAPTER II

REVIEW OF LITERATURE

This review is a comprehensive amalgamation of the literature that has shaped the current knowledge base of sport-related concussion. The first part of this review includes the most recent prevalence and incident estimates for concussion in high school and collegiate athletics. This information is followed by an overview of the commonly used definitions of concussion and the underlying biomechanical and pathophysiological mechanisms that have been proposed to occur during this injury. Next, the advancements in the management of sport-related concussion are detailed with a separate section dedicated to neurocognitive testing.

The remaining portion of this review discusses the factors (e.g., age, sex, and history of previous concussion) that have been found to influence the risk and associated recovery outcomes from sport-related concussion. In particular, the published studies that have investigated the potential cumulative effects of concussion is covered and subsequently critiqued. In response to these criticisms, a rationale for using fMRI to better evaluate the potential long-term effects of multiple concussions is provided.

Concussion in High School and Collegiate Athletics

Sport-related concussion continues to be a serious public health concern (Thurman, Branche, & Sniezek, 1998), as both incidence of injuries and athletic participation rates are on the rise (DeHaas, 2009; NFHSA, 2008). The Centers for Disease Control (CDC) have recently estimated that approximately 1.6 to 3.0 million concussions occur annually in the United States, an estimate that has increased from 300,000 per year in the 1990's (CDC, 2006). Considering these statistics along with

current record-setting participation rates for high school and collegiate male and female athletes (DeHaas, 2009; NFHSA, 2008), it is expected that the annual incidence of sport-related concussion will continue to rise relative to these increases in sport participation (Lovell, 2008).

Recent studies have shown increases in the prevalence and incidence of concussion in both high school and collegiate athletic populations (Gessel et al., 2007; Hootman et al., 2007). Gessel and colleagues (2007) reported that approximately 8.9% of all high school athletic injuries were concussions, which is higher for this age group than the previously reported 5.5% (Powell & Barber-Foss, 1999) and 7.5% (Schulz et al., 2004). These increases are likely due to the increased awareness about the signs and symptoms of concussion. Moreover, Hootman and colleagues (2007) recently summarized the previous 16 years (1988 – 2004) of injury data collected by the National Collegiate Athletic Association Injury Surveillance System (NCAA ISS) in 15 NCAA sports. The NCAA ISS revealed incidence rates for concussion in collegiate athletes range from 5.0% to 18.0% (Gessel et al., 2007; Hootman et al., 2007). It should be noted that women's ice hockey accounted for the upper limit (18%) of the range of concussion incidence in collegiate athletes. This estimate may be misleading (i.e., outlier) as data were only collected for three years (2000-2003) on this sport versus 16 years among the other sports (Hootman et al., 2007). The NCAA ISS began data collection on women's ice hockey in 2000, therefore only three years of data were analyzed for this study. However, these recent injury estimates for college athletes by Gessel et al. (2007) and Hootman et al. (2007) are comparable to previous epidemiological reports that found

concussion comprising 5.9% to 6.2% of all collegiate athletic injuries (Covassin, Swanik, & Sachs, 2003a; Covassin et al., 2003b).

At first glance it seems that sport-related concussion comprises a higher percentage of total injuries among high school compared to college populations. However, these two groups are more similar when considering the actual rates of injury (e.g., athletic exposures). The injury rates for sport-related concussion range from 0.28 (Hootman et al., 2007) to 0.43 (Gessel et al., 2007) concussions per 1,000 athlete-exposures (A-Es) for collegiate athletes and 0.23 concussions per 1,000 A-Es for high school athletes (Gessel et al., 2007). These data suggest that collegiate athletes may have slightly higher injury rates than high school athletes, but concussions most likely represent a greater proportion of injuries at the high school level (Gessel et al., 2007).

Researchers have also examined the sport setting (practice versus competition) in which concussive injury occurs. Gessel et al. (2007) reported that 65.4% of concussions at the high school level occurred during competition whereas only 34.6% occurred during practice. The overall total for high school A-E data indicated a similar trend for concussion incidence, with more concussions occurring during competition (0.53 concussions per 1000 A-Es) than practice (0.11 concussions per 1000 A-Es) (Gessel et al., 2007). Moreover, Gessel et al. (2007) reported higher injury rates for college athletes compared to high school athletes in both competition (1.02 concussions per 1,000 A-Es) and practice (0.28 concussions per 1,000 A-Es). Overall, these data suggest that concussions occur more often in competition than practice.

Certain sports have been identified as having a high incidence rate of concussion. Results from a large database of 396 sport-related concussions, found that the sports of

football (40.5%), girls' soccer (21.5%), boys' soccer (15.4%), and girls' basketball (9.5%) comprised the highest percentage of the total number of concussions, respectively (Gessel et al., 2007). These rankings, with the exception of wrestling and football, are similar to earlier findings by Powell and Barber-Foss (1999) who reported football (63.4%), wrestling (10.5%), boys' soccer (6.2%), girls' soccer (5.7%), and girls' basketball (5.2%) comprised the highest incidence of concussion in high school sports. These findings should not be surprising given that sports with the highest incidence of concussion are primarily contact and/or collision sports such as American football.

Epidemiological studies by Covassin et al. (2003a) and Hootman et al. (2007) utilized the NCAA ISS database to examine the incidence of concussion with respect to all other sports injuries (e.g., ankle sprains, anterior cruciate ligament injury). These investigations revealed that women's ice hockey (18.3%), women's lacrosse (6.3% - 13.9%), women's soccer (5.3% - 11.4%), men's ice hockey (7.9% - 10.3%), men's lacrosse (5.6% - 10.1%), football (6.0% - 8.8%), women's basketball (4.7% - 8.5%), field hockey (3.9% - 7.2%), men's soccer (3.0% - 7.0%), and wrestling (3.3% - 6.6%) had the highest percentage of concussive injuries with respect to all reported athletic injuries. It should be noted that these data collectively suggest a trend that indicate women's sports may have higher prevalence and incidence of concussion among high school and collegiate sports. These sex differences in the risk and rate of concussion will be covered later in this review.

Due to several reasons, estimating the true prevalence and incidence rates for sport-related concussion is a challenging task for both researchers and sports medicine professionals. The lack of consensus on the definition of concussion and its on-field

markers (e.g., LOC, amnesia, confusion) (Aubry et al., 2002); along with the reliance on athletes to self-report their symptoms (McCrea et al., 2004) has made estimating injury rates difficult. The wide range of published epidemiological findings can be attributed to methodological differences across studies including study design (retrospective vs. prospective); different sources of data collection (athletic trainers, coaches, parents); differences between sample populations (age groups, leagues, rules); different definitions of injury; and varying methods of calculating injury rates (per 100 players, A-E). As researchers and clinicians improve efforts to define and detect this injury, future epidemiological studies will be more accurate in determining the prevalence and incidence of concussion.

Definition of Concussion

The term "concussion" has historical roots. Early physicians attempted to describe a head injury that produced a transient change in mental status, brief paralysis, and/or temporary loss of consciousness (LOC) without observable skull fracture (Levin, Benton, & Grossman, 1982). The derivation of the word "concussion" is from the Latin "*concutere*" referring to a clashing together, an agitation, disturbance, or shock of impact (Bailes & Cantu, 2001). This term is synonymous with the older expression "*commotio cerebri*" that has also been used to describe a sudden temporary LOC (Ommaya & Gennarelli, 1975). Ambrose Paré (1510-1590), a French military surgeon, is often credited with popularizing the term "concussion" in his writings where he referred to the "concussion, commotio, or shaking of the brain" (Denny-Brown & Russell, 1941; Verjaal & Van 'T Hooft, 1975). In addition to this brief historical account, The Traumatic Brain Injury Act (1966) introduced the term "traumatic brain injury (TBI)" into federal law in

1966 (Maroon et al., 2000). As a result of the TBI act, concussions are also referred to as mild traumatic brain injury (MTBI). The wide variety of symptom presentation, inconsistent cognitive impairments, and the unclear mechanisms and pathophysiological events that underlie concussion have made defining this injury difficult. The difficulty of this task persists today in the lack of consensus for a universal definition of concussion.

There have been many proposed definitions of concussion that have been constantly revised due to the increasing knowledge about this injury. One of the more long-standing definitions was published more than 40 years ago by the committee on head injury nomenclature of the Congress of Neurological Surgeons (1966). This committee defined a concussion as "a clinical syndrome characterized by the immediate and transient post-traumatic impairment of neural function such as alteration of consciousness, disturbance of vision or equilibrium, etc., due to brainstem dysfunction" (Congress of Neurological Surgeons, 1966, p. 386). However, this definition was criticized for having a number of limitations that included: failure to account for the common symptoms of concussion (e.g., amnesia, confusion); too focused on brain stem dysfunction and LOC; and failure to recognize the role of other affected brain structures (e.g., cortical areas) that may result in persistent physical and/or cognitive symptoms (Aubry et al., 2002; Lovell, 2009).

Two definitions currently used in the literature and by sports medicine professionals have attempted to remedy these limitations. In 1997, the American Academy of Neurology (AAN) defined a concussion as a traumatically induced alteration in mental status (e.g., confusion, amnesia) that may or may not include LOC (AAN, 1997). The most recent definition as proposed by the Concussion in Sport (CIS) group

define a concussion as a "complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" (Aubry et al., 2002, p. 56). Both of these definitions offer a universal description of an injury that is characterized by its individualized presentation in each athlete (Bailes & Cantu, 2001).

The CIS group published five common features of concussion that incorporate clinical, pathological, and biomechanical constructs to supplement the definition of this injury. These defining features of sport-related concussion include: 1) concussion can be caused by direct impacts to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted toward the head; 2) concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously; 3) concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than structural injury; 4) concussion results in a graded set of clinical syndromes that may or may not involve LOC; and 5) concussion is typically associated with grossly normal structural neuroimaging studies (Aubry et al., 2002, p. 7). These supplemental features have expanded the criteria for defining and detecting sport-related concussion to include the different signs and symptoms that accompany this injury. The different signs and symptoms of concussion are determined by both the biomechanical forces associated with concussive trauma and the locally affected brain structures.

Biomechanical Aspects of Concussion

The early work of Denny-Brown and Russell (1940; 1941) paved the way for the future biomechanical investigation of concussion. These pioneering researchers in concussion attempted to experimentally reproduce concussion in the lab by delivering

calculated blows to animals' heads that were either stabilized to a surface or allowed to freely move upon impact. Denny-Brown and Russell (1940; 1941) found it difficult to concuss an animal when its head was stabilized, but successfully induced concussion when animal's skulls were allowed to move freely upon impact. They concluded that the sudden change in the velocity of head movement was essential to consistently produce concussion in animals, and possibly humans.

The differences between these two conditions (stabilized, non-stabilized) involve the nature of the transfer of kinetic energy from a blow to the head. When the animals' heads were stabilized, the kinetic energy simply passed through the head and was transmitted to the fixed surface, leaving the brain unharmed and its function intact (Shaw, 2002). However, these types of impacts typically caused more traumatic structural injuries (e.g., skull fractures and crushing type of injuries) rather than mild (i.e., concussion) internal brain injuries. In contrast, allowing the animals' heads to move freely upon impact caused the kinetic energy from the blow to be entirely absorbed by the head, causing movement of the brain inside the skull. Denny-Brown and Russell (Denny-Brown & Russell, 1941) concluded that the contact between the skull and the brain was the most likely mechanism of concussive injury.

Later studies expanded on the findings of Denny-Brown and Russell (1940; 1941) by describing the brain movement inside the skull during concussive impacts. Holbourn (1943; 1945) categorized the observed vector outcomes following a concussive blow to be either linear (translational) or rotational (angular). An inertial force (e.g., collision with a goalpost or a direct blow to the face) applied linearly to the skull accelerates or decelerates the skull in a straight line. Linear forces imparted to the skull most likely

result in the compression and stretching of axons that led to the disruption and eventual separation of nerve fibers (diffuse axonal injury: DAI) (Povlishock, 1993; Povlishock, Becker, Cheng, & Vaughan, 1983; Povlishock & Christmas, 1995; Povlishock & Coburn, 1989). In contrast, when an inertial rotational force is sustained, the impact can accelerate or decelerate the skull around the midline axis of the body causing cortical shearing and stretching injuries to the brain. Rotational forces commonly occur from a side or lateral impact (e.g., a hook punch in boxing). Later experimental studies were conducted to better examine the subsequent brain movement inside the skull following both linear and rotational impacts.

Holbourn (1943) studied these forces by constructing wax models of a skull that contained a brain-like gelatinous substance. These models were subjected to rotational and linear accelerations that produced shearing and stretching forces on the brain-like gelatinous substance. In his research, Holbourn reported that the brain was mostly resistant to compression during linear acceleration, but susceptible to deformation when accelerated in a rotational manner. Holbourn (1945) also concluded that rotational motion was a significant precursor for producing concussion, as it likely caused axonal shearing and stretching injuries at the cortical surface (i.e., white-gray matter junction). These conclusions were later supported by other researchers who directly observed the movement (e.g., shifting and swirling) of the brain beneath the skull in monkeys (Pudenz & Shelden, 1946). Later studies (Ommaya & Genneralli, 1974) also found consistent success producing concussion in monkeys when subjecting their heads to rotational acceleration forces, which further confirms Holburn's (1943) conclusions.

Acceleration/deceleration concussions can occur from either impact or impulse forces (Ommaya & Gennarelli, 1976; Ommaya & Genneralli, 1974). Impact acceleration/deceleration concussion occurs when the head makes direct contact with an external object that either accelerates or decelerates the head causing injury (Denny-Brown & Russell, 1941). For example a football player making helmet-to-helmet contact with another player, would be classified as an impact acceleration/deceleration injury. In contrast, an impulse injury occurs when the head is indirectly accelerated or decelerated from impacts elsewhere on the body (e.g., whiplash) (Ommaya & Genneralli, 1974). Impact and impulse injuries can injure the brain from the stresses and strains of inertial loading on the brain from sudden movement of the head. However, impact injuries require actual contact between the skull and some external object. This contact can result in skull bending, fracture, and intracranial pressure (ICP) wave propagation (Goldsmith, 1970). The ICP wave propagation, or momentary compression or depression of the skull without fracture, can result in a rapid decrease in intracranial volume with an accompanying increase in pressure (Goldsmith, 1970). This increased pressure then sweeps across the cortical surface and throughout the cranium compromising the integrity of neuronal function along the way (Gurdjian, 1972).

Cerebrospinal fluid (CSF) has been suggested by researchers to play a role in the biomechanical events that underlie concussion (Shelden, Pudenz, Restarski, & Craig, 1944). Within the subarachnoid space, CSF cushions the brain and provides it with the ability to shift or move slightly in response to sudden changes in the velocity of head movement by oscillating, gliding, rotating, swirling, and/or spinning (to a lesser degree) within the cranial vault (Shelden et al., 1944). The CSF converts focally applied external

stress to compressive stress because the fluid follows the contours of the sulci and gyri and distributes the force in a uniform fashion (Pudenz & Shelden, 1946; Shelden et al., 1944). The CSF offers the brain protection during minimal movement, but when the momentum becomes more forceful the brain will come into violent contact with the skull and its bony protuberances (Bailes & Cantu, 2001). This interaction of the brain and skull can result in the compressive, tensile, and shearing stresses on neural tissue and axons commonly seen in concussive injury (Cantu, 1992). More severe movement can even result in contusions or lacerations of neural tissue, as observed in more severe forms of TBI (Shaw, 2002).

Cerebrospinal fluid does not totally prevent shearing forces from being imparted to the brain. When rotational forces are applied, there are three contact areas between the brain and the skull in which shearing forces occur where rotational gliding is hindered. Cantu (1992) reported that at the floor of the frontal and middle fossa; the dura mater-brain attachments (e.g., midline falx cerebri and the tentorium cerebelli); and the dissipation of CSF between brain and skull are areas where rotational gliding of the brain is hindered and pose possible sites for injury.

The dissipation of the CSF between the brain and skull offers an explanation of the mechanism of coup and contre-coup injuries commonly observed in concussive injury. Coup injuries occur primarily to neural tissue directly beneath the skull at the point of impact (Bailes & Cantu, 2001). This injury occurs when the head is in a resting state and is forcibly struck by another object such as an opponent's football helmet (Cantu, 1992). When the head is stationary there is no brain lag or disproportion of CSF (Cantu, 1992). However, following a concussive impact the brain abruptly shifts inside

the skull squeezing away CSF, thus allowing the brain to contact the skull (Cantu, 1992). The resulting shearing stresses are greatest at the site of cranial impact, which better explain the mechanism of the coup injury (Cantu, 1992). Contre-coup injuries commonly occur opposite to the site of cranial impact, but can also occur elsewhere in the brain (Bayly et al., 2005). A contre-coup injury usually occurs when a moving head collides with a non-moving object, such as an athlete falling over backward and striking his or her head on the ground (Cantu, 1992). When the head is moving prior to impact, the brain lags towards the trailing surface which squeezes away the protective CSF. This action allows excess CSF to accumulate in the opposite surface, and permits the shearing forces to be maximal at the site where CSF is thinnest (Cantu, 1992). In conclusion, coup injuries likely result from accelerative forces, whereas contre-coup injuries are likely associated with the deceleration of the skull (Cantu, 1992).

In summary, concussion is best characterized as a mild form of diffuse axonal brain injury that results from the linear or rotational acceleration/deceleration of the skull (Chason, Hardy, Webster, & Gurdjian, 1958; Denny-Brown & Russell, 1941; Gennarelli, 1993; Plum & Posner, 1980). Diffuse axonal injury is better described as an injury to the gray-white matter junction that leads to axonal dysfunction (Gean, 1994). The contact between the brain's cortical surface and the skull's bony protuberances causes a subsequent series of pathophysiological events that occur in the brain.

Pathophysiology of Concussion

Concussive injury usually resolves over a period of three to 14 days (Lovell et al., 2003; McClincy, Lovell, Pardini, Collins, & Spore, 2006) and shows minimal intracranial pathology (Jantzen et al., 2004). Therefore, it has been suggested that concussion

primarily involves temporary neuronal disruption rather than cell death (Giza & Hovda, 2001). Many of the pathological and physiological changes that occur in the concussed brain, or more specifically at the cellular level, have been discovered in both experimental and human studies. These studies indicate that the temporary neuronal dysfunction that follows concussion most likely results from ionic shifts, altered cerebral metabolism, impaired connectivity among brain regions, and/or changes in neural transmission. Giza and Hovda (2001) have described these events as the "neurometabolic cascade" of concussion (See Figure 1).

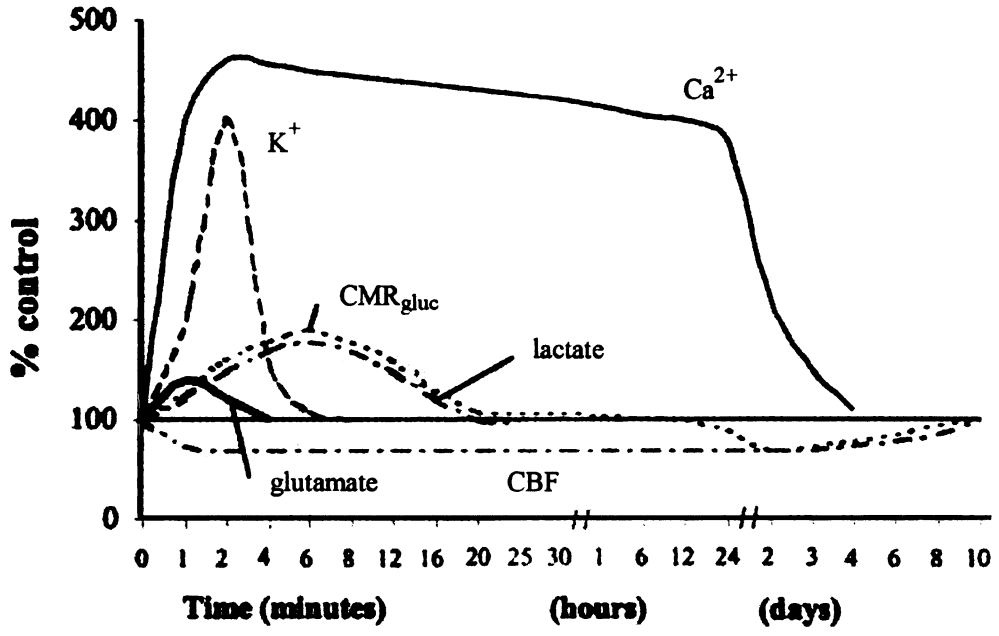

Figure 1. *The neurometabolic cascade following experimental concussion. K^+, potassium; Ca^{2+}, calcium; CMRgluc, oxidative glucose metabolism; CBF, cerebral blood flow.* (Reprinted with permission. Giza C., Hovda D. Ionic and metabolic consequences of concussion. In: Cantu RC, Cantu RI, 2001, *Neurologic Athletic Spine Injuries.* St. Louis, MO: WB Saunders Co; 2000: 80-100.).

The pathophysiological events that occur in the brain following a concussive impact include abnormal ionic fluxes accompanied by an unchecked release of neurotransmitters resulting from axonal stretching, neuronal membrane disruption, and the opening of normally voltage-dependent potassium (K^+) channels (Giza & Hovda, 2001). While the resting membrane potential of the neuron relies on the ratio of extracellular to intracellular K^+ (Sugaya, Takato, & Noda, 1975), concussive trauma can cause depolarization and neural firing that opens K^+ channels leading to the excessive accumulation of extracellular K^+ (Julian & Goldman, 1962; Katayama, Becker, Tamura, Tamura, & Hovda, 1990; Takahashi, Manaka, & Sano, 1981). The nonspecific depolarization causes the release of the excitatory amino acid glutamate, which further facilitates the efflux of K^+ by activating kainate, N-methyl-D-aspartate (NMDA), and D-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors (Giza & Hovda, 2000). The activation of NMDA receptors forms a pore which allows an influx of calcium (Ca^{2+}) into the cell (Cortez, McIntosh, & Noble, 1989). The efflux of K^+, influx of Ca^{2+}, and release of excitatory neurotransmitters together lead to an ionic imbalance in the brain (Katayama et al., 1990).

The concussed brain undergoes a roller coaster of hyper- and hypo-metabolic events in an effort to restore homeostasis in damaged neurons. In an attempt to correct the ionic imbalance, membrane pumps (e.g., K^+, Na) are activated, which require large amounts of adenosine triphosphate (ATP) (Hovda et al., 1999; Rosenthal, LaManna, Yamada, Younts, & Somjen, 1979). This abrupt demand for energy is best met by an increase in glycolysis, which places the brain in a state of accelerated metabolism (i.e.,

hyperglycolysis) (Sunami et al., 1989). Research has shown that increases in glucose utilization occur almost immediately in the concussed rat and last up to 30 minutes for mild concussive injury, and as long as four hours for brain injuries that result in a cerebral contusion (Yoshino et al., 1991). After the initial period of hyperglycolysis the brain enters an energy crisis due to diminished cerebral blood flow (CBF) and a decreased supply of glucose (Giza & Hovda, 2000). The influx of Ca^{2+} into the cells impairs mitochondrial function, ultimately leading to the failure of sufficient energy production (i.e., hypoglycolysis) (Xiong et al., 1998). Cerebral glucose metabolism diminishes in the first 24 hours post-concussion and can remain in this depressed state for five to ten days (Yoshino et al., 1991).

As mentioned above, changes in CBF also contribute to the depressed state of physiological function following concussion. Specifically, changes in CBF cause the brain to experience dysautoregulation (i.e., neurometabolic cascade) that reduces oxygen, blood flow, and glucose (Giza & Hovda, 2001). Normally CBF works in conjunction with neuronal activity and cerebral glucose metabolism (Giza & Hovda, 2001), however researchers (Velarde, Fisher, & Hovda, 1993; Yamakami & Mcintosh, 1989; Yuan, Prough, Smith, & Dewitt, 1988) have found that CBF may be reduced to 50% of normal levels following concussion. Yuan et al. (1988) examined CBF changes in concussed rats and found a significant decrease in CBF in all brain regions immediately after injury. More specifically, hemispheric CBF decreased more than CBF in the brainstem and cerebellum regions. Non-injured control group comparisons revealed reductions in CBF ranging from 5% to 50% between paired brain regions. Yuan and colleagues (1988)

concluded that changes in CBF following brain injury may stem from an increased permeability of cerebral capillaries which causes cerebral edema.

The pathophysiological events that occur after concussion are not fully understood. Many of the abovementioned studies have used various methodologies due to inconsistent methodological designs, limitations inherent to using animal models, and lack of uniform characteristics that accompany injury (e.g., severity, symptom presentation, and cognitive impairments). In addition to these shortcomings and limitations, researchers have also questioned whether concussion is a structural injury or functional disturbance.

Nature of Concussive Injury: Structural or Functional?

Numerous researchers have suggested that concussive injury should be considered a disturbance of neural function rather than a structural injury (Aubry et al., 2002; Chen et al., 2004; Denny-Brown & Russell, 1941; Johnston, Ptito, Chankowsky, & Chen, 2001; Lovell, 2009; Ptito et al., 2007; Verjaal & Van 'T Hooft, 1975). This position is rooted in the frequent presentation of symptoms and cognitive deficits reported by concussed athletes with grossly normal structural neuroimaging (e.g., CT and MRI scans) (Aubry et al., 2002; Bazarian, Blyth, & Cimpello, 2006; McAllister et al., 1999). Moreover, due to the diffuse nature of concussive injury (i.e., DAI), researchers have claimed that structural scans such as CT and MRI contribute little to concussion evaluation (Aubry et al., 2002; Kant, Smithseemiller, Isaac, & Duffy, 1997), but should be used whenever possible to rule out any structural brain lesions (Lovell, 2009). However, functional neuroimaging techniques (e.g., functional magnetic resonance imaging: fMRI, positron emission tomography: PET, single photon emission computed

tomography: SPECT) that examine the metabolic/physiological state of the brain have shown promise as functional brain abnormalities have been found in concussed athletes in absence of any structural damage (Chen et al., 2004; Jantzen et al., 2004; Lovell et al., 2007; McAllister et al., 1999; McAllister et al., 2001).

Signs and Symptoms of Concussion

Concussed athletes present a wide variety of signs and symptoms that may go unrecognized by sports medicine professionals, or even the athletes themselves (Collins & Hawn, 2002). More importantly the signs and symptoms of concussion may occur alone or in combination with each other, thus making every concussed athlete a unique case. When an athlete sustains a concussion he or she may present any of the following on-field signs of injury: dazed and/or vacant facial expression; confusion and/or failure to remember sport responsibilities or assignments; disorientation to the game situation (e.g., score); inappropriate emotional reaction (e.g., laughing, crying); display of incoordination or clumsiness; delayed response to questions; LOC; and/or changes in typical behavior or personality (Aubry et al., 2002; Collins & Hawn, 2002; Kontos, Collins, & Russo, 2004; Lovell & Collins, 1998).

Two of the more recognizable on-field markers of sport-related concussion are LOC and PTA. Sport-related LOC is best described as a state of brief coma in which the eyes are typically closed and the athlete is unresponsive to external stimuli (Symonds, 1962). On-field PTA is typically represented by the length of time between concussion and the point at which the athlete regains normal continuous memory function (Russell & Smith, 1961; Symonds, 1962). There are two types of PTA: retrograde amnesia and anterograde amnesia. Retrograde amnesia is defined as the inability to recall events

occurring during the time immediately preceding concussion, whereas anterograde amnesia refers to the inability to recall events immediately following concussion (i.e., difficulty in forming new memories) (Kontos et al., 2004). It should be noted that disorientation, another common on-field marker, is not associated with memory loss and should not be confused with PTA.

In addition to these commonly observed signs of concussion, athletes may self-report a variety of somatic, neurobehavioral, and neurocognitive symptoms following injury. Somatic symptoms commonly reported by concussed athletes include: headache, nausea, vomiting, balance problems, sensitivity to light/noise, and/or numbness/tingling (Barth et al., 1989; Cantu, 1998a; Maddocks & Dicker, 1989). In addition to somatic symptoms, neurobehavioral symptoms often include: sleeping more/less than usual, drowsiness, fatigue, sadness, and nervousness. Additional neurocognitive symptoms may also include: feeling "slowed down," mental fogginess, difficulty concentrating, and memory difficulties (Aubry et al., 2002; Collins & Hawn, 2002; Kontos et al., 2004; Lovell, Iverson, Collins, McKeag, & Maroon, 1999; Piland, Motl, Guskiewicz, McCrea, & Ferrara, 2006).

The signs and symptoms that are observed and/or reported following concussion are localized to the underlying affected brain structures (Bailes & Cantu, 2001; Collins & Hawn, 2002; Kontos et al., 2004). Therefore an athlete who sustains a blow to either side of the cranium (right or left temporal lobe) may experience memory disturbance (i.e., amnesia) and/or confusion. Similarly, a blow to the frontal region of the head (i.e., frontal lobes) may result in subtle mood/personality changes, planning difficulties (e.g., failure to execute sport assignments), and overt confusion. Athletes who sustain trauma to the

back of the head will most likely present slowed processing, dizziness, photophobia, tinnitus, and possible visual disturbances (e.g., double or blurry vision). Interestingly, concussive impacts to the back of the head more likely result in LOC, due to the close proximity of this area to deeper cortical structures (Collins & Hawn, 2002; Kontos et al., 2004). It should be noted that in the case of a contre-coup injury, trauma would likely occur to the site opposite of injury in these examples.

The role that LOC has in the detection and diagnosis of concussion has been debated, as recent studies suggest that this on-field sign is not as prevalent as once thought (Aubry et al., 2002; Collins, Grindel et al., 1999; Gessel et al., 2007; Guskiewicz et al., 2000; Lovell, Collins, Iverson et al., 2004; Lovell et al., 1999). Guskiewicz and colleagues (2000) recorded self-reported symptoms following 1,003 diagnosed concussions in a sample of college and high school football players. Over a three-year period only 8.9% of concussions actually resulted in LOC, while 27% of concussions were associated with PTA. More importantly, Guskiewicz and colleagues (2000) found that headache (86%) was the most commonly reported symptom followed by dizziness (67%), and confusion (59%). These findings have been supported by other studies that have found LOC not to be as prevalent or the most significant predictor of concussion (Collins et al., 2003; Gessel et al., 2007). In response to these findings, LOC has been suggested to be a relatively uncommon sign of concussion and should not be the sole criterion in defining this injury (Aubry et al., 2002; Collins et al., 2003; Guskiewicz et al., 2005; Guskiewicz et al., 2000).

The signs and symptoms of concussion usually resolve within seven to ten days (Field et al., 2003), but memory difficulties have been documented up to two weeks post-

concussion (McClincy et al., 2006). However, approximately 10% of people who sustain a concussion can remain symptomatic for three to six weeks post-injury (Willer & Leddy, 2006). Post-concussion syndrome (PCS) is defined as 1) cognitive deficits in attention or memory, and 2) at least three or more of the following symptoms that last at least three months: fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, apathy, or personality change (Boake, McCauley, & Levin, 2005). Athletes who develop PCS can have their lives drastically affected as persisting symptoms can influence academic performance (persisting headache, attention and concentration difficulties) and overall well-being. There is currently no scientifically-validated treatment for PCS besides rest and cognitive rehabilitation (Willer & Leddy, 2006). Furthermore, the diagnosis of PCS is controversial, as these lingering symptoms are common among the general population (Willer & Leddy, 2006).

Sports medicine professionals responsible for detecting, diagnosing, managing, and making return-to-play decisions make these assessments from the signs and symptoms presented and/or reported by the concussed athlete. Their reliance on athletes being forthright, honest, and knowledgeable of the symptoms of concussion has made detecting, diagnosing, and managing this injury very difficult. It is not surprising that many concussions go undetected due to the failure of athletes to report or even minimize concussion symptoms (Bailes & Cantu, 2001).

The underreported nature of concussion symptoms has received attention from recent researchers (Delaney, Lacroix, Leclerc, & Johnston, 2002; Kaut, DePompei, Kerr, & Congeni, 2003; McCrea et al., 2004). McCrea et al. (2004) administered an end-of-season survey to 1,532 high school football players that inquired whether they

experienced any signs or symptoms associated with concussion during the previous season. After being briefed on the signs and symptoms of concussion, approximately 15% (n = 229/1,532) of athletes indicated that they most likely sustained a concussion; while less than half (47.3%) of these athletes reported their signs and symptoms (McCrea et al., 2004). A similar study by Kaut et al. (2003) surveyed 461 collegiate athletes over a six-year period, and found that over 25% of athletes reported experiencing a blow to the head causing somatic symptoms (e.g., seeing stars, nausea/vomiting, headache, etc...). However, only 19% reported their symptoms while the remaining athletes continued to participate in sport. These studies better quantify the under-reported nature of concussion in both high school and collegiate populations, and have led researchers to investigate plausible explanations for these behaviors.

There are numerous reasons why athletes do not report symptoms of concussion (Garrick, 2005; Kaut et al., 2003; McCrea et al., 2004; Williamson & Goodman, 2006). These reasons include: symptoms not severe enough to warrant medical attention; fear of being withheld from competition; lack of awareness or knowledge of the signs and symptoms of concussion; and not wanting to let teammates down by being injured (Kaut et al., 2003; McCrea et al., 2004). Kaut and colleagues (2003) also reported that over half (56%) of surveyed athletes did not know the possible consequences that can occur from unreported head injury (i.e., playing with a concussion). Therefore, athletes themselves may not be sufficiently aware of the signs, symptoms, and potential catastrophic effects of concussion.

Athletes who fail to report a probable concussion place themselves at an increased risk for more serious consequences if they sustain a second head injury before their

symptoms fully resolve (Cantu, 1992, 1998a; Cantu & Voy, 1995; McCrory & Berkovic, 1998; Saunders & Harbaugh, 1984). The primary concern in this regard is the potential for catastrophic injury, such as second-impact syndrome (SIS) (Cantu, 1992; Cantu & Voy, 1995; McCrory & Berkovic, 1998; Saunders & Harbaugh, 1984). Second-impact syndrome is best described as diffuse cerebral swelling leading to the rapid development of cerebral vascular congestion, which in turn causes increased intracranial pressure that often results in brainstem herniation and death (Cantu, 1992, 1998a; Cantu & Voy, 1995; McCrory & Berkovic, 1998).

Cantu (2003) summarizes the events from three athletes who sustained a second concussive blow resulting in SIS. Cantu (2003) emphasizes that the second concussive injury can be minor, such as a whiplash injury that snaps the athlete's head causing accelerative forces to the brain. The injured athlete, although appearing stunned, seldom loses consciousness and may be able to walk off the playing field. However, within seconds to minutes of impact the athlete collapses to the ground, semicomatose with rapidly dilating pupils, loss of eye movement, and evidence of respiratory failure (Cantu, 1992). The pathophysiological events that follow include the loss of autoregulation of cerebral blood supply leading to vascular engorgement within the cranium (Cantu, 2003). An immediate increase in intracranial pressure follows, which in turn lead to brainstem herniation, coma, and eventual respiratory failure (Cantu, 2003).

Second-impact syndrome most commonly occurs in younger athletes between the ages of 12 to 18 years old (Cantu, 1998a, 2001; Cantu & Voy, 1995). The development of the brain during adolescence has been suggested to be a time of increased risk of adverse consequences following concussion (Field et al., 2003). This increased risk is most likely

due to the biomechanical, pathophysiological, and anatomical differences between younger and older athletes. These age differences will be expanded upon later in this literature review. Nonetheless, proper management of sport-related concussion helps to lessen the risk of catastrophic consequences such as SIS.

Management of Sport-Related Concussion

The management of sport-related concussion has seen vast improvement over the past decade. Results from empirical studies have increased the knowledge and awareness of sport-related concussion that has refined management strategies, benefitting both sports-medicine professionals and injured athletes. More specifically, this progress has seen the suggested abolishment of historically utilized concussion grading scales, improved diagnostic methods, individual case management recommendations, and the utilization of computerized neurocognitive test batteries to improve the management of this injury (Aubry et al., 2002; McCrory et al., 2005).

Grading scales and return-to-play guidelines. When an athlete presents and/or reports signs and symptoms of concussion, sports medicine professionals take certain steps to begin managing this injury. These steps, or protocols, have the purpose of assessing the severity of the injury and making a determination of when the athlete may safely return to play. The severity of concussion has been traditionally assessed by "grading," or assigning a numerical value (e.g., Grade 1 (Mild); Grade 2 (Moderate); Grade 3 (Severe) to the injury. Researchers have suggested that a concussion of greater severity (e.g., Grade 3) would most likely result in a greater number and duration of symptoms and cognitive impairments during the acute (i.e., sideline) and prolonged (i.e., days or weeks post-injury) recovery period (Guskiewicz et al., 2000). In addition, the

majority of these grading scales correspond to a return-to-play guideline that provides recommendations on when the concussed athlete may return to play. In theory, these guidelines make concussion management a uniform process that manages all injuries the same within their respective "grade" or numerical classification. However, researchers have criticized grading scales for their lack of consensus among sports-medicine professionals on which one to use; the over-reliance on LOC as a primary marker of severity (Kelly, Lissel, Rowe, Vincenten, & Voaklander, 2001), inability to account for individual recovery rates and symptom presentations (Aubry et al., 2002; McCrory et al., 2005), and lack of empirical support (Collins, Lovell, & McKeag, 1999). Nonetheless, it is important that the more common grading scales and return-to-play guidelines are reviewed, as they have formed the foundation of concussion management strategies used today.

There are approximately 17 grading scales and 14 return-to-play guidelines currently available to sports medicine professionals (Cantu, 1998b; Collins, Lovell et al., 1999). The more widely used management guidelines are the American Academy of Neurology (AAN) (1997), Cantu's Grading Scales (1986; 2001), and the Colorado Medical Society Guidelines (1994) (See Tables 1 and 2). These grading scales are similar with respect to recognizing the presence of on-field LOC and PTA as primary markers of severity, but differ on the duration of these two symptoms. Similarly the return-to-play guidelines permit mildly concussed athletes to return to the same game they were injured in, a practice that has been recently questioned (Aubry et al., 2002). These management guidelines offer a protocol for assessing concussion, but researchers have since questioned their utility in accurately assessing the severity of injury and

determining when an athlete can safely return to play (Cantu, 2001; Collins & Hawn, 2002; Collins, Lovell et al., 1999; Lovell et al., 1999).

It should be noted that a revision of Cantu's (Cantu, 1986) grading system was published in 2001 (Cantu, 2001). This revision included "observed signs and symptoms" in each numerical grading classification as well as a delineation of on-field PTA to specifically include retrograde and anterograde amnesia. While this revision better reflects the wide variety of symptomology associated with concussion, these guidelines are still a rigid, uniform approach to assessing concussion severity and primarily base return-to-play decisions on LOC and PTA.

Table 1

Description of AAN (1997), Cantu (1986; 2001), and Colorado Medical Society (1994) Grading Scales

	Severity of Grade		
Guideline	1	2	3
Cantu (1986)	(1) No LOC (2) PTA lasts < 30 min	(1) LOC lasts < 5 minutes. OR (2) PTA lasts > 30 minutes	(1) LOC lasts > 5 minutes. OR (2) PTA lasts > 24 hours
Cantu Revised (2001)	(1) No LOC (2) PTA* or post-concussion signs and symptoms lasts less than 30 min	(1) LOC lasts < 1 minute OR (2) PTA* lasts > 30 minutes, but < 24 hours	(1) LOC lasts > 1 minute OR (2) PTA* lasts > 24 hours OR (3) Symptoms lasting > 7 days
Colorado	(1) Confusion without amnesia (2) No LOC	(1) Confusion with amnesia. (2) No LOC	(1) LOC (any duration)
AAN	(1) Transient confusion (2) No LOC (3) Concussion symptom or mental status change resolves in < 15 minutes.	(1) Transient confusion (2) No LOC (3) Concussion symptom or mental status change resolves in > 15 minutes.	(1) LOC (brief or prolonged)

*retrograde or anterograde

Table 2

Description of AAN (1997), Cantu (1986; 2001), and Colorado Medical Society (1994) Return-to-Play Guidelines

	Severity of Grade		
Guideline	1	2	3
Cantu (1986)	Athlete may return to play that day in select situations if normal clinical examination at rest and exertion. If symptomatic, athlete may return to play in 7 days.	Athlete may return to play in 2 weeks if asymptomatic at rest and exertion for 7 days.	Athlete may return to play in 1 month if asymptomatic at rest and exertion for 7 days.
Cantu Revised (2001)	No LOC; PTA* or PCS < 30 min.	LOC lasting < 1 min.; PTA* or PCS > 30 min., but < 24 hrs.	LOC > 1 min. or PTA* > 24 hrs.; PCS > than 7 days
Colorado	Remove athlete from contest and evaluate immediately and every 5 minutes. Permit athlete to return if amnesia or symptoms do not appear for 20 minutes.	Remove athlete from contest and disallow athlete to return. Permit athlete to return to practice after 1 week if asymptomatic.	Transport athlete to hospital. Perform neurological examination and observe overnight. Permit athlete to return to play after 2 week if asymptomatic.
AAN	Examine athlete immediately for mental status changes. Return to contest if no symptoms or mental status changes at 15 minutes.	Remove athlete from game and disallow to return. Athlete can return in 1 week if asymptomatic.	Remove athlete from contest and transport to hospital. Permit athlete to return to play if asymptomatic 1 week (if LOC was brief) or 2 weeks (if prolonged LOC).

*retrograde or anterograde

The previously reviewed guidelines refer to a single concussive episode, which may not be applicable to injured athletes with a history of previous concussions. Sports medicine professionals are responsible for determining when an athlete should miss significantly more time from competition or even be disqualified for the remainder of the season or career. The management guidelines for athletes with a previous history of concussion are described in Table 3 (Cantu, 2001). These guidelines offer sports medicine professionals a framework in which to base their decisions from, however, of note is their predominant reliance on the existing grading scales, which has been questioned similar to the previously reviewed management guidelines (Aubry et al., 2002; Cantu, 2001).

Table 3

Guidelines for Return to Play after Multiple Concussions (Cantu, 2001)

	First concussion	Second concussion	Third concussion
Grade 1 (Mild)	May return to play if asymptomatic for 1 week	Return to play in 2 weeks if asymptomatic for 1 week	Terminate season; may return to play next season if asymptomatic
Grade 2 (Moderate)	Return to play after asymptomatic for 1 week	Minimum of 1 month; may return to play then if asymptomatic for 1 week; consider terminating season	Terminate season; may return to play next season if asymptomatic
Grade 3 (Severe)	Minimum of 1 month; may then return to play if asymptomatic	Terminate season; may return to play next season if asymptomatic	

It is well documented that concussion management guidelines are anecdotal in nature and predominantly based on expert opinion rather than on empirical data (Collins, Lovell et al., 1999). Furthermore, there is a lack of consensus among sports medicine professionals on which management guidelines to use. This lack of concordance increases the subjectivity of concussion management decisions and the risk of prematurely returning a concussed athlete back to competition. Researchers have also investigated on-field LOC and PTA as predictors of symptom presentations and cognitive

outcomes following concussion, as they are a center-piece to the previously reviewed grading scales.

Studies conducted in populations of MTBI patients failed to report any post-injury differences on measures of cognitive performance when using on-field LOC as a grouping variable (Kelly et al., 2001; Leninger, Gramling, Farrell, Kreutzer, & Peck, 1990; Lovell et al., 1999). Lovell et al. (1999) administered a battery of neurocognitive tests to a sample of mild head injury patients (approximately 28 years of age) within a week of injury. More specifically, these researchers compared neurocognitive performance between two groups of patients, those who experienced LOC at the time of injury and those who did not experience LOC. As hypothesized all head injury patients demonstrated poor neurocognitive performance on measures of language, concentration, learning, memory, and executive functioning due to effects from injury. However these performance decrements were not significantly different between the LOC and no LOC groups. Lovell and colleagues (1999) concluded that there is no more support for weighing LOC more heavily than other on-field markers (e.g., amnesia or confusion). These results are supported by Leninger, Gramling, Farrell, Kreutzer, and Peck (1990) who also found no differences between LOC and symptomatic mild head injury patients on a battery of neurocognitive tests. These findings question the use of on-field LOC as hallmark symptom of concussion severity, but are also limited in their generalizeability to athletic populations.

McCrea et al. (2002) investigated both acute (i.e., sideline) and long-term (i.e., days following injury) neurocognitive outcomes associated with on-field presentations of LOC and PTA. Using a sample of concussed high school and collegiate football players,

McCrea et al. (2002) prospectively examined neurocognitive function at the approximate time of injury and at post-injury intervals of approximately 15 minutes, 48 hours, and 90 days post-concussion. Concussed athletes were separated into three groups (LOC, PTA, no LOC/PTA) with respect to their on their on-field markers of injury. The Standardized Assessment of Concussion (SAC) was used to assess cognitive orientation, concentration, and immediate and delayed memory. At the time of injury and at 15-minutes post-injury, all athletes (regardless of group) presented immediate and delayed memory impairment relative to baseline scores. These impairments were not evident at 48 hours or 90 days post-concussion, which suggests a recovery within 48 hours of injury.

Further analyses by McCrea et al. (2002) revealed between-group differences on overall SAC performance immediately following concussion. Athletes who experienced LOC were more severely impaired on the SAC immediately following injury than the other two groups (PTA and no LOC/PTA). In addition, athletes who experienced PTA performed worse than the no LOC/PTA group. Although neurocognitive impairments for all groups were resolved by 48 hours post-concussion, athletes who did not experience LOC or PTA demonstrated cognitive recovery within the first 15 minutes. In contrast, the LOC and PTA groups remained impaired at 15 minutes, but recovered by 48 hours. These findings suggest that LOC is likely associated with early deficits following concussion, but may not specifically imply injury severity as measured by recovery time (Erlanger et al., 2003; McCrea et al., 2002).

Researchers have suggested that PTA may be more predictive of long-term impairments and symptoms than LOC (Collins et al., 2003; Erlanger et al., 2003). Collins, Iverson, Lovell, McKeag, and Norwig et al. (2003) investigated the relationship

between on-field markers of concussion (disorientation, PTA, LOC) and neurocognitive performance. Seventy-eight athletes were administered a computerized neurocognitive test battery (ImPACT) and symptom inventory during preseason (i.e., baseline) and approximately 2 days post-concussion. Concussed athletes were classified into two groups based on post-concussion neurocognitive performance and symptoms. Athletes in the "good" post-injury group did not demonstrate any measureable change on these post-injury neurocognitive measures when compared to their baseline, while the "poor" group was comprised of athletes who demonstrated a significant decline in memory performance and an increase in reported symptoms. Results indicated that athletes in the "poor" post-injury group were over 10 times more likely to exhibit retrograde amnesia following concussive injury when compared to the 'good' group (Collins et al., 2003). Moreover, the "poor" post-injury group was over four times more likely to exhibit PTA and present at least five minutes of mental status change at the time of injury. Strikingly there were no differences between groups in terms of on-field LOC, which suggests that LOC may not be as predictive of post-concussion impairments at 2 days post-injury as once thought.

Using a sample of 47 high school and collegiate athletes, Erlanger and colleagues (2003) found LOC to only be associated with initial (i.e., sideline) estimates of severity, as this on-field marker did not associate with the total number of symptoms at 2 days post-injury or the overall duration of symptoms. Similar to Collins et al. (2003), Erlanger and colleagues (2003) reported that on-field PTA was a better predictor of severity at 2 days post-injury. These findings collectively suggest that predicating concussion

management strategies around LOC may not be advantageous for assessing severity, or making appropriate return-to-play decisions (Collins et al., 2003; Erlanger et al., 2003).

Determining when an athlete can safely return to play following concussion has been a germane issue among both clinicians and researchers. At the center of this debate lies the issue of whether or not to return a mildly concussed athlete to the same game/practice he or she was injured. Athletes often refer to a mild concussion as a "bell-ringer" or "ding" (Guskiewicz et al., 2004; Lovell, Collins, Iverson et al., 2004). This terminology is commonly used by athletes and even coaches to describe a very brief and short-lasting episode of concussion symptoms (e.g., headache, disorientation, confusion, etc...) that dissipate rather quickly and may even go unreported by the injured athlete. Return-to-play guidelines permit mildly concussed athletes (i.e., Grade I) to return to the same game if they did not experience any LOC or PTA, symptoms resolve on the sideline within 15 minutes, and successfully complete all sideline mental assessments (American Academy of Neurology, 1997; Cantu, 2001; Colorado Medical Society, 1994). However researchers have questioned returning athletes with a Grade I concussion to the same contest, as memory impairments have been found days later (Lovell, Collins, Iverson et al., 2004).

Lovell, Collins, Iverson, Johnston, and Bradley (2004) prospectively assessed neurocognitive function and post-concussion symptom reporting in a sample of high school athletes who sustained a Grade I concussion. These researchers found declines in memory performance and increased symptom reporting at approximately 36 hours post-injury, which raises concern for allowing athletes with a "mild" concussion to return to the same game/practice they were injured. Other studies have indicated that 33% (10/30)

of concussed athletes who were permitted to return to the same contest they were injured in, later reported a delayed onset of symptoms at 3 hours post-concussion, while only 12.6% (20/158) of concussed athletes who were not permitted to return experienced delayed symptoms (Guskiewicz et al., 2003). These results suggest that return-to-play recommendations for Grade 1 concussions may be too liberal, and directly question the decision to permit a mildly concussed athlete back to the same competition/practice he or she was injured in (Aubry et al., 2002; McCrory et al., 2005). Moreover, the terms "bell-ringer" or "ding" may trivialize the seriousness of concussive injury, even in mild cases (Guskiewicz et al., 2004).

Sport-related concussion consensus and position statements. The criticisms and shortcomings of management guidelines have been addressed in more recent consensus papers and position statements (Aubry et al., 2002; Guskiewicz et al., 2004; McCrory et al., 2005). The CIS group was assembled at the 1st International Symposium on Concussion in Sport held in Vienna, Austria in 2001 (Aubry et al., 2002), and more recently convened in Prague, Czech Republic in 2004 (McCrory et al., 2005). This panel of medical experts, from the fields of neurology, neuropsychology, and athletic training, convened with the purpose of amalgamating current literature to form the basis of a comprehensive systematic approach for managing sport-related concussion. Published summaries of these symposiums, along with a recent position statement from the National Athletic Training Association (NATA) (Guskiewicz et al., 2004), have revised traditionally used sport-related concussion management protocols (Aubry et al., 2002; Guskiewicz et al., 2004; McCrory et al., 2005).

The recommendations made by the CIS group question the last decade of clinical practice with respect to grading scales. These experts recognized the limited empirical support for grading scales and in turn, recommended abolishing these management practices (Aubry et al., 2002; McCrory et al., 2005) or grading concussions retrospectively (Guskiewicz et al., 2004). In addition, it was agreed upon that any athlete who sustains a concussion and is still demonstrating signs and symptoms of concussion should not to be returned to the same contest (Aubry et al., 2002; Guskiewicz et al., 2004). Concussed athletes should also be regularly monitored for any signs of deterioration and receive a full medical evaluation following injury (e.g., clinical exam, posturography, neurocognitive testing) (Guskiewicz et al., 2004). In the event of a more serious injury (prolonged LOC; focal neurological deficit; seizure activity; or persistent post-concussive symptoms) structural neuroimaging should be employed to rule out subdural or epidural hematoma, structural lesion, or skull fracture (Guskiewicz et al., 2004). However, it was recognized by the CIS group that these conventional imaging methods (CT, MRI) are not useful in detecting the subtle effects of sport-related concussion (Aubry et al., 2002).

The return-to-play recommendations made by the CIS Group, and similarly the NATA position statement, are centered on a medically supervised step-wise process (Aubry et al., 2002; Canadian Academy of Sport Medicine Concussion Committee, 2000; McCrory et al., 2005). These stages are based on the possibility of symptoms returning from progressive physical and sport-specific exertion (Guskiewicz et al., 2004). The recommended return-to-play stepwise process following a concussion includes: 1) No activity, complete rest until asymptomatic, 2) Light aerobic exercise such as walking or

stationary cycling, no resistance training, 3) Sport specific exercise and progressive addition of resistance training, 4) Non-contact training drills, 5) Full contact training after medical clearance, and 6) Game play (Aubry et al., 2002; McCrory et al., 2005). The CIS group recommends that injured athletes should continue to proceed to the next level if they remain asymptomatic at the current stage. If concussion symptoms reappear, the athlete should revert back to the previous asymptomatic stage and resume the progression after 24 hours (Aubry et al., 2002). These guidelines allow for a more individualized approach when returning an athlete back to competition from concussion.

Consensus statements and position papers have stressed that sports medicine professionals should take a multidisciplinary approach when managing concussion (Aubry et al., 2002; Guskiewicz et al., 2004). It is imperative that persons (coaches, parents, teachers, teammates, medical staff, etc...) directly involved in the lives of concussed athletes be cognizant of the post-concussion sequelae, and is respectful and compliant with medical decisions. Student-athletes recovering from concussion may need to be excused from academic classes and commitments, as activities that tax the brain may exacerbate symptoms and delay recovery (McCrory et al., 2005).

Lastly, experts recommend that the management of sport-related concussion take a multifaceted (sideline assessment, clinical exam, posturography, follow-up neurocognitive testing) approach (Aubry et al., 2002; Guskiewicz et al., 2004; McCrory et al., 2005). The NATA position statement recommends utilizing a wide variety of these valid and reliable concussion management tools, as concussion often presents in many different ways (Guskiewicz et al., 2004). One tool that has received increased attention is

neurocognitive testing, as it adds objectivity to return-to-play decisions and has been suggested to be the "cornerstone" of concussion management (Aubry et al., 2002).

Neurocognitive testing and sport-related concussion. Neurocognitive testing has been suggested to reveal a more complete picture of the cognitive sequelae that follows sport-related concussion; that can be missed by only assessing reported symptoms and post-injury behaviors (Kontos et al., 2004). This management tool has also proven valuable in assessing the long-term cognitive recovery from concussion (Guskiewicz et al., 2004). Since concussive injury may affect different anatomical areas of the brain, neurocognitive test batteries administered to concussed athletes should evaluate multiple aspects of cognitive function (Collins & Hawn, 2002). For a review of neurocognitive batteries see Grindel, Lovell, and Collins (2001). The neurocognitive domains most susceptible to change in the days following concussion include attention and concentration, cognitive processing speed/efficiency, learning and memory, working memory, executive function and verbal fluency (Guskiewicz et al., 2004). More specifically, the domains of attention, concentration, and memory function are most sensitive to the acute effects of concussion (Echemendía, Putukian, Mackin, Julian, & Shoss, 2001; Guskiewicz, Ross, & Marshall, 2001; Macciocchi, Barth, Alves, Rimel, & Jane, 1996; Macciocchi, Barth, & Littlefield, 1998).

The benefits of employing neurocognitive testing following MTBI has been documented in earlier studies by Rimel, Giordani, Barth, Boll, and Jane et al. (1981) and Yarnell and Lynch (1970). Rimel et al. (1981) is credited as one of the first studies to emphasize the importance of neurocognitive testing for MTBI. Using a large sample of MTBI patients, Rimel and colleagues (1981) found neurocognitive impairments in the

domains of higher level cognitive function (e.g., memory, planning, and reaction time) problem-solving, attention, and concentration at approximately 3-months post-injury. Another study by Yarnell and Lynch (1970) assessed memory retention in four concussed football players. Injured athletes did not demonstrate any retrograde amnesia for approximately 1 to 3 minutes following concussion. However, retrograde amnesia progressively developed at approximately 3 to 20 minutes post-injury. Both these researchers concluded that neurocognitive testing is a valuable tool for measuring cognitive recovery following MTBI, and similarly concussion. However, these studies were conducted retrospectively, which limits their ability to determine cognitive changes and/or improvement from pre-injury (i.e., baseline) to post-injury.

The increased utilization of neurocognitive test batteries following concussion has prompted researchers and clinicians to identify the best practices for using this tool. Researchers have suggested employing baseline testing whenever possible; as it provides a benchmark for comparing post-concussion neurocognitive performance to athletes "normal" pre-injury scores (e.g., prospective design methodology) (Guskiewicz et al., 2004). Baseline testing also has athletes serve as their own controls, which minimizes any confounding factors such as age (Field et al., 2003), sex (Covassin et al., 2007), learning disability (Collins, Grindel et al., 1999), education level, and/or hyperactivity disorders. In addition, sports medicine professionals agree on two general approaches for re-administering neurocognitive tests following concussion. As per the NATA position statement, it is recommended that sports medicine professionals can either re-administer neurocognitive testing only when the athlete is asymptomatic or at fixed time points following concussion (e.g., every 24 to 48 hours) until symptoms and cognitive

performance returns to baseline (Guskiewicz et al., 2004). Regardless of which clinical approach is taken, baseline neurocognitive testing is the key to maximizing the benefits of this tool when assessing the subtle cognitive effects and recovery of concussed athletes (Van Kampen et al., 2006).

A hallmark study conducted by Barth, Alves, Ryan, Macciocchi, and Rimel et al. (1989) was one of the first to prospectively examine changes in neurocognitive performance following sport-related concussion. Approximately 2,300 college football players from 10 universities were baseline tested on four paper-and-pencil neurocognitive tests (Paced Auditory Serial Addition Test, Trail-Making Test A and B, and Digit Symbol Test). There were 183 athletes who sustained a concussion during the four-year study. In an attempt to examine the cognitive recovery from concussion, Barth and colleagues (1989) re-administered neurocognitive testing within 24 hours, 5 days, and 10 days post-injury. Post-concussion neurocognitive performance was compared to 48 age-matched non-injured controls. Significant neurocognitive impairments were reported in the domains of sustained auditory attention and visuomotor speed at 24 hours post-concussion when compared to controls. However, these cognitive deficits were resolved by day 5 and concussion symptoms were resolved by 10 days post-injury. This study was the first to prospectively examine changes in neurocognitive performance following sport-related concussion. However, the controls used in this study were not athletes, which may bias these findings if the groups were different with respect to normative scores. Nonetheless this benchmark study by Barth and colleagues (1989) prompted later researchers to prospectively examine cognitive recovery from sport-related concussion.

In the mid-to-late 1990's, traditional paper-and-pencil neurocognitive tests were used by researchers to examine cognitive recovery time and symptom resolution following sport-related concussion (Collins, Grindel et al., 1999; Hinton-Bayre, Geffen, Geffen, McFarland, & Friis, 1999; Macciocchi et al., 1996; Maddocks & Saling, 1996; McCrory, Bladin, & Berkovic, 1997). These studies targeted older collegiate and professional athletes that participated in sports with a high risk of concussion (e.g., football, rugby). Collins et al. (1999) prospectively administered a battery of eight paper-and-pencil neurocognitive tests to a large sample (n=393) of collegiate football players. Sixteen concussed athletes were re-administered neurocognitive tests within 24 hours of injury, and at 3, 5, and 7 days post-concussion. Significant impairments in verbal learning and delayed memory, with moderate declines in executive function and processing speed, were found at 24 hours and 3 days post-concussion. The researchers reported that cognitive decrements and post-concussion symptomology were resolved by 5 to 7 days and 3 to 5 days, respectively. These findings are in agreement with other researchers who also found impairments in cognitive processing speed and verbal memory that resolved at 7 days post-injury (McCrea et al., 2003), and slowed reaction times that resolved within 5 days post-concussion (Maddocks & Saling, 1996). These studies are among the first to suggest that the recovery time from concussion is approximately 5 to 10 days following injury.

Researchers have identified problematic issues associated with using formal paper-and-pencil neurocognitive test batteries in concussed athletes for both clinical and research purposes (Collie, Darby, & Maruff, 2001). Although these tests offer a more individualized, and empirically-supported approach to managing concussion, they are

also costly, time-consuming, and susceptible to learning effects (Hinton-Bayre et al., 1999). Researchers have responded to these issues by advocating the use of computerized neurocognitive test batteries for examining the subtle cognitive changes in the days following sport-related concussion (Aubry et al., 2002; McCrory et al., 2005).

Computerized neurocognitive testing has been shown to be effective in identifying the subtle changes in cognitive function following concussion (Iverson, Brooks, Collins, & Lovell, 2006; Iverson, Lovell, & Collins, 2005; Lovell & Collins, 2002; Lovell, Collins, Fu, Burke, & Podell, 2001). The use of this tool has allowed for more individualized and empirically-based injury management than traditional LOC-based grading scales (Cantu, 2006; Van Kampen et al., 2006). This method of assessing neurocognitive function offers increased consistency in administration and scoring, the ability to create alternate forms, and the ability to measure several different types of responses at one time (Kane & Kay, 1992). Furthermore, computerized neurocognitive testing is a timely and cost-effective alternative to the paper-and-pencil neurocognitive test batteries, which often require lengthy administrations and the expertise of a licensed neuropsychologist (Goldstein, 1990). From a practical perspective, computerized neurocognitive test batteries make baseline testing more efficient, as many athletes can be tested at one time (Van Kampen et al., 2006). These commercially available computerized neurocognitive tests are listed and described in Table 4.

Table 4

Description of Subtests/Tasks for Available Computerized Neurocognitive Test Batteries

	CogSport	CRI	ImPACT
Subtests/Tasks	Simple/Choice/Complex RT, Monitoring, 1-back, Matching, Incidental & Associate Learning	Simple RT, Cued RT, Visual Recognition, Symbol Scanning, Decoding	Word Discrimination, Visual Working Memory, Sequencing, Visual Attention Span, Symbol Matching, Choice RT

In sum, computerized neurocognitive testing has been a valuable addition for both sports medicine professionals and researchers. Factors such as age (Field et al., 2003), sex (Covassin et al., 2007), learning disability (Collins, Grindel et al., 1999), and concussion history (Iverson, Gaetz et al., 2004) have all been found to influence the risk and recovery from concussion. Not only do these management batteries provide additional information on the cognitive recovery of the concussed athlete, but it has also provided a means for researchers to identify and examine factors that may influence the risk and recovery of sport-related concussion.

Age Differences and Sport-Related Concussion

High school athletes have been found to demonstrate a slower neurocognitive and symptom recovery following concussion than collegiate athletes (Field et al., 2003; Lovell et al., 2003; McCrea et al., 2003; Sim, Terryberry-Spohr, & Wilson, 2008). In a hallmark study, Field et al. (2003) prospectively examined cognitive recovery and

symptom resolution in a sample of concussed high school and collegiate athletes, as well as non-injured controls. High school athletes demonstrated significant memory impairment up to 7 days post-concussion, while memory declines were only observed for the first 24 hours post-concussion in collegiate athletes. In addition to these findings, high school athletes also reported more concussion symptoms than college athletes at 24 hours, 3 days, and 5 days post-injury (Field et al., 2003). Similarly, Lovell et al. (2003) found significant declines in memory performance at 4 and 7 days post-concussion in high school athletes when compared to non-injured athlete controls. The findings by Field et al. (2003) and Lovell et al. (2003) have been supported by other studies that has found age-related differences in recovery time following concussion (Iverson, Brooks, Collins et al., 2006; McClincy et al., 2006).

More recent studies suggest that high school athletes may take longer than 5 to 7 days as previously reported by Field et al. (2003) and Lovell et al. (2003). Iverson et al. (2006) found that 37% (11/30) of concussed high school athletes were still clinically impaired on two or more neurocognitive measures (verbal memory , visual memory, reaction time, processing speed) at 10 days post-concussion. Similarly, McClincy, Lovell, Pardini, Collins, and Spore (2006) found memory impairments for verbal and visual memory, reaction time lasting up to 14 days post-concussion in a sample of concussed high school and collegiate athletes. Unfortunately, a between-group analysis could not be performed because of the very small number of concussed college athletes (n=14) compared to high school athletes (n= 76); however the mean age of the sample was 16.11 years (SD = 1.89), which is of high school age. Nonetheless, these studies suggest that high school athletes may take as long as 2 weeks to recover from concussion.

In contrast to high school athletes, collegiate athletes have been found to demonstrate a faster neurocognitive recovery from sport-related concussion. Macciocchi, Barth, Alves, Rimel, and Jane (1996) prospectively examined neurocognitive function in a sample of 183 concussed collegiate athletes and matched controls. Neurocognitive impairments in sustained auditory attention and visuomotor speed were observed at 24 hours post-concussion and were resolved within 5 days of injury. More recent studies have supported this finding as both McCrea et al. (2003) and Field et al. (2003) did not report any neurocognitive impairments past 5 days post-injury in college athletes. These results suggest that college athletes generally experience a rapid resolution of cognitive impairments following concussion.

Age-related biomechanical differences. In accounting for these age-related differences, researchers have suggested that the immature or developing brain places younger athletes at risk for more adverse outcomes following concussion. Developmental differences in biomechanical and pathophysiological factors have been offered to account for these findings (Buzzini & Guskiewicz, 2006; Field et al., 2003; McCrory, Collie, Anderson, & Davis, 2004). These age-related differences have been suggested to be predicated on the anatomical and physical differences between the adolescent and adult brains as well as the susceptibility of long-term impairments of the developing adolescent brain from head trauma (McCrory et al., 2004).

Developmental factors specific to the immature brain appear to play a role in predisposing youth to adverse outcomes following concussion. Specifically, brain-water content, cerebral blood volume (CBV), level of myelination, and skull geometry have been suggested to affect the biomechanics of concussive injury in younger athletes (Baur

& Fritz, 2004; Gefen, Gefen, Zhu, Raghupathi, & Margulies, 2003; Prins & Hovda, 2003; Thibault & Margulies, 1998). Other contributing factors such as larger head-to-body ratio, thinner skull, larger subarachnoid space in the cranium (e.g., allowing more room for brain movement), and weaker neck muscles have also been identified to lead to more adverse outcomes from concussion in younger athletes (Tierney et al., 2008; Tierney et al., 2005).

Immature musculoskeletal systems have also been shown to play a role in influencing the dynamics of a concussive injury in younger (i.e., weaker and smaller) athletes (Tierney et al., 2008). The kinetic energy transferred to the skull upon impact not only needs to be of sufficient mass and acceleration, but must be absorbed directly by the head in order for a concussion to occur (Shaw, 2002). Younger athletes usually have weaker, less-developed, neck muscles which does not allow them to transfer energy from concussive impact that is directed toward the head throughout the body, thus increasing their risk of concussion (Tierney et al., 2008; Tierney et al., 2005).

Age-related pathophysiological differences. The immature brain has also been shown to be up to 60 times more sensitive to glutamate-mediated *N*-methyl-D-aspartate (NMDA) excitotoxic brain injury (a prevalent neurotransmitter released in the neurometabolic cascade that follows concussion) (McDonald & Johnston, 1990; McDonald, Silverstein, & Johnston, 1988). McDonald, Silverstein, and Johnston (1988) found that immature rats demonstrated a 21 times larger neurotoxic lesion in the brain compared to adult rats after injection of NMDA into the corpus striatum. This hypersensitivity to NMDA may increase the susceptibility to the ischemic and injurious

effects of excitatory amino acids in developing adolescents who sustain a concussion (Biagas, Grundl, Kochanek, Schiding, & Nemoto, 1996; Grundl et al., 1994).

These pathophysiological and biomechanical differences between the developing and the adult brains are plausible explanations for the age-related differences in the risk and recovery of concussion. These differences call attention to the previously reviewed concussion management and return-to-play guidelines, as they assume that the speed of recovery is uniform between younger and older athletes (Field et al., 2003; Sim et al., 2008). Moreover, these guidelines also manage male and female concussed athletes the same. However, recent studies have demonstrated sex differences in the risk and recovery (i.e. symptoms resolution and cognitive recovery) from sport-related concussion (Broshek et al., 2005; Covassin et al., 2007; Covassin et al., 2003b).

Sex Differences and Sport-Related Concussion

There has been a steady increase in female sport participation at both the high school and collegiate levels (DeHaas, 2009; NFHSA, 2008). The National Federation of State High School Associations annual participation report indicates that a record setting 3 million females participated in high school athletics during the 2007-2008 academic year (NFHSA, 2008). All time highs for female sport participation were also found in the college population with 175,994 women athletes participating across all NCAA divisions in the 2007-2008 academic year (DeHaas, 2009). This increase in female sport participation has prompted researchers to investigate sex differences in the prevalence and incidence of sport-related concussion in high school and collegiate populations (Covassin et al., 2003a; Covassin et al., 2006; Gessel et al., 2007; Hootman et al., 2007; Powell & Barber-Foss, 1999).

Studies conducted by Covassin et al. (2003a; 2003b) and Hootman et al. (2007) both identified sex differences in the incidence of sport-related concussion among collegiate athletes. Examining injury data across 15 sports collected by the NCAA from 1997 – 2000, Covassin and colleagues (2003b) found females to be at a greater risk of concussion than males in sports played by both sexes. More specifically, concussions comprised a greater percentage of total injuries for the women's sports of lacrosse (13.9%), soccer (11.4%), and basketball (8.5%) than the men's sports of lacrosse (10.1%), soccer (7.0%), and basketball (5.0%) (Covassin et al., 2003a, 2003b). Hootman and colleagues (2007) recently summarized 16 years (1988-2004) of NCAA injury data and also found differences in the incidence of concussion between male and female athletes. These researchers reported a greater percentage of total injuries in women's soccer (5.3%), basketball (4.7%), and lacrosse (6.3%) when compared to men's soccer (3.9%), basketball (3.2%), and lacrosse (5.6%). These data clearly suggest sex differences in the risk of concussion at the collegiate level, with female athletes having a higher risk. These sex differences have also been explored in high school populations.

There is a dearth of research that has investigated sex differences in the incidence and prevalence of sport-related concussion among high school athletes. However, the few studies that have been published have also found similar epidemiological trends as observed in collegiate populations (Covassin et al., 2003a, 2003b; Hootman et al., 2007). Gessel and colleagues (2007) used an internet-based surveillance system (Reporting Information Online: RIO) to collect injury and exposure data across nine high school sports at 100 high schools in the United States during the 2005-2006 academic year. This data collection period yielded 4,431 sport-related injuries of which 8.9% of them were

concussions. In sports played by both sexes (soccer and basketball), girls had a higher incidence of concussion than boys. Specifically, girls' soccer (21.5%) and basketball (9.5%) had a higher incident of concussion than boys' soccer (15.4%) and basketball (2.81%) (Gessel et al., 2007). These data represent higher estimates than previously reported by Powell and Barber-Foss (1999) who also found higher incidence of concussion in girls soccer (6.2%) and basketball (5.2%) compared to boys soccer (5.7%) and basketball (4.2%). This increase in incidence rates may be due to increased awareness of the signs and symptoms of concussion.

The sex differences in the risk of sport-related concussion have called attention to exploring differences in cognitive outcomes and symptom presentation following this injury. Since males and females differ on cognitive measures of verbal memory,(Boden, Kirkendall, & Garrett, 1998; Covassin et al., 2006; Kimura & Clarke, 2002; Lewis & Kamptner, 1987) perceptual motor speed, (Heaton, Ryan, Grant, & Matthews, 1996; Lewis & Kamptner, 1987) and visuospatial tasks (Beatty, Mold, & Gontkovsky, 2003; Covassin et al., 2006; Lewis & Kamptner, 1987), it is not out of context to explore the nature of these differences following concussion. This disparity in cognitive performance may contribute to different recovery patterns between sexes when neurocognitive testing is being employed (Broshek et al., 2005). Unfortunately empirical work in this area is scant, but the initial findings are promising and warrant further investigation (Broshek et al., 2005; Covassin et al., 2008; Covassin et al., 2006).

Broshek and colleagues (2005) administered a computerized neurocognitive test battery (Concussion Resolution Index: CRI) to 94 male and 37 female athletes prior to (i.e., baseline) and approximately 3 to 4 days following concussion. Post-injury sex

comparisons on neurocognitive measures indicated that female athletes demonstrated significantly more severe cognitive declines (relative to baseline scores) than males in simple and choice reaction time. Significantly more symptoms were also self-reported by females compared to males following concussion. Also females demonstrated cognitive impairment 1.7 times more often than males in simple and choice reaction time. These findings are among the first to suggest that sex differences may exist following sport-related concussion, however athletes in this study were from both high school and collegiate levels with significantly fewer women (28%) than men (72%) which is a limitation to these findings. Nonetheless, more recent studies have also highlighted sex differences in sport-related concussion outcomes.

Covassin et al. (2007) examined sex differences on measures of cognitive performance and self-reported symptoms following sport-related concussion. Similar to Broshek et al. (2005), Covassin and colleagues (2007) also employed a computerized neurocognitive test battery (i.e., ImPACT) at baseline and at approximately 2 and 8 days post-concussion to a sample of 79 (41 male; 38 female) concussed collegiate athletes. These authors found an expected decrease in cognitive performance in male and female athletes at both 2 and 8 days following concussion. However, sex differences in one of four cognitive domains were noted, as concussed females performed significantly worse in visual memory than concussed males at 2 days post-concussion. In contrast, concussed male athletes reported significantly higher symptom scores for sadness and vomit than females. These findings are inconsistent with previous researchers that has shown females, not males, to self-report more symptoms following concussion (Brooks, 2004; Broshek et al., 2005). These differing post-injury outcomes between concussed male and

female athletes have been attributed to various differences in hormonal systems, cerebral organization, and musculature that may influence females' risk for more adverse outcomes following concussion (Broshek et al., 2005).

Factors that account for sex differences on concussion outcomes. There has long been a debate in the literature as to whether estrogen, the primary female sex hormone, has a detrimental or a protective effect on the risk and outcome from brain injury. Animal models have shown that estrogen treatment prior to experimentally-induced brain injury (e.g., fluid percussion brain injury) has had protective effects for male rats but detrimental effects for female rats (Emerson, Headrick, & Vink, 1993). In contrast, Kupina, Detloff, Bobrowski et al. (2003) found estrogen to have a neuroprotective effect, as female mice demonstrated a better outcome compared to male mice following experimental brain injury. Specifically, males had a 20% mortality rate, whereas no deaths were recorded among female mice.

The sex-based differences in neuroanatomy and cerebrovascular organization are well established and may account for varying outcomes between sexes following concussion. De Courten-Myers (1999) reported that males had a greater number of cortical neuronal densities, while females had a greater area of neuropil (i.e., containing unmyelinated neuronal processes). Esposito, Van Horn, Weinberger, and Berman (1996) found that females have a greater cerebral blood flow rate, coupled with a higher basal rate of glucose metabolism. These two differences could yield a more exacerbated neurometabolic cascade (ionic fluxes followed by hypoglycolysis in brain) following concussion. In addition, the decrease in cerebral blood flow and increase in metabolic

demands caused by brain injury may interact with the already increased metabolic demands in females (Broshek et al., 2005).

A weaker neck musculature may also predispose females to an increased risk of concussion. Tierney and colleagues (2005) investigated sex differences in head-neck strength. These authors found that sex differences exist in head-neck segment dynamic stabilization during head angular acceleration (similar to concussive acceleration/deceleration forces). Females exhibited significantly greater head-neck segment peak acceleration and displacement than males. These authors concluded that females' heads are susceptible to higher speeds of acceleration and greater displacement following an externally applied force.

The research suggesting there are differences in age (e.g., high school vs. college) and sex on the risk and recovery from concussion is conclusive. Findings have been replicated and are becoming generally accepted across the field of sports medicine. Moreover, varying risks and recovery on these two variables have direct influence on the management of concussion. In contrast, there is still debate on the cumulative effects associated with history of concussion. It is commonly known that once an athlete gets his or her first concussion, it is likely he or she will sustain future concussions. The long-term effects of concussion are in debate as the literature on this topic is less conclusive.

Cumulative Effects of Concussion

There is vested interest from coaches, parents, and sports medicine professionals to ensure the safety of athletes upon their return to play following concussion. Determining when an athlete can resume sports participation may be a time of concern and deliberation when the athlete has a history of concussion(s), due to the growing body

of evidence suggesting possible detrimental effects of previously sustained concussions (Iverson, Gaetz et al., 2004). The question, "How many is too many?" is still a debated topic among sports medicine professionals and researchers. Empirical studies have continued to investigate the assumption that a history of multiple concussions are predictive of a lowered threshold (i.e., increase in risk) and worse outcome (i.e., increased symptoms and prolonged cognitive impairments) following subsequent concussion (Collins et al., 2002). The existing literature on this topic is primarily themed around addressing three questions: 1) Do athletes with a history of concussion have a higher risk for subsequent concussion?; 2) Do athletes with a history of concussion take longer to recover from another concussion?; and 3) Are there any cumulative, or long-term neurocognitive effects associated with a history of multiple concussions? These questions will be addressed in the following sections.

Do Athletes with a History of Concussion Have a Higher Risk for Subsequent Concussion?

Albright, McAuley, Martin, Crowley, and Foster (1985) was one of the first studies to suggest a possible association between previous history of concussion and risk of future concussive injury. Incoming freshman college football players self-reported their history of any head and/or neck injury that was defined as at least one day of removal from participation in high school football. These athletes were given a physical examination and x-ray screening to evaluate any pre-existing abnormalities associated with previous head or neck injury. Albright and colleagues (1985) collected head and neck injury data over an 8-year period (1975 -1982). Results from this study revealed that college football players with a history of previous head injury had a two-fold increase in

their risk of sustaining another head injury during their college career than those without a history of previous head injury. In addition, the average time loss from participation for concussed athletes with a history of concussion was 4.89 days, while concussed athletes without a history of concussion only lost 2.31 days of participation. These researchers did not find a significant relationship between history of concussion and severity of subsequent concussion.

The Albright et al. (1985) study supports a relationship between history of concussion, risk, and outcome from future concussive injury. However, these data are most likely a conservative estimate as time loss from sport participation was the sole criterion for defining previous history of concussion and determining severity of concussions (i.e., the more days removed from sport, the more severe the concussion) sustained during the study. More recent studies have found higher estimates for the risk of concussion in both high school and collegiate athletes with a history of concussion (Guskiewicz et al., 2000; Zemper, 2003).

Zemper (2003) investigated the incidence of sport-related concussion in both high school and college football players with a history of concussion. Athletes with a medical record of concussive injury sustained in the previous five years were prospectively studied for a 2-year period to assess risk of future concussion. Zemper (2003) found that high school and college football players with a history of concussion were 5.8 times more likely to sustain a concussion than those without a history of concussion, which is higher than previously reported by Albright et al. (1985). Interestingly, high school football players with a history of concussion had a slightly higher risk (6.6 times greater) for subsequent concussion than collegiate football players (5.3 times greater) with a history

of concussion. This finding failed to support the authors' hypothesis that collegiate athletes would be at a higher risk of concussion due to a longer involvement in sport than high school athletes. However, it complements other studies that have found age-related differences on concussion risk and outcomes that are attributed to the on-going cognitive and physical development of high school athletes (Field et al., 2003). It should be noted that the severity of concussions sustained during this 2-year period did not differ between high school and college athletes, which is in agreement with previous findings by Albright et al (1985).

The findings of Zemper (2003) indicate that history of concussion is associated with an increased risk for subsequent concussion in both high school and college football players. Stated another way, 1 in 35 athletes without a history of concussion will sustain a concussion over a 5 year span, whereas approximately 1 in 6 athletes with a history of concussion will sustain a subsequent concussion over a 5 year span (Zemper, 2003). In addition, other studies have found both high school and collegiate athletes who sustain a concussion are three times more likely to incur another concussion in that same season (Guskiewicz et al., 2000).

There seems to be a general consensus on the relationship between history of concussion and an increased risk for future concussions. However the previously reviewed studies have failed to address the actual number of previously sustained concussions (Zemper, 2003), and inadequately assessed severity of previous concussion (Albright et al., 1985). Zemper (2003) only made a dichotomous (history versus no history) comparison among athletes with a history of concussion, as this author did not report the actual number or severity of previously sustained concussions. Other

researchers used time loss (from participation) as criteria for reporting concussion history and determining severity (Albright et al., 1985), which is an out-dated approach that likely resulted in an overly conservative estimation. Other researchers have considered how the severity of previously sustained concussion(s) influences the risk and outcome from future concussion (Collins et al., 2002; Gerberich, Priest, Boen, Straub, & Maxwell, 1983).

Researchers have examined the relationship between the severity of previously sustained concussions (i.e., on-field markers: LOC and PTA) and the subsequent risk of re-injury (Collins et al., 2002; Gerberich et al., 1983). Gerberich and colleagues (1983) surveyed 103 high school football teams with the purpose of investigating the relationship between history of concussion and LOC. The results indicated that athletes with a history of concussion involving LOC were four times more likely to experience another concussion involving LOC than those who never had a concussion. These results suggest that previous concussions involving LOC may influence the risk of future injury.

A related study by Collins et al. (2002) evaluated the relationship between history of multiple concussions and severity of subsequent concussion in high school athletes. As with previous research (Gerberich et al., 1983), Collins and colleagues (2002) were specifically interested in on-field concussion severity markers (e.g., LOC, PTA, confusion, disorientation) presented with subsequent concussion. High school athletes with a history of three or more concussions were more likely to experience on-field LOC (6.7 times), confusion (4.1), and anterograde amnesia (3.8 times) associated with subsequent concussion than athletes without a history of multiple concussions. Additionally, high school athletes with three or more previous concussions were over

nine times more likely to experience any combination of three to four on-field, abnormal markers associated with subsequent concussion than athletes with no history of concussion.

Similar to Gerberich et al. (1983), Collins and colleagues (2002) found only 5% of athletes (n = 88) with no history of concussion experienced a concussion involving LOC, while 26% (n = 88) of athletes with a history of three or more concussions experienced another concussive injury involving LOC (Collins et al., 2002). These data suggest that a history of three or more concussions may be associated with more severe subsequent concussions as measured by on-field markers of injury in high school athletes. These findings may be suggestive of a lowered protective threshold (i.e., "reserve") that may increase the risk for more severe subsequent concussive injury (Collins et al., 2002). This relationship may be predicated on the actual number of previously sustained concussions, as college athletes with a history of two or more concussions did not have a greater likelihood of sustaining a more severe concussion (Covassin et al., 2008).

A "dose-response" relationship between the number of previous concussions and the risk of future concussion has been suggested by researchers (Guskiewicz et al., 2003). Guskiewicz and colleagues (2003) conducted a 3-year study that examined the cumulative effects associated with recurrent concussion in a large sample of collegiate football players. These researchers found an association between the reported number of previous concussions and the likelihood of incident concussion. Specifically, athletes with a history of three or more previous concussions were 3.4 times more likely to sustain a concussion than those without a previous history of concussion. Additionally, athletes

with two previous concussions were 2.8 times more likely and athletes with only one previous concussion were 1.5 times more likely to sustain a subsequent concussive injury than athletes without a previous history of concussion. These researchers also concluded that 1 in 15 athletes who sustain a concussion may incur another concussion in the same season. Moreover, these re-injuries typically take place within a 7 to 10 day period following concussion (Guskiewicz et al., 2003). These researchers concluded that college football players with a history of concussion are likely to have future concussive injuries, and support a dose-response effect for the number of previous concussions and subsequent risk of injury.

There seems to be a general consensus among the previously reviewed studies suggesting a relationship between history of concussion and risk for sustaining another concussive injury. More importantly, this increase in risk may be dependent on the number of previous incidences of concussion (i.e., dose response). This dose-response relationship may also be associated with long-term neurocognitive consequences following future concussive injury and previous concussions.

Do Athletes with a History of Concussion Take Longer to Recover From Subsequent Concussion?

Long-term neurocognitive impairments are rarely associated with a single uncomplicated concussion (Macciocchi et al., 2001). Macciocchi et al. (2001) prospectively examined the neurocognitive consequences associated with two concussions in a small sample of college football players (n = 24). These researchers purposefully compared neurocognitive performance on measures of visual and auditory attention and processing speed (Paced Auditory Serial Addition Task, Trail-Making Tests

A and B, and Symbol Digit Test) and self-reported symptom presentation between athletes who sustained two concussions with athletes who sustained only one concussion during the study. Of note, athletes who sustained two concussions were further divided into two groups: two concussions sustained in the same season (n = 5) and two concussions sustained in consecutive seasons (n = 5). Athletes who sustained a concussion in the same season had a mean separation of 33 days, while athletes with concussions occurring in consecutive years had a mean separation of 532 days (Macciocchi et al., 2001).

Macciocchi and colleagues (2001) reported that athletes with a single concussion did not differ significantly on any neurocognitive measures from those sustaining two concussions. Athletes who sustained two concussions demonstrated similar neurocognitive performance following each injury. A subsequent comparison between pre-season and post-concussion (i.e., after second concussion) neurocognitive performance yielded no significant differences. Lastly, athletes who sustained two concussions in one season demonstrated similar neurocognitive performance to athletes who sustained two concussions in consecutive seasons. In addition to these findings, subsequent analyses on total reported symptoms revealed that the number of players reporting symptoms increased significantly after 1 or 2 injuries, but returned to baseline at 10 days post-concussion (Macciocchi et al., 2001).

Macciocchi and colleagues (2001) concluded that athletes with a history of a single concussion do not take any longer to recover from subsequent injury than athletes who are injured for the first time. However, it should be noted that this study used a small sample size (n = 24) which could have affected statistical power. In this regard, the

statistical comparison between athletes with a single concussion compared to athletes with two concussions approached significance on the measures of attention and processing speed ($p = .06$). These results have not been supported by other researchers who found that a history of two or more concussions is associated with prolonged recovery and symptom resolution following subsequent injury (Covassin et al., 2008).

Covassin and colleagues (2008) prospectively administered a computerized neurocognitive test battery (ImPACT) and self-reported symptom checklist in a sample of concussed collegiate athletes at 2 and 5 days post-concussion. Post-injury comparisons were made between athletes with and without a history of two or more concussions on measures of verbal and visual memory, reaction time, processing speed, and total symptoms. Approximately two days after concussion, all concussed athletes (regardless of concussion history) demonstrated decreased neurocognitive performance in verbal memory, visual memory, reaction time, processing speed, and reported significantly more symptoms. It should be noted that there were no differences between groups at 2 days post-injury on any neurocognitive measures, and all injured athletes showed significant improvement on these measures by 5 days post-injury. However, at approximately 5 days post-concussion, athletes with a history of two or more concussions demonstrated lower performance on verbal memory and slower reaction times compared to athletes without a history of concussion. The researchers (Covassin et al., 2008) found no differences at 2 or 5 days post-concussion in reported symptoms between athletes with and without a history of two or more concussions. These results suggest that athletes with a history of two or more concussions may take longer to recover than athletes with no history of previous concussion.

Researchers have also examined the neurocognitive recovery (ImPACT) from concussion between athletes with and without a history of three or more concussions (Iverson, Gaetz et al., 2004). Concussed athletes with a history of three or more concussions have been found to demonstrate significant memory impairment at 2 days post-injury compared to concussed athletes without a history of concussion (i.e., recovering from their first injury). Athletes with a history of multiple concussions were also 7.7 times more likely to demonstrate a major decrease in memory performance than athletes with no previous concussion 2 days post-injury. These results are in agreement with previous literature that found athletes with a history of three or more concussions presented a greater number of post-concussion symptoms (Gaetz, Goodman, & Weinberg, 2000) and take longer for symptoms to resolve (Guskiewicz et al., 2003) than athletes without a history of concussion.

These studies collectively suggest that a dose response relationship between the number of previous concussions and outcome from subsequent concussion likely exists (Guskiewicz et al., 2003; Iverson, Gaetz et al., 2004). In other words, athletes with a history of a single concussion do not demonstrate any worse neurocognitive or symptom outcomes following subsequent injury (Macciocchi et al., 2001). In contrast, athletes who have sustained at least two prior concussions have been found to demonstrate a more prolonged neurocognitive and symptom recovery (Covassin et al., 2008; Iverson, Gaetz et al., 2004). The research is conclusive in suggesting that the risk and outcome associated with future concussive injury are a likely function of the number of previous concussions. Unfortunately studies investigating more long-term cumulative effects of multiple

concussions are less conclusive (Bruce & Echemendia, 2009; Iverson, Brooks, Lovell et al., 2006; Iverson, Gaetz et al., 2004; Moser & Schatz, 2002; Moser et al., 2005).

Are There Any Cumulative, or Long-Term, Neurocognitive Effects Associated with a History of Multiple Concussions?

The potential for long lasting, or permanent neurocognitive impairment resulting from multiple concussions are a central concern for athletes, families, coaches, and sports medicine professionals (Iverson, 2006). In addition, the recent media attention from the suggested association between late-life cognitive impairment (e.g., memory) associated with multiple concussions found in retired professional football players has caused concern for amateur athletes (Guskiewicz et al., 2005). Consequently, researchers have employed formal paper-and-pencil and computerized neurocognitive test batteries to assess cognitive function in high school (Moser et al., 2007; Moser & Schatz, 2002), collegiate (Collins, Grindel et al., 1999; Killam, Cautin, & Santucci, 2005), and professional athletes (Guskiewicz et al., 2007; Wall et al., 2006) with a history of multiple concussions. Unfortunately these studies have produced conflicting results, leaving this important issue still in debate.

College athletes with a history of multiple concussions have been found to demonstrate poor performance on more formal paper-and-pencil neurocognitive test batteries and increased symptoms (Collins, Grindel et al., 1999; Killam et al., 2005). Collins et al. (1999) assessed verbal learning, delayed memory, attention, concentration, visual scanning, executive functioning, processing speed and self-reported symptoms in a large sample of college football players. These athletes were separated into three groups (none, one, two or more previous concussions) according to self-report of concussion

history. The results of this study indicated a significant difference between groups for total reported baseline symptoms. More specifically, baseline symptoms increased as the number of previously sustained concussions increased (Collins, Grindel et al., 1999). Other findings revealed that athletes with two or more concussions performed significantly worse than the other two groups on Trail-Making Test B and the Symbol Digit Modalities test (Collins, Grindel et al., 1999). These researchers concluded that history of multiple concussions are associated with long-term deficits in executive function and information processing speed. Specifically, a history of a single concussion does not appear to result in long-term neurocognitive impairment as seen in athletes with a history of two or more concussions.

It should be mentioned Collins et al. (1999) also observed an interaction between learning disability and concussion history. Interestingly, athletes with a learning disability and history of concussion performed worse than athletes with a history of concussion and no learning disability. These findings not only suggest a relationship between learning disability and history of concussion, but also highlight the importance of considering diagnosed learning disability in neurocognitive assessment.

The findings of Collins et al. (1999) are salient to the existing literature that promotes a cause for concern regarding the long-term neurocognitive outcomes of athletes with a history of multiple concussions. However these findings are not without limitations, as the time since last concussion and severity of previous concussions were not addressed. This information may directly influence these findings and conclusions. Other researchers have addressed these limitations and have attempted to better control

for the time since last concussion in order to better identify potential residual neurocognitive impairment (Killam et al., 2005).

Killam, Cautin, and Santucci (2005) administered the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), post-concussion syndrome checklist, and the Stroop Task to four groups of collegiate athletes participating in ice hockey, field hockey, lacrosse, or soccer with and without a history of recent concussion. Specific comparisons on these measures were made between athletes with a non-recent (i.e., more than two years since last diagnosed concussion) history of concussion; athletes with a recent history of concussion (i.e., two years or less since last concussion); athletes without a history of concussion; and non-athletes without a history of concussion. Killam and colleagues (2005) found no differences between any of the groups on neurocognitive measures of visuospatial construction, language, attention or symptoms. However, athletes with a history of concussion and recently concussed athletes demonstrated impairments in immediate and delayed memory when compared to non-athletes without a history of concussion. Interestingly, the three groups of athletes (i.e., regardless of concussion history) had lower total RBANS scores than the non-athlete/non-concussed controls. These results suggest there may be mild neurocognitive impairments associated with participation in contact sports, and the possibility of increased vulnerability to cumulative mild concussive effects associated with undiagnosed concussion.

Killam and colleagues (2005) concluded that there may be prolonged (i.e., cumulative effect) neurocognitive impairment in immediate memory associated with concussive injuries sustained during a prior two-year time span. However, these impairments were not observed in delayed memory in the recently concussed athletes.

There was also a non-significant trend toward a positive relationship between number of years since last concussion (less than 2 years) and immediate memory scores, suggesting that this impairment likely recovers with time (greater than 2 years). Killam et al. (2005) concluded that delayed memory likely resolves during athlete's removal from participation, but deficits in immediate memory may be more prolonged. These results, while seemingly important, should be interpreted with caution as this study was limited to a small sample size (n = 28).

In contrast to the previous studies, other researchers using similar neurocognitive measures have failed to find any evidence of impaired cognitive function in collegiate athletes with and without a history of multiple concussions (Guskiewicz, Marshall, Broglio, Cantu, & Kirkendall, 2002). Guskiewicz et al. (2002) examined neurocognitive performance between college soccer players. Collegiate soccer players have been found to demonstrate similar performance on a battery of neurocognitive tests (i.e., Hopkins Verbal Learning, Wechsler Digit Span, Stroop Test, Trail-Making B, and Symbol Digit Modalities Test) compared to other collegiate athletes (e.g., baseball, women's lacrosse and field hockey) and student controls (Guskiewicz et al., 2002). An initial examination of the groups revealed a higher incidence rate for concussion in the collegiate soccer athletes, with 49.5% reporting a history of one or more concussions compared to 29.2% and 15.1% of the non-soccer athletes and student controls, respectively. In addition, soccer athletes were significantly more likely to sustain repeat concussions than the other groups. These researchers also examined the effects of multiple concussions within the soccer athletes (i.e., between-group comparisons among none, one, or two or more previous concussions). The results revealed that soccer athletes with a history of two or

more concussions were no more likely to have impaired neurocognitive performance than those with no history of concussion (Guskiewicz et al., 2002). These findings suggest that there are no cumulative effects associated with multiple concussions. However, this study used collegiate soccer players whereas the majority of previous studies have primarily been conducted on college football players.

Very few studies have considered the cumulative effects of multiple concussions in high school athletes, which is surprising due to the increased vulnerability and prolonged recovery times from concussion seen in this younger population (Field et al., 2003). However the published studies that do exist reveal there may be a cause for concern for these younger athletes, as there is documented evidence that suggests a history of multiple concussions may be associated with decreased neurocognitive function. Moser and colleagues (2005) examined neurocognitive function (RBANS, Trail-Making Tests A and B) in high school athletes. Based upon self-report of concussion history, athletes were assigned to the following groups: no previous concussion; one previous concussion; two or more previous concussions; and recently concussed (within the past 7 days). The authors noted that all athletes, regardless of their concussion history were asymptomatic for the past 6 months, with exception of the recently concussed group (who endorsed a greater number and intensity of symptoms than the other three groups). These recently concussed athletes performed significantly worse on measures of attention, concentration, processing speed, and cognitive flexibility than those in the no concussion history or one previous concussion groups. Strikingly, there were no statistical differences on any of these measures of cognitive ability between recently concussed athletes and athletes with a history of two or more concussions. These

findings support previous work of Moser et al. (2002) who also found no differences between recently concussed athletes and athletes with a history of two or more previous concussions on overall neurocognitive performance. These results suggest that a history of two or more concussions may lead to decreased neurocognitive function; however, these studies did not assess concussion severity in any group, which may limit these findings. Further studies exploring the potential cumulative effects in high school and collegiate athletes are warranted.

In contrast to these studies that suggest a relationship between history of multiple concussions and decreased neurocognitive performance, other studies employing computerized neurocognitive test batteries have failed to support this claim (Broglio et al., 2006; Bruce & Echemendia, 2009; Collie et al., 2006; Guskiewicz et al., 2002; Iverson, 2006). Interestingly these studies have made two conclusions based on their findings: 1) there are no cumulative effects associated with multiple concussions, or 2) computerized neurocognitive tests used in these studies may not be sensitive enough to detect any subtle effects associated with a previous history of multiple concussions.

Iverson et al. (2006) used a computerized neurocognitive test battery (ImPACT) that assessed verbal memory, visual memory, reaction time, and processing speed in a large sample of male high school and college athletes. Based on self-report, athletes were grouped into none, one, and two previous concussion groups. The results from this study indicated no differences on any of the measures of neurocognitive function between any of the groups. A similar study using a different computerized neurocognitive test battery (CRI) also reported no observed differences on baseline performance between groups of athletes with zero, one, two or three or more previous concussions (Collie et al., 2006).

These authors concluded that if there is a cumulative effect from a history of concussion it is probably very small and possibly undetectable by computerized neurocognitive testing (Collie et al., 2006; Iverson, 2006).

The results from Iverson et al. (2006) and Collie et al. (2006) have been supported by other studies that have used multiple neurocognitive test batteries to assess not only the cumulative effects of concussion, but also to better evaluate these instruments as appropriate measures for detecting any long-term neurocognitive deficits associated with previous multiple concussions (Broglio et al., 2006; Bruce & Echemendia, 2009). Broglio et al. (2006) retrospectively examined baseline performance of collegiate athletes on two computerized neurocognitive test batteries (CRI = 235 subjects; ImPACT = 264 subjects) and found no differences between groups of athletes with zero, one, two, or three previous concussions on CRI or ImPACT. These authors have questioned the utility and sensitivity of these measures to detect possible lingering neurocognitive decrements that may be associated with multiple concussions (Broglio et al., 2006).

Bruce and Echemendia (2009) recently conducted a series of three related studies that investigated the association between self-reported concussion history and performance on both paper-and-pencil and computerized neurocognitive tests. In the first study a computerized neurocognitive test battery (ImPACT) was administered to 858 male collegiate athletes who were grouped according to their self-reported history of concussion (no previous concussion = 292; one = 196; two = 42; three or more = 60). There were no differences between any of the groups on verbal or visual memory, reaction time, or processing speed. Consequently these researchers concluded that college athletes with a previous history of one or more concussions demonstrate a

complete recovery, or experience very mild, undetectable neurocognitive deficits (Bruce & Echemendia, 2009). These authors also mentioned that computerized neurocognitive test batteries may not be sensitive enough to detect long-term deficits compared to previous findings using paper-and-pencil tests (Collins, Grindel et al., 1999; Killam et al., 2005). Furthermore, these two forms of neurocognitive assessment can measure vastly different neurocognitive constructs such as free recall memory assessment versus forced-choice recognition memory paradigms used in computer forms of neurocognitive assessment (Bruce & Echemendia, 2009).

These differences between paper-and-pencil neurocognitive tests provided a rationale for two follow-up studies by Bruce and Echemendia (2009). Similar to the first study, Bruce and Echemendia (2009) administered a traditional paper-and-pencil neurocognitive test battery to 479 male collegiate athletes who were grouped according to their self-report concussion history (none = 292; one = 119; two = 41; three or more = 27). Contrary to Collins et al. (1999) and Killam et al. (2005), there were no significant differences in cognitive performance between college athletes with and without a history of concussion on traditional neurocognitive measures. Bruce and Echemendia (2009) concluded that differences (i.e. confounders) between the samples used in the first two studies could account for the lack of significant findings. Therefore, a third, and final study was conducted to examine the association between concussion history and cognitive performance in a separate sample of athletes who received both computer and paper-and-pencil neurocognitive tests.

A large sample of 175 male collegiate athletes with and without a history of multiple concussions (none = 118; one = 43; two or more = 14) were administered both a

computerized (ImPACT) and paper-and-pencil neurocognitive test battery to examine neurocognitive function. All athletes included in this study did not sustain a concussion in the previous six months, and were asymptomatic at the time of data collection. As with the previous studies, no significant differences in neurocognitive performance were found on either computerized or traditional paper-and-pencil test batteries.

Researchers have thoroughly examined the relationship between history of concussion and the subsequent risk and outcome from future concussive episodes. In sum, athletes with a history of at least two or more concussions have been found to be at a higher risk for subsequent concussion, and are likely to demonstrate a prolonged recovery from future concussive injuries (Guskiewicz et al., 2003; Moser & Schatz, 2002; Moser et al., 2005). However, the extant literature investigating more long-term or residual cognitive impairments associated with a history of multiple concussions has uncovered many issues and left many questions unanswered. The concern that neurocognitive test batteries may not be sensitive enough to detect the potential long-term effects in athletes with a history of multiple concussions has warranted the continued investigation of this topic (Bruce & Echemendia, 2009). Functional MRI has been recently suggested to be sensitive to the acute effects of concussion, as differences in brain activation patterns have been documented in the absence of neurocognitive impairment (Jantzen et al., 2004; Lovell et al., 2007; McAllister et al., 1999; McAllister et al., 2001; Mendez, Hurley, Lassonde, Zhang, & Taber, 2005). This tool may also prove valuable in assessing residual neurocognitive impairment in athletes with a history of multiple concussions.

Overview of Functional Magnetic Resonance Imaging

Until recently, the majority of functional neuroimaging studies conducted on concussed athletes and MTBI patients have primarily used positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) (Masdeu, Van Heertum, & Kleiman, 1994; Ruff, Crouch, & Troster, 1994). Resting metabolic measurements used by these imaging methods have shown perfusion deficits in traumatic brain injured patients that have not been detected with CT or MRI (Abdel-Dayem et al., 1987; Alavi et al., 1987; Jansen et al., 1996; Langfitt et al., 1986; Newton et al., 1992). However, these imaging techniques require a radioactive tracer which is invasive and has been suggested to limit clinical application (Chen et al., 2004). In contrast to these limitations, fMRI does not require radioactive exposure, has temporal resolution limited only by brain hemodynamics, and spatial resolution comparable to conventional MRI (Ptito et al., 2007). Moreover researchers have begun to utilize this tool to study the neurophysiological and functional sequelae of concussive injury (Ptito et al., 2007).

Functional MRI has afforded researchers the ability to measure changes in neuronal activity (i.e., brain activation) during the completion of various neurocognitive tasks (Lovell, Collins, Fu, & Stump, 2004). The measurement of neuronal activity is derived from increases or decreases in the level of blood oxygenation (e.g., ratio of oxyhemoglobin to deoxyhemoglobin), which are influenced by the metabolic demands of active neurons during cognitive processes (Huettel, Song, & McCarthy, 2004). The different magnetic properties of oxygenated hemoglobin (diamagnetic) and deoxygenated hemoglobin (paramagnetic) can be measured using MRI. The contrast seen in MRI with regard to changes in the ratio of oxygenated hemoglobin to deoxygenated hemoglobin is

known as "blood oxygenation-level dependent" (BOLD) contrast (Pike & Hoge, 2000). More specifically, changes in the BOLD response can be observed using T_2* weighted imaging. In summary, fMRI has allowed researchers to not only examine brain activation patterns elicited from various cognitive tasks, but to also identify the functional connectivity of brain regions that are responsible for these cognitive processes.

Many concussed athletes demonstrate cognitive impairment and deterioration in the domains of planning and memory which are primarily localized to the frontal, temporal, and hippocampal areas (Ptito et al., 2007). The few studies that have employed this tool have investigated a wide variety of research questions that range from examining brain activation in the acute time period (e.g., one week) of concussion to one-month post-concussion (Lovell et al., 2007; McAllister et al., 2001). While these studies are different with respect to their research agenda (sample selection, research questions and design) most have used some variant of a working memory paradigm. The following section will provide a general overview of working memory and the neural correlates involved in this cognitive process. The N-back working memory task will also be reviewed as it has been widely used for fMRI and concussion (Lovell et al., 2007; McAllister et al., 1999; McAllister et al., 2001).

Overview of Working Memory and N-back Paradigm Used for fMRI

Baddeley and Hitch (1994) describes working memory as the "on-line" storage of information (e.g., digits, words, names, etc...) necessary for performing cognitive processes. More specifically, working memory involves the active maintenance (e.g., rehearsal) of a limited amount of information for a brief period of time until it is manipulated either physically or mentally (E. E. Smith & Jonides, 1998). An example of

actively maintaining information is attempting to remember a phone number by repeating the numbers over and over until it is dialed. An example of manipulation is the creation of a mental map of a particular geographical area when given directions on how to find a certain house (E. E. Smith & Jonides, 1998). The manipulation feature of working memory has been suggested to be the cornerstone of higher cognitive processes that includes reasoning, decision making, problem solving, and language understanding (Jonides, 1995; E. E. Smith & Jonides, 1998). The key feature to working memory is the amount of information or "working memory load" that must be maintained to solve a particular problem. Smith and Jonides (1998) indicate that approximately one to 10 items can be maintained or kept active in working memory, whereas the storage duration lasts from zero to 60 seconds.

The current multi-component model of working memory (Baddeley, 2000) is derived from earlier unitary models of short-term memory (Atkinson & Shiffrin, 1968; Broadbent, 1958). However, the well-documented findings indicating that verbal and spatial information is localized to different cortical brain regions, has led to the abandonment of this unitary system in favor of a multi-component model of working memory (Baddeley, 1986, 2000; Baddeley & Hitch, 1994). The work of Baddeley and Hitch (1994) suggests that working memory is comprised of three subcomponents: the phonological loop for verbal information; visuospatial sketchpad for visual information, and a central executive system for attentional control.

The phonological loop has been described as an acoustic store where verbal working memory decays after about 2 seconds unless it is refreshed by subvocal rehearsal (Baddeley & Hitch, 1994). Separate cortical areas localized to the left hemisphere are

involved in the storage and rehearsal of verbal material that include the dorsolateral prefrontal cortex (Petrides, 2000), left posterior parietal cortex (Oztekin, McElree, Staresina, & Davachi, 2008), premotor area, and the supplementary motor area (SMA) (Awh et al., 1996; Chein, Ravizza, & Fiez, 2003; Chung, Han, Jeong, & Jack, 2005; Cohen et al., 1997; D'Esposito, Aguirre, Zarahn, Ballard, & Shin, 1998). The posterior parietal cortex (left hemisphere) has been functionally dissociated from frontal areas as it has been found to be the site of storage for verbal material (Awh et al., 1996), while the other activated areas are involved in planning and speech production (e.g., Broca's Area), which may involve the subvocal rehearsal component of working memory (Oztekin et al., 2008; E. E. Smith & Jonides, 1998).

The visuospatial sketchpad is similar only to the phonological loop in the sense that it also temporarily holds information that is continually refreshed to prevent memory decay (Baddeley & Hitch, 1994). In contrast to the phonological loop, the visuospatial sketchpad holds visual, spatial, and kinesthetic material. Interestingly, activations in the right hemisphere have been found on visual working memory tasks that include areas in the posterior parietal, occipital, and frontal cortex (Baddeley & Hitch, 1994). Similar to verbal working memory, separate regions in the right hemisphere are specific for the storage and rehearsal of visual information. The inferior posterior parietal area and anterior occipital area have been suggested to mediate the storage function of spatial working memory (E. E. Smith, Jonides, & Koeppe, 1996).

\ The last subcomponent of Baddeley's working memory model (2000) is the central executive system for attentional control. The executive system is the most complex and least well understood component of working memory (Baddeley & Hitch,

1994). The executive processes housed in the frontal lobes have been assumed to regulate the operations of working memory (Baddeley, 2000). The operations of inhibition, attentional switching, and contextual coding and checking are all functions of the prefrontal cortex (Petrides, 2000). More recently this component was revised to include an episodic buffer that serves as a temporary interface between the phonological loop, visuospatial sketchpad and long-term memory (Baddeley, 2000). The function of this buffer is for binding information from a number of sources (e.g., mnemonic and sensory) into coherent episodes that are consciously retrievable (Rudner & Ronberg, 2008).

In sum, working memory is comprised of a multi-component system that actively holds information for retrieval, and both verbal and spatial information have been found to have different neural correlates. Furthermore, both of these systems have distinct memory stores that are dissociated from their rehearsal components (e.g., parietal areas store verbal information while Broca's Area is responsible for actively maintaining this information via subvocal rehearsal) (E. E. Smith et al., 1996). The N-back working memory task has been widely used in neuroimaging studies to identify these localized brain regions that have a role in working memory processes. The fact that the brain regions elicited by this working memory task have been consistently found across many studies has made this working memory paradigm a popular choice for examining changes in the brain when comparing different pathological states such as concussion. More importantly, working memory has been suggested to sub-serve higher order cognitive function which adds to the value of using these paradigms in injured populations (Owen, McMillan, Laird, & Bullmore, 2005; Ptito et al., 2007).

The N-back working memory task involves the continual monitoring of a series of stimuli and a response to stimuli that are the same as the one presented "n" trials previously, where "n" is a predetermined integer that is usually 1, 2, or 3. These predetermined integers, or conditions, represent an increase in memory load (i.e., 3-back is the highest load). This demanding working memory task incorporates all components of Baddeley's working memory (1994) as it requires the continual adjustment of presented information held in working memory in conjunction with incorporating newly presented stimuli while simultaneously rejecting distant stimuli (Owen et al., 2005). The stimuli used for this task can be either verbal or non-verbal. Moreover, the type of monitoring for these tasks can be identity (e.g., was this trial the same as the trial presented n trials before) or location (e.g., is this stimuli in the same location as the stimuli presented n trials before).

The N-back task uses all parts of Baddeley's (1994) multi-component model of working memory. The cortical regions that are activated during this task include the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), rostral prefrontal cortex (frontal pole), premotor cortex (bilateral and medial), and posterior parietal cortex (bilateral and medial) (Owen et al., 2005). Activity in each of these regions has been found to correspond to the cognitive processes that are required to complete the N-back working memory task. More specifically, activity in the DLPFC has been found to contribute to the strategic reorganization (e.g., "chunking") and control of working memory contents (Bor, Cumming, Scott, & Owen, 2004; Bor, Duncan, Wiseman, & Owen, 2003; D'Esposito et al., 1998; Ericcson, Chase, & Falloon, 1980; Owen, 1997). Moreover, the attentional changes and switching that occur when stimuli

are presented, inspected, and compared with previously shown stimuli activates the regions of the VLPFC, rostral prefrontal, and premotor areas (Dove, Rowe, Brett, & Owen, 2001; Owen, 2000; Owen et al., 2005). In contrast to the above mentioned frontal regions, consistent activation in posterior parietal areas has been found in studies using the N-back (Jonides, Schumacher, & Smith, 1998; Owen et al., 2005; E. E. Smith & Jonides, 1998; E. E. Smith, Jonides, Marshuetz, & Koeppe, 1998). According to Baddeley's multi-component model, the posterior parietal cortex serves as a site for the temporary storage of information. These areas of the brain that contribute to the cognitive processes of working memory, relevant to fMRI N-back working memory paradigms, have been implicated following sport-related concussion.

Functional MRI is a relatively novel approach to exploring the neurophysiological basis of concussive injury, as these studies are very expensive and the equipment required for this research is not readily available (Lovell et al., 2007). Nonetheless, the few researchers that have used fMRI to study the underlying neurophysiological basis of concussive injury have produced exciting results. Specifically, fMRI studies have focused on identifying functional networks of the brain that may be implicated in the acute-time period following concussion (Jantzen et al., 2004; Lovell et al., 2007). A detailed review of these studies will help form the basis of identifying and proposing how this technology could be valuable in addressing the unresolved issue of long-term effects associated with a history of multiple concussions.

Functional MRI and Sport-Related Concussion

Researchers have specifically used fMRI to explore the neurophysiological basis of the symptomology and neurocognitive impairments that occur in the acute time period following concussion (Jantzen et al., 2004; Lovell et al., 2007). Lovell and colleagues (2007) studied the relationships between neurocognitive performance, post-concussion symptoms, and brain activation patterns in a sample of concussed high school and college athletes (n = 28). Concussed athletes and a separate sample of non-injured controls (n = 13) were administered a computerized neurocognitive test battery (ImPACT) and fMRI at approximately 6 days and 1-month post-concussion. A working memory paradigm (N-back) was used for fMRI to elicit changes in BOLD response.

The neurocognitive testing and symptom inventory comparisons made by Lovell and colleagues (2007) revealed that concussed athletes performed significantly worse than controls at 6-days post-injury on verbal and visual memory, reaction time, and processing speed. These between-group differences were also observed for total reported symptoms. However, at 1-month post-concussion no differences on any neurocognitive or symptom assessments were reported which suggests the concussed athletes had recovered from injury. Subsequent results from fMRI analyses also yielded interesting relationships between neurocognitive and symptom recovery and regional changes in brain activation (Lovell et al., 2007).

Functional MRI results by Lovell et al. (2007) reported neuronal activation in frontal and parietal regions that are expected to be involved in working memory. These researchers used an alternative approach to measure changes in brain activation relevant to the increasing difficulty of the memory task (i.e., comparing 0-back to 2-back

condition). Instead of separately examining brain activation in brain regions of interest (e.g., functional specialization), Lovell and colleagues (2007) grouped the activated brain regions into three functionally-connected networks to determine the relative contribution of each network to the symptoms and neurocognitive recovery from concussion. The first network included medial, frontal, and right temporoparietal gyri. The second network was comprised of the right frontal and anterior temporal regions, and the third network included the bilateral posterior parietal cortex.

Subsequent analyses on these networks revealed that the posterior parietal cortex was significantly correlated with symptomology and delayed memory (i.e., neurocognitive performance following concussion. Interestingly, symptom severity was negatively associated with activation in this area. In addition to these results, brain activation in temporoparietal regions (e.g., Brodman's Area 6) was associated with recovery (i.e., return to competition). Concussed athletes with the highest level of activation in this area approximately 1-week post-concussion took approximately 26 days, or twice as long, to return to play than other athletes with less activation in this area.

Lovell et al. (2007) is recognized as one of the first studies to directly measure the relationship between brain physiology, symptomology and neurocognitive function in concussed athletes. These researchers concluded that post-concussive impairments and symptoms are associated with changes in regional brain activation. Furthermore, it appears that the magnitude of these changes is related to the recovery from sport-related concussion. The working memory task used in this study elicited activation in dorsal

attentional system that was also found to be related to the clinical recovery from concussion.

While this study is valuable, there are several limitations that warrant attention. Lovell and colleagues (2007) used a small sample that was primarily comprised of male, high-school aged athletes, which limits the application of these findings to older athletes (e.g., collegiate) and females. In addition, the average number of previously sustained concussions in this sample was less than one (M = .86), which limits the generalizeability of these findings to athletes with a history of multiple concussions. Unfortunately, this study did not report fMRI data from the second scanning time period, as previous researchers have observed differences in brain activation patterns at one-month post-concussion in the absence of any neurocognitive impairments (McAllister et al., 1999). Functional MRI was also administered retrospectively (i.e., there was no baseline/pre-injury comparison) which is not the most sensitive approach to account for the degree of change in brain activation from pre to post-concussion time periods (Collins, Grindel et al., 1999; Jantzen et al., 2004). In response to this limitation, other researchers have prospectively used fMRI to better examine neurophysiological changes following concussion (Jantzen et al., 2004).

The importance of the baseline assessment has been emphasized by numerous researchers who have examined changes in neurocognitive performance and symptomology following concussion (Collins, Grindel et al., 1999; Schatz & Zillmer, 2003). Conversely this methodology has been a novel approach in the area of functional neuroimaging due to the increased utilization of resources (e.g., financial, equipment,

time) for mass baseline assessments that may or may not prove useful for post-concussion assessment (i.e., cannot predict who will get a concussion).

In contrast to these feasibility issues, Jantzen et al. (2004) conducted a prospective study using eight college football players who were identified by their playing position (e.g., running backs, linebackers) for high risk of concussive injury. Seven out of eight athletes completed a baseline fMRI assessment that included: finger sequencing, serial calculation, and digit span task functional paradigms. Only four out of the eight athletes sustained a concussion during the season and participated in post-concussion fMRI and neurocognitive evaluations approximately one week after injury. Unfortunately, the one athlete without a baseline measure sustained a concussion. This athlete completed the 1-week post-injury measures, but was later administered a baseline assessment at the end of the season upon reporting asymptomatic for an extended period of time (3 months). The remaining four athletes who did not sustain a concussion were also retested at the conclusion of the season and served as a control group.

Jantzen and colleagues (2004) found no differences between baseline or post-concussion performance on the finger sequencing, serial calculation, and digit span test for concussed athletes. Moreover, this performance did not differ from controls for either baseline or post-concussion tests. Although these athletes were diagnosed with a concussion by sports medicine professionals there were no impairments on any of these measures, which led the researchers to question this neurocognitive battery's sensitivity to concussion (Jantzen et al., 2004). However, fMRI yielded expected areas of activation relevant to the neurocognitive test battery that included frontal and parietal areas. Within-subject increases in BOLD signal intensity were found on a subset of tasks that produced

striking differences between concussed athletes and controls. More specifically, controls had a small increase in activation that was restricted to the SMA and a small region on the left dorsal premotor cortex, whereas concussed athletes demonstrated large extensive increases in SMA, bilateral premotor cortex, superior and inferior parietal regions and areas of the cerebellum. These additional regions of activation were associated with executive domains including working memory and planning (Jantzen et al., 2004). A region of interest (ROI) analysis was performed to further evaluate these within-group differences.

Jantzen and colleagues (2004) identified nine ROIs relevant to the behavioral tasks that included: SMA and cingulate motor area; prefrontal cortex; inferior and superior parts of the parietal cortex; and left and right cerebellum. These areas were used to calculate the extent and amplitude of within-subject brain activation increases. Comparisons between concussed athletes and controls revealed that the number of activated voxels from baseline to post-injury was greater for concussed athletes than controls, especially for the finger sequencing task. Concussed athletes yielded more than twice the area of increased activation than controls in the medial frontal region and cerebellum areas (Jantzen et al., 2004). Similarly, the average increase in signal intensity from baseline to post-concussion was more prominent in concussed athletes especially in the areas of frontal and parietal ROIs. These findings suggest that the frontal and parietal areas may be especially sensitive to concussion (Jantzen et al., 2004), which has also been reported by other researchers (Lovell et al., 2007).

The study by Jantzen et al. (2004) demonstrates differences in brain activation between concussed and non-concussed athletes in absence of neurocognitive impairment.

Furthermore, concussed athletes demonstrated a pattern of hyperactivation in brain regions that were not observed in controls. These authors concluded that the brain may need additional resources (i.e., alternative recruitment) to compensate for injury, which has been found in other studies (Chen et al., 2004; McAllister et al., 1999; McAllister et al., 2001). Nonetheless, this study is valuable as it is the first to employ a prospective methodology using fMRI in concussed athletes. As such, these researchers concluded that prospective designs using fMRI and neurocognitive measures may be the most sensitive methodology to detect the effects of concussion, compared to solely relying on neurocognitive testing (Jantzen et al., 2004).

The results reported by Jantzen et al. (2004) are not without limitations. First, these researchers used a very small sample size that included only eight athletes who were all college-aged males. Second, these researchers did not report any characteristics of concussion such as severity, symptoms, and/or number of previous concussions. Finally, this study did not assess recovery time as measured by fMRI (i.e., a recovery data point was not included). These limitations should be noted, and further research is warranted to explore if these increased brain activation patterns seen in concussed athletes are observable in long-term time periods.

Lovell et al. (2007) and Jantzen et al. (2004) both examined the neurophysiological changes in the brain during the acute time period following concussion. The findings of these studies collectively suggest that concussed athletes show increased brain activation areas not observed in controls. However, other fMRI studies investigating brain activation patterns in concussed athletes have not examined athletes in the acute time period following concussion. Instead they have retrospectively

used fMRI to detect changes in brain activation patterns approximately 1 month post-injury (Chen et al., 2004; McAllister et al., 1999; McAllister et al., 2001).

Chen and colleagues (2004) examined changes in brain activation patterns in concussed athletes compared to non-concussed controls. A verbal and visual working memory task was used for fMRI in a sample of 16 concussed athletes and 8 non-injured controls. The time elapsed between the date of concussion and participation in this study ranged from one to 14 months. Of note, all but one of the concussed athletes reported symptomatic at the time of the study. These researchers found no between-group differences on either verbal or visual working memory tasks. In contrast, results from fMRI demonstrated that concussed athletes exhibited alternative and/or increased areas of activation compared to controls in the absence of the aforementioned similarity in behavioral performance.

Group analyses by Chen et al. (2004) found discrepancies in brain activation patterns between concussed athletes and controls relevant to areas involved in verbal and visual working memory. While both groups exhibited activation in the mid-dorsolateral prefrontal cortex, concussed athletes had significantly less activation in this area than controls. Additional analyses of the BOLD signal change across time (i.e., baseline to working memory condition) in the right dorsolateral prefrontal cortex revealed expected patterns of activation for controls, but not the concussed athletes. Differences in the mean percentage of BOLD signal change from baseline to working memory conditions revealed that concussed athletes had significantly less signal increase compared to controls.

Individual analyses by Chen and colleagues (2004) found high variability in working memory performance and activated brain regions within the group of concussed athletes. None of the concussed athletes, regardless of how well they performed on the working memory task, showed brain activation in all areas of interest with respect to controls. Additional clusters of activation were observed in temporal and parietal areas for all but three of the concussed athletes. Concussed athletes also demonstrated less activation in the dorsolateral prefrontal cortex and other frontal regions compared to controls. In addition to these findings, the strength of the percent signal change in the BOLD response from baseline to working memory was used to determine if the BOLD response of each individual concussed athlete was within the range of the controls. Thirteen out of the 16 concussed athletes had at least one ROI with a BOLD response that significantly differed from controls. Chen and colleagues concluded that the concussed athlete's performance on working memory did not correlate well with expected regions of brain activity. These findings are in agreement with other studies that have found this pattern of alternative neural recruitment in concussed athletes.

Of important note, Chen and colleagues (2004) retested several concussed athletes approximately three months later when symptoms had resolved. Again, there were no differences on behavioral measures for this testing occasion and controls. In contrast, the brain activation patterns were more localized to frontal areas similar to controls, which is tentative evidence that indicates a neurophysiological recovery may exist following concussion. This protracted fMRI assessment has not been conducted in other studies (Jantzen et al., 2004; Lovell et al., 2007), thus leaving the concept of a neurophysiological recovery relatively unaddressed.

The results from Chen et al. (2004) suggest that concussed athletes who are still symptomatic demonstrate varying task-related neurophysiological responses when compared to non-concussed controls. Moreover, these differences in brain activation patterns may change in time, with respect to the resolution of symptoms. The sample used by Chen et al. (2004) included many concussed athletes with a previous history of concussion (ranging from one to five or more). Unfortunately, these researchers did not consider concussion history or the actual number of previous concussions as a grouping variable for fMRI analyses.

McAllister et al. (1999; 2001) conducted two related studies with the purpose of examining the effects of MTBI on brain activation patterns during a working memory task. In the first study, these researchers examined the relationship between brain activation patterns and working memory processing load in an older sample of MTBI patients (30 years of age) and healthy age-matched controls (McAllister et al., 1999). At the time of study MTBI patients reported significantly more symptoms (e.g., memory, concentration, occupational difficulties) than controls. Interestingly within 1-month of MTBI, patients and controls showed similar behavioral performance and regional areas of activation on an auditory working memory task (e.g., auditory N-back). As the task difficulty increased (e.g., from baseline to 2-back condition), both the groups activated more frontal and parietal brain areas in response to increased working memory load.

McAllister and colleagues (1999) reported differences between the two groups with respect to the degree of increased brain activation when progressing from low to high difficulty. More specifically, the control group showed an almost maximal increase in activation from a 0-back (baseline condition) to 1-back task (i.e., low difficulty), and a

smaller increase in activation from the 1-back to the 2-back task (i.e., moderate difficulty). In contrast the MTBI group demonstrated less activation from the 0-back to the 1-back task compared to the controls. Strikingly, the greatest activation occurred when moving from the 1-back to the 2-back condition. In other words, MTBI patients showed greater activation with moderate working memory difficulty than controls. The areas of activation relevant to the increased load of the working memory task was the right frontal and right parietal regions, both found to be involved in working memory (E. E. Smith et al., 1998).

McAllister et al. (1999) concluded that the differing degrees of activation between controls and MTBI patients in response to a moderate working memory load may reflect differences in the ability to "turn on" processing resources. However, since this memory task only involved a moderate load (e.g., 2-back), it was unknown whether controls had more processing resources to draw from than MTBI patients. A follow-up study was designed to further explore this question (McAllister et al., 2001).

In 2001, McAllister and colleagues added another level of difficulty (e.g., 3-back) to the working memory paradigm to better examine brain activation patterns at higher processing loads (McAllister et al., 2001). Expanding on the results of the previous study (McAllister et al., 1999), McAllister et al. (2001) hypothesized that controls may have additional processing reserves to draw upon than MTBI patients, which would be supported by further increases in brain activation in a 3-back working memory condition. These researchers further hypothesized that MTBI patients would allocate most of their available processing resources in the moderate working memory load (2-back) and show little increase from moderate to higher load (3-back). Therefore, if MTBI patients have

the inability to recruit additional processing resources, they would be expected to perform worse than controls on a 3-back working memory load task.

The follow-up study by McAllister et al. (2001) included 18 MTBI patients and 12 non-injured controls that were studied with fMRI (N-back working memory task) and a brief neurocognitive test battery (Trail-Making Test, Wisconsin Card Sorting Test, Stroop Interference Test, California Verbal Learning Test, Wechsler Memory Scale) at approximately 27 days post-injury. Preliminary analysis for both groups revealed no structural abnormalities; however MTBI patients reported significantly more memory problems (i.e. complaints) than controls. In addition, both groups demonstrated similar performance on neurocognitive measures of attention, executive function, and memory. Contrary to the authors' hypotheses, there were no significant behavioral differences between groups on any condition of the N-back working memory test including the task of high processing load (3-back). However, there were significant differences in brain activation patterns relevant to these four working memory conditions.

Mild TBI patients and non-injured controls demonstrated increased activation in bilateral frontal and parietal regions that are associated with working memory. A between-group difference for brain activation associated with increased processing load was also documented. In concordance with previous research (McAllister et al., 1999), the MTBI group displayed a greater extent of activation for the moderate working memory load (2-back) than controls in bilateral frontal and parietal regions. However, brain activation for the high load condition was associated with less of an increase in MTBI when compared to controls. The control group had a greater increase in brain activation patterns, particularly in parietal cortical areas, bilaterally. These results were

confirmed by a subsequent voxel-by-voxel comparison that depicted greater increases in activation in all brain regions of interest (left parietal, right inferior parietal, left middle frontal, right superior frontal) for the MTBI patients than controls when progressing from low to moderate load. In contrast, when progressing from moderate to high working memory load, controls showed significantly greater increases in activation in most brain regions.

The two studies by McAllister and colleagues (McAllister et al., 1999; McAllister et al., 2001) accentuate the differences in brain activation between MTBI patients and non-injured controls associated with increased working memory load. These researchers have proposed two cognitive-neural mechanisms to account for these findings that include differences in working memory capacity and allocation of processing resources (McAllister et al., 2001).

Mild TBI or concussive injury may directly impair working memory capacity that is only manifested under increased working memory or processing demands (McAllister et al., 2001). More specifically, McAllister et al. (2001) suggested that the 3-back condition is not difficult enough to tease out these between-group differences. This supposition is based on the assumption that MTBI patients recruit additional processing resources to compensate for injury when moving from the 1-back to the 2-back condition, whereas this is not the case for controls. Non-injured controls activated more processing resources when progressing from the zero to the 1-back condition, with little further activation in the 2-back condition. McAllister et al. (2001) concluded that controls were not challenged by the 2-back condition, whereas the 3-back condition produced increased activation in this group. This finding suggests that this greater working memory load was

sufficient enough to recruit additional processing reserves. In contrast, MTBI patients did not show this additional recruitment for the 3-back memory task, which could suggest that they have already used the majority of their processing resources or reserves for the 2-back (McAllister et al., 2001). These authors contend that a higher-load such as a four-back may provide support for this assumption. More specifically, if MTBI patients showed additional activation on an even higher working memory demand (i.e., four-back) this would suggest that they have additional processing resources to draw from. On the contrary if no further activation was observed, then it could tentatively suggest that MTBI impairs working memory capacity or processing reserves.

Another explanation for the findings of McAllister et al. (1999; 2001) are in regard to the inability for MTBI patients to appropriately match processing resources to processing load (McAllister et al., 2001). This inability to allocate processing resources appropriately would suggest impairment of the central executive component of working memory which is localized to prefrontal areas of the brain (E. E. Smith & Jonides, 1998). These areas of the brain also subserve higher order cognitive function (i.e., learning, planning, memory) that is implicated following concussive injury (Ptito et al., 2007). The dysfunction of the central executive system would likely "over-match" processing resources to moderate processing loads, thus leaving little resources for additional demand (e.g., 3-back) (McAllister et al., 2001). The dysfunction of the central executive component may also account for the increased recruitment of additional neural resources seen in the acute time period following concussion in athletes (Jantzen et al., 2004; Lovell et al., 2007).

Unfortunately, comparing and contrasting the existing fMRI studies on concussive injury is not an easy task, as each have addressed very different questions and used different sample populations and methodological designs. A common finding from these studies are observed changes in fMRI in absence of neurocognitive impairment, which suggests that fMRI may have value in detecting more subtle changes not evidenced by neurocognitive testing. Therefore fMRI may be valuable in assessing possible long-term effects of concussion in athletes with a history of multiple concussions.

CHAPTER III

METHODOLOGY

Research Design

A paired, case-control design was used to compare neurocognitive function, working memory performance, and brain activation patterns between asymptomatic male and female high school and collegiate athletes with and without a history of two or more concussions. The independent variable was history of concussion (no previous concussion, history of two or more previous concussions) and working memory load (0-back, 1-back, 2-back, 3-back). The dependent variables were neurocognitive test scores, working memory scores, and brain activation patterns from images acquired by fMRI. More specifically, computerized neurocognitive test scores included verbal and visual memory, processing speed, and reaction time (RT). Paper-and-pencil neurocognitive test scores included RT for Trail-Making Test Forms A and B and the number correct for the Symbol Digit Modality Test. Working memory included reaction time and percent correct on all four N-back working memory loads. Brain activation patterns included percent BOLD signal change from functional region of interest analyses and whole brain analyses.

Participants

This study received approval from the Institutional Review Board of Michigan State University (MSU) prior to recruiting participants. The participants selected for this study were 14 high school or college athletes with a previous history of two or more concussions and 14 controls matched on age and sex with no history of previous

concussion. All participants were selected from MSU's on-going sport-concussion surveillance study.

Michigan State University Sport-Related Concussion Surveillance Study

Researchers at MSU have been collecting baseline and post-concussion data at MSU and eight local high schools in the mid-Michigan region for the previous three years. To date, approximately 3,000 male and female athletes participating in the sports of football, wrestling, soccer, basketball, ice hockey, baseball, volleyball, softball, lacrosse, and gymnastics have completed a baseline computerized neurocognitive test battery (ImPACT). This pre-season measure collects both cognitive performance and medical history that includes previous history of concussion. Sports medicine personnel at each participating institution have been responsible for referring any athlete who sustains a concussion for follow-up neurocognitive testing. The Vienna guideline concussion criteria have been used by sports medicine personnel to diagnose a concussion at all participating institutions. By this criterion, a concussion is defined as "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" (Aubry et al., 2002, p. 58). Concussed athletes were evaluated by a certified athletic trainer and/or a team physician. Concussed athletes were then referred to the research team for follow-up ImPACT testing at 2, 7, 14, 21, and 30 days post-concussion. One hundred high school and collegiate athletes have sustained a concussion during this research project, with 42 of these having a previous history of two or more concussions. From these 42 athletes, 14 with a history of two or more concussions who meet specific inclusionary criteria were selected to participate in the current study.

Inclusionary Criteria for Athletes with a History of Two or More Concussions

To be included in this study, athletes with a history of two or more concussions met the following criteria: 1) athletes must be participating in the current MSU sport-concussion program, 2) athletes must have incurred at least their second concussion within the past 2 years (i.e., during the on-going MSU concussion study), 3) athletes who sustained a concussion must have completed at least two post-concussion ImPACT tests, 4) athletes who sustained a concussion must have demonstrated at least one neurocognitive impairment on any of the ImPACT composite scores. Neurocognitive impairments are determined by ImPACT on the clinical exam report. ImPACT designates any neurocognitive composite score that has at least 1 reliable change (RCI), indicating clinical significance, and 5) athletes must be medically cleared from their last diagnosed concussion by their school's sport medicine staff (i.e. no concussion symptoms and cognitive impairments) and remain asymptomatic and injury-free (i.e. without incurring another diagnosed concussion) for at least 3 months.

Exclusionary Criteria for Athletes with a History of Two or More Concussions

Any athlete who met the following exclusionary criteria were not asked to participate in this study: 1) any athlete who does not participate in the current MSU sport-concussion program, 2) any athlete who did not sustain at least their second concussion during the previous 2 years, 3) any athlete who did not complete at least two ImPACT post-concussion follow-up assessments, 4) any athlete who has not been medically cleared to play for the past 3 months, 5) any athlete with a history of learning disability; color blindness, psychological disorder, brain surgery, or a major neurological condition (demylinating disease, acute disseminated encephalomyelitis), 6) any athlete with a

severe history intracranial pathology (e.g., subdural hematoma) as determined by a positive CT or MRI, 7) any athlete with hypertension, sickle cell disease, diabetes, and migraines, 8) any athlete who is pregnant, and 9) any athlete who is not compatible with the MRI (i.e., braces or other dental appliances, non-removable ferromagnetic material) (See Appendix A).

Selection of Control Subjects

Athletes who do not have a history of concussion, and are participating in the current MSU sport-concussion program were eligible to serve as control subjects for the current study. Fourteen of these athletes were matched on height, weight, age and sex to athletes with a history of two or more concussions participating in the study. .

Any control athlete who met the following exclusionary criteria was not recruited to participate in this study: 1) any athlete with a history of learning disability, color blindness, psychological disorder, brain surgery, or a major neurological condition (demylinating disease, acute disseminated encephalomyelitis), 2) any athlete with a history of severe intracranial pathology (e.g., subdural hematoma) as determined by a positive CT or MRI, 3) any athlete with hypertension, sickle cell disease, diabetes, and migraines, 4) any athlete who is pregnant, and 5) any athlete who is not compatible with the MRI (i.e. braces or other dental appliances, non-removable ferromagnetic material) (See Appendix B).

Operational Definitions

The following operational definitions were used in this study:

Blocked design – the separation of experimental conditions into distinct blocks, so that each condition is presented for an extended period of time (Huettel, Song, & McCarthy, 2004)

Concussion – "complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" (Aubry et al., 2002, p. 58)

Functional magnetic resonance imaging (fMRI) – a neuroimaging technique that uses standard MRI scanners to investigate changes in brain function over time (Huettel et al., 2004)

N-back working memory task – a popular working memory experimental paradigm commonly used for fMRI. Subjects are asked to monitor the identity or location of a series of verbal or nonverbal stimuli and to indicate when the currently presented stimulus is the same as the one presented "n" trials previously (Owen et al., 2005)

Neurocognitive performance – scores on a battery of scientifically-validated computerized tests that measure memory, reaction time, and processing speed

Reaction time – the time required for someone to make a simple motor response to the presentation of a stimulus (Huettel et al., 2004)

T_1-weighted (T_1-dependent) – images that provide information about the relative T_1 values of tissue; also known as T_1 images

T_2*-weighted – images that provide information about the relative T_2* values of tissue. T_2* -weighted images are commonly used for BOLD-contrast fMRI (Huettel et al., 2004)

Instrumentation

Immediate Post Concussion Assessment Cognitive Testing (ImPACT) 5.0.

ImPACT version 5.0 is a computer-based program that is designed to run from both desktop PC and a laptop using Windows 95 or higher and has been frequently used to assess cognitive function following concussion (Lovell, 2006). The ImPACT program consists of three main categories. In the first category, athletes use the keyboard and external mouse to input demographic and descriptive information through a series of easy-to-follow instructional screens. The demographics section includes: years experience playing sport, history of alcohol and drug use, learning disabilities, attention deficit hyperactive disorder, major neurological disorder, and previous concussion history. These factors may contribute to scores achieved after suffering a concussion; however, with a baseline assessment one can potentially eliminate these confounding variables. The second category consists of 22 concussion symptoms that are rated using a 7-point Likert scale. Athletes self-rate their concussion symptoms by clicking on a number between 0 (not experiencing this symptom) and 6 (severely experiencing this symptom) using an external mouse. The third category consists of six neurocognitive modules that are described below.

ImPACT module one. The first module evaluates attention processes and verbal recognition memory. Athletes are presented twice with a list of 12 words that remain on a screen for 750 ms at a time. Athletes are then tested for immediate recall by answering "yes" or "no" when presented a list of 24 words. At the end of the sixth module (approximately 20 min) athletes are presented with the same 24 words and asked to

answer "yes" or "no." This test measures delayed memory of athletes. Tests are scored based on a total percentage of correct answers.

ImPACT module two. The second module measures visual recognition memory and attentional processes. Athletes are presented with 12 designs that remain on the screen for 750 ms at a time. Athletes are then tested for immediate recall by answering "yes" or "no" when presented 24 designs. At the end of the sixth module (approximately 20 min) athletes are presented with the same 24 designs and asked to answer "yes" or "no." This test measures delayed memory and is scored on total percentage correct.

ImPACT module three. The third module evaluates visual working memory and visual processing speed by using a distractor task (choice reaction time) and memory task (visual memory). Athletes are asked to right click if a red circle is presented and left click if a blue square is presented for the distractor task. Athletes are then presented a random screen of X's and O's with three yellow X's and/or O's. Athletes are presented the distractor test, followed by the same memory screen minus the yellow X's and/or O's. The athlete is asked to click on the three previously illuminated yellow X's and/or O's. Athletes complete this module four times. They receive a score for the number of errors on the distractor test, reaction time for the distractor test, and correct identification of yellow X's and O's.

ImPACT module four. The fourth module measures visual processing speed, learning, and memory. Athletes are presented nine symbols matched with nine numbers (1 to 9) on a screen. Below these pairings, a symbol is randomly presented. The athlete clicks on the matching number as quickly as possible while at the same time remembering the number/symbol pairings. When an athlete clicks on the correct number,

the number will light up green. If the number was incorrect it will light up red. The athlete completes 27 trials. The second phase to this test consists of the symbols disappearing from the top grid, and then randomly reappearing below the grid. The athletes click on the number that matches the symbol. Athletes receive an average reaction time score and a score for memory recall.

ImPACT module five. The fifth module measures choice reaction time. Athletes are presented with the words one at a time: red, green, and blue. If the word appears in the correct color, athletes click the left mouse button as fast as they can. Athletes receive a reaction time score and a score for the number of errors.

ImPACT module six. The sixth module measures visual motor response speed and working memory. Athletes are presented with three random letters on the screen. Athletes are then asked to click in backwards order numbers "25" through "1" from a randomized 5 X 5 grid. Athletes are asked to type in the three letters that appeared on the screen before the last number grid. Athletes complete this module five times. Athletes receive a score for the correct number of letters and clicked numbers.

Reliability and Validity of ImPACT

Test-retest reliability for ImPACT was assessed over eight days across four test administrations, yielding correlation coefficients ranging from .66 to .85 for the verbal memory index, .75 – .88 for the processing speed, and .62 to .66 for the reaction time (Lovell, Collins, & Podell, 2001). Using reliable change indices, repeated administrations over a two-week period revealed no practice effects (Iverson, Lovell, Collins, & Norwig, 2002). Correlations between ImPACT visual and verbal memory composites with the Brief Visual Spatial Memory Test-Revised total score (r=.50) and the delayed recall score

(r=.85) have been established (Iverson, Franzen, Lovell, & Collins, 2004). The processing speed composite score was also shown to correlate with the Trail-Making Tests A (r= -.49) and B (r= -.60), and the Symbol-Digit Modalities test (r=.68) (Iverson, Franzen et al., 2004). Schatz and colleagues (2006) documented a combined sensitivity of 81.9% for ImPACT indices and total symptom score, and a specificity of 89.4%; positive likelihood ratio was approximately 8:1 and negative likelihood ratio was 2:1.

Trail-Making Test Form A and B

The Trail-Making Test Forms A and B assesses complex visual scanning, motor speed, divided attention, and cognitive flexibility and ability to shift strategy (Lezak, Howieson, & Loring, 2004; Reitan & Wolfson, 1993). Form A of the Trail-Making Test requires subjects to draw lines to connect consecutively numbered circles on one worksheet. Form B of this measure requires the subject to connect the same number of consecutively numbered circles and letters on another worksheet by alternating between the two sequences.

Symbol Digit Modality Test

The Symbol Digit Modalities Test (SDMT) (A. Smith, 1982, 1968) is a brief paper-and-pencil neurocognitive test battery that involves a simple substitution task requiring the examinee to use a reference key to pair specific numbers with given geometric figures as fast as possible for 90 seconds. This altered, inverse form of the Digit Symbol Test (Wechsler, 1955) assesses attention, visual scanning, and motor speed. Correlations between the SDMT and the Digit Symbol Test are .80 for healthy subjects (Lezak et al., 2004). This neurocognitive measure has been extensively used in the

concussion literature to examine neurocognitive function following concussive injury (Collins, Grindel et al., 1999).

Functional Magnetic Resonance Imaging (fMRI)

The experiment was conducted on a GE 3T Signa® HDx MR scanner (GE Healthcare, Waukesha, WI) with an 8-channel head coil. This system has an actively shielded short-bore (2.06 m width x 1.72 m length) magnet, a fast gradient system that provides high-speed brain imaging for fMRI as well as regular body imaging, a powerful volume reconstruction engine that enables virtually real-time image generation, even when massive parallel imaging datasets are involved, as well as multinuclear spectroscopy hardware. The short-bore magnet provides a low incidence of claustrophobia. Parallel imaging technology allows echo-planar images (EPI) to be acquired with higher temporal resolution and with less distortion for fMRI studies and other EPI-based image acquisitions.

Procedures

Participant recruitment, consent, and pre-screening for fMRI and Neurocognitive Testing

This study was approved from the Michigan State University Institutional Review Board. Written informed consent/assent was obtained from each recruited participant prior to their voluntary participation in this study. Any minors (e.g., high school athletes) selected to participate in this study were recruited by the researchers and his or her school's certified athletic trainer. Specifically, the minor and his or her parent or guardian was contacted to discuss participation in the study. All risks and benefits were discussed and questions were answered. Athletes completed the fMRI compatibility form (see

Appendix B). Upon consenting to participate and being compatible with fMRI imaging, athletes were enrolled in the study and scheduled for data collection.

Session 1: Neurocognitive Testing

Upon arrival to MSU Radiology, all female athletes were required take a pregnancy test to ensure they were not pregnant prior to the fMRI scan (in the second data collection session). Participants then reported to a designated computer testing room at MSU Radiology on a pre-arranged time and day. Athletes were administered a baseline ImPACT test, Trail-Making Test Form A and B, Symbol Digit Modalities Test, and a practice test of the N-back working memory task (approximately 1 hour). If possible, athletes had the opportunity to visit the fMRI scanner model to become familiar with the surroundings and could ask questions of the researcher and radiology technician(s) prior to their second visit for scanning. Prior to leaving MSU Radiology, participants were scheduled for their second visit to be scanned.

Session Two: fMRI Scanning

Participants were instructed to arrive approximately 15 minutes prior to their scheduled scanning time to be prepped for fMRI imaging. Prior to participation all athletes were asked a set of questions that assessed sleep, caffeine, exercise, etc (See Appendix B). These questions were used to further corroborate inclusionary and exclusionary criteria about each participant. The following imaging sequences were conducted during an approximate one hour and fifteen minute scanning session: 1) localizer (10 minutes); 2) Asset Calibration; 3)Axial T_2* (10 minutes); 4) higher-order shim; 5) fMRI working memory task (30 minutes); 4) Resting scan (8 minutes); 5) DTI

scan (12 minutes); 6) anatomical T_1scan (10 minutes); and 7) Sagittal FLAIR cube (5 minutes).

Data Acquisition

Functional MRI N-Back Working Memory Paradigm:

The N-back task is a commonly used test of working memory. This task requires the athlete to watch and attempt to remember sets, or blocks, of 12 upper and lowercase letters that appear one at a time on the computer screen. Athletes were required to respond accordingly by pressing their right index finger when they identify a target, and their right middle finger for non-targets. There are four conditions, or working memory loads, of this task that included: 0-back, 1-back, 2-back, and 3-back. Each of these conditions increases in difficulty from the 0-back to 3-back. In the 0-back condition, a pre-designated letter (e.g., "x") was identified as the target letter. All other letters represented a non-target. When a letter appears, athletes were required to execute either a target or non-target response as fast as possible. The 1-back working memory load requires the athlete to remember and identify any letter that is the same as the one shown before it, as this is a target. Any letter that is not the same as the one shown before it is a non-target. The 2-back working memory load is similar to the 1-back, but now the athlete must look for a letter that is the same as the one shown exactly two letters before it. The 3-back working memory load is the most difficult and requires the athlete to remember and identify a letter that appeared exactly three letters before it. Examples of each of these conditions are depicted in Figure 2.

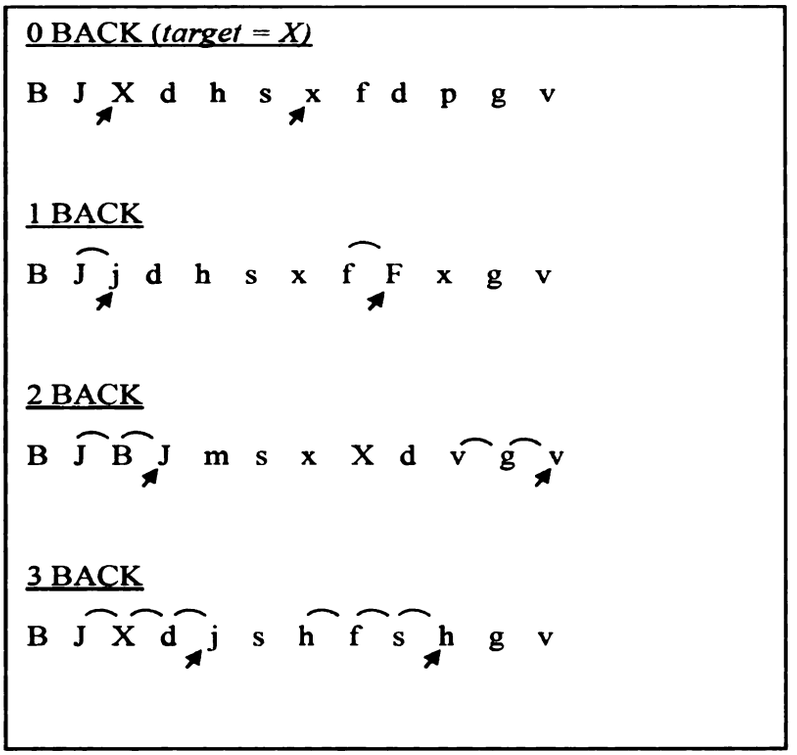

Figure 2. Examples of the 0-back, 1-back, 2-back, and 3-back N-back task working memory loads. Bold arrows indicated targets. Each letter was presented for 500 ms followed by a blank screen for 2000 ms.

E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA) was used to create the N-back working memory paradigm for the current study. The creation of this paradigm was similar to the N-back paradigm used by previous researchers (Ravizza, Delgado, Chein, Becker, & Fiez, 2004). Thirty-six consonant letters (both upper and lowercase) that included: B, C, D, F G H, J, K, M, N, P, Q, R, S, T, V, X, and Z were used as a "letter-bank" for creating each of the four N-back working memory loads. All N-back working memory loads were comprised of 96 letters that were randomly selected (with replacement) from the "letter-bank." Of the 96 letters, 32 were positioned pseudo-randomly as targets and 64 were positioned pseudo-randomly as non-targets across four runs.

The working memory paradigm was implemented as a block design that included four 6.15 minute runs during fMRI. Fifteen seconds of fixation preceded the start of the first stimuli block in each run, and this data period was discarded. Each of the four runs was counterbalanced and included eight (four conditions that repeat) stimuli blocks (see Figure 3). Each stimulus block contained 12 letters that appeared one at a time for 500 ms followed by a blank screen that remained for 2000 ms. All stimuli blocks were 30 seconds long alternating with 15 second fixation periods between them (see Figure 3 below). The fixation periods included a white "plus" sign presented on a black background. It is important to note that targets were pseudo-randomly positioned within and across all runs and blocks (e.g., it is possible that one block could have no targets and all non-target letters). Distractor foils (e.g., 1-back targets appearing during the 2-back condition) were also "pseudo-randomly" positioned within and across all four runs. There were no foils in the 0-back condition, as it served as a control. However in the 1-back working memory load there were eleven 2-back foils and six 3-back foils. The 2-back working memory load had nine 1-back and ten 3-back foils. The 3-back working memory load had eleven 1-back and six 2-back foils.

	N-back Conditions							
Run 1:	0	1	2	3	0	1	2	3
Run 2:	3	2	1	0	3	2	1	0
Run 3:	0	1	2	3	0	1	2	3
Run 4:	3	2	1	0	3	2	1	0

Figure 3. Presentation order of the N-back stimulus blocks.

Stimuli were displayed on a 640×480 LCD monitor mounted on top of the RF head coil. The LCD was subtended 12°×16° of visual angle. The paradigm was controlled by E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA). A pair of 5-button MR-compatible keypads with this system was used to record participant responses.

Pilot Behavioral Data for N-back

Thirteen high school and collegiate athletes without a self-reported history of concussion volunteered to pilot test the N-back working memory paradigm. This group consisted of 7 males (M = 19.14 years, SD = 1.95) and 5 females (M = 20.33 years, SD = 1.21). One-way ANOVAs were conducted to examine performance differences in accuracy and reaction time for each of the N-back conditions. Results revealed significant differences for accuracy ($p = .001$) and reaction time ($p = .001$). Post-hoc comparisons for accuracy found significant differences between the 0-back and 3-back working memory loads ($p = .001$), 1-back and 3-back working memory loads ($p = .001$), and the 2-back and 3-back working memory loads ($p = .001$) (See Figure 4). Additional post-hoc comparisons for reaction time also revealed significant differences between 0-back and 3-back ($p = .002$) and the 1-back and 3-back ($p = .002$) working memory loads (See Figure

5). These results indicate an effect for increased working memory load as subjects progressed from the 0-back to 3-back working memory loads.

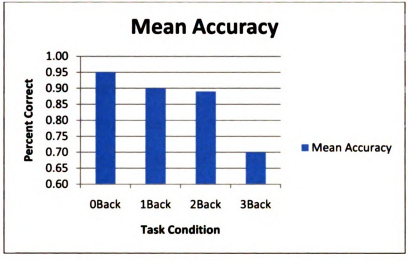

Figure 4. Behavioral pilot data for accuracy on the N-back working memory paradigm (n = 13).

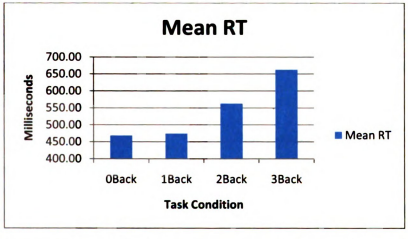

Figure 5. Behavioral pilot data for reaction time on the N-back working memory paradigm (n = 13).

Imaging Acquisition

During each session, images were acquired for the purpose of localization, and then first and higher-order shimming procedures were carried out to improve magnetic field homogeneity. To study brain function, echo planar images (EPI), starting from the most inferior regions of the brain, were acquired with the following parameters: 36 contiguous 3-mm axial slices in an interleaved order, TR/TE = 2500/27.7 ms, flip angle = 80°, FOV = 220 mm, matrix size = 64 × 64, voxel-size = 3.4375 x 3.4375 x 3 mm, with the first four data points discarded. Each volume of slices were acquired 144 times during each of the four functional runs while athletes viewed the stimuli and pressed a pre-designated button to indicate target or non-target, which resulted in a total of 576 volumes of images over the course of the entire experiment. After the functional data acquisition, high-resolution volumetric T_1-weighted spoiled gradient-recalled (SPGR) images with cerebrospinal fluid suppressed were obtained to cover the whole brain with 180 contiguous 1mm sagittal slices, TR/TE = 8.596/3.828ms, flip angle = 8°, FOV = 240mm, matrix size = 256 x 256. These images were used to register subject functional data to normalized stereotactic space.

Data Analysis

Functional MRI Data Pre-processing

FMRI and MRI data were preprocessed and analyzed using FMRIB's Software Library (FSL) fMRI Expert Analysis Tool (FEAT) (S. M. Smith et al., 2004). Functional data were brain-extracted (S. M. Smith, 2002), motion-corrected to the median functional image using b-spline interpolation (4 df), high-pass filtered (60s), and spatially smoothed (9mm full width at half maximum (FWHM), isotropic). The anatomical volume was

brain-extracted and registered to the standard space T1 MNI template using tri-linear interpolation with FMRIB's Linear Image Registration Tool (FLIRT, 12 df; (Jenkinson & Smith, 2001)). The median functional image was registered to the anatomical volume, and then transformed to the MNI template.

First Level Subject Analysis

Statistical images were created using FEAT with an improved General Linear Model (GLM). Regressors were created by convolving blocked time-course files for each condition with a canonical HRF. Time-course files were generated separately for each of four working memory loads (0-back, 1-back, 2-back, 3-back). Each regressor was entered into the GLM along with their temporal derivative and 6 rigid body movement parameters (motion in x, y, z, roll, pitch, and yaw directions) which were modeled as nuisance covariates.

Group Analysis

Statistical maps were entered into a 2 group (history of concussion, control) x 4 working memory load (0-back, 1-back, 2back, 3-back) repeated measures ANOVA. Paired samples T-test contrasts for within and between effects were performed in a second-level GLM. For all within-subjects comparisons individual subject beta-images were entered along with a regressor per subject to account for subject-specific variance. Group analyses were performed using FSL's FLAME higher-level analysis tool (Beckmann, Jenkinson, & Smith, 2003), and all f- and t-statistics were converted to unit-normal z-statistics.

Functional ROI analysis:

Functional ROI's were defined by clusters surviving voxel-wise thresholding at FWE-corrected $p < 0.05$ with a minimum extent of 10 contiguous voxels. Percent signal-change values were extracted from individual subject beta-maps within ROI's functionally defined by the second level contrast results, group-averaged, and subjected to offline analysis.

Data Analyses for Evaluation of Hypotheses

H1: There will be no differences on ImPACT verbal memory performance between asymptomatic athletes with and without a history of two or more concussions.

An independent samples t-test was conducted to evaluate differences on verbal memory performance between asymptomatic athletes with and without a history of two or more concussions. Statistical significance was set at $p \leq .05$.

H2: There will be no differences on ImPACT visual memory performance between asymptomatic athletes with and without a history of two or more concussions.

An independent samples t-test was conducted to evaluate differences on visual memory performance between asymptomatic athletes with and without a history of two or more concussions. Statistical significance was set at $p \leq .05$.

H3: There will be no differences on ImPACT reaction time between asymptomatic athletes with and without a history of two or more concussions.

An independent samples t-test was conducted to evaluate differences on reaction time between asymptomatic athletes with and without a history of two or more concussions. Statistical significance was set at $p \leq .05$.

H4: There will be no differences on ImPACT motor processing speed between asymptomatic athletes with and without a history of two or more concussions.

An independent samples t-test was conducted to evaluate differences on motor processing speed between asymptomatic athletes with and without a history of two or more concussions. Statistical significance was set at $p \leq .05$.

H5: There will be no differences in performance on the Trail-Making Test Form A between asymptomatic athletes with and without a history of two or more concussions.

An independent samples t-test was conducted to evaluate differences on the Trail-Making Test Form A between asymptomatic athletes with and without a history of two or more concussions. Statistical significance was set at $p \leq .05$.

H6: There will be no differences in performance on the Trail-Making Test Form B between asymptomatic athletes with and without a history of two or more concussions.

An independent samples t-test was conducted to evaluate differences on the Trail-Making Test Form B between asymptomatic athletes with and without a history of two or more concussions. Statistical significance was set at $p \leq .05$.

H7: There will be no differences in performance on the Symbol Digit Modalities Test between asymptomatic athletes with and without a history of two or more concussions.

An independent samples t-test was conducted to evaluate differences on the Symbol Digit Modalities Test between asymptomatic athletes with and without a history of two or more concussions. Statistical significance was set at $p \leq .05$.

H8: There will be no differences in reaction time on the N-back working memory task between asymptomatic athletes with and without a history of two or more concussions.

Reaction time (milliseconds) for the N-back working memory task was assessed with a 2 group (concussion history, no concussion history) X 4 working memory load (0-back, 1-back, 2-back, 3-back) ANOVA with repeated measures on the last factor. Post-hoc comparisons were explored using separate independent t-tests. Statistical significance was set at $p \leq .05$.

H9: There will be no differences in accuracy on the N-back working memory task between asymptomatic athletes with and without a history of two or more concussions.

Accuracy (percent correct) for the N-back working memory task was assessed with a 2 group (concussion history, no concussion history) X 4 working memory load (0-back, 1-back, 2-back, 3-back) ANOVA with repeated measures on the last factor. Post-hoc comparisons were explored using separate independent t-tests. Statistical significance was set at $p \leq .05$.

H10: There will be differences in regional patterns of activation, indicative of brain "reorganization" and/or "compensation," between asymptomatic athletes with and without a history of two or more concussions.

H11: There will be differences in the amount of "engagement" in working memory brain regions between asymptomatic athletes with and without a history of two or more concussions.

Hypothesis 10 (i.e., the "compensation hypothesis") and 11 (i.e., the "engagement hypotheses" were evaluated by several statistical analyses. First, a whole-brain 2 group (history of concussion, control) X 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated measures ANOVA was performed to identify any brain regions that interacted between group and working memory load. Resulting ROIs from this analysis

could be interpreted in support of H10 if interactions were characterized by increased activity in the history of concussion group with load in regions outside of those that increase with load in the control group. Alternatively, ROIs from this analysis could be interpreted in support of H11 if no regions were found to be uniquely activated by history of concussion group, but regions that increased in activity with load in the control group did not increase, or to the same degree, in the history of concussion group.

Second, another method to assess whether the brain regions used by the control group was also used, and to the same degree, by the history of concussion group a more sensitive functional ROI mask (Family-Wise Error: FWE corrected $p < .05$) was derived by using 3-back > 0-back contrast from controls. Percent signal-change was then extracted from these regions in both groups (all subjects) and tested offline using SPSS. This analysis was done in order to accept a more liberal significance threshold of uncorrected $p < 0.05$ by looking at summarized data offline, and was explored in support of H11. A Bonferroni correction was used to control for an inflation of Type I error due to multiple ANOVAs being conducted on the ROIs.

Third, in order to ensure that the functional ROI localization based on the control group was unbiased, a functional ROI mask (FWE-corrected, $p < .05$) using the 3-back > 0-back contrast was derived from the history of concussion group and percent signal-change was subsequently extracted from these regions in both groups and tested offline using SPSS. A Bonferroni correction was used to control for an inflation of Type I error due to multiple ANOVAs being conducted on the ROIs. This analysis was performed to explore if peak activation regions used by the history of concussion group were used to the same degree as controls. In addition to confirming that peak activations from the

history of concussion functional ROI mask were in common regions with those derived from the control mask, this analysis could result in regions that increased with load in the history of concussion group not found in the control mask (i.e., support for H10).

Fourth, for purposes of quantitative comparison, between-group whole-brain independent t-tests were conducted for 0-back, 1-back, 2-back and 3-back to identify any regions that are significantly different at any of these working memory loads. This analysis could provide a sensitive comparison of activity that varied between groups at any working memory load level.

Finally, whole-brain paired t-tests were performed on the 1-back > 0-back; 2-back > 1-back; and 3-back > 2-back contrasts to examine regional activation differences with respect to increases in working memory load between both groups (i.e., evaluating differences of "the differences"). Similar to the methods of McAllister et al. (1999; 2001) these contrast maps were displayed at a $z > 2.33$ ($p < 0.01$) in order for qualitative comparisons (i.e., test of ocularity) to be made. A subsequent contrast map of this analysis was also displayed at a $z > 3.1$ ($p < .001$), k > 10 voxels, which represents the study's minimum whole-brain significance criteria in cases where FWE-corrected $p < 0.05$ was thought likely to result in a Type II error.

EQ 1: Are there brain deactivation differences between asymptomatic athletes with and without a history of two or more concussions?

A functional ROI mask (FWE-corrected, $p < 0.05$) based on deactivating regions (i.e., 0-back > 3-back contrast) was derived from the control group. This mask was used to extract percent signal-change for these brain regions in both groups and tested offline using SPSS. Similar to the functional ROI mask derived by the contrast of 3-back > 0-

back, these data were examined to demonstrate whether regions deactivated with increases in load in the control group consequently deactivated, and to the same degree, in the history of concussion group. A Bonferroni correction was used to control for an inflation of Type I error due to multiple ANOVAs being conducted on the ROIs.

CHAPTER IV

RESULTS

Demographic Information

There were a total of 30 athletes who participated in this study; however two athletes were excluded from study due to negative MRI results. Therefore 28 athletes comprised the sample. Fourteen athletes (8 male, 6 female) with a history of at least two concussions were matched on age, height, and weight with 14 athletes (8 male, 6 female) without a history of concussion. All athletes participating in this study were asymptomatic at the time of study. The history of concussion group was comprised of 9 collegiate athletes and 5 high school athletes, while the control group was comprised of 6 collegiate athletes and 8 high school athletes. This discrepancy is due to the ages of 17 and 18 years being represented as both a high school senior and college freshman. The sports of football, wrestling, softball, basketball, hockey, and soccer were represented in this sample. Athletes were not directly matched on sport, due to multiple sports played by high school athletes. Independent t-tests were conducted to evaluate potential matching differences on age, height, and weight. There were no significant differences between the history of concussion group and controls regarding age (t (26) = .00, p =1.00), height (t (26) = -1.45, p =.16), and weight (t (26) = .09, p=.93). A summary of demographic data for age, height, and weight can be found in Table 5.

Table 5

Demographic Information for Asymptomatic Athletes with a History of Two or More Concussions (n = 14) and Controls (n = 14)

	Age (yrs)		Height (cm)		Weight (kg)	
Group	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
History of Concussion						
Males	18.00	±1.85	175.90	±6.60	73.43	±10.07
Females	18.50	±2.88	164.67	±4.65	66.76	±10.26
Total	18.21	±2.26	171.09	±8.08	70.57	±10.34
Controls						
Males	18.00	±2.33	180.67	±7.62	77.34	±12.70
Females	18.50	±2.74	169.34	±6.76	60.55	±6.38
Total	18.21	±2.42	175.79	±9.09	70.14	±13.29

The history of concussion group had a reported average of 2.43 previous concussions (*SD* = ± .65) that ranged from 2 to 4 previous injuries. All athletes in the concussion history group were recovered (asymptomatic) for at least 3 months since their last concussion. Specifically, the average time since recovery from their last concussion was approximately 9 months (*SD* = ± 6.67) with a range from 3 to 26 months. Additional self-reported information on the total number of concussions that involved LOC was also collected. A complete summary of these data for the entire group of athletes with a previous history of concussion can be found in Table 6.

Table 6

Descriptive Data on Previous Concussions for Asymptomatic Athletes with a History of Two or More Concussions (n = 14)

Athlete	No. of Concussions	No. of Concussions Involving LOC	Time Since Last Concussion (months)
1	2	1	4
2	2	1	14
3	3	0	26
4	2	1	8
5	2	1	4
6	2	1	10
7	3	3	8
8	2	2	6
9	2	0	8
10	2	0	14
11	3	1	4
12	3	0	3
13	2	0	3
14	4	0	18

Evaluation of Hypotheses: Behavioral Results

The following behavioral results (H1 through H9) are combined into the categories of computerized neurocognitive test results, paper-and-pencil neurocognitive test results, and behavioral data from the N-back working memory task completed during scanning.

Computerized Neurocognitive Testing Results (Hypotheses 1 – 4):

There will be no differences on computerized neurocognitive test performance (ImPACT Composite Scores: verbal and visual memory, motor processing speed, reaction time) between asymptomatic athletes with and without a history of two or more concussions.

Hypotheses 1 through 4 were supported as the results from separate independent t-tests revealed no significant differences between asymptomatic athletes with a history of two or more concussions and controls on verbal memory (t (26) =.15, p =.88), visual memory (t (26) = -.96, p =.34), motor processing speed (t (26) =.06, p =.95), and reaction time (t (26) = -.30, p =.77). The means and standard deviations for each ImPACT composite score can be found in Table 7.

Table 7

Mean and Standard Deviations for ImPACT Composite Scores for Asymptomatic Athletes with a History of Two or More Concussions (n=14) and Controls (n=14)

	History of Concussion		Controls	
ImPACT Composite	*Mean*	*SD*	*Mean*	*SD*
Verbal Memory	.89	± .10	.89	± .10
Visual Memory	.83	± .09	.86	± .08
Motor Processing Speed	43.27	± 6.41	43.13	± 5.60
Reaction Time	.53	± .07	.54	± .05

Paper-and-Pencil Neurocognitive Testing Results (Hypotheses 5 – 7):

There will be no differences on paper-and-pencil neurocognitive test performance (Trail-Making Test Form A and B, Symbol Digit Modalities Test) between asymptomatic athletes with and without a history of two or more concussions.

Hypotheses 5 through 7 were supported as the results from separate independent t-tests did not reveal any significant differences between asymptomatic athletes with a history of two or more concussions and controls for the Trail-Making Test Form A (t (26) = 1.35, p = .19), Trail-Making Test Form B (t (26) = .64, p = .53), or the Symbol Digit Modalities Test (t (26) = .69, p = .50). The mean and standard deviation scores for these tests can be found in Table 8.

Table 8

Means and Standard Deviations of Paper-and Pencil Neurocognitive Test Battery Scores for Asymptomatic Athletes with a History of Two or More Concussions (n = 14) *and Controls* (n = 14)

	History of Concussion		Controls	
Neurocognitive Test Battery	*Mean*	*SD*	*Mean*	*SD*
Trail-Making Test Form A	16.86	± 2.31	15.37	± 3.45
Trail-Making Test Form B	38.45	± 12.18	35.96	± 7.99
Symbol Digit Modalities Test	62.86	± 13.25	60.14	± 6.64

N-back Working Memory Task Results (Hypotheses 8 – 9):

There will be no differences on reaction time and accuracy on the N-back working memory task between asymptomatic athletes with and without a history of two or more concussions.

Hypothesis 8 was supported as the results from a 2 group (concussion history, control) x 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated measures ANOVA revealed no significant between group differences (F [1,26] = .64, p =.43, η^2 = .02) for reaction time on the N-back working memory task. The group x working memory load interaction was also not significant (*Wilks* λ =.97, F [3,24] = .25, p =.86, η^2 = .03). However, there was a significant within-subject main effect for working memory load (*Wilks* λ =.31, F [3,24] = 17.89, p =.000, η^2 = .69) (See Figure 6). Subsequent pairwise comparisons with a Bonferroni correction revealed significant differences in reaction time between 0-back and 1-back (p = .01), 1-back and 2-back (p = .03), and 2-back and

3-back (p = .00) working memory loads. The means and standard deviations for N-back reaction times are shown in Figure 7.

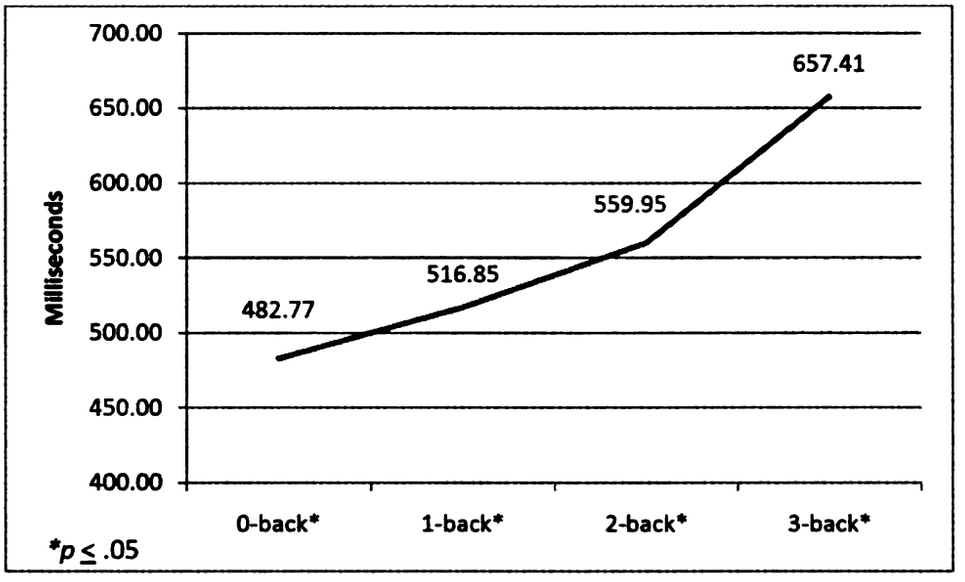

Figure 6. Significant within-groups effect for N-back reaction time across the working memory loads (N = 28).

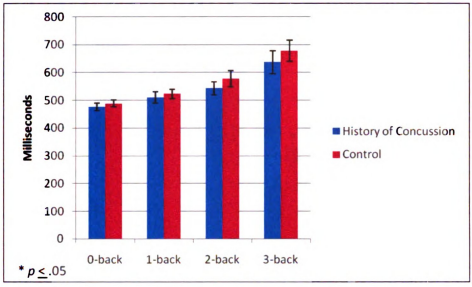

Figure 7. Means and standard deviations for reaction time on the N-back working memory task for asymptomatic athletes with a history of two or more concussions (n=14) and controls (n=14).

Hypothesis 9 was not supported as the results from a 2 group x 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated measures ANOVA revealed significant differences between asymptomatic athletes with a history of two or more concussions and controls for N-back accuracy (i.e., percent correct) (F [1,26] = 14.92, p =.001, η^2 = .37). A series of post-hoc independent t-tests were performed to identify group differences at each working memory load. Specifically, there were no between-group differences at the 0-back working memory load (p=.70). However, controls demonstrated better accuracy than the history of concussion group at the 1-back (p=.01), 2-back (p=.04), and 3-back (p=.02) working memory loads. The means and standard deviations for accuracy on the N-back is shown in Figure 8.

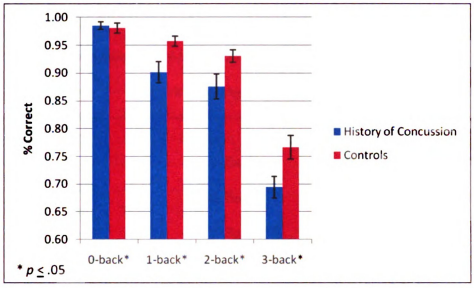

Figure 8. Mean accuracy (percent correct) and standard deviations for N-back working memory performance between asymptomatic athletes with a history of two or more concussions (*n = 14)* and controls (*n* = 14).

A significant within subjects main effect for accuracy on working memory load (*Wilks* λ =.08, F [3,24] = 88.77, p =.000, η^2 = .92) was also found. Subsequent pair-wise comparisons with a Bonferroni correction revealed significant differences for accuracy between the 0-back and 1-back (p = .01) and the 2-back and 3-back (p=.000) working memory loads. The within group comparisons of accuracy for the 1-back and 2-back working memory loads were not significant (p=.62). These values can be found in Table 9.

Table 9

Pair-wise Comparisons of N-back Working Memory Loads for Accuracy (n= 28)

	N-Back Working Memory Load	*p*
0-back	1-Back	.001*
	2-Back	.000*
	3-Back	.000*
1-back	2-Back	.62
	3-Back	.000*
2-back	3-Back	.000*

*$p \leq .05$

A significant interaction was also revealed for group and working memory load (*Wilks* $\lambda = .66$, $F\,[3,24] = 4.16$, $p = .02$, $\eta^2 = .34$). The control group correctly identified more targets than the history of concussion group for the 1-back, 2-back, and 3-back working memory loads. This interaction is depicted in Figure 9.

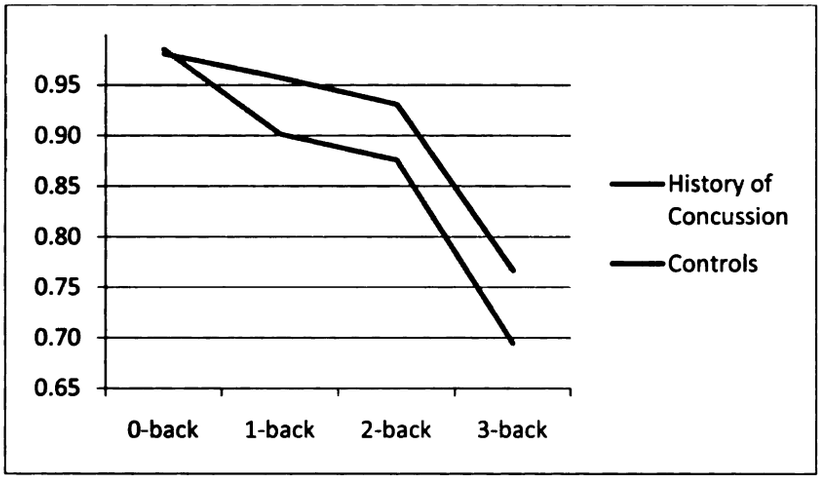

Figure 9. Interaction between asymptomatic athletes with a history of two or more concussions and controls on N-back accuracy.

In addition to calculating percent correct for the 32 target trials, false alarm rates (i.e., a subject pressing target during a non-target trial) were calculated for each working memory load. A comparison of the mean false alarm rates between the two groups can be found in Table 10. The results from an independent samples t-tests revealed no significant differences between groups for the 0-back (t (26) = .29, p = .78), 1-back (t (26) = 1.21, p = .24), 2-back (t (26) = .99, p = .33), or 3-back (t (26) = .83, p = .41) false alarm rates.

Table 10

Mean and Standard Deviations for False Alarm Rates (percent) on the N-back Working Memory Task for Asymptomatic Athletes with a History of Two or More Concussions (n = 14) and Controls (n = 14)

	History of Concussion		Controls	
N-back Working Memory Load	*Mean*	*SD*	*Mean*	*SD*
0-back	.01	±.02	.01	±.01
1-back	.03	±.02	.02	±.02
2-back	.06	±.03	.05	±.04
3-back	.07	±.06	.05	±.04

Evaluation of Hypotheses: Imaging Results

Functional MRI Results (Hypotheses 10 and 11):

There will be differences in regional patterns of activation that are indicative of brain compensation or engagement differences between asymptomatic athletes with and without a history of two or more concussions.

Results from Whole-Brain 2 X 4 Repeated Measures ANOVA

The results from a whole-brain 2 group (history of concussion, controls) X 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated measures ANOVA revealed no significant interaction between group and working memory load or main effect for group (See Figures 10 and 11, respectively). However, there was a within subjects main effect for working memory load. Post-hoc whole-brain paired t-tests for all athletes were conducted for both activation (i.e., 3-back > 0-back) and deactivation (i.e., 0-back >3-back) contrasts to further identify which brain regions demonstrated an increase or decrease in response to working memory load. Brain regions of activation were found in the right inferior parietal lobe (R IPL), left middle frontal gyrus (L MFG), right inferior frontal gyrus (R IFG), left inferior frontal gyrus (L IFG), anterior cingulate cortex (ACC), right middle frontal gyrus (R MFG), left inferior parietal lobe (L IPL), precuneus, and cerebellum. Brain regions of deactivation were also found in the dorsal anterior cingulate cortex (Dorsal ACC), right temporal parietal junction (R TPJ), left insula, left posterior cingulate gyrus (L PoCG), left inferior parietal lobe (L IPL), and left hippocampus. The activated and deactivated brain regions are displayed in Figure 12 and listed in Table 11.

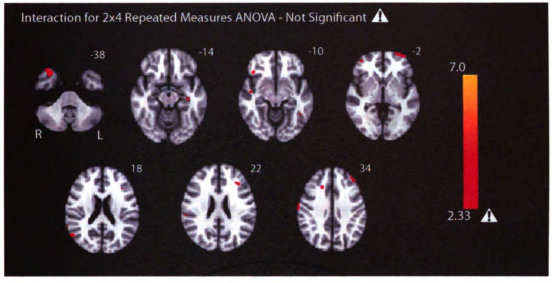

Figure 10. The whole-brain Group x Load interaction. This analysis failed to reach significance in any region of the brain. Overlay is shown at a nominal uncorrected threshold of $p < 0.01$ for display purposes only.

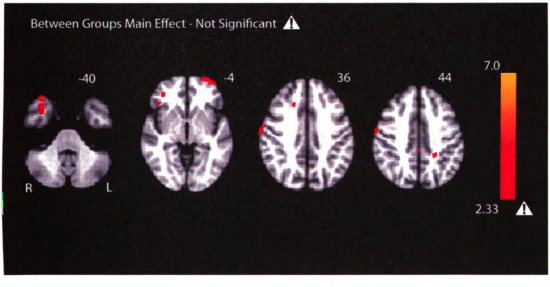

Figure 11. The whole-brain main effect for group. This analysis failed to reach significance in any region of the brain. Overlay is shown at a nominal uncorrected threshold of $p < 0.01$ for display purposes only.

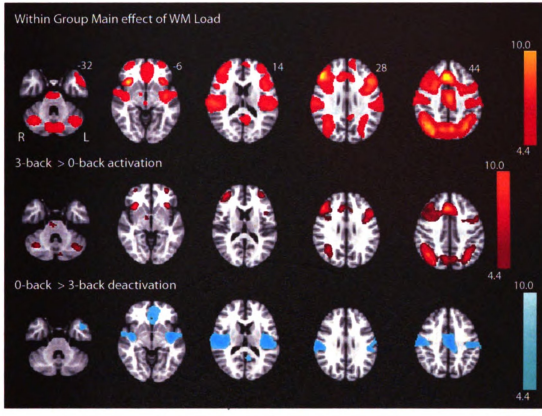

Figure 12. (Row 1) Results of the whole-brain within group main effect for working memory load. (Row 2) Regions showing increased activation between 3-back > 0-back contrasts are shown in red. (Row 3) Regions showing deactivation between 0-back > 3-back contrasts are shown in light blue. Across groups several bilateral regions of activation were found in prefrontal and parietal cortices common to previous fMRI studies of working memory.

Table 11

Results of the Whole-Brain 2X4 Repeated Measures ANOVA (n = 28)

	Brodmann Area	#Voxels	Z-max	MNI coordinates		
				X	*Y*	*Z*
Within-subjects effect						
Activated Regions						
R IPL (SMG, Angular)	19, 39, 40	1952	9.53	38	-64	46
L MFG	10	208	7.4	-30	60	0
R IFG	47	244	9.19	34	22	-6
L IFG	44, 46	1031	8.87	-44	18	24
ACC	8, 32	904	10.4	2	26	42
R MFG	9	884	10.3	48	32	26
R MFG (R DLPFC)	8	874	10.1	28	10	52
L IPL (SMG, Angular)	19, 39, 40	862	9.29	-32	-58	36
Precuneus	7	696	8.29	-6	-70	44
L IFG	47	80	7.82	-32	24	-4
R MFG	10	329	8.28	40	46	10
L MFG(L DLPFC)	6, 8	241	8.41	-28	2	48
Cerebellum		74	7.52	34	-62	-36
Cerebellum		28	7.26	-34	-62	-36
Deactivated Regions						
Dorsal ACC	24, 31	606	8.74	-2	-12	44
R TPJ	40	1419	8.07	60	-24	20
L Insula/L TPJ	22, 40, 47	1096	7.73	-40	-8	-4
L PoCG	3	86	7.29	-42	-22	54
L IPL, L PoCG	2, 40	56	7.08	-52	-24	36
L Hippocampus	28	18	6.95	-26	-16	-22
Between-subjects effect		*No significant activation*				
Interaction		*No significant activation*				

Overall the results of the whole-brain 2X4 repeated measures ANOVA revealed no significant main effect for group or an interaction between group and working memory load. Nonetheless, there was clearly an effect of working memory load as indicated in the within-subject activation and deactivation contrasts. The lack of a significant whole-brain interaction suggests that both groups behaved similarly. However, to assure that this conclusion is not a Type II error, an additional (and more sensitive) functional region of interest (ROI) analysis was performed. This analysis allowed for a more liberal significance criterion of $p < 0.05$ uncorrected for multiple comparisons to be accepted.

Functional Region of Interest Approach Analyses

A functional ROI approach was used to compare percent signal change in the BOLD response between the two groups of athletes. More specifically two analyses (i.e., approaches) were used to extract percent signal change. First control group activation contrasts between the high-load (3-back) and the no-load condition (0-back) were family-wise error (FWE) corrected at $p < .05$ and used as a functional mask. This mask was used to extract BOLD percent signal-change estimates from each subject's parametric maps at each working memory load. Subsequent offline statistical analyses were then conducted on percent signal-change estimates using SPSS. Second, the history of concussion group activation contrasts between the between the high-load (3-back) and the no-load condition (0-back) were FWE corrected at $p < .05$ and were also used as a functional mask. As with the prior approach, this mask was used to extract BOLD percent signal-change estimates from each subject's parametric maps at each working memory load and also tested offline using SPSS. Following a series of 2 group (history of concussion,

control) x 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated measures ANOVAs, a Bonferroni correction was used to control for inflation of Type I error rate ($p \leq .004$). These functional ROI masks are overlaid on a standard template in Figure 13, and the coordinates for the extracted brain regions for controls and history of concussion group are also listed in Tables 12 and 13 respectively.

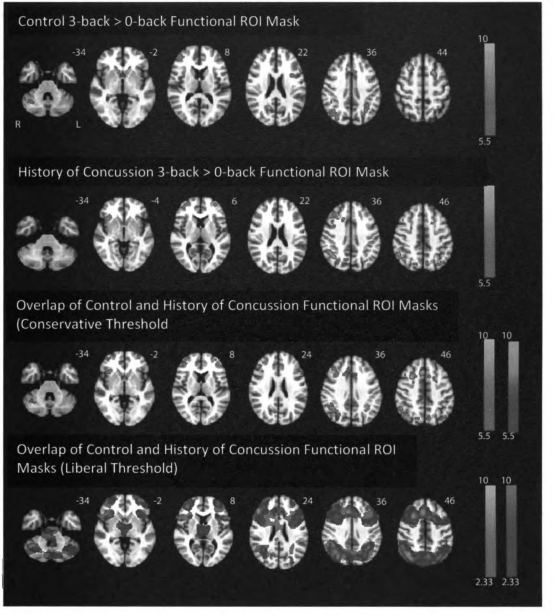

Figure 13. (Row 1) Functional ROI mask derived from contrast of control 3-back > 0-back. (Row 2) Function ROI mask derived from contrast of concussed 3-back > 0-back. (Rows 3 + 4) Overlap of both history of concussion (Red) and control groups (Blue) Functional ROI masks at conservative and liberal thresholds, respectively. There was a high degree of overlap in the Functional ROI masks derived from each group. This degree of overlap is particularly evident at the liberal threshold of $p < 0.01$. Percent signal-change estimates for offline analyses were extracted from the conservative threshold of FWE-corrected $p < 0.01$.

Table 12

Locations of Peak Activations in Brain Regions from the 3-back > 0-back Contrast Derived from Controls (n=14)

Brain Region	Brodmann Area	# Voxels	Z-max	MNI coordinates		
				X	Y	Z
1. R IPL	19, 40	490	9.81	34	-72	46
2. ACC/SMA	8, 32	374	12.4	4	24	42
3. R MFG (R DLPFC)	6, 8	299	12.2	28	14	52
4. R MFG	8	135	10.7	48	32	26
5. L MFG (L DLPFC)	8	112	9.51	-26	4	50
6. R MFG	46	95	8.02	38	44	16
7. Angular Gyrus	19, 39	90	8.43	-32	-62	38
8. L MFG	10	32	7.55	-34	58	-2
9. L IFG	44	30	7.92	-38	8	22
10. Cerebellum		24	7.02	38	-58	-34
11. L IFG	44, 46	19	7.36	-54	18	26
12. L Precuneus	7	11	6.45	-6	-70	44

Table 13

Locations of Peak Activations in Brain Regions from the 3-back > 0-back Contrast Derived from Asymptomatic Athletes with a History of Two or More Concussions (n=14)

Brain Region	Brodmann Area	# Voxels	Z-max	MNI coordinates		
				X	Y	Z
1. R IPL (SMG)	40	875	10.4	36	-60	38
2. R MFG (R DLPFC)	46	458	8.07	48	32	24
3. R MFG	10	245	6.53	38	50	0
4. R IFG	47	231	6.45	38	22	-6
5. ACC/SMA	8, 32	165	5.88	10	28	40
6. L MFG	10	140	5.66	-32	52	4
7. L IPL	19, 40	115	5.41	-36	-68	42
8. R Precuneus	7	59	4.78	-8	-72	46
9. L IFG	47	21	4.23	-32	24	-6
10. L MFG (L DLPFC)	9	13	4.07	-18	10	46
11. R MFG	9	12	4.05	24	2	46

Results from Functional ROI Analyses Derived from Control 3-back > 0-back Activation Contrasts. A series of separate 2 group (concussion history, control) x 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated-measure ANOVAs were conducted to compare BOLD percent signal changes in each of the 12 extracted brain regions. A Bonferroni-corrected level of significance ($p \leq .004$) was used to identify statistical significance.

The results from the repeated measures ANOVAs conducted on the R IPL (p = .97), ACC/SMA (p = .36), R MFG (R DLPFC) (p = .56), R MFG (p = .89), L MFG (L DLPFC) (p = .74), R MFG (p = .83), Angular gyrus (p = .90), L MFG (p = .58), L IFG (p = .41), Cerebellum (p = .91), L IFG (p = .83), and the L Precuneus (p = .67) did not reveal any statistically significant differences (Bonferroni-corrected $p \leq .004$) between athletes with a history of concussion and controls for BOLD percent signal change. However there was a significant within-subjects effect for working memory load in every brain region. The means and standard deviations for these regions can be found in Table 14 listed in Appendix C, and results from separate repeated measures ANOVAs are listed in the following Tables (15 – 26) and Figures (14 – 25).

Table 15

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R IPL

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.85	44.02	3	.00*	.85
Group	N/A	.00	3	.97	.00
WM load X Group	.01	.06	3	.99	.01

*$p \leq .004$

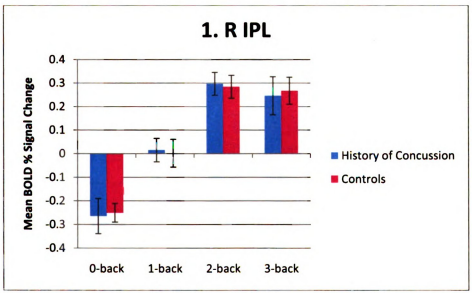

Figure 14. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R IPL.

Table 16

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the ACC/SMA

	Wilks λ	*F*	*df*	*P*	η^2
WM load	.87	55.30	3	.00*	.87
Group	N/A	.87	3	.36	.03
WM load X Group	.06	.50	3	.68	.06

*$p \leq .004$

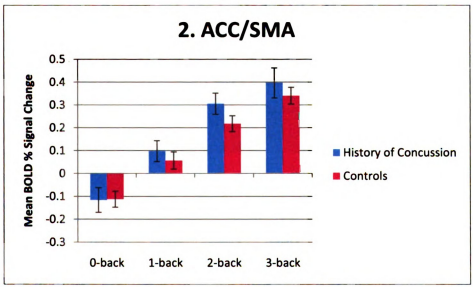

Figure 15. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the ACC/SMA.

Table 17

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R MFG (R DLPFC)

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.81	34.95	3	.00*	.81
Group	N/A	.35	3	.56	.01
WM load X Group	.11	.94	3	.43	.11

*$p \leq .004$

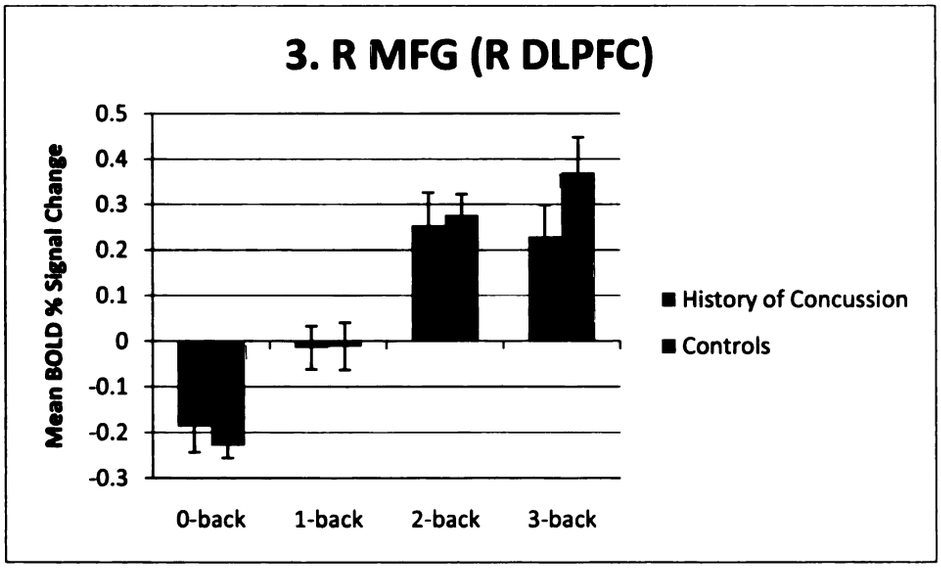

Figure 16. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R MFG (R DLPFC).

Table 18

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R MFG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.86	49.44	3	.00*	.86
Group	N/A	.02	3	.89	.00
WM load X Group	.04	.30	3	.82	.04

*$p \leq .004$

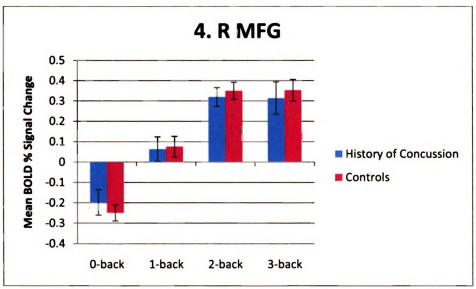

Figure 17. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R MFG.

Table 19

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the L MFG (L DLPFC)

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.80	32.69	3	.00*	.80
Group	N/A	.11	3	.74	.00
WM load X Group	.03	.24	3	.87	.03

*$p \leq .004$

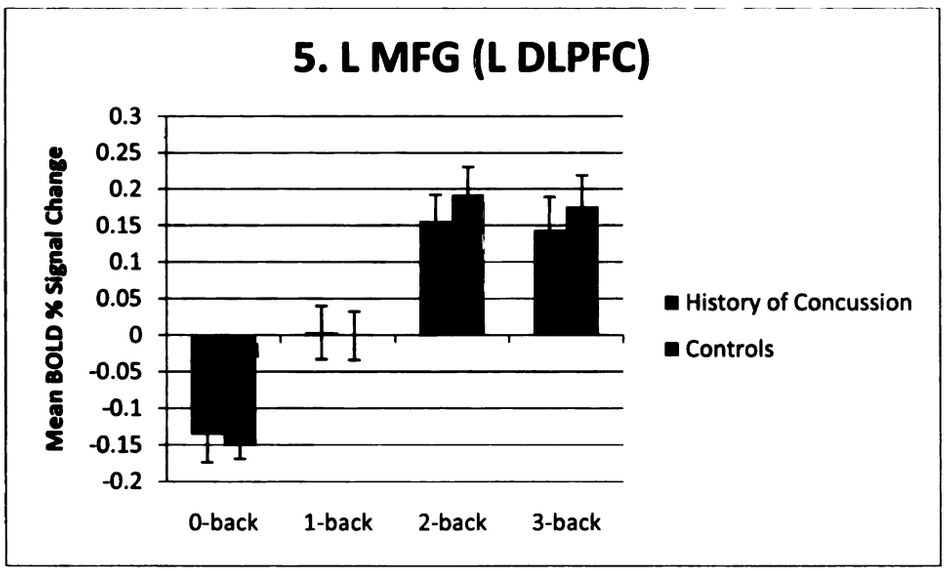

Figure 18. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L MFG (L DLPFC).

Table 20

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R MFG

	Wilks λ	*F*	*df*	*P*	η^2
WM load	.76	24.83	3	.00*	.77
Group	N/A	.05	3	.83	.00
WM load X Group	.08	.66	3	.58	.08

*$p \leq .004$

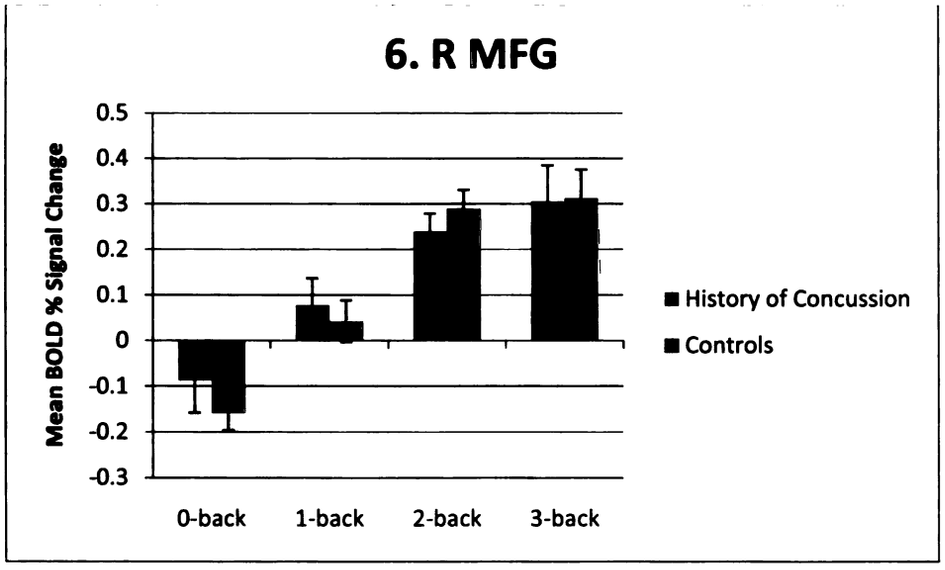

Figure 19. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R MFG.

Table 21

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the Angular Gyrus

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.89	65.76	3	.00*	.89
Group	N/A	.02	3	.90	.00
WM load X Group	.09	.78	3	.52	.09

*$p \leq .004$

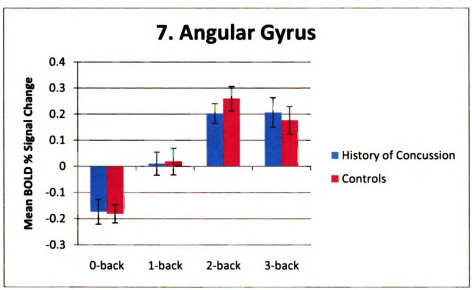

Figure 20. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the Angular Gyrus.

Table 22

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the L MFG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.43	10.43	3	.00*	.57
Group	N/A	.32	3	.58	.01
WM load X Group	.33	3.18	3	.02	.33

*$p \leq .004$

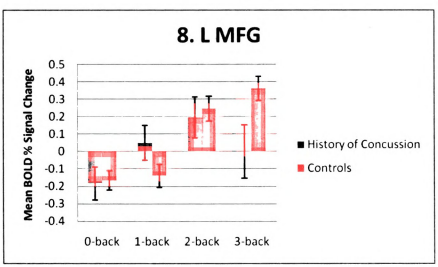

Figure 21. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L MFG.

Table 23

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the L IFG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.27	22.09	3	.00*	.73
Group	N/A	.72	3	.41	.03
WM load X Group	.97	.29	3	.83	.04

*$p \leq .004$

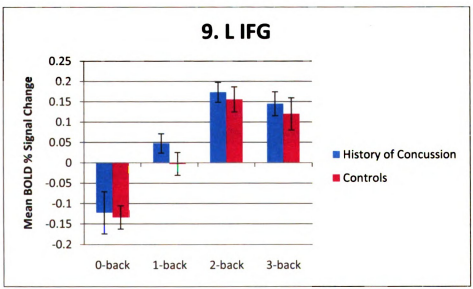

Figure 22. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L IFG.

Table 24

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the Cerebellum

	Wilks λ	*F*	*df*	*P*	η^2
WM load	.63	13.35	3	.00*	.63
Group	N/A	.01	1	.91	.00
WM load X Group	.03	.25	3	.86	.03

*$p \leq .004$

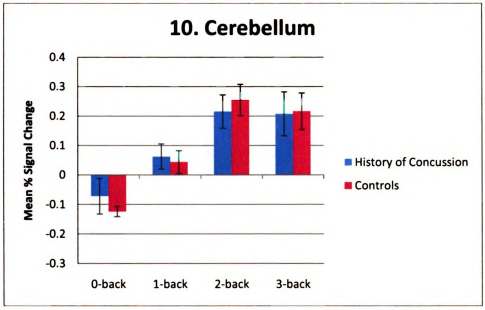

Figure 23. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the Cerebellum.

Table 25

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the L IFG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.29	19.52	3	.00*	.71
Group	N/A	.05	3	.83	.002
WM load X Group	.96	.38	3	.77	.05

*$p \leq .004$

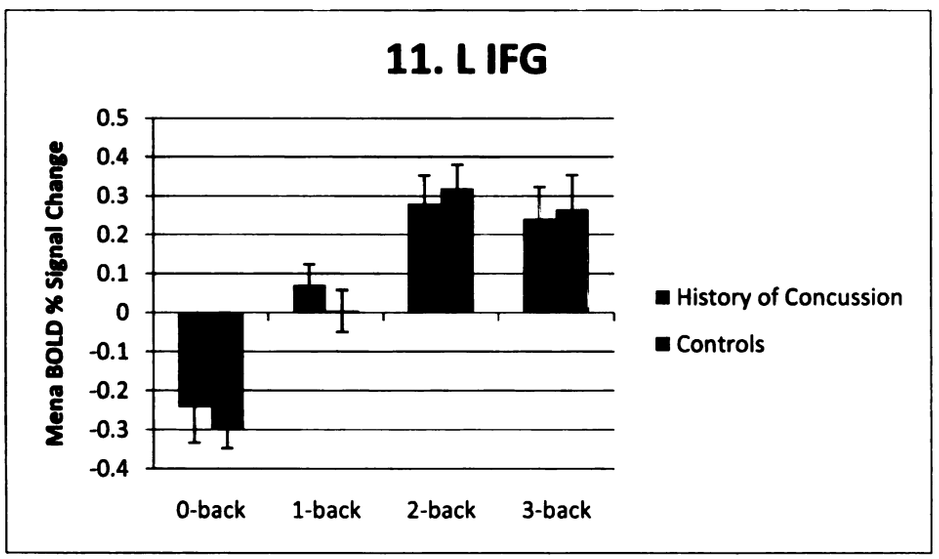

Figure 24. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L IFG.

Table 26

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the L Precuneus

	Wilks λ	*F*	*df*	*P*	η^2
WM load	.82	35.52	3	.00*	.82
Group	N/A	.19	1	.67	.01
WM load X Group	.24	2.50	3	.08	.24

*$p \leq .004$

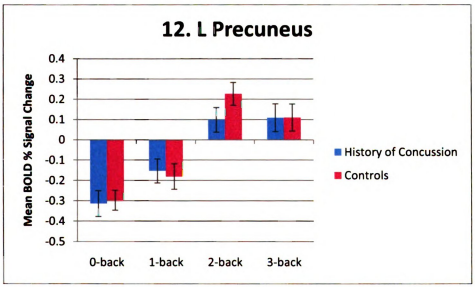

Figure 25. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L Precuneus.

Results from Functional ROI Analyses Derived from History of Concussion

Group 3-back > 0-back Activation Contrasts. A series of separate 2 group (concussion history, control) x 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated-measure ANOVAs were conducted to compare BOLD percent signal changes in each brain region when using the 3-back minus 0-back contrast Functional ROI mask derived from the history of concussion group. As with the previous analyses, a Bonferroni-corrected level of significance was used ($p \leq .01$). The results from the repeated measures ANOVAs conducted on the R IPL ($p = .88$), R MFG (R DLPFC) ($p = .61$), R MFG ($p = .81$), R IFG ($p = .26$), ACC/SMA ($p = .59$), L MFG ($p = .98$), L IPL ($p = .95$), R Precuneus ($p = .74$), L IFG ($p = .33$), L MFG (L DLPFC) ($p = .96$), and the R MFG ($p = .42$) did not reveal any statistically significant differences between athletes with a history of concussion and controls for BOLD percent signal change. However there was a significant within-subjects effect for working memory load in every brain region. There were also no significant interactions in any of these brain regions. The means and standard deviations for BOLD % signal change in these brain regions can be found in Table 27 listed in Appendix D. The ANOVA results for these brain regions are listed in Tables 28 – 38 and Figures 26 – 36.

Table 28

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R IPL/SMG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.15	45.73	3	.00*	.85
Group	N/A	.02	3	.88	.00
WM load X Group	.98	.20	3	.90	.02

*$p \leq .01$

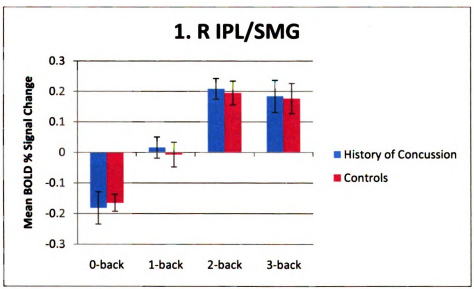

Figure 26. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R IPL/SMG.

Table 29

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R MFG (R DLPFC)

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.12	58.63	3	.00*	.88
Group	N/A	.27	3	.61	.01
WM load X Group	.99	.12	3	.95	.01

*$p \leq .01$

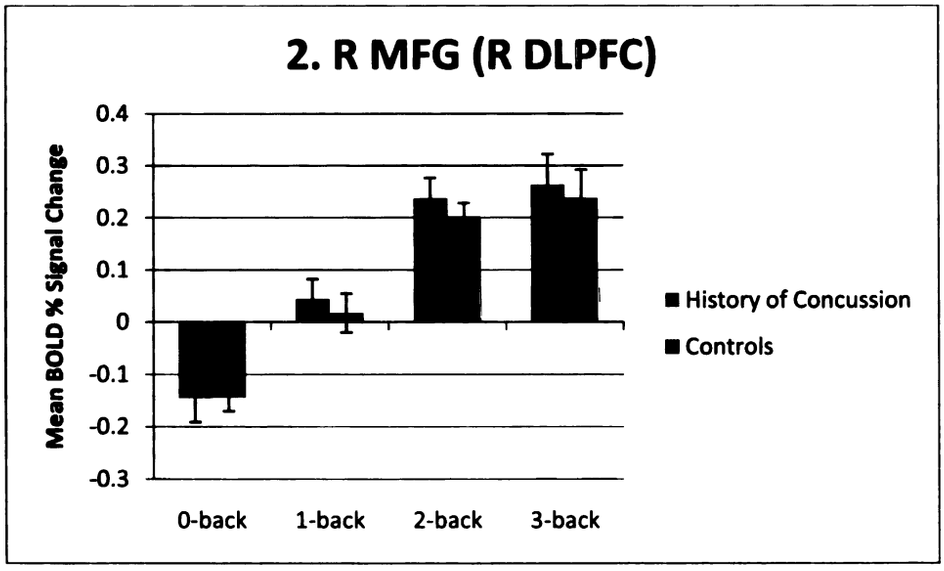

Figure 27. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R MFG (R DLPFC).

Table 30

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R MFG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.32	16.79	3	.00*	.68
Group	N/A	.06	3	.81	.00
WM load X Group	.92	.72	3	.55	.08

*$p \leq .01$

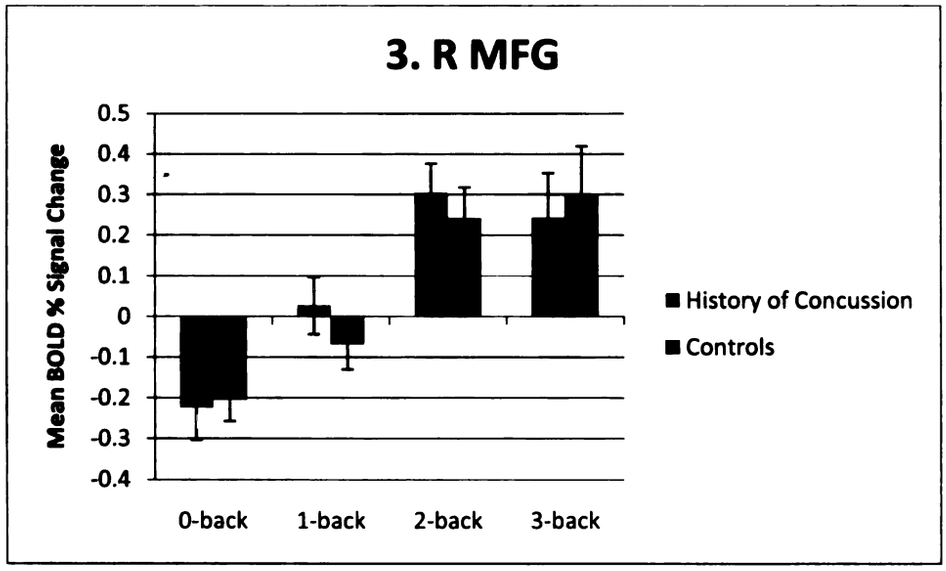

Figure 28. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R MFG.

Table 31

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R IFG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.27	21.40	3	.00*	.73
Group	N/A	1.35	3	.26	.05
WM load X Group	.97	.64	3	.60	.07

*$p \leq .01$

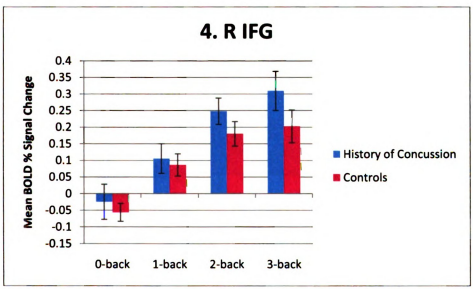

Figure 29. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R IFG.

Table 32

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the ACC/SMA

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.13	53.78	3	.00*	.87
Group	N/A	.29	3	.59	.01
WM load X Group	.82	1.77	3	.18	.18

*$p \leq .01$

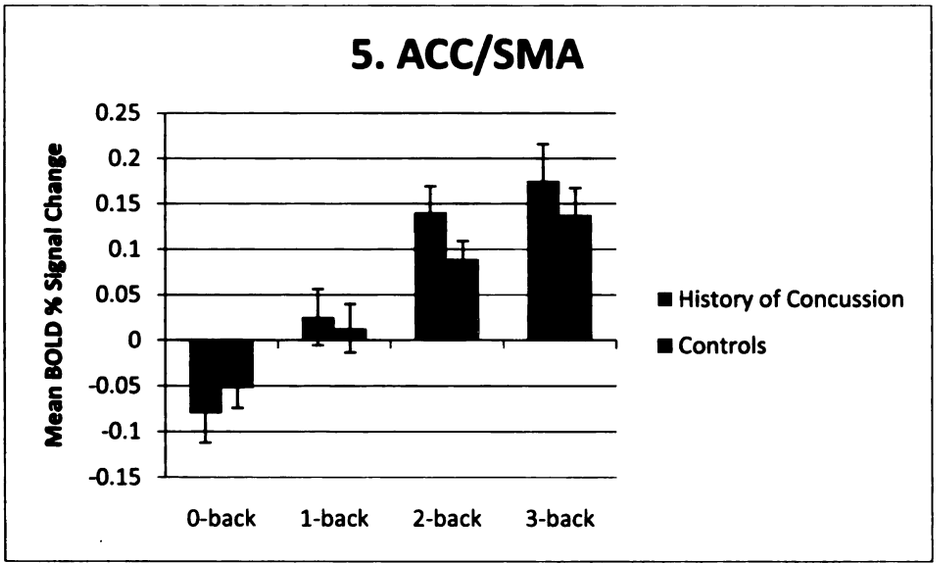

Figure 30. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the ACC/SMA.

Table 33

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the L MFG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.26	23.20	3	.00*	.74
Group	N/A	.00	3	.98	.00
WM load X Group	.90	.85	3	.48	.10

*$p \leq .01$

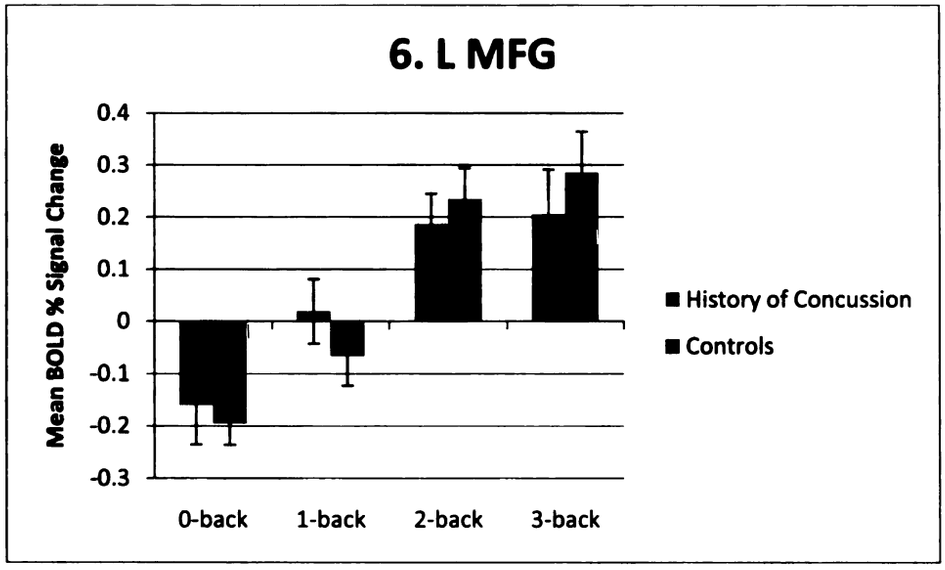

Figure 31. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L MFG.

Table 34

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the L IPL

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.26	22.83	3	.00*	.74
Group	N/A	.00	3	.95	.00
WM load X Group	.95	.46	3	.71	.06

*$p \leq .01$

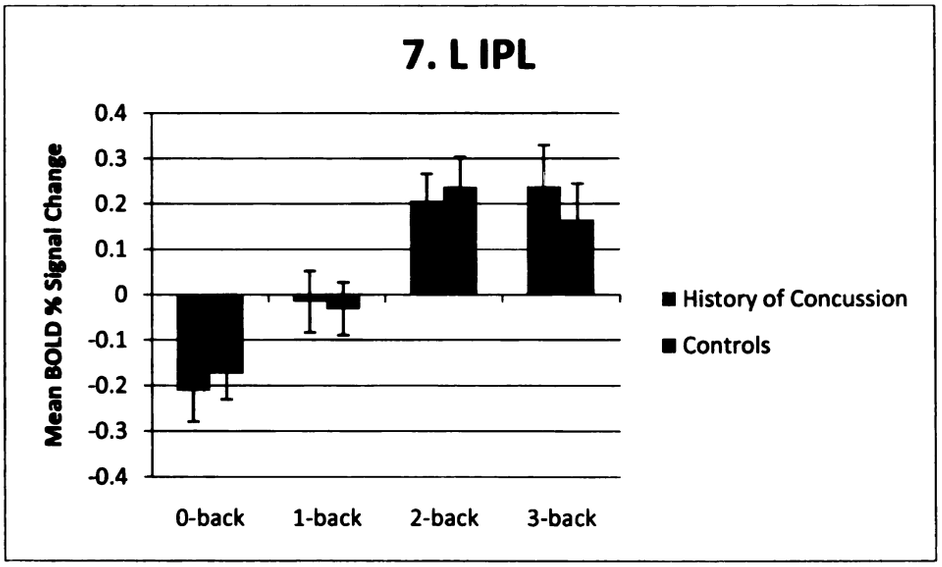

Figure 32. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L IPL.

Table 35

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R Precuneus

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.18	37.71	3	.00*	.83
Group	N/A	.11	3	.74	.00
WM load X Group	.76	2.56	3	.08	.24

*$p \leq .01$

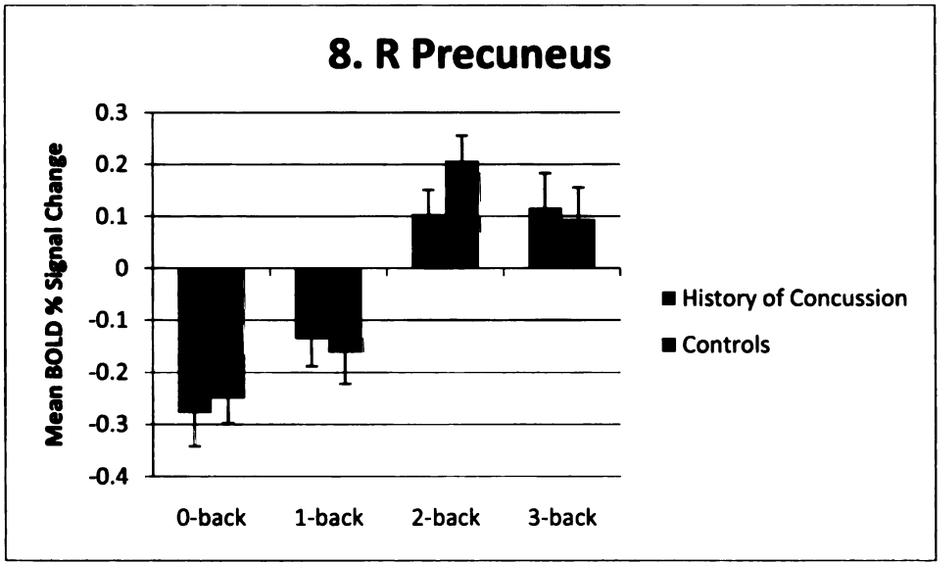

Figure 33. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R Precuneus.

Table 36

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the L IFG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.23	27.45	3	.00*	.77
Group	N/A	.98	3	.33	.04
WM load X Group	.99	.12	3	.95	.02

*$p \leq .01$

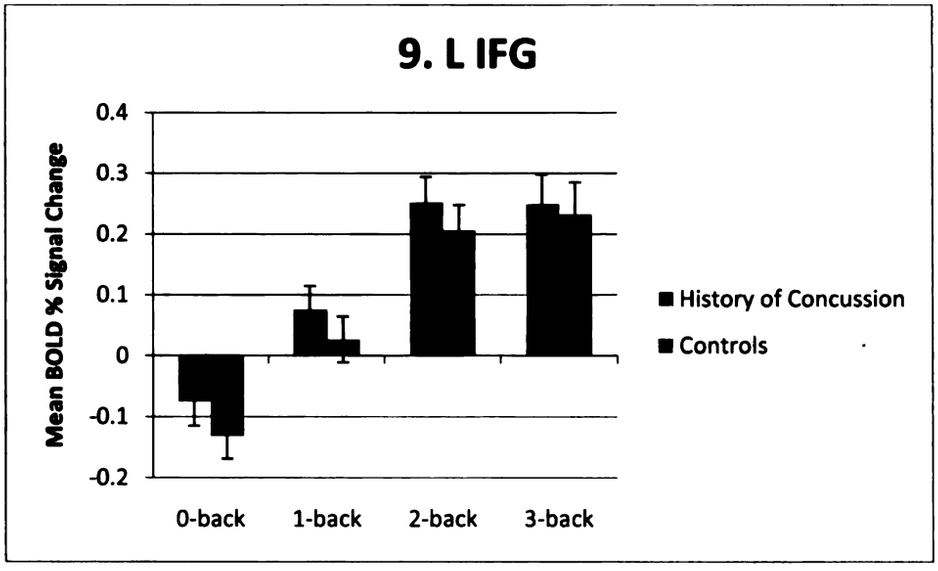

Figure 34. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L IFG.

Table 37

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the L MFG (L DLPFC)

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.28	20.20	3	.00*	.72
Group	N/A	.00	3	.96	.00
WM load X Group	.99	.12	3	.95	.01

*$p \leq .01$

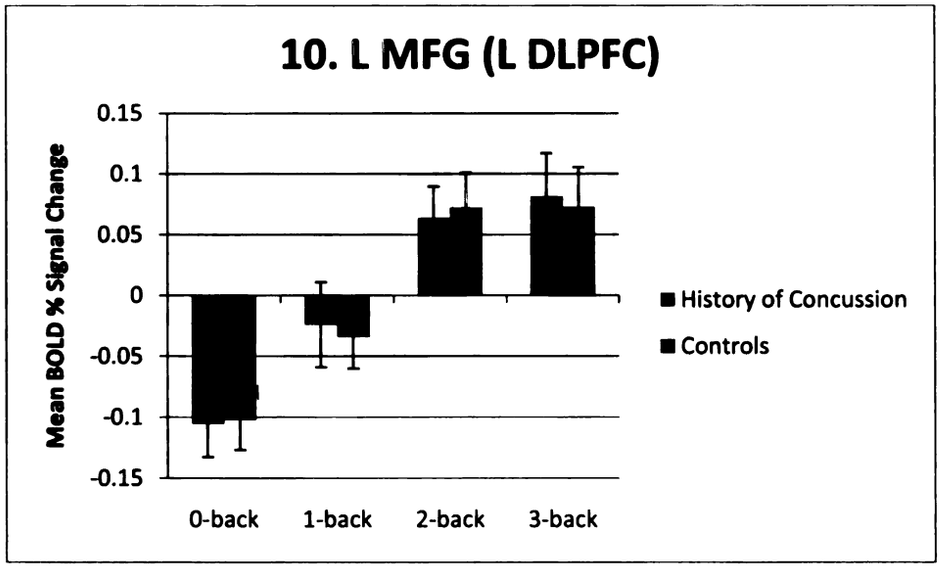

Figure 35. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L MFG (L DLPFC).

Table 38

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the R MFG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.23	27.26	3	.00*	.77
Group	N/A	.67	3	.42	.03
WM load X Group	,95	.38	3	.77	.05

*$p \leq .01$

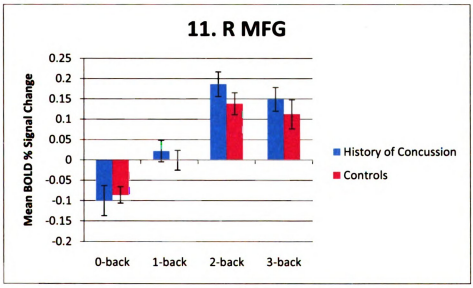

Figure 36. The means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R MFG.

Whole-Brain Independent T-Tests

Between-group comparison at each working memory load. The results of a series of whole-brain between-group independent t-tests were conducted at each working memory load to identify any regions of activation that may be used more by either group. The results indicated that there were no significant differences between groups in brain activation at any working memory load. In addition to these analyses further exploration of the data was conducted by examining between-group differences (i.e., whole-brain independent t-tests) for the following working memory contrasts: 1-back > 0-back; 2-back > 1-back; and 3-back > 2-back.

Between-group comparison of 1-back > 0-back working memory load. The results of an independent t-test revealed that both groups showed similar activation when advancing from the 0-back to the 1-back working memory load. Moreover there were no significant differences at the nominal $p \leq .01$ level which indicates that neither group demonstrated different activation. These overlapping brain regions are presented in Figure 37.

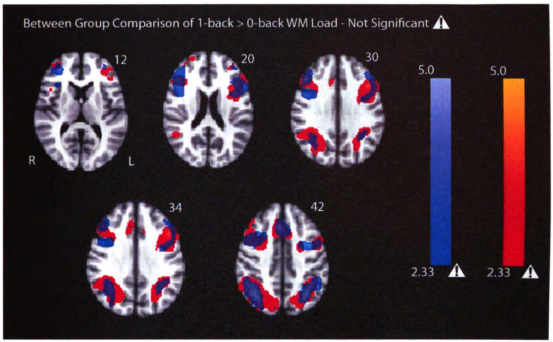

Figure 37. Results of an independent t-test comparing increases in brain activation when increasing from baseline (i.e., 0-back) to low (i.e., 1-back) working memory loads between history of concussion (Red) and control (Blue) groups. Overlay is shown at a nominal uncorrected threshold of $p < 0.01$ for display purposes only.

Between-group comparison of 2-back > 1-back working memory load. The results of an independent t-test revealed that both groups showed similar activation when advancing from the 1-back to the 2-back working memory load. Moreover there were no significant differences at the nominal $p \leq .01$ level, which indicates that neither group demonstrated different activation. These overlapping brain regions are displayed in Figure 38.

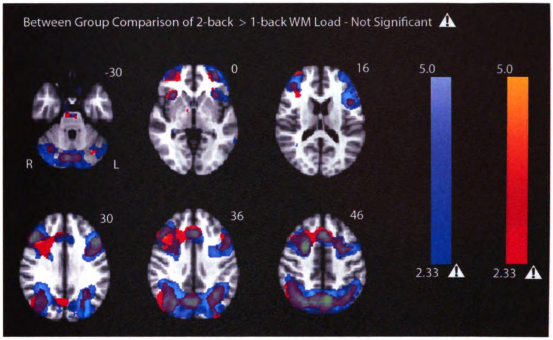

Figure 38. Results of an independent t-test comparing increases in brain activation when increasing from low (i.e., 1-back) to moderate (i.e., 2-back) working memory loads between history of concussion (Red) and control (Blue) groups. Overlay is shown at a nominal uncorrected threshold of $p < 0.01$ for display purposes only.

Between-group comparison of 3-back > 2-back working memory load. The results of an independent t-test revealed that both groups showed similar activation when advancing from the 2-back to the 3-back working memory load. Interestingly, at first glance it seems that the two groups activated different brain regions when responding to the high working memory load of the 3-back condition. However these differences were only apparent at the nominal $p \leq .01$ level. When increasing the threshold to this study's minimum acceptance criteria of $Z > 3.1$, $p \leq .001$ no regions survive a more conservative threshold. These comparisons are displayed in Figure 39.

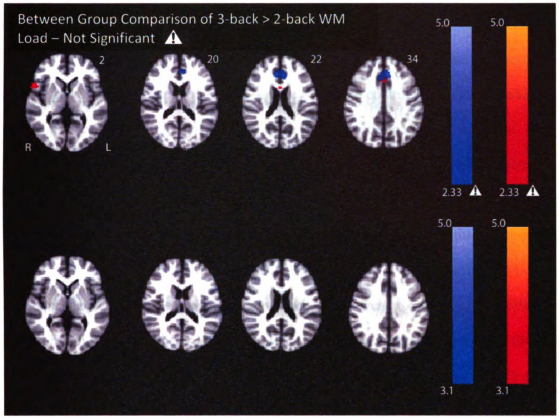

Figure 39. Results of an independent t-test comparing increases in brain activation when increasing from moderate (i.e., 2-back) to high (i.e., 3-back) working memory loads between history of concussion (Red) and control (Blue) groups. Row 1 overlay is shown at a nominal uncorrected threshold of $p < 0.01$ for display purposes only. Row 2 overlay is shown at a threshold of $p < 0.001$ and reveals no significant activations that this level.

Exploratory Analyses: Task-Induced Deactivations

A Functional ROI approach was also used to compare percent signal changes in the BOLD response between the history of concussion and control groups for the brain regions that were found to deactivate during the N-back working memory task. The control group deactivation contrasts between the 0-back and the 3-back working memory loads were FWE-corrected at $p < .05$ and used as a functional mask (See Figure 40 and Table 39). This mask was used to extract BOLD percent signal-change estimates from each subject's parametric maps at each working memory load level. Subsequent offline statistical analyses were then conducted on percent signal-change estimates using SPSS. Several off-line 2 group (history of concussion, control) x 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated measures ANOVAs were performed on each of the eight extracted brain regions. A Bonferroni correction ($p \leq .01$) was used to control for inflated Type I error rate due to multiple analyses performed on these brain regions.

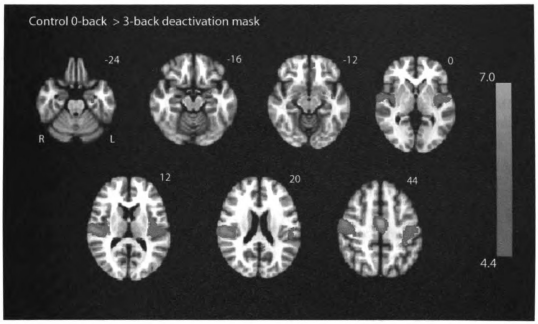

Figure 40. Functional ROI mask for deactivation brain regions derived from control's 0-back > 3-back contrast. Percent signal-change estimates for offline analyses were extracted from the conservative threshold of FWE corrected $p < .05$.

Table 39

Brain Regions of Deactivation Using the 0-back > 3-back Contrast from Controls (n= 14)

	Brodmann Area	# Voxels	Z-max	MNI coordinates		
				X	Y	Z
1. R PoCG/R TPJ/Angular Gyrus	3, 4, 40	3723	6.3	64	-16	36
2. L Insula/L TPJ	22, 40, 47	1420	5.87	-40	-8	-4
3. Dorsal ACC	24	1311	6.98	-2	-8	44
4. L PoCG	3, 4	1200	6.01	-40	-22	58
5. L N. Accumbens/Amygdala	28, 34	57	5.07	-24	-4	-18
6. L Hippocampus	28	44	6.53	-26	-16	-22
7. MedFG	10	38	5.97	-4	54	-8
8. PCC	29	20	4.1	-6	-48	20

A series of separate 2 group (concussion history, control) x 4 working memory load (0-back, 1-back, 2-back, 3-back) repeated-measure ANOVAs were conducted to compare BOLD percent signal changes in each extracted brain region. The results from the repeated measures ANOVAs conducted on the Right Posterior Central Gyrus/Right temporal-parietal junction/Angular Gyrus (R PoCG/R TPJ/Angular Gyrus) (p = .17); Left Insula/Left temporal-parietal junction (L Insula/L TPJ) (p = .35); Dorsal Anterior Cingulate Cortex (Dorsal ACC) (p = .40); Left Posterior Cingulate Gyrus (L PoCG) (p = .46); Left Nucleus Accumbens/Amygdala (p = .58); Left Hippocampus (p = .86); Medial Frontal Gyrus (MedFG) (p = .90); and the Posterior Cingulate Cortex (PCC) (p = .99) revealed no significant differences between groups. There were also no significant interactions among these brain regions for BOLD percent-signal change. However there was a significant within-subjects effect of working memory load in all deactivated brain regions. The means and standard deviations for BOLD percent-signal change can be found in Table 40 listed in Appendix E. The results from these analyses are displayed in Tables 41 - 48 and Figures 41 - 48.

Table 41

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent ignal Change in the Right Po CG/TPJ/Angular gyrus

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.84	40.64	3	.000*	.84
Group	N/A	.1.98	3	.17	.07
WM load X Group	.19	1.90	3	.16	.19

*$p \leq .01$

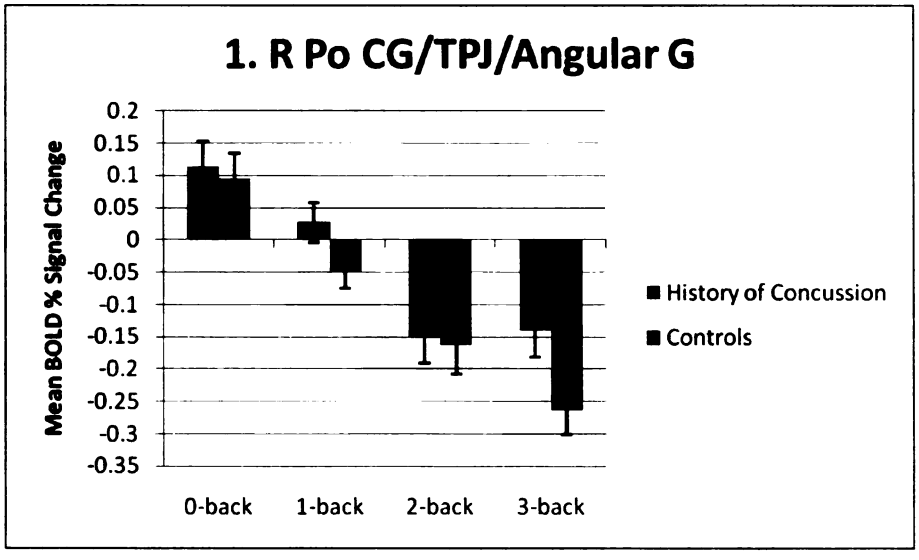

Figure 41. The deactivation means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the R Po CG/TPJ/Angular gyrus.

Table 42

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the Left Insula/TPJ

	Wilks λ	*F*	*df*	*p*	η^2
WM load	..80	31.13	3	.000*	.80
Group	N/A	.92	3	.35	.03
WM load X Group	.19	1.89	3	.16	.19

*$p \leq .01$

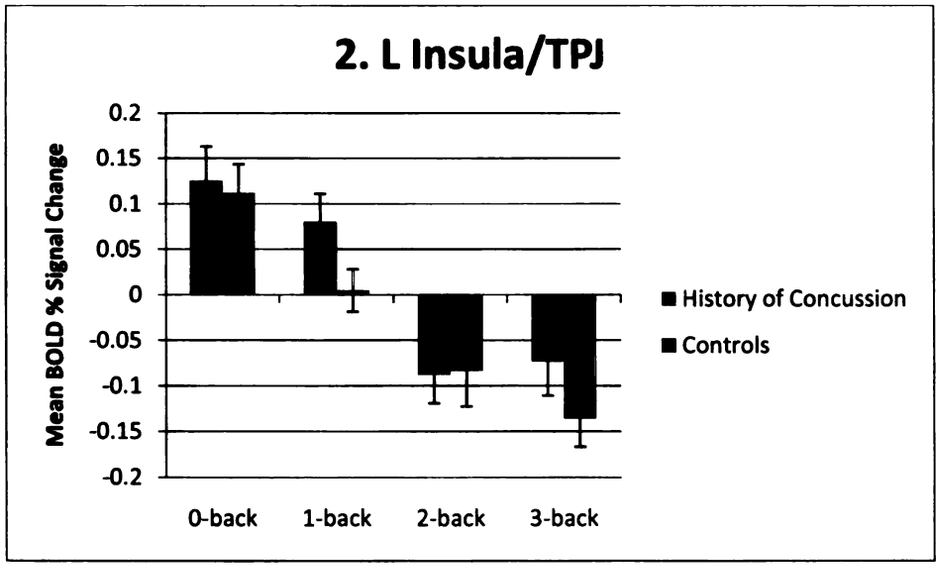

Figure 42. The deactivation means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L Insula/TPJ.

Table 43

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the Dorsal ACC

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.10	18.65	3	.000*	.70
Group	N/A	.73	3	.40	.03
WM load X Group	.30	2.84	3	.06	.26

*$p \leq .01$

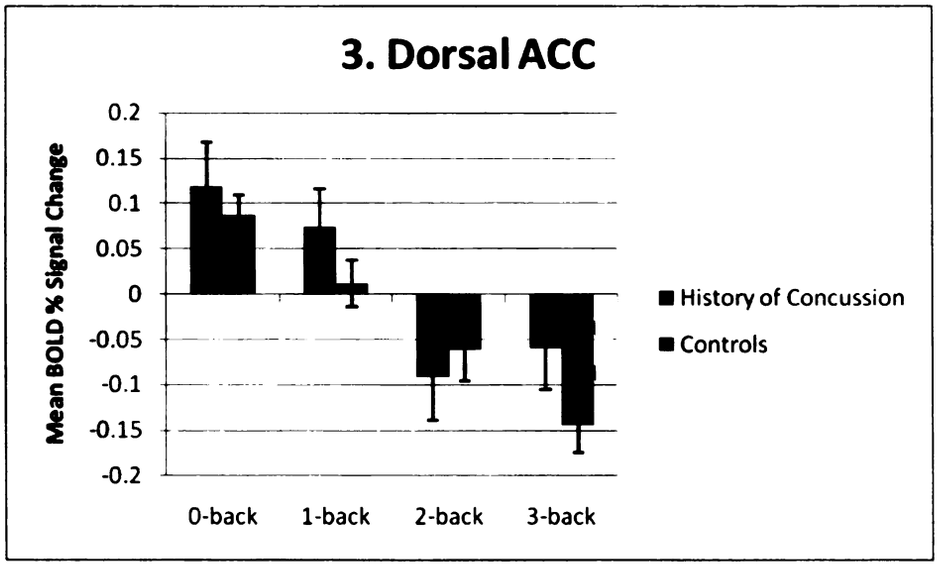

Figure 43. The deactivation means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the Dorsal ACC.

Table 44

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the Left Po CG

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.74	22.60	3	.000*	.74
Group	N/A	.57	3	.46	.02
WM load X Group	.21	2.11	3	.13	.21

*$p \leq .01$

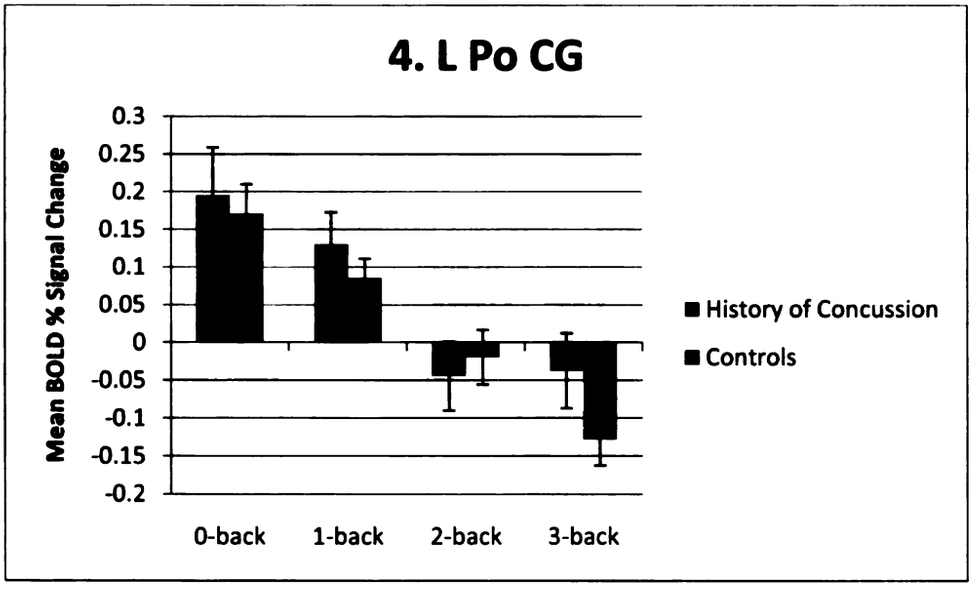

Figure 44. The deactivation means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L Po CG.

Table 45

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the Left Nucleus Accumbens/Amygdala

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.64	13.90	3	.000*	.64
Group	N/A	.32	3	.58	.01
WM load X Group	.11	1.00	3	.41	.11

*$p \leq .01$

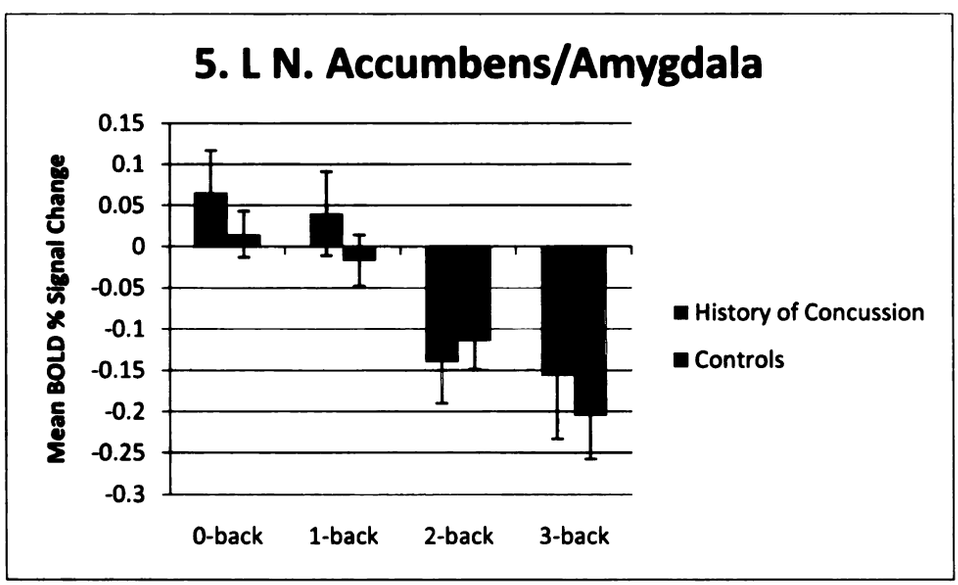

Figure 45. The deactivation means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L Nucleus Accumbens/Amygdala.

Table 46

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the Left Hippocampus

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.63	13.84	3	.000*	.63
Group	N/A	.03	3	.86	.00
WM load X Group	.14	1.34	3	.29	.14

*$p \leq .01$

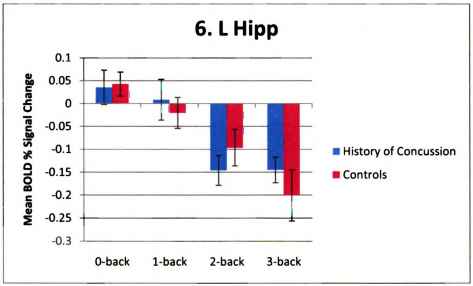

Figure 46. The deactivation means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the L Hipp.

Table 47

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the Medial Frontal Gyrus

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.71	19.42	3	.000*	.71
Group	N/A	.02	3	.90	.00
WM load X Group	.11	1.00	3	.43	.11

*$p \leq .01$

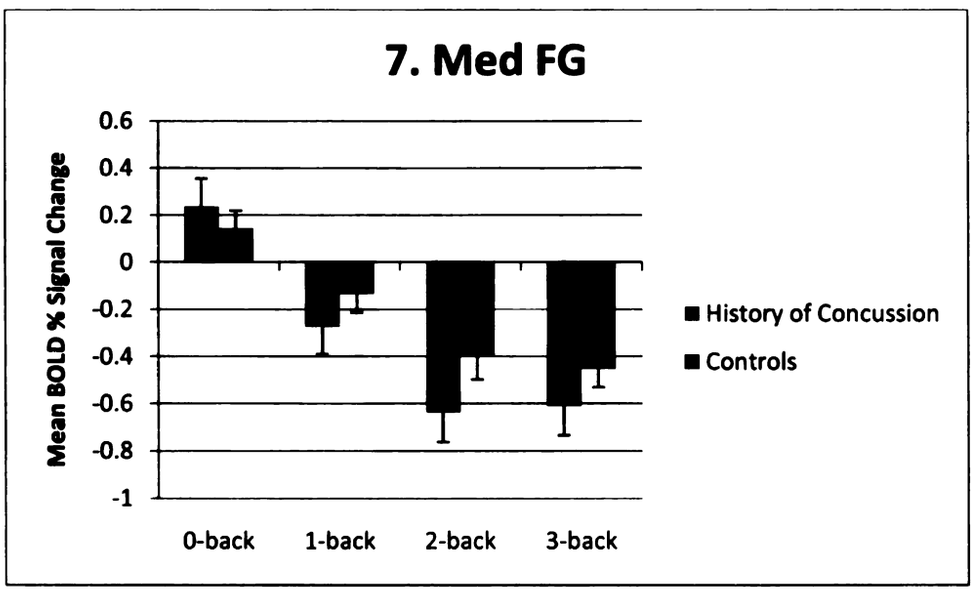

Figure 47. The deactivation means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the Med FG.

Table 48

Results from a 2 Group (Concussion History, Control) x 4 Working Memory Load (0-back, 1-back, 2-back, 3-back) Repeated Measures ANOVA for BOLD Percent Signal Change in the Posterior Cingulate Cortex

	Wilks λ	*F*	*df*	*p*	η^2
WM load	.66	15.56	3	.000*	.66
Group	N/A	.00	3	.99	.00
WM load X Group	1.00	.88	3	.46	.10

*$p \leq .01$

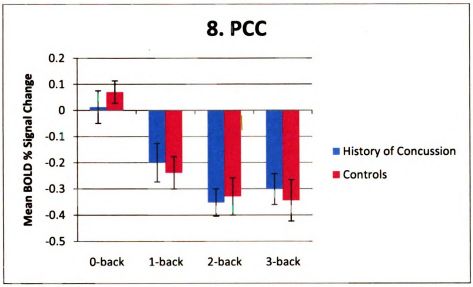

Figure 48. The deactivation means and standard errors of BOLD % signal change across all N-back working memory conditions for athletes with a history of concussion and controls in the PCC.

Other Analyses

Post-hoc power analysis. The observed statistical power of this study ranged from .06 to .75. The small sample size ($N = 28$) of this study warrants consideration as some of the analyses may lack adequate statistical power. Therefore post-hoc power analyses were conducted for each of the offline statistical analyses used for the three Functional ROI approaches (e.g., control, concussion, deactivation) to determine sample sizes required to achieve adequate statistical power. The effect sizes for interactions were used to calculate sample size using G-Power statistical software (Erdfelder, Faul, & Buchner, 1996). Specifically the low, median, and high effect sizes were used to calculate subsequent sample size using $p = .05$. The results of this post-hoc power analysis can be found in Table 49.

Table 49

Calculated Sample Sizes from Post-Hoc Power Analyses for the Functional ROI Analyses

Analysis	Effect Size	N
Control Functional ROI Mask	.01	N/A
	.05	860
	.28	30
History of Concussion Functional ROI Mask	.01	N/A
	.06	598
	.24	40
Deactivation Functional ROI Mask from Controls	.10	216
	.17	76
	.26	34

Other exploratory analyses. It warrants mentioning that other additional analyses were performed to explore relationships among the neuroimaging data and between the behavioral N-back data and activation patterns. These efforts, while outside the original scope and proposal of this project, did not yield results that significantly added to the present results. Therefore these analyses were omitted from the present results. A list of these analyses and a brief summary of the findings can be found in Table 50 listed in Appendix F.

CHAPTER V

DISCUSSION

Introduction

This chapter will provide a general overview of the results found in the present study and discuss them in relation to the relevant literature on sport-related concussion. First, the findings from the neurocognitive measures will be reviewed and discussed. Second, the behavioral results from the N-back working memory paradigm will be compared and contrasted with similar studies that have used this paradigm to evaluate working memory in MTBI patients and concussed athletes. Third, the neuroimaging results will be discussed and subsequently compared and contrasted to the few studies that have used fMRI to examine brain activation patterns associated with sport-related concussion. Finally, clinical implications of these findings and suggestions for future research will be proposed.

General Discussion of Results

The purpose of the current study was to evaluate brain activation patterns in asymptomatic athletes with and without a history of two or more concussions. More specifically this study wanted to evaluate neurocognitive performance on both paper-and-pencil and computerized test batteries and examine brain activation patterns that may indicate compensatory and/or engagement differences elicited from a working memory paradigm. Asymptomatic athletes with a previous history of two or more concussions (i.e., history of concussion group) did not differ from matched-control athletes without previous concussion on paper-and-pencil or computerized neurocognitive tests. Moreover, behavioral performance on the N-back working memory task was similar

between the groups for reaction time; however the two groups differed on accuracy. Specifically, the history of concussion group identified fewer correct targets at the low (i.e., 1-back), moderate (i.e., 2-back), and high (i.e., 3-back) working memory loads. The findings from fMRI revealed that both groups used the same brain regions to perform the working memory task, which does not support the earlier findings of compensatory brain activation patterns by Chen et al. (2004). In addition, asymptomatic athletes with a previous history of concussion and controls showed similar magnitude of activations in these regions with the exception of a non-significant trend found in the left middle frontal gyrus. When the working memory task increased in difficulty from the moderate working memory load to the high working memory load, controls showed additional activation in this region to meet increased working memory demand. However this increase in activation was not observed in the history of concussion group; rather this group demonstrated a decrease in activation relative to this high working memory load. While this trend may suggest an activation difference in a frontal brain region that is proposed to comprise part of the executive component of working memory (Baddeley, 2000), interpretations of this finding should be tenuous. As this study was constrained by a small sample size and this finding was not replicated by other whole-brain analyses.

Overall the findings of this study suggest that a previous history of two or more concussions is not indicative of long-term neurocognitive impairment. In addition, fMRI results also suggest that there is no compensatory effect in asymptomatic athletes with a history of concussion and controls as previously reported (Chen et al., 2004). These findings will now be discussed in relation to the extant literature salient to sports-related concussion and the residual effects of multiple concussions.

Behavioral Performance on Neurocognitive Test Batteries

Overall the neurocognitive test results from the present study indicate that asymptomatic athletes with a history of two or more concussions demonstrate similar performance to athletes without a history of concussion. More specifically, there were no differences between the groups on either paper-and-pencil (e.g., Trail-Making Test Form A and B, Symbol Digit Modalities Test) or computerized neurocognitive (e.g., ImPACT) test batteries. Therefore these findings suggest that a history of multiple concussions does not produce deficits in neurocognitive function that are measureable with more traditional paper-and-pencil or computerized neurocognitive test batteries.

Paper-and-pencil neurocognitive testing. The present study's findings on the two paper-and-pencil neurocognitive tests are in contrast to the majority of studies that support the premise that a history of multiple concussions are associated with prolonged declines in neurocognitive function (Collins, Grindel et al., 1999; Killam et al., 2005; Moser & Schatz, 2002; Moser et al., 2005). Collins et al. (1999) found that collegiate athletes with a history of two or more concussions demonstrated worse performance on the Trail-Making Test Form B and the Symbol Digit Modalities Test than athletes with zero or one previous concussion. Similarly, Moser and colleagues (2002; 2005) also found poor performance on paper-and-pencil neurocognitive measures (Trail-Making Test Form A and B) for high school athletes with a history of two or more concussions compared to high school athletes with zero or one previous injury. These researchers concluded that there may be a decline in neurocognitive function associated with a history of multiple concussions.

The contrast in findings between the current and the aforementioned studies could be due to sample selection criteria such as symptomology and time since last concussion. Specifically athletes with a history of concussion in the current study were all asymptomatic and incurred their last concussion approximately 9 months before participation. It should be noted that athletes with a history of concussion in the Collins et al. (1999) and Moser et al. (2002; 2005) studies were symptomatic at the time of study. Therefore, the differences in findings between the current study and these previous studies could be due to residual symptoms reported by their samples. Even though athletes were reporting symptoms, Moser et al. (2002; 2005) required athletes with a history of concussion to be injury-free for at least 6 months since their last concussion. However, Collins et al. (1999) did not report time since last concussion. Athletes who participated in the current study were asymptomatic and did not incur a concussion for approximately 9 months prior to study. Differences in these time periods could allow for further resolution of any lasting cognitive deficits and could potentially explain discrepancies between the findings of the current study and Moser et al. (2002; 2005).

While the previously discussed studies concluded that there are residual cognitive decrements associated with a history of multiple concussions, other researchers using similar paper-and-pencil neurocognitive measures have not replicated these findings, which support the results of the present study (Guskiewicz et al., 2002). Guskiewicz and colleagues (2002) found no differences between athletes and controls with and without a history of one, two, or more than two previous concussions on a neurocognitive test battery that included the Trail-Making Test Form B and the Symbol Digit Modalities Test. Unfortunately these researchers did not disclose any information on the time since

last concussion for their sample. Nonetheless, Guskiewicz et al. (2002) is in agreement with the current study's results that conclude there are no residual cognitive impairments in asymptomatic athletes with a history of multiple concussions.

Computerized neurocognitive testing. In regard to computerized neurocognitive testing athletes with a history of concussion and controls demonstrated similar (i.e., no significant differences) performance on the ImPACT neurocognitive test battery. These results are in concordance with other researchers who also employed similar computerized neurocognitive measures (Broglio et al., 2006; Bruce & Echemendia, 2009; Chen et al., 2007; Collie et al., 2006; Covassin et al., 2008; Iverson, Brooks, Lovell et al., 2006). Studies by Covassin et al. (2008) and Iverson et al. (2006) found no baseline performance differences on ImPACT between athletes with and without a history of multiple concussions. Other studies also reported no significant differences between athletes with and without a history of one, two, or three previous concussions on ImPACT, CRI (Broglio et al., 2006), and CogSport (Collie et al., 2006) computerized neurocognitive baseline assessments. It warrants mentioning none of these studies reported information on symptoms or time since last concussion which limit their comparison to the current study's results.

Chen, Johnston, Collie, McCrory and Ptito (2007) administered a computerized neurocognitive test battery (CRI) to athletes with a history of at least three concussions and lingering post-concussion symptoms and a control group. These athletes were studied approximately five months since their last injury. Similar to the findings of the current study, Chen and colleagues (2007) reported no significant differences between athletes

with a history of concussion and controls on the computerized neurocognitive test battery.

The results of Chen et al. (2007) and the findings from the current study suggest that there are no cognitive deficits, as measured by computerized neurocognitive test batteries, in both symptomatic and asymptomatic athletes with a history of at least two or more concussions. However, these findings should be interpreted with caution as both Chen et al. (2007) and the present study had small sample sizes. Moreover, there are numerous studies that have found computerized neurocognitive testing to be a valuable tool that has proven useful in detecting cognitive impairment in the acute time period following concussion (Collins et al., 2002; Covassin et al., 2008; Iverson, Gaetz et al., 2004). However, the utility of these measures for detecting long-term impairments in athletes with a history of concussion remains enigmatic.

Neurocognitive test batteries and residual effects from multiple concussions. The present study's findings from both the paper-and-pencil and computerized neurocognitive test batteries address an issue in current debate among researchers in the field of sports medicine. Specifically, it seems that researchers who employ more traditional paper-and-pencil neurocognitive measures report significant differences in performance between asymptomatic athletes with and without a history of concussion, while others employing computerized neurocognitive measures do not find athletes demonstrate neurocognitive impairments. Therefore, the sensitivity of both paper-and-pencil and computerized versions of neurocognitive assessment have been questioned in their ability to detect the potential subtle differences that may or may not exist in asymptomatic athletes with a history of concussion (Broglio et al., 2006; Bruce & Echemendia, 2009).

The current study administered both paper-and-pencil and computerized versions of neurocognitive tests and did not find any differences between asymptomatic athletes with a history of concussion and controls. These findings are in agreement with other researchers who also used both versions of neurocognitive testing to evaluate cognitive performance in athletes with and without a history of concussion (Bruce & Echemendia, 2009). Bruce and Echemendia (2009) conducted a large-scale study using both paper-and-pencil and computerized (ImPACT) versions of neurocognitive assessment and found no differences between groups of athletes with and without a history of concussion (e.g., one, two, three or more). Furthermore, none of the athletes in Bruce and Echemendia (2009) were concussed in the prior six months before their study, which is three months earlier than the present study. Unfortunately these researchers did not disclose information on the symptomology of their history of concussion group. Overall the results from Bruce and Echemendia (2009) support the current study's findings that revealed similar neurocognitive performance as measured by the Trail-Making Test Form A and B, Symbol Digit Modalities Test, and ImPACT between asymptomatic athletes with and without a history of two or more concussions.

N-back Working Memory Task

The N-back working memory paradigm was used in the present study to elicit brain activation patterns in all participants. The findings from the behavioral data on the N-back task revealed that asymptomatic athletes with a history of two or more concussions performed the task just as fast as controls, but were significantly less accurate at every working memory load (i.e., 1-back, 2-back, 3-back) except the 0-back. This is an interesting finding as the few published studies that utilized fMRI to study

concussion in both MTBI patients (McAllister et al., 1999; McAllister et al., 2001) and athletes (Chen et al., 2007; Chen et al., 2008; Chen et al., 2004) found no behavioral differences on working memory tasks similar to the N-back.

There are many differences in sample selection characteristics and criteria between the present study and McAllister et al. (1999; 2001) that could account for the discrepancy in the results of N-back accuracy between these studies. The two studies by McAllister and colleagues (1999; 2001) did not find accuracy differences on an auditory N-back performance at the low, moderate, or high loads, as MTBI patients demonstrated similar N-back performance as controls. The sample used by McAllister et al. (1999; 2001) consisted of MTBI patients who were asymptomatic at the time of study, which was approximately 1-month following their injury. It should also be noted that a small number of MTBI patients were athletes who had sustained a concussion. Nonetheless, a direct comparison between the results of the current study and McAllister et al. (1999; 2001) is difficult as the present study collected data only on asymptomatic athletes following an approximate nine month time period. McAllister et al. (1999; 2001) collected data primarily on MTBI patients who sustained their injuries outside the sport setting (i.e., motor vehicle accidents, falls, etc...). Therefore, the mechanisms of injury between these two studies are not directly comparable. Moreover no information regarding the number of previous head injuries sustained were given in McAllister et al. (1999; 2001). Finally, the task used by McAllister and colleagues (1999; 2001) was an auditory N-back task which is slightly different from the visual presentation of the N-back task used in the present study.

Chen and colleagues (2007; 2008; 2004) also used a working memory paradigm (verbal and visual design memory task) to elicit brain activation changes in symptomatic athletes with a history of multiple concussions. Similar to the findings in the present study, Chen et al. (2008; 2004) did not find behavioral differences on accuracy or reaction time on a working memory paradigm. However the study published by Chen and colleagues in 2007 found that symptomatic athletes with a history of three or more previous concussions had significantly faster reaction times on a verbal working memory task than controls. However these two groups did not differ on accuracy.

The present study's findings revealed that asymptomatic athletes with a history of two or more concussions are less accurate than controls on N-back working memory performance; however they are just as fast as controls. A possible explanation may be a speed-accuracy tradeoff. More specifically, the history of concussion group sacrificed accuracy to perform the task at the same speed of controls. This finding could also indicate that a subtle deficit in working memory may exist in the history of concussion group not seen in controls.

The N-back working memory paradigm detected a performance difference between groups while the other administered neurocognitive measures did not reveal any differences in performance. Differences between these tests, and the cognitive domains they evaluate, may offer an explanation for these findings. The entire neurocognitive battery used in the present study (i.e., Trail-Making Test Form A and B, Symbol Digit Modalities Test, and ImPACT) assessed a wide variety of cognitive functions that included attention, learning, spatial organization, motor speed, visuospatial scanning, reaction time, and memory. While these tests evaluated many of the same domains of

cognitive function, none of these batteries exclusively measured verbal working memory in such a manner as the N-Back (i.e., exclusively loading working memory for a prolonged period of time). The Trail-Making Test Form A and B requires limited working memory resources as these tests primarily rely on rote memory for sequential numbers and letters. Similarly, the Symbol Digit Modalities Test assesses attention, visual scanning, and motor speed, and does not involve a high demand of working memory. Moreover, four of the six modules that comprise the ImPACT neurocognitive test battery involve memory for verbal or visual items. However, none of these batteries exclusively evaluates working memory performance with the progressive loading of verbal items that are required to be kept "online" like the N-back working memory task. Therefore, it is likely that the N-back is a more thorough and difficult measure of working memory than the Trail-Making Test Form A and B, Symbol Digit Modalities Test, and ImPACT. Nonetheless, the present study's results should be interpreted with caution and considered exploratory due to small sample size.

Functional MRI Findings

One of the primary focal points of the present study was to use fMRI to study brain activation patterns between asymptomatic athletes with and without a history of two or more concussions. This objective was addressed in several ways as this study identified and validated brain regions that have been previously found to be involved in working memory; statistically tested for between-group differences in these regions; and evaluated two previously published hypotheses proposed by McAllister et al. (1999; 2001) (i.e., engagement hypothesis) and Chen et al. (2007; 2004) (i.e., compensation hypothesis) that have offered an explanation for the brain activation patterns seen in

MTBI patients and symptomatic athletes with a history of concussion. The present study is the first to examine brain activation patterns in asymptomatic athletes with and without history of two or more concussions.

All athletes in the current study showed task-induced activations in brain regions that have been well-documented to be involved in working memory (Jonides, Schumacher, & Smith, 1997; Jonides et al., 1998; Owen et al., 2005; E. E. Smith & Jonides, 1998; E. E. Smith et al., 1998). Specifically, this study found bilateral activations in the middle and inferior frontal gyri (BA 6/8/9/10) and bilateral activation in parietal areas including inferior parietal regions with supramarginal and angular gyri (BA 19/39/40). Additional activation was also observed in anterior cingulate cortex (BA 8/32), precuneus (BA 7), and cerebellar regions. These brain regions activated by both the history of concussion group and controls validate the N-back working memory paradigm used for the current study, and allowed for further between-group comparisons to identify any abnormal activation between these groups that would be evident of compensation.

The current study found that relevant to increases in working memory load, asymptomatic athletes with a history of two or more concussions activated the same brain regions as controls. Therefore the compensation brain activation patterns between symptomatic athletes with a history of multiple concussions and controls documented in previous studies (Chen et al., 2004) are not evident in asymptomatic athletes. This "non-significant" finding is important as it is suggestive of a neurophysiological recovery following concussion. This "recovery effect" was also documented in the prior work of Chen et al. (2004).

In their primary analysis, Chen and colleagues (2004) found abnormal brain activation patterns indicative of compensation between controls and symptomatic athletes with a history of multiple concussions. Controls demonstrated task-related (i.e., verbal working memory) activations in the bilateral middle frontal gyrus (BA 9/46), right cingulate (BA 32), and left temporal gyrus (BA 21) while symptomatic athletes showed less task-related activation in the mid-dorsolateral prefrontal cortex (BA 9/46) and an increased number of activation peaks outside regions used by controls in both temporal and parietal areas. These additional brain regions used by the symptomatic athletes in their study was interpreted to be a compensatory effect that may result from previous concussion and reported post-concussive symptoms. However Chen et al. (2004) collected data three months later following resolution of symptoms on several athletes (i.e., now asymptomatic) and found that their task-related activation was similar to activation observed in controls, thus showing an effect of recovery as measured by brain activation. Interestingly these asymptomatic athletes in this follow-up analysis by Chen and colleagues (Chen et al., 2004) were studied approximately 9 months post-concussion, which is the same time period used in the present study. Moreover the brain regions used by both the "recovered" (i.e., asymptomatic) athletes and controls in Chen et al. (2004) included the same brain regions observed in the present study.

While the fMRI findings from the present study did not yield brain activation patterns suggestive of compensation, it appears that both asymptomatic athletes with a history of two or more concussions and controls also use these brain regions largely to the same degree. Therefore there is no substantial evidence from this study that would support engagement differences within common brain regions as reported previously by

McAllister et al. (1999; 2001). However it should be noted that a non-significant trend was found in one frontal brain area. More specifically the history of concussion group demonstrated a disproportionate amount of activation in the left middle frontal gyrus (BA 10) at the high working memory load compared to controls. While the controls showed increased activation in this brain region at every working memory load the history of concussion group did not activate this brain region when progressing from the moderate to the high working memory load. This was the only brain region that approached statistical significance before the Bonferroni correction was performed.

In the studies conducted by McAllister and colleagues (1999; 2001), both MTBI patients and controls showed increases in brain activation in response to each increase in working memory load, but this relationship was found to be different between groups. Specifically at the moderate (2-back) working memory load the MTBI group demonstrated a greater extent (i.e., they were more "engaged" at this level) of activation than controls in bilateral frontal and parietal brain regions. When the task difficulty increased to the high working memory load (3-back) the MTBI group showed less of an increase in activation (in right frontal and parietal areas), whereas controls demonstrated a greater increase in activation (in bilateral parietal areas). These authors concluded that differences in working memory capacity or improper allocation of resources could explain these findings.

The methodological similarities and differences between the current study and the previous work of McAllister et al. (2001) warrant review. McAllister et al. (2001) used a qualitative approach or "test of ocularity" that entailed the visual inspection and comparison of working memory contrasts (e.g., 1-back > 0-back, 2-back > 1-back, 3-back

> 2-back) between MTBI and controls rather than actually statistically testing for differences. The results of these visual comparisons were displayed at a very liberal uncorrected threshold (p = .05) which does not accurately account for the multiple comparisons issue (i.e., increased probability of Type I error) associated with whole-brain analyses. In response to this methodological weakness, the current study employed a more quantitative approach by statistically testing for group differences between each of these contrasts. These results were displayed at both an uncorrected liberal threshold similar to McAllister et al. (2001) and a more conservative threshold (p = .001) to decrease the probability of Type I error. These comparisons revealed between-group differences at the liberal threshold, but not for the more conservative threshold. Therefore, when statistically testing for between-group differences between working memory contrasts and using a corrected threshold the current study did not replicate the engagement differences previously reported in McAllister et al. (2001). However when the Functional ROI analysis was employed a non-significant trend suggestive of engagement differences was found in the left middle frontal gyrus.

The disproportionate activation between groups found in the left middle frontal gyrus was significant at the nominal $p \leq .05$ level only for the Functional ROI approach derived from the controls 3-back > 0-back contrast mask. It is important to note that disparity in activation was not found in any whole-brain analysis and was not replicated when using the history of concussion group Functional ROI 3-back > 0-back contrast mask, which may indicate that this finding is a spurious result. Moreover in light of the many analyses performed on numerous brain regions a Bonferroni correction method was

performed to control for inflation of Type I error rate. This statistical decision is an appropriate treatment for this data, which clearly warrants further study.

Discussion of Exploratory Analyses: Task-Induced Deactivations

In addition to examining increases in activation relevant to higher working memory demand, the current study also identified brain regions that demonstrated a decrease in activity (i.e., higher neural activity at baseline than at working memory load) during the N-back task. These "deactivated" brain regions are thought to comprise a default mode of brain function (i.e., default-mode network) that is active at rest and suppressed during externally cued tasks (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001; Shulman et al., 1997). The brain regions consisting of the posterior cingulate/precuneus, bilateral inferior parietal cortex, left dorso-lateral prefrontal cortex, left lateral inferior frontal cortex, left inferior temporal gyrus, medial frontal regions running along the dorsal-ventral axis, and right amygdala have been found to make up this default-mode network (Greicius et al., 2003; Raichle et al., 2001). This network of brain regions have been consistently found during baseline/resting states (e.g., eyes closed) and during the presentation of a passive stimulus (e.g., a checkerboard design) using a wide variety of cognitive paradigms (Greicius et al., 2003). The specific brain regions (e.g., posterior cingulate) that comprise the default-mode network have been posited to serve a functional purpose of continually gathering information about the external environment and internal thoughts (Raichle et al., 2001).

The current study found deactivations in bilateral post-central/angular gyrus, bilateral temporal-parietal junctions, and dorsal and posterior cingulate regions which have been reported in previous studies (Greicius et al., 2003). Interestingly there are very

few studies to date that has examined deactivated brain regions in concussed athletes. Chen et al. (2007) found reduced deactivations in medial frontal and temporal regions in concussed athletes who were experiencing depression symptoms. However the brain deactivation patterns examined in the current study between asymptomatic athletes with a history of two or more concussions and controls and did not reveal any statistical differences. While both groups used these regions to the same extent this specific area of study may be one of promise for future research as the patterns of deactivations in these regions approached statistical significance in several analyses.

Implications of Findings

This study's findings are a timely and important piece of the current knowledge base on sport-related concussion. There is an on-going discussion and debate on the potential residual effects associated with multiple concussions in both the scientific and popular media communities. This study suggests that there are no residual effects, as measured by neurocognitive testing and functional neuroimaging among asymptomatic athletes with a previous history of two or more concussions. These findings directly relate and influence the sports-medicine practitioner's pre-season evaluation of concussion history, management of this injury, and return-to-play decisions as a history of two or more concussions may not be linked to long-term changes in cognitive performance. However, previous studies that provide evidence for an increase in risk and prolonged recovery times (from incident concussion) associated with a history of two and three previous concussions should not be ignored. Nonetheless, this study's findings indicates an effect of recovery, as two or more concussions were not found to have a lasting effect on cognitive function.

Limitations

The interpretation of the findings from the present study is bound by certain limitations. First, and foremost the study's small sample size compromises its external validity. Thus caution should be taken when attempting to generalize the findings. In addition, the formation of groups (i.e., history of concussion and controls) were solely based on self-report of concussion history or a lack thereof. It is possible that some control athletes sustained an undiagnosed/undetected concussion at some prior point in their career. This possibility is a potential confounder in the current study and future studies should include an additional non-athlete control group. Finally, this study grouped the actual number of previous concussions into one group. Some studies have found more of a cumulative effect for three or more concussions than two (Collins, Grindel et al., 1999).

Suggestions for Future Research

This study is the first to explore brain activation patterns in asymptomatic athletes with a history of two or more concussions and have provided an impetus for future study ideas and suggestions. Given the small sample size of the current study, additional data should be collected to increase the statistical power of this project. It would also be beneficial to add a non-athlete control group, as this would better control for the possibility of undiagnosed concussions in athlete controls who self-report they never had sustained a previous concussion. In addition, academic achievement is a variable that could also be a potential confounder, and should be considered in future studies of this kind.

Expanding this dataset should keep in mind the possibility of exploring sex differences and age differences (e.g., high school vs. college ages) with respect to zero, one, two, and/or three previous concussions. A cross-sectional study of this kind would adequately address the other factors (sex and age) that have been suggested to influence outcomes following concussion. Other future studies could use imaging methodology to examine brain activation patterns in a more complete and longitudinal fashion. For example, studying brain activation changes in the acute and long-term time periods (e.g., 3-days, 1 week, 1 month, 3 months, and 6 months) following concussion would provide data that would be valuable to understanding the time course of the pathophysiological changes that may occur in the brain during recovery. In addition, other cognitive tasks that may prove valuable should include attentional tasks that may relate to the task-induced deactivations seen in the present study. These tasks could include visual search tasks, color-word Stroop Task, selective attention (dichotic presentation), and dual-task paradigms. Finally, future fMRI studies could work to corroborate concussion symptom clusters and localization of brain-skull impacts.

Conclusions

This research project was the first to employ functional neuroimaging to study brain activation patterns in asymptomatic athletes with a history of multiple concussions who have no residual neurocognitive deficits. While compensatory brain activation patterns have been observed in symptomatic athletes with a history of multiple concussions, the current study did not find these activation patterns of compensation in athletes with a history of two or more concussions who were asymptomatic. According to these current findings, compensatory brain activation patterns are not permanent and

likely resolve with symptomology. In addition to compensation, other researchers have found "engagement" differences in the amount of activation within common brain regions used by both symptomatic MTBI patients and controls while performing a working memory task. These "engagement" differences were also found in the present study, as asymptomatic athletes with a history of two or more concussions failed to demonstrate increased activation in the left middle frontal gyrus when a high demand was placed on working memory. This finding suggests that a history of multiple concussions, even when asymptomatic, may be associated with reduced working memory capacity and a potential dysfunction of frontal brain regions that may improperly allocate working memory resources. Finally, asymptomatic athletes with a history of two or more concussions demonstrated less accurate performance on the N-back working memory task than controls. In lieu of the similar neurocognitive performance between these groups, the N-back working memory task may be a more thorough and specific assessment of verbal working memory and may be useful for future studies examining the subtle memory impairments that may exist in athletes with a history of multiple concussions.

APPENDICES

APPENDIX A

Magnetic Resonance (MR) Procedure Screening Form for Research Subjects

Date: _____

Please indicate if you have any of the following:

Yes ☐ No ☐ Aneurysm clips
Yes ☐ No ☐ Cardiac Pacemaker
Yes ☐ No ☐ Implanted cardioverter defibrillator (ICD)
Yes ☐ No ☐ Electronic Implant or device
Yes ☐ No ☐ Magnetically-activated implant or device
Yes ☐ No ☐ Neurostimulation system
Yes ☐ No ☐ Spinal Cord Stimulator
Yes ☐ No ☐ Internal electrodes or wires
Yes ☐ No ☐ Bone growth/bone fusion stimulator
Yes ☐ No ☐ Cochlear, otologic, or other ear implant
Yes ☐ No ☐ Insulin or infusion pump
Yes ☐ No ☐ Implanted drug infusion device
Yes ☐ No ☐ Any type of prosthesis (eye, penile, etc.)
Yes ☐ No ☐ Heart valve prosthesis
Yes ☐ No ☐ Eyelid spring or wire
Yes ☐ No ☐ Artificial or prosthetic limb
Yes ☐ No ☐ Metallic stent, filter or coil
Yes ☐ No ☐ Shunt (spinal or intraventricular)
Yes ☐ No ☐ Vascular access port and/or catheter
Yes ☐ No ☐ Radiation seeds or implants
Yes ☐ No ☐ Medication patch (nicotine, nitroglycerine)
Yes ☐ No ☐ Any metallic fragment or foreign body
Yes ☐ No ☐ Wire mesh implant
Yes ☐ No ☐ Tissue expander (e.g., breast)
Yes ☐ No ☐ Surgical staples, clips, or metallic sutures
Yes ☐ No ☐ Joint replacement (hip, knee, etc.)
Yes ☐ No ☐ Bone/joint pin, screw, nail, wire, plate, etc.
Yes ☐ No ☐ IUD, diaphragm, or pessary
Yes ☐ No ☐ Dentures or partial plates
Yes ☐ No ☐ Tattoo or permanent makeup
Yes ☐ No ☐ Body piercing jewelry
Yes ☐ No ☐ Hearing aid
Yes ☐ No ☐ Other implant _____

APPENDIX B

Name (First and Last): _____

Age: _____

Handedness: R L Both

Have you had a DIAGNOSED concussion in the last three months (can be sport or non-sport related)?

Y N

Have you had any direct (knock to the head, fall on your head, etc...) or indirect (like whiplash from a car accident) head impact in the last three months? Y N

If YES – wait another 3 months—

If NO – ask the following questions as a check...

How many hours of sleep did you get last night?

Did you consume any caffeine in the last 24 hours?

Did you exercise in the last 24 hours?

Have you taken any medications in the last 24 hours?

Do you have a diagnosed learning disability?

Do you have a history of migraines?

Treatment for headaches?

Family history of migraines?

APPENDIX C

Table 14

Means and Standard Deviations for BOLD % Signal Change in Extracted Brain Regions Using 3-back > 0-back contrast from Controls

	0-back		1-back		2-back		3-back	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1. R IPL								
Hx	-.26	±.28	.01	±.19	.30	±.18	.25	±.30
Control	-.25	±.15	.00	±.22	.28	±.18	.27	±.22
2. ACC/SMA								
Hx	-.12	±.20	.10	±.17	.31	±.17	.40	±.25
Control	-.11	±.13	.06	±.14	.22	±.13	.34	±.14
3. R MFG (RDLPFC)								
Hx	-.19	±.21	-.01	±.18	.25	±.27	.23	±.26
Control	-.23	±.11	-.01	±.19	.28	±.17	.37	±.29
4. R MFG								
Hx	-.20	±.23	.06	±.22	.32	±.17	.31	±.30
Control	-.25	±.15	.08	±.19	.35	±.16	.35	±.20
5. L MFG (LDLPFC)								
Hx	-.14	±.14	.00	±.14	.16	±.13	.14	±.17
Control	-.15	±.07	.00	±.12	.19	±.14	.18	±.16
6. R MFG								
Hx	-.09	±.26	.08	±.22	.24	±.14	.31	±.29
Control	-.16	±.04	.04	±.17	.29	±.15	.31	±.23
7. Angular Gyrus								
Hx	-.17	±.18	.01	±.16	.20	±.14	.21	±.21
Control	-.18	±.13	.02	±.19	.26	±.18	.18	±.20
8. L MFG								
Hx	-.18	±.35	.05	±.38	.20	±.44	.00	±.57
Control	-.17	±.20	-.14	±.25	.25	±.27	.36	±.26
9. L IFG								
Hx	-.12	±.19	.05	±.09	.17	±.09	.14	±.11
Control	-.13	±.11	.00	±.10	.16	±.12	.12	±.15
10. Cerebellum								
Hx	-.07	± .22	.06	±.16	.21	±.21	.21	±.28
Control	-.12	± .06	.04	±.15	.25	±.20	.22	±.23
11. L IFG								
Hx	-.24	±.34	.07	±.20	.28	±.27	.24	±.30
Control	-.30	±.19	.00	±.20	.32	±.23	.27	±.33
12. L Precuneus								
Hx	-.31	±.24	-.15	±.22	.10	±.23	.11	±.23
Control	-.30	±.18	-.18	±.23	.23	±.21	.11	±.25

APPENDIX D

Table 27

Means and Standard Deviations for BOLD % Signal Change in Extracted Brain Regions Using 3-back > 0-back contrast from Asymptomatic Athletes with a History of Two or More Concussions

	0-back		1-back		2-back		3-back	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1. R IPL								
Hx	-.18	±.20	.02	±.13	.21	±.13	.18	±.20
Control	-.17	±.10	-.01	±.15	.19	±.15	.18	±.18
2. R MFG (R DLPFC)								
Hx	-.15	±.17	.04	±.14	.24	±.15	.26	±.22
Control	-.14	±.10	.02	±.14	.20	±.10	.24	±.20
3. R MFG								
Hx	-.10	±.14	.02	±.10	.19	±.11	.15	±.11
Control	-.09	±.08	.00	±.09	.14	±.10	.11	±.13
4. R IFG								
Hx	-.02	±.20	.11	±.17	.25	±.15	.31	±.22
Control	-.06	±.10	.09	±.13	.18	±.14	.20	±.18
5. ACC/SMA								
Hx	-.08	±.12	.03	±.12	.14	±.12	.18	±.15
Control	-.05	±.08	.01	±.10	.09	±.07	.14	±.11
6. L MFG								
Hx	-.16	±.28	.02	±.23	.19	±.22	.21	±.32
Control	-.20	±.15	-.07	±.21	.23	±.22	.29	±.30
7. L IPL								
Hx	-.21	±.25	-.02	±.25	.21	±.22	.24	±.34
Control	-.17	±.21	-.03	±.22	.24	±.25	.16	±.30
8. R Precuneus								
Hx	-28	±.24	-.14	±.19	.10	±.17	.12	±.25
Control	-.25	±.18	-.16	±.22	.21	±.18	.09	±.23
9. L IFG								
Hx	-.08	±.15	.07	±.15	.25	±.16	.25	±.18
Control	-.13	±.14	.03	±.14	.21	±.16	.23	±.20
10. L MFG (L DLPFC)								
Hx	-.11	±.10	-.02	±.13	.06	±.10	.08	±.13
Control	-.10	±.09	-.03	±.10	.07	±.11	.07	±.12
11. R MFG								
Hx	-.22	±.30	.01	±.26	.30	±.27	.24	±.41
Control	-.21	±.19	-.07	±.23	.24	±.28	.30	±.44

APPENDIX E

Table 40

Means and Standard Deviations for Deactivated Brain Regions

	0-back		1-back		2-back		3-back	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1. R PoCG/TPJ/Angular Gyrus								
Hx	.11	±.15	.03	±.11	-.15	±.14	-.14	±.16
Control	.09	±.15	-.05	±.10	-.16	±.17	-.26	±.14
2. L Insula								
Hx	.13	±.14	.08	±.12	-.09	±.12	-.07	±.14
Control	.11	±.12	.00	±.09	-.08	±.14	-.14	±.12
3. Dorsal ACC								
Hx	.12	±.18	.07	±.16	-.09	±.18	-.06	±.16
Control	.09	±.08	.01	±.10	-.06	±.13	-.14	±.11
4. L PoCG								
Hx	.20	±.24	.13	±.16	-.04	±.17	-.04	±.19
Control	.17	±.15	.09	±.10	-.02	±.13	-.13	±.13
5. L N. Accumbens/Amygdala								
Hx	.07	±.19	.04	±.19	-.14	±.19	-.16	±.28
Control	.01	±.10	-.02	±.12	-.12	±.13	-.20	±.20
6. L Hipp								
Hx	.04	±.14	.01	±.17	-.15	±.12	-.15	±.11
Control	.04	±.10	-.02	±.13	-.10	±.15	-.20	±.21
7. Med FG								
Hx	.24	±.44	-.27	±.43	-.64	±.47	-.61	±.46
Control	.14	±.28	-.14	±.30	-.40	±.40	-.45	±.29
8. PCC								
Hx	.01	±.23	-.20	±.27	-.35	±.19	-.30	±.22
Control	.07	±.16	-.24	±.23	-.33	±.26	-.33	±.29

APPENDIX F

Table 50

Other Analyses Performed to Explore Behavioral and Neuroimaging Data in Addition to Those Reported in Results

Question	Exploratory Analysis Performed
Are there between group differences in activation means at any working memory load?	Between-group independent t-tests for 0-back, 1-back, 2-back, and 3-back for all brain regions *(Non Significant)*
Does N-back accuracy predict activation better in either group?	Split-file (group) regression with N-back accuracy as predictor and activation as dependent variable for each brain region at each working memory load *(Non Significant)*
Are there group differences in overall working memory activation? (Note: 1-back, 2-back, 3-back BOLD % signal change values were combined into one mean score)	Between-group independent t-test *(Non Significant)*
Are there group differences for combined 0-back activation and combined BOLD % signal change values?	2 group X 2 working memory load ANOVA (Note: significant within-subjects effect for load, no between-group effect or interaction)

Are there group differences in combined working memory load? (Note: 0-back, 1-back, 2-back, 3-back BOLD % signal change values for brain regions were combined into four mean scores)	2 group X 4 working memory load ANOVA (Note: significant within-subjects effect for load, but no significant between-group effect or interaction)
Does BOLD % signal change predict N-back accuracy better in either group? (Note: this was performed separately for each working memory load)	Four split-file (group) multiple regressions with BOLD % signal change for all brain regions as predictors and N-back accuracy as dependent variable. *(Non Significant)*
Which brain region predicts accuracy at each working memory load between groups?	Four split-file (group) multiple regressions (one for each WM load) using brain regions as predictors and accuracy as dependent variable. *(Non Significant)*
Is there a relationship between N-back accuracy and % BOLD signal change in any brain region?	Split-file (group) Correlation analyses performed using accuracy and activation for each working memory load. Note: 0-back accuracy was negatively correlated with 0-back activation in ACC/SMA (p = .01); R MFG (p = .04); R DLPFC (p = .01) for Hx group and negatively correlated in L Precuneus (p = .01) for controls. 2-back accuracy was negatively correlated with 2-back activation in R DLPFC (p = .05) and L MFG (p = .03)
Did brain activation predict accuracy overall for the total sample (N = 28) for all working memory loads?	Four regressions (one for each working memory load) conducted with BOLD % signal change in brain regions as predictors and N-back accuracy as dependent variable. *(Non Significant)*

Did N-back accuracy predict brain activation for the total sample (N = 28) for all working memory loads?	Four multiple regressions (one for each working memory load) conducted with N-back accuracy as predictors and BOLD % signal change in brain regions as dependent variable. *(Non Significant)*
For the history of concussion group did time since last concussion predict activation in any brain region for the 3-back working memory load?	Regression analyses were performed for each extracted brain region using time since last concussion as the predictor and activation as the dependent variable. *(Non Significant)*
Is there a relationship between the number of previous concussions, LOC, time since last concussion, and N-back accuracy at any working memory load?	Separate correlations were performed for these given variables. *(Non Significant)*
Are there group differences in combined working memory load for deactivations? (Note: 0-back, 1-back, 2-back, 3-back BOLD % signal change values for brain regions were combined into four mean scores)	Separate 2 group x 2 WM Load repeated measures ANOVAs performed for each WM load level. *(Non Significant)*
Are there group differences in combined total working memory load for deactivations? (Note: 0-back, 1-back, 2-back, 3-back BOLD % signal change values for brain regions were combined into one total WM score)	A 2 group x 2 (0-back, total WM deactivation) repeated measures ANOVA performed. *(Non significant)*

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