The effects of concussive and sub-concussive head impacts on brain activity

By

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Kinesiology)
in the University of Michigan
2016

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Acknowledgements

I would like to thank all of the committee members for their support and mentoring through the dissertation process. Additionally, I would like to thank Ashley Rettmann, Brandon Moore and Chris Reams for their contributions to data collection. Thank you to Drs. Jeffrey Kutcher and Andrea Almeida for serving as the supervising physicians for this study. Lastly, I would like to acknowledge and thank the coaches, parents and players for their constant involvement in the study and for allowing us to collect data with them and making me a part of their family.

Table of Contents

List of Abbreviations

ATP	Adenosine triphosphate
BESS	Balance Error Scoring System
CBF	Cerebral blood flow
CCAT	Computerized Cognitive Assessment Tool
CDC	Center for Disease Control and Prevention
CNS	Central nervous system
CRT	Clinical reaction time
CT	Computed tomography
CTE	Chronic traumatic encephalopathy
DTI	Diffuse tensor imaging
EEG	Electroencephalogram
ERP	Event-related potential
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
GCS	Glasgow Coma Scale
GSC	Graded Symptom Checklist
HBI	Health behavior inventor
HIT	Head Impact Telemetry
HRQOL	Health Related Quality of Life
ICC	Intraclass correlation coefficient
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing
MD	Mean diffusivity
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
mTBI	Mild traumatic brain injury
NAA	N-acetyl aspartic acid
NFHS	National Federation of State High School Associations
NFL	National Football League
NFT	Neurofibrillary Tangle
NOSCAE	National Operating Committee on Standard for Athletic Equipment
PCI	Post-Concussion Syndrome
SAC	Standard Assessment of Concussion
SCAT	Sport Concussion Assessment Tool
SOT	Sensory Organization Test
SWL	Satisfaction With Life
TBI	Traumatic Brain Injury

List of Tables

List of Figures

Abstract

Context: 7 million athletes participate in high school sports annually. Approximately 1 million of these athletes participate in football, which is associated with repetitive head impacts. Concussion literature suggests sub-concussive impacts may lead to declines in brain function across a season of football. Furthermore, recent research suggests following clinical concussion recovery, metabolic and neurophysiological recovery may not be complete.

Objective: The purpose of this study was to monitor head impacts and cognitive function during (72hour, asymptomatic) and after concussion and longer term over a full football season (pre-season, mid-season, post-season).

Participants: 106 male adolescent (46 football-athletes, 42 controls for football-athletes, 9 concussed-athletes, 9 controls for concussed-athletes).

Outcome measures: The Head Impact Telemetry System encoder was used to track the location and magnitude of head impacts during football participation. Psychophysiology was measured using Electroencephalography and was quantified using a 256 channel system to record brain activity during an auditory oddball task. All Participants completed Axon neurocognitive testing, clinical reaction time task (CRT), symptom inventory and two Health Related Quality of Life Surveys (Health Behavior Inventory, Satisfaction with Life) throughout the above testing time-points.

Results: Football-athletes sustained a mean of 482 head impacts during all practices and games. Mixed measures ANOVA indicated a significant decrement on one BNA output score, Target amplitude, with lower post-season scores ($p<0.05$). No other BNA output scores, Axon, CRT, SWL, or HBI measurements showed significant deficits post-season ($p>0.05$). Furthermore, P3a amplitudes were significantly larger and N2 latency was longer during post-season testing. Mixed measured ANOVAs indicated no significant deficits in BNA output scores, Axon performance, CRT, and HRQOL, for concussed and matched controls across post-injury time points. Additionally, there was a significantly longer P3a latency post-season latencies across groups and smaller P3a amplitudes at post-season for concussed compared to controls ($p<0.05$).

Conclusion: Overall, these findings suggest electrophysiology changes between pre and post-season testing among football athletes and control participants without concussion, with the majority demonstrating improved cognitive function. Therefore, no negative effects may be associated with repeated head impacts in one season of football. Furthermore, no cognitive deficits were present during asymptomatic testing following concussion.

Chapter 1 Introduction

Statement of problem

Adolescent sport participation has been shown to improve perceived quality of life,[1] and benefit cognitive functioning.[2] With increased concern for stagnation of physical activity in youth, the benefits of sports participation are vital for health related outcomes. In the United States, it is estimated that 7 million athletes participate in high school sports annually.[3] Consequently, due to the physical nature of contact sports, athletes are at greater risk to sustain an injury than a non-sport participating adolescent. High school athletes sustain roughly 2.6 injuries per 1,000 athlete exposures per year.[4] Of those injuries, on average 23.1% of all high school injuries are concussions.[4]

Furthermore, roughly 1 million adolescent athletes participate in high school football alone.[4] As such, football has the highest overall incidence of injuries compared to all sports with an estimated 600,000 injuries sustained a year.[4] In particular, it has been estimated that high school football athletes sustain 6.4 concussions per 10,000 athlete exposures.[5]

Football participation also results in a high number of head impacts. While a concussion may occur in following some impacts, the majority are considered sub-concussive. Sub-concussive head impacts are impacts that do not produce a discernable injury and more notably do not elicit a clinical presentation of a concussion, but may demonstrate harmful brain effects.[6] A high school football athlete sustains an estimated 650 head impacts per player per season.[7-9] Further, there is a significant concern regarding the quantity of head impacts sustained over the course of a football career, and as a result any negative effects head impacts impose on brain

health. Recent research suggests sub-concussive impacts may result in negative brain function changes.[10-14] In particular, Talavage et al[14] examined the brain functioning of high school athletes following sub-concussive head impacts sustained during a football season using a standard cognitive test for concussion and functional MRI measures while completing visual working memory tasks. These authors[14] reported decreased brain activation in the dorsal lateral prefrontal cortex. Results from the study found neurocognitive and neurophysiologic deficits in individuals without a reported concussion, and therefore raises concerns regarding the effects of repeated head impacts on brain function.[14] Cognitive declines were associated with the number of head impacts athletes sustained in the week prior to imaging.[14] The authors noted that the study participants were likely to continue to participate in football, even though brain changes were found because of the lack of concussion symptoms present. In addition, Bazarian et al[15] studied a small cohort of high school hockey and football athletes and measured white matter changes in the brain using Diffusion Tensor Imaging (DTI). The study concluded significant white matter changes were present following pre-season and post-season testing in athletes compared to controls.[15] The above studies use advanced neuroimaging techniques to demonstrate changes in brain activation following repeated head impacts. Monitoring brain activity following a cognitive stimulus, may further add to the sub-concussive body of literature. More specifically, EEG research has been used to understand the neural process following concussion, in which recovery patterns were demonstrated. EEG may be sensitive enough to be used to monitor brain activity following repeated head impact exposure, and measure the cognitive effects of sub-concussive head impacts impose on brain health.

Following repeated head impact exposure, concussions can occur. Research has suggested that those with a concussion history are 2-5.8 times more likely to sustain another

concussion.[16,17,18] As such, there is concern for properly returning athletes back to sports participation to decrease the risk of repeat injury, and decrease the risk of sustaining a more severe secondary injury. Furthermore, youth athletes, in particular, are a population of concern with beginning contact sport participation at a young age and accumulating numerous head impacts over a playing career. Research has suggested following a concussion, adolescent athletes may have a prolonged recovery compared to adults with a greater number of reported symptomatic days (7 to 15 days).[19, 20] Additionally, since the brain is still developing during high school, there is a greater concern for the effects concussions have on cognitive function throughout the recovery process. [21-23]

Concussion management remains a subjective process with a clinical evaluation serving as the best diagnostic tool. Concussion sideline assessments are used largely as aides to measures cognitive deficits following injury.[24] Following acute concussion, immediate deficits in cognition and motor control are noted.[25-27] The majority of these deficits return back to pre-season levels within 7 to 10 days of injury,[28] However, research has suggested that despite improvements in cognitive performance following injury, persistent effects may still exist following clinical recovery.[29] This suggests that despite being asymptomatic and returning back to pre-season clinical assessment testing scores, athletes may not be completely recovered. Therefore, increasing the risk of repeat injury and secondary injury complications. Improving the sensitivity of brain function assessment techniques may assist in decreasing the risk of repeat injuries during the critical concussion recovery period,[30] as well as decreasing the number of poor outcomes following returning to athletics too soon.[31] Therefore, it is necessary to develop and further enhance current assessment tools to be able to accurately and effectively identify when it is safe to return an athlete back to physical activity following concussion.

Electroencephalography (EEG) has been recently used to measure brain activity following concussion. Specifically, Event Related Potentials (ERP's) have been used to identify brain responses following a specified task. Research has shown the utility of ERPs following sport-related concussion and the ability for ERPs to identify continued concussion deficits.[22,23,32-35] Specifically, research suggests decreased P3 and N2 amplitudes and longer P3 latencies following concussion, suggesting individuals have a harder time allocating attentional resources during tasks.[22,23,32-37] Further, ERP use following concussion has identified working memory deficits.[37] These studies further support the use of ERP following concussion.

Furthermore, a study using EEG has identified a relationship between concussion symptom presentation and concussion recovery.[34] Dupuis et al[34] found participants with increased number of reported symptoms and an increased symptom severity, displayed smaller P3 amplitudes. Additionally, Gosselin et al[38] found that participants displayed the same negative correlation with self-reported headaches and ERP P3 amplitude. Results suggest P3 and N2 components may be used as an objective measure to identify cognitive impairments and recovery patterns following concussion. However, it still remains unclear how the N2 and P3 components change with concussion recovery. Evidence suggests following a concussion and post-injury, decreased P3 amplitude, decreased N2 amplitudes, and longer P3 latencies are present. Further understanding the concussion recovery timeline is important for concussion management patterns and to be able to better comprehend concussion as a transient injury.

A novel EEG method, Brain Network Activation (BNA), records ERP during a cognitive task to understand the neural network activity of brain function and dysfunction.[39-42] Further, the novel BNA algorithm incorporates neural network connectivity through time, location, amplitude and frequency to process data into network clusters and derives a similarity score. The similarity

score compares individual scores to normative data. BNA has recently shown to recognize working memory deficits, and brain activation changes in health and unhealthy subjects.[39,40,42,43] A recent study researched post-traumatic migraine following concussion and showed decreased BNA performance in the post-traumatic migraine group three weeks post injury.[43] The BNA algorithm may have early implications to monitoring brain activation changes following concussion and generalize neural network patterns to gauge physical and functional neural connections and neural communication strength during cognitive function.

In all, EEG research has identified deficits in brain activation following a concussion. The ability to further monitor and depict recovery patterns following a concussion despite clinical resolution will enhance concussion management protocols and add to the body of literature to show effects of concussion. EEG research has shown to be a sensitive measure to detecting brain activation changes following concussion and may be more sensitive than common clinical concussion assessment tools. Using EEG following concussion may be a helpful tool for return to play guidelines and decision-making processes following concussion. Furthermore, monitoring sub-concussive head impacts and outlining a relationship between number and intensity of impacts and brain activation will further the body of literature on brain health following repeated head impacts.

Statement of purpose and hypotheses

The purpose of this investigation is to evaluate the relationship of sub-concussive impacts on brain activity, clinical cognitive function and symptom reports in high school athletes throughout a football season. Further, a second purpose of this investigation is to evaluate the relationship of concussive impacts on brain activity, clinical cognitive function and symptom reporting in high school football athletes following a sport-related concussion.

Aim 1: Determine the effect of sub-concussive head impacts on brain activity (Brain Network Activation, Event-Related Potentials), clinical cognitive function, and symptom reporting in high school football athletes.

Hypothesis 1A: Football athletes will demonstrate a significant decline in brain network activity (BNA) following pre-season and post-season testing. Matched controls will demonstrate no changes in brain network activity performance across time-points

Hypothesis 1B: Football athletes will demonstrate a decline in P3 amplitude, and increase in P3 latency, as well as a decline N2 amplitude and an increase in N2 latency between pre-season and post-season testing, suggesting attention, cognition and allocation deficits are present following a season of high school football. Matched controls will demonstrate no changes in P3 amplitude, P3 latency, N2 amplitude, and N2 latency

Hypothesis 1C: *Hypothesis 1A*: Football athletes will not demonstrate a significant decline in the less sensitive clinical measures of cognitive function or symptom reports. Matched controls will demonstrate no changes in clinical cognitive assessment tools across time-points

Hypothesis 1D: There will be a negative relationship between the number and volume (e.g. cumulative acceleration) of head impacts recorded by the HIT System and both brain network activity (BNA) and event-related potentials (P3a, P3b, N2 amplitudes and latencies), while we do not expect a negative relationship in the less sensitive clinical measure of cognitive function or symptom reports.

Significance of Aim 1: Research has suggested that sub-concussive impacts have a negative effect on cognition.[14,44] However, it is still largely unclear how sub-concussive impacts effect brain activity following a season of high school football.

Aim 2: To evaluate the effects sport-related concussions impose on brain activity (BNA, ERP), cognitive function, and symptom reporting within 72 hours of injury, when asymptomatic and at the conclusion of the season.

Hypothesis 2A: Concussed athletes will demonstrate significant declines in brain network activity (BNA), cognitive performance, and increased symptom reporting within 72 hours of injury compared to their own baseline evaluation and controls.

Hypothesis 2B: Concussed athletes will demonstrate restored cognitive function following asymptomatic and post-season testing, but continued brain network activity (BNA) impairments compared to their baseline evaluation and controls.

Hypothesis 2C: Concussed athletes will demonstrate significant declines in P3 amplitude, increased P3 latency, decreased N2 amplitude and increased N2 latency within 72 hours of injury compared to their own baseline evaluation and control athletes.

Hypothesis 2D: Concussed athletes will continue to demonstrate a decline P3 amplitude, increased P3 latency, decline in N2 amplitude, and an increase N2 latency following

asymptomatic and post-season testing time points compared to concussed athletes baseline evaluation.

Significance of Aim 2: Current research has suggested that despite athletes reporting symptom recovery, lingering cognitive impairments may still be present. Aim 2 is outlined to capture brain activity changes following concussion symptom resolution that may not be regularly detected on clinical assessment measures.

Chapter 2 Literature Review

The purpose of this literature review is to discuss the epidemiology, pathophysiology, sub-concussive concerns, acute management and long-term effects of concussion. Throughout the literature concussion will be defined using the following definitions: In 1997, the American Academy of Neurology defined concussion as a "trauma induced alteration in mental status that may or may not involve loss of consciousness."[45] [46] The concussion in sport group in 2012 clarified the definition of concussion to "a complex pathophysiological process affecting the brain, induced by biomechanical forces."[25,47]

2.1 Epidemiology

In the United States, there are over 7.5 million high school sports athletes,[4] with high school sport participation annually improving.[4] Although sport participation is beneficial to both physical and social development, injury during sports participation occurs,[48] with estimates of 1.3 million high school athletes treated annually for sports injuries.[4] According to the 2012-2013 high school injury surveillance study, head/face injuries, strain/sprains, contusion, and fractures are the most common injury types sustained during sport participation.[4]

Furthermore, sport and recreation related concussions are responsible for an estimated 1.6-3.8 million injuries in the United States.[49] Data from 2012-2013 academic year shows an estimated 300,000 concussions occur in high school athletics,[4,50] meaning roughly 23% of all high school injuries were concussions.[4] Twenty-seven percent of concussions are sustained during competition, while 18% are sustained during practices.[4] More specifically, football has

seen roughly 150,000- 250,000 concussions per year, resulting in 25% of overall injuries are concussions.[4,51] The majority of football concussions sustained are due to tackling (25%) or being tackled (35%).[4]

The number of reported concussions continually increases. Concussion incidence rates vary by sport and level of participation,[16,17,52-54] with high school athletes reporting a higher number of concussions compared to college athletes in identical sports.[55] Although a recent review by Giza et al[46] exposed a higher incidence rate of concussions in both male and female athletes at the college level compared to the high school level per 1,000 game exposures.[55,56] Gessel et al,[55] suggested 1.55 concussions per 1,000 games in high school football athletes compared to 3.02 concussions per 1,000 games in college football athletes. Following football, incidence rates for college ice hockey (1.96), male (.59) and female (.97),[56] and high school soccer, and male (1.38) and female (1.80)[55] college soccer followed with the highest incidence rate of concussions per 1,000 games.[46] Rosenthal et al[57] recently examined concussion rates by sport during the 2005-2006 and 2010-2011 academic years in high school athletics. Results from the study demonstrated that football continues to have a high concussion exposure rate, with track and field, girl's volleyball, swimming/dive and baseball reporting the lowest concussion rate per 1,000-athlete exposures.[57,58]

In 2012, Marar et al[5] reported 2.5 concussions per 10,000-athlete exposures in high school athletes.[5] This number has increased exponentially with Rosenthal et al[57] reporting overall concussion rates of 0.51 per 1,000-athlete exposures.[57] From the 2005-2006 to 2010-2011 academic years, high school football has increased from 0.47 to 0.94 concussions per 1,000 athlete exposures.[57] In addition, both men and women soccer have increased incidence rates at 0.22 to 0.41 and 0.36 to 0.73 concussions per 1,000-athlete exposures respectively.[57]

Additionally, when comparing male and female athletes in the same sports, female athlete have higher rates of concussion compared to their male counterparts.[5,52,57,59,60] Understanding incidence rates of concussive episodes is important to understand the greater concern concussions pose on late life health. Due to the large number of high school athletes and increased exposure rates, high school aged athletes are an important population to conduct research in, to allow research translation to effect a large subset of the youth athletic population.

2.2 Physiology

2.2.1 Acute Phase

During a concussion, the brain experiences neuronal stretching due to the impact forces.[61,62] Subsequently, the brain experiences a neurometabolic cascade resulting in neuronal dysfunction,[62] and changes to the cellular functioning including ionic shifts, metabolic changes and impaired neurotransmission.[61,62] Normal signal transmission across neurons results from the release of neurotransmitters and is followed by a controlled regulation of the ionic changes of sodium and potassium. However, following a concussive injury the regulation of ions is significantly interrupted.

During normal brain function, glutamate release is regulated by neurons and serves as an energy source.[63] However, research has demonstrated that following a concussive impact, neurotransmitters are released resulting in an excessive release of glutamate into the brain.[61,62] The release in glutamate overly excites the surrounding cells, resulting in significant changes in normal ion balance. The ionic flux results in depolarization, which triggers the voltage gated ion channels to open, and potassium to flow out of the cell.[62] The change in potassium levels causes the brain to work harder in attempts to regulate the ion levels throughout the cell.[61,62,64] In order for the neuron to fire again, homeostasis needs to be restored. To reestablish equilibrium, the sodium-potassium pump is activated, requiring increasing amounts of ATP, which triggers an

increase in glucose metabolism.[61] The initial ionic flux and hyperglycolysis causes a "depression-like state,"[61,62] further causing a deeper energy crisis.

In addition to the changes in sodium and potassium levels in the cell, calcium is also affected.[61,64] When functioning normally, calcium is not damaging to brain function. However, following injury there is a change in calcium levels, causing calcium to rush inside the cells through the opened channels.[61] The influx of calcium in the cell results in greater mitochondrial calcium accumulation and impaired oxidative metabolism.[61,62] The impairment results in further metabolism dysfunction and potentially worsening the cellular crisis.[61]

During normal brain functioning, cerebral blood flow, cerebral glucose metabolism, and neuronal activity are highly dependent on one another.[62] Following injury, cerebral blood flow has been noted to decrease.[65] This decrease may be due to the cerebral blood flow unable to adequately respond to a stimulus as normal, due to the increase in cerebral glucose metabolism occurring as a result of impact. Due to the combination of hyperglycolysis and decreased cerebral blood flow, a change in energy demand occurs in the brain, resulting in an increased energy crisis.[61,62]

Research has shown that following the initial period of hyperglycolysis and within 24 hours of injury, cerebral glucose consumption diminishes,[62] and has also been shown to last 7-10 days post-injury in adult animals. This state of hyperglycolysis results in a state of impaired metabolism during that period.[62,66,67] Thomas et al[68] examined prolonged effects of the metabolic period in both adult and adolescent rats. Researchers found that the younger rats showed a metabolic depression resolution occurring within 3 days,[68] compared to 10 days found in adult rats by Yoshino and colleagues.[67] This research suggests that injury recovery differs by age of rats. In conclusion, following injury to the brain, an immediate change in neuronal firing occurs.

The neurons have to recover following damage, which takes time, suggesting immediate removal from potential secondary injury is important to allow for recovery. Despite evidence of the immediate effects of concussion, research is still searching for answers as to how multiple impacts to the head cause physiological or structural changes to the brain. Lastly, it is important to understand and recognize the metabolic recovery process following a concussion to appropriately return an athlete back to sports participation.

2.2.2 Sub-clinical/ Sub-concussive impacts

To date, research has primarily focused on concussive impacts, management and the recovery following concussions. Few research studies have focused on sub-concussive head impacts and the effect on the brain and cognitive functioning.[69,70] Sub-concussive impacts are classified as head impacts that do not result in a concussion, or other serious head injuries.[12] An athlete who sustains one or more sub-concussive head impacts may experience changes in brain function without a clinical concussive presentation.[14]

Human and animal research has identified changes to the central nervous system and pathophysiological brain changes to occur following sub-concussive head impacts.[71-73] However, to date, the influence of sub-concussive impacts on cognitive functioning has been mixed. Some studies have demonstrated altered brain function following repeated head impacts experienced during a football season.[14 ,44,74] An investigation by Bazarian et al,[15] tested nine high school hockey and football athletes without a diagnosed concussion, one individual with a concussion and six control subjects. All subjects underwent Diffusion Tensor Imaging pre and post-season. The researchers found a significant structural brain change in fractional anisotropy. Changes in white matter percentages were highest in the individuals who sustained a diagnosed concussion, intermediate with sub-concussive individuals and lowest in the control subjects.[15] The sub-concussive participants white matter changes over the three-time points at an increased rate than

controls.[15] However, more research should be conducted to further understand the effect of white matter changes on the brain and identify the relationship to sub-concussive and concussive head impacts. Another investigation by Talavage et al,[14] reported on twenty-one high school football athletes. Researchers found mix results with four of the subjects showing no in-season ImPACT score changes, while the remaining four displayed significant declines in ImPACT. Additionally, this subset of players displayed decreased fMRI activation levels in the dorsal lateral prefrontal cortex, and cerebellum.[14] Breedlove et al[44] studied twenty-four high school football players over two seasons using fMRI and computerized neurocognitive testing to measures cognitive function. Results from this study suggest that repeated head impact exposure is related to pathologically altered neurophysiology.[44] Findings from both Talavage et al[14] and Breedlove et al[44] provide some evidence that sub-concussive head impacts may lead to cognitive and neurophysiological changes. However, repeat studies are needed to further investigate sub-concussive impacts.

Similarly, Johnson et al[75] studied the acute effects of sub-concussive head impacts on brain functioning during a resting-state in twenty-four male and female collegiate rugby players. Each subject underwent a resting state fMRI 24 hours before a game and then 24 hours following a game. Results found an increase in connectivity in the "left supramarginal gyrus to bilateral orbitofrontal cortex as well as a decrease in connectivity from the retrosplenial cortex and dorsal posterior cingulate cortex following pre and post game scans."[75] Additionally, concussion history was a factor for differences found in functional activity. Those with a concussion history displayed a decrease in functional connectivity following sub-concussive head impacts, and those without a concussion history displayed an increase in connectivity.[75] McAllister et al[74] examined whether exposure to repeated head impacts over a season of Division I football and ice

hockey in 214 athletes affects white-matter diffusion measurements. The results for this study showed a group difference between contact athletes and non-contact athletes for mean diffusivity in the corpus callosum. Results also showed that contact athletes displayed worse performance on tests for learning and that a poorer score on post-season cognitive testing correlated with greater head impact exposure. These results suggest a relationship may be present between white-matter diffusion changes, cognition and head impact exposure.[74] Overall, there is evidence that suggests repeated head impact exposure without a diagnosed concussion results in negative brain changes.

Conversely, a few studies have not found brain changes following sub-concussive head impacts. Specifically, Gysland et al[69] reported no difference on neurocognitive tests following a football season in a group of 46 male collegiate athletes. Gysland and colleagues examined five clinical neurologic measurements (ANAM, SOT, SAC, BESS, and Graded Symptom scales) before and after a season of play.[69] The subjects showed no clinically meaningful changes from pre-season to post-season testing on any of the clinical neurological measurements.[69] Miller et al[70] examined 58 Division III football players who had no known concussions. The athletes underwent Standardized Assessment of Concussion (SAC) and ImPACT testing pre-season, mid-season and post-season. Miller et al[70] found no significant changes in test scores at any of the time points, suggesting sub-concussive impacts did not influence cognitive changes. Overall, longitudinal research should look for a direct association repeated head impacts and cognitive health while factoring normal age cognitive declines. Currently, the relationship among repeated head impacts, and brain health is not clear. Therefore, this study will monitor repeated head impacts throughout a season of football and identify any changes to cognitive function.

2.3 Concussion Assessments

2.3.1 Injury Concerns for the Adolescent athlete

Adolescent athletes participating in sports are at a risk for sustaining a concussion. In particular, some research suggests size and strength related factors increase concussion risk. More specifically, head to body size ratio is larger in a child's head compared to an adult head. The variation in head proportion, and a weaker neck creates a combination that makes it difficult for children to resist larger impacts, resulting in a whiplash mechanism.[76,77,78] There is also evidence that suggests the unmyelinated fibers in the brain are more vulnerable or susceptible to biomechanical injury than myelinated fibers.[79]

Furthermore, adolescents also have structural and functional disadvantages after sustaining head trauma. Since the brain of a young athlete is still developing, direct head trauma may result in prolonged brain development and may place youth at a greater risk for life threating conditions.[76] Pre-clinical research has suggested that following a traumatic brain injury; an immature brain can be more vulnerable to neurotransmission plasticity impairments to the brain.[77,80] Literature has suggested that recovery from concussions at the cellular level may take longer in younger athletes compared to college-aged athletes.[68,77,80] There has been some concern that the young brain may not have the ability to adapt to changes following injury. Therefore, the National Athletic Trainers Association recommends implementing additional management protocols when working with younger athletes.[24,81] A developing brain may take longer to heal than a fully developed brain, and implementing more frequent check-ups, proceeding with caution and conservatism during the return-to-play protocol is suggested.[76] While it has yet to be determined which structural or functional differences factor into age related changes, any of these or a combination of several may be responsible.

Concussions at any age or level of participation should be reported immediately. However, an unreported concussion or improper management, especially at the youth level, can result in a premature return-to-play and the potential for Second Impact Syndrome (SIS). SIS is described as a second head injury occurring before a previous head injury is fully recovered resulting in vascular engorgements and progressive cerebral swelling.[31,82,83,31,84] This injury can result in an immediate collapse and a rapid deterioration that may result in death. However, there is significant controversy regarding if SIS exists. The debate revolves around whether the nature of cerebral swelling is due to the second head impact or if it is a progression from the initial injury. Additionally, researchers are conflicted on how far apart first and second head impact need to be in order to result in SIS, and if developing a subdural hematoma result in the rapid edema production. Lastly, the United States reports the highest number of SIS cases in the world, therefore there is a questioning as to why the United States has so many more cases.[85] In all, despite debate as to if SIS exists, in order to prevent any further injury, concussions need to be recognized early, and properly managed.[83,82]

Concussion management should differ between adolescent athletes and adults. Overall, concussion management should implement early detection and proper management despite the age of the athlete. However, when managing a concussive injury for adolescent athletes, it is important to proceed with more caution and remove the athlete from play in order to decrease the chances of that athlete developing more serious conditions by continuing to participate in sports.[86] It is important to include age appropriate assessment tools for the symptom inventory checklist, neurocognitive function, and balance. Age appropriate assessment tools incorporate parent involvement and have guidelines for a gradual return-to-learn.[87]

2.3.2 Concussion Assessment

A medical professional diagnoses concussion through a clinical exam, which is supported by a variety of assessments tools.[25,46] Consensus suggests concussion evaluation and management should be a multifaceted approach.[24,25,88] Concussion assessment emphasizes self-report symptoms, an assessment of cognitive functioning (e.g. mental status tests) and balance and coordination evaluations. McCrory et al[26] suggests the player should be medically evaluated on site and immediately following injury. The on-field assessment should be systematic in nature ruling out a more severe or life threatening injury first. This assessment should include 1.) A head and neck palpation to rule out cervical fracture or facial fractures, 2.) A dental exam to rule out any teeth or mouth injuries, 3.) A pupillary exam to examine the constriction and dilation of the pupils and if they are equal in size, 4.) A cranial nerve assessments to assess neurological deficits, 5.) A muscular skeletal strength and sensation exam to assess neurological deficits, 6.) Balance and gait assessment to assess postural control and proprioception, 7.) A symptom inventory and cognitive function assessment. On field concussion assessment is the first step towards concussion diagnosis. If any of the above exams results in abnormal findings, the athlete is to be removed from play immediately and follow-up testing should ensue. This protocol is implemented in the below study for immediate removal from play and used during a concussion diagnosis.

2.3.3 Return to play

Once an athlete is asymptomatic they may begin a stepwise approach to return back to sports participation.[25] This return-to-play protocol incorporates a day-to-day progression with 24-hour time frames between each step. An athlete must be symptom-free, and must have returned back to daily school attendance prior to beginning the return to play protocol. The protocol begins with light aerobic exercise, and gradually increases intensity to sport specific exercise,

non-contact sport participation, a full contact practice, and finally return to play.[25] Light aerobic exercise includes walking, swimming, or stationary biking while keeping the athletes maximum predicted heart rate under 70%. Sport-specific exercise incorporates sport specific training drills into exercise (i.e. routes, dribbling, skating). Following sport specific drills, a non-contact practice participation follows. During the non-contact participation day, the athlete participates in more complex training drills that would be similar to a game situation without player contact. For example, passing drills in football or hockey. Following a medical clearance, a full contact practice will ensue and would be a normal training practice. An athlete would be allowed to participate in a competition following a full contact practice.[25] If at any point during the return to play progression, an athlete has symptoms, the athlete is to stop and rest. Following another 24hour symptom-free window, the athlete would be able to return to the progression a step below where they left off.[25] The above return to play protocol is best practices for concussion management and was implemented in the below study during concussion management.

2.4 Acute

2.4.1 Symptoms

Concussions are associated with various clinical signs and symptoms.[26] Concussion signs and symptoms may occur immediately following injury or may be delayed up to a few days.[25-27] Some observed signs include feeling dazed, confused, repeating questions, difficulty remembering concussive episode, forgetful and loss of consciousness.[89] The athlete may experience headaches, the feeling of built up pressure in their head, trouble focusing or concentrating, hard time remembering, feeling slowed down, feel as though they are in a "fog", nausea, vomiting, dizziness, fatigue, may have a sensitivity to light, noise, and may "not feel

right." Further, emotional changes may develop as increased irritability, sadness, increased anxiety or nervousness and may increase their need for sleep, or demonstrate a lack of sleep.[89,90]

Recent research has grouped concussive symptoms into cognitive, somatic, affective/ emotional, and sleep disturbance.[91] Cognitive symptoms include confusion, post-traumatic amnesia, retrograde amnesia, clouded decision-making, lack of focus, delayed motor function and excessive drowsiness. Somatic symptoms include headache, fatigue, disequilibrium, nausea/vomiting, visual disturbances and phono-phobia. Affective/ Emotional symptoms include emotional or irritability. Sleep disturbance includes trouble falling asleep, sleeping more or less than usual. [91] Headache is the most commonly reported concussion symptom (93%)[58,16,17] followed by dizziness (67%) and confusion (59%).[16,17,92,93] These symptoms may appear following a concussion, however, each concussion may present differently with varying symptoms. Roughly only 4.6% of concussions result in a loss of consciousness.[58] Additionally, 1.5% of concussions result in prolonged symptoms.[58]

Concussion symptomology is important for concussion assessment. Typically, symptoms are self-reported or administered by an interview. A common symptom checklist is the Graded Symptom Checklist (GSC). [94] This checklist grades 22 items on a 0-6 rating scale. A zero score is defined as no symptoms while a score of 6 defines symptoms as severe. The graded symptom checklist has a sensitivity of 64%-89%[88] and a specificity of 91%-100%[46] and is widely used in concussion management and clinical practice. A graded symptom checklist is recommended in current consensus guidelines.[24-26,46] Identifying concussion symptoms can help develop individualized concussion management plans to reduce the chances of symptom exacerbation,[95] and to begin the return to play and return to learn process following injury. Due to consensus

recommendations for symptom inventory use following concussions, the below study will incorporate the use of the 22 item symptom checklist throughout testing.

2.4.2 Neurocognitive Function

Literature suggests that cognitive function is impaired following a concussion.[92,96-99,100] Neurocognitive testing can detect subtle impairments following a concussion[94,99] using both paper and pencil and computerized testing.[92,96,97,100-104,105,106,107] Makdissi et al[100] validated the Axon computerized task for clinical response change scores.[100] Computerized neurocognitive testing is most commonly used during concussion assessment testing. Some of the most widely used testing programs include Axon Sports/ CogSport, Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), Automated Neuropsychological Assessment Metris (ANAM), CNS Vital Signs. This investigation will use the Axon Sports Computerized Cognitive Assessment Tool.

The Axon by CogState is a common clinical assessment tool that measures speed and accuracy of processing speed, attention, learning, and working memory. Each test incorporates four tasks that use virtual playing cards and takes <15min to complete. The four tasks include simple reaction time, choice reaction time through identification and visual attention, continuous learning assessing recognition and attention, followed by recall assessing working memory and attention. Axon CogState has been researched to have a good test-rest reliability.[108,109] The neurocognitive test has a high sensitivity (71%) to cognitive declines following a concussion.[100] Louey et al[110] studied Cogstate Axon Sports and suggest that the computerized task is a reliable tool for baseline testing with 96% sensitivity. In 2001, Collie et al[111] validated Cogstate Axon Sports to be used for testing with a high to very high reliability of 0.69-0.90 respectively.[112] Limited studies have been conducted in the high school population, and significantly less have

analyzed Cogstate Axon computerized test. Axon computerized neurocognitive test is a widely used concussion clinical assessment tool following injury. Therefore, this study will use the Axon computerized neurocognitive tests throughout testing time points to identify if deficits are present in processing speed, attention, learning and working memory.

2.4.3 Reaction Time

Research has suggested that following a concussion, reaction time is impaired resulting in a slower reaction time, but gradually improves during the recovery period.[100,106,108,112-119] Reaction time is a sensitive cognitive change.[112,118,120] Reaction time can be examined in two ways, computerized or a clinical assessment. Computerized reaction time has been commonly seen using neurocognitive testing and has shown mixed reliability. The Cogstate computerized test, identification task and One-back tasks displayed a 0.66 ICC, while working memory tasks displayed a low reliability with 0.55 and 0.40 ICC respectively.[121]

The University of Michigan developed a clinical reaction time tool that can be used on the sideline.[122] The clinical reaction time tool displays both a cognitive and motor aspect of motor control. The reaction time tool is a 1.3m long rod, with markings at 0.5cm increments and stabilized to a weighted disk.[109,122] Refer to chapter 3 for detailed clinical reaction time testing protocol. The clinical reaction time task is an inexpensive and efficient method to capture reaction time. There have been multiple studies looking at clinical reaction time and capturing subtle changes.[109,122-124] Eckner et al studied 28 controls and 28 concussed participants and reported a slower reaction time following concussion compared to baseline testing.[122] MacDonald et al[121] compared clinical reaction time and computerized reaction time and found that they were positively yet weakly correlated and both had marginal test-retest reliability (ICC=0.61 and 0.69). Despite, the few studies above, clinical reaction time assessment following

a concussion is a relatively easy approach. Further, clinical reaction time has bee shown to increase and be hindered following a concussion. Clinical reaction time is incorporated into common neurocognitive assessments and simple reaction time. Therefore, this study will use the Michigan developed clinical reaction time stick drop throughout study testing time points to be able to identify when reaction time deficits are present.

2.6 Concussive Biomechanics

2.6.1 Principles of head impacts

A concussive injury results from a "direct blow to the head, neck or body with forces transmitted to the head."[25] The rapid change in acceleration can cause brain tissue deformation through direct physical damage or metabolic damage from ionic disruption.[61] Beyond the initial physical damage to neurons from shearing forces, the unregulated metabolic cascade compromises brain function and is associated with the clinical symptomatology of concussion.[61] Motivated to quantify impact magnitude and frequency, multiple accelerometers have been developed for in vivo use in athletics.

Researchers have used accelerometers to define, and quantify head impacts sustained in sports participation, as well as explore injury diagnostics. Research has been mixed regarding a set concussion threshold.[125-128] Currently, there is no consensus on whether there is a linear and/or rotational concussive threshold. Head impact accelerometers calculate peak linear acceleration, estimate rotational acceleration, and calculate the quantity of head impacts sustained. Research on head impact exposure has raised concern for the negative effects of sub-concussive impacts on brain connectivity[75,129] and neurocognitive performance.[130] Leveraging multiple components of an impact, algorithms can estimate impact severity measures, including the Head Impact Telemetry severity profile,[131] head injury criterion (HIC15),[132] and Gadd Severity Index.[133]

2.6.2 In vivo head impact studies

The first *in vivo* head impact research monitored football head acceleration during games and was by Moon[134] and Reid[135] in the 1970's. Moon et al[134] found over all average peak acceleration of the player's head to be 776.2g using a 750hz filter and 353.93g for a 250hz filter. Reid et al[135] found linear acceleration between 40g and 230g in collegiate athletes. More recently, Naunheim et al[136] implemented a single tri-axial accelerometer inside high school hockey and football helmets. The researchers recorded an average peak linear acceleration value of 29.2g in football athletes and 35g for ice hockey. Using a single accelerometer affixed to the head or helmet gathers limited biomechanical detail. To enhance head impact monitoring abilities, the Head Impact Telemetry (HIT) System was developed to produce impact data and measure impacts sustained to the helmet during sport participation.[137,138] In 2005, the HIT system was used by Duma et al[139] to capture real time data, and employ the HIT system in a large number of athletes.[139] Now, the majority of sport-concussion biomechanics research encompasses the use of the HIT system. The HIT system technology (developed by Simbex, Lebanon, NH, and marketed commercially as a Sideline Response System by Riddell Inc, (Elyria, OH)) was designed to identify, monitor and quantify head impact biomechanical factors. The HITS uses six triaxial accelerometers embedded into the helmets themselves and measures real- time head acceleration. Refer to Chapter 3 for additional details regarding the HIT system.

2.6.3 Impact frequency, and magnitude

2.6.3.a College

Research has been conducted at all levels of play monitoring and examining head impact biomechanics.[53,127,139-148] At the collegiate team level, football teams have recorded head impacts ranging from 3,312-190,054 per team per season.[9,131,149,150] More specifically, on average college football athletes sustain between 223-800 head impacts per player per season.[139,151-154] A

substantial portion of head impact literature has focused on linear acceleration following impact because of its relationship with pressure gradients and concussion risk.[155] Impact magnitude, however, varies by level of participation. At the collegiate level, the average linear acceleration of the head during football season ranges from 20g to 35g.[9,139,151,152] Additionally, McAllister et al[130] recorded max linear acceleration to be 132g. In a mixed sample of high school and collegiate football players by Greenwald et al,[131] linear acceleration was recorded at 65.5g-84.2 and 103.45g-127.8g for the top 5% and 1% of impacts respectively.[131,9]

Furthermore, rotational acceleration has been hypothesized to contribute to the diffuse injury seen in mild traumatic brain injuries, resulting from shearing of cerebral tissue.[156] College football head impact biomechanics research suggests the mean rotational acceleration of head impacts range between 1,187-6,990.5 rad/sec^2,[131,157,158] with the top 5% between 3,147 rad/s^2-5,805 rad/s^2 and top 1% 6,990.5 rad/sec^2.[131,157,158]

2.6.3.b High school

Similarly to the college population, researchers have continued to monitor head impact frequency and intensity in the high school football setting.[7-9,144,145,153,159] Researchers have recorded total team head impacts to range between 8,326 to 101,000 across multiple seasons.[9,131] More specifically, high school football players have sustained between 413-652 head impacts per player per season.[9,144] The mean linear acceleration has been reported to range from 21.7g[160] to 29.3g in high school football players.[127,136,145,161] While, rotational acceleration values for high school football have been reported from 973 rad/sec^2 to 7,701 rad/sec^2.[8,145,160]

2.6.3.c Youth

Head impact monitoring has been performed at the youth football level to gain a better understanding of the distribution of head impacts from the start of a playing career. Youth football teams have recorded head impacts ranging from 748-11,978 total head impacts per

team.[140,162-164] The average youth athlete sustains between 106.9-275 head impacts per player per season.[140,162-164] Overall, youth athletes sustain fewer head impacts during a football season than both high school and college athletes, but additional monitoring is needed to ascertain whether there is a cumulative impact burden during an amateur football career.

Average linear acceleration magnitudes range from 16g to 22g at the youth level[140,142,163,165,166] with the top 5% of impacts exceeding 38g,[140,162,163] and the top 1% of impacts at 86g.[162] Rotational acceleration ranges from 7 to 12,322 rad/s^2 [164,140,162,163] with median rotational acceleration values to have been reported at 1,407.4 rad/s^2 [164] and top 5% reported at 2,481 rad/s^2.[160] In all, rotational acceleration values for youth and high school athletes are lower than college athletes and are attributable to the differences in size and strength of players at different ages. Athletes at the college level are stronger than at the youth level and therefore sustain head impacts with a greater magnitude.

2.6.3.1 Position

In addition to age differences, researchers have also monitored head impacts by football position. Overall, research suggests linemen sustain the majority of impacts during a football season compared to any other position.[8,9,144] Specifically, Schnebel et al[9] examined both high school and college athletes and found that skill players, which includes any position other than nose tackle, defensive tackle, or offensive linemen, sustain 24.6% of all head impacts while linemen sustained 75.4% of all head impacts. Studies by Crisco et al[141] and Broglio et al[8,145] found college and high school football linemen sustained more head impacts per practice (college: 11.5 impacts per practice; high school: 10.7 impacts and game (college: 29.8 impacts; high-school 28.7 impacts) compared to other positions .

Similar to impact count, linear acceleration values significantly vary by football position and which side of the ball the athlete plays on (offensive or defensive player). [145,152] Offensive

lineman (22.89g) sustained higher average linear acceleration impacts than defensive linemen (21.56g). Similarly, offensive backs (22.93g) and linebackers (22.67g), sustained higher magnitudes than defensive lineman and defensive backs.[152] Broglio et al[145] found the greatest average linear acceleration values among high school quarterbacks (27.0g for practices and 28.6g during games), followed by tight ends (25.5g for practices and 27.1g for games); wide receivers, cornerbacks, and safety positions (27g for practices and 26.6g for games); linemen (24.4g for practices, 25.1g for games). When viewed collectively with the impact frequency results, it becomes evident that while football linemen sustain a greater number of impacts relative to the other positions, skill players receive impacts of greater magnitude.

Rotational acceleration by position has not been reported in all levels of play. However, some research suggests the mean rotation acceleration value was consistent during practice sessions amongst linemen (1,572.9 rad/sec^2), quarterbacks (1,506.0 rad/sec^2), wide receivers/cornerbacks (1,571.4 rad/sec^2) and tight end, running back and linebackers (1,632.5 rad/sec^2)[8]. However, differences emerged during game participation, with the tight end; running backs; and linebackers sustaining the greatest rotational acceleration values (1,789.4 rad/s^2). Quarterbacks followed a similar pattern, with rotational acceleration values of 1,786.9 rad/s^2, while wide receiver/cornerbacks sustained rotational values of 1,771.1 rad/sec^2 and linemen recording the lowest rotational acceleration values of 1,658.5 rad/s^2.[8] This research suggests that rotational acceleration values are higher in linemen during practice sessions, but are greatest in tight tends, running backs, and linebackers during game situations. Following the same pattern with linear acceleration, rotational acceleration values vary by sport position with skill players receiving impacts of greater rotational acceleration magnitudes.

2.6.3.2 Location

Furthermore, head impact location has been researched. Mihalik et al[152] and Daniel et al[162] reported greater likelihood of sustaining impacts to the top of the head than impacts sustained to the front, back left, or right sides of the head among collegiate football players. While, Munce et al[164] recorded the majority of head impacts in youth athletes were located to the front of the head (42.5%), while hits to the back (26.1%), top(13.3%) , left (7.7%) and right (10.4%) of the helmet followed suite. Overall, head impacts location distribution can be valuable tool for clinicians to use in educating players and coaches to improve tackling techniques, note specific drill issues and adjust practice schedules.

2.6.4 Concussion Threshold

Researchers have been exploring the utility of head biomechanical data for predicting concussive injury. However, current research suggests that there is no singular concussion threshold.[125,126,146,167] More specifically, concussions sustained during college football participation have been recorded to be between 55.7 -168g and between 3,620- 7,235 rad/s^2.[168,151,9,131] Guskiewicz et al[168] reported on 13 collegiate level concussions occurring over varying impact magnitudes (60.5-168.7g and 163.4-15,397.1rad/s^2), although the mean peak linear and rotational accelerations were 102.8g and 5311.6 rad/s^2 respectively. As noted, the research on concussive injuries in the college setting varies and no set intensity of impact defines when a concussion will occur.

Among younger athletes, concussion research at the high school level has shown linear acceleration values to range from 74g to 146g with mean linear acceleration reported at 105g.[140,142,148,165,169] Rotational acceleration values for concussive injuries have been recorded to range from 5,582.6 rad/s^2 and 9,515.6 rad/s^2 .[140,142,148,165,169] These data suggest that concussion threshold varies among individual high school football players.[127] However, it is still unclear as

to why so many impacts at similar magnitudes do not result in a concussive injury, eluding that the injury threshold changes within individuals.[127] Since the concussion threshold is dynamic, other covariates such a gender, age and concussion history should be considered to help improve the predictive ability of impact biomechanics. Overall, head impact biomechanics helps to identify concussive injuries sustained during sport participation. This information can contribute to the body of literature, showing how each athlete responds differently to each head impact sustained. In addition, head impact biomechanics serve as a platform to quantify cumulative head impacts to be able to use in accordance with cognitive function assessments to identify effects sub-concussive head impacts. In particular, the HIT system will be used in the study outlined below to calculate frequency and intensity of repeated head impacts and quantify concussive impacts to contribute further to the body of literature.

2.7 Chronic

2.7.1 Post-concussion syndrome

Post concussion syndrome is a long-term effect of concussion. Post-concussion syndrome is a symptom complex associated with somatic, cognitive, sleep and affective symptoms following a concussion.[170] Post-concussive syndrome is defined as prolonged concussion symptoms lasting longer than 30 days[171] and affects between 1.5% and 15% of concussed individuals.[172-175] Post concussion syndrome can alter an athlete's daily life, including Health Related Quality of Life (HRQOL), and can result in greater academic compensation. The academic compensations can result in decreased school performance from an increase in school absences and greater stresses from limited school participation. Post concussion syndrome can also hinder social participation with friends and family.[176] Post-concussion syndrome produces long-term impairments for individuals and can present significant deficits to daily living. Further

understanding of post-concussion syndrome will help identify long-term impairments following concussion.

2.7.2 Health Related Quality of Life

Health Related Quality of Life (HRQOL) refers to the "physical, psychological and social domains of health, seen as distinct areas that are influenced by a persons experiences, beliefs, expectations and perceptions."[177] HRQOL outcome measures can vary between general and specific disease oriented measures, and specific to age of disease population (i.e. adolescent, adult, geriatric). HRQOL is a supplemental objective measure that captures unique clinical data that compliments the clinical exam and can help the athletic trainer with injury management. Understanding and implementing patient rated outcome measures in sport injuries will not only assist athletic trainers in returning athletes back to participation, but will ensure athletes are treated and managed properly. It is well known that concussive injuries have a negative effect on symptom reporting, cognitive functioning, and postural control[178] and recent research has also demonstrated HRQOL declines following a concussion.[179-181] Valovich McLeod et al[179] found lower Social functioning scores and lower global Pediatric Outcomes Data Collection Instrument HRQOL scores after an adolescent athlete self-reported an injury. This suggests that a recent injury can affect the individual beyond physical impairments and can negatively affect HRQOL.[179] To date, no research has evaluated the relationship between HRQOL and exposure to sub-concussive head impacts in a youth population. Therefore, this study will incorporate two HRQOL surveys into the study testing timeline. Monitoring HRQOL throughout testing will gain insight into the effects that sub-concussive head impacts impose on HRQOL, while also gaining more understanding into health deficits following concussion.

2.7.3 Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease affecting the brain. Martland et al[182] first described CTE in 1928 classified as "punch drunk." CTE has also been recognized as "dementia pugilistica"[183] and " the psychopathic deterioration of pugilists."[184] Most research suggests that CTE to be a direct effect of sustaining multiple concussions and a result of repeated sub-concussive head impacts.[185] Research has suggested that CTE is primarily found in individuals who have participated in contact sports over a lifetime (e.g. football, hockey, boxing) and usually begins 8-10 years after repetitive mild traumatic brain injuries. [186]

CTE is defined by the build-up of the protein Tau in the brain. Tauopathy is characterized by the development of neurofibrillary tangles in the brain.[185] The tauopathy neurofibrillary tangles are in the relative absence of β -amyloid deposits. In addition to the presence of tauopathy, CTE development characteristics include brain weight decreases, frontal lobe atrophy, enlarged ventricles, and white matter changes.[10] CTE symptoms have been noted to be an insidious onset and include severe mental and physical disabilities, depression, including thoughts of suicide, attention-deterioration (Memory, poor judgment, confusion, lack of insight), paranoia, aggression, irritability, and tremors.[186] There may be disruption to many pathways in the brain, including the cortical spinal tract, mamillothalamic tract, limbic function in general, and the medial forebrain bundle. These areas are associated with motor functions, cognition, and emotional responses among a few. Currently, research has been inconclusive of CTE incidence rates. However, the majority of research has suggested that it is more prevalent in retired NFL athletes compared to the general population.[186] Recently, Bieniek et al[187] examined the brains of 1,721 men whom donated their brain for research. Researchers found that 21 of 66 former athletes demonstrated tau pathology.[187] Despite this being the largest sample of brains examined for CTE, additional studies should include brains from alternative sources that are not primary

sources for Alzheimer's, Parkinson's, or ALS. Further research is needed to create a clearer picture into which patient population is most susceptible to develop CTE, to identify any predisposing factors, and to evaluate the influence of repeated head impacts on the development of CTE.

2.8 Electroencephalogram/event related potentials

Electroencephalogram (EEG) has been used in a variety of settings to examine electrical activity of the brain. EEG was discovered by Hans Berger in 1929,[188] by demonstrating that human brain activity could be monitored through scalp electrode use and plotting the voltage change from an amplified signal. EEG has been useful for both scientific and clinical use. One component of EEG is the ability to record Event Related Potentials (ERPs). ERP's have allowed researchers to further explore cognitive function following injury. Following response to, or in preparation for, a stimulus, ERPs show voltage change patterns. ERP's have good temporal resolution and can identify cognitive functions that occur between a stimulus and response to the stimulus.

In 1935, Pauline and Hallowell Davis[189] became the first to measure ERP recordings in live humans. This particular finding of ERP's was discovered prior to the usage of computerized EEG recordings. In 1964, Grey Walter and colleagues[190] reported on what is now the cognitive ERP component, or what they called as Contingent Negative Variation (CNV). CNV was the first to display consistent patterns of amplitude and electric responses despite EEG background noise and distinguish an expectant cognitive response.

Another advancement and component of ERPs was the discovery of the P300 or P3 component. The P3 component was discovered in 1965 by Sutton and colleagues and is the component elicited during the decision making process.[191] When the subject could not predict the upcoming stimulus a large P3 component peaked at 300ms post-stimulus. When the stimulus was predictable there was much smaller P3 peak.[191] P3 can be divided into 2 components P3a and P3b. P3a occurs at an unexpected event in the frontal area and is mainly associated with working memory, while P3b occurs after an expected but infrequent event and typically transmitted through the temporal and parietal structures.[192] Peak latency is thought to demonstrate speed and the amount of time required to detect a target stimuli.[192-194] Tasks that require greater attention resources would demonstrate smaller P3 amplitude with longer peak latency as processing resources are used during task performance.[195,196] Passive stimuli typically show smaller amplitudes compared to active stimuli because stimuli and attention abilities reduce amplitude.[192] Shorter P3 latency has been associated with better cognitive performance.[192,197,198] P3 latency alters with cognitive abilities and is more sensitive to task processing demands.[192] The use of ERP amplitude and latency following oddball task paradigms has shown a test re-test correlation of 0.50-0.80 for amplitude and 0.40-0.70 for peak latency.[196,199-201]

An additional component to ERP analysis is the inclusion of N2. Unlike the P3 component, the N2 is a negative-going wave. In an Oddball paradigm the N2 component is observed following a rare stimulus.[202] For an auditory component, N2 has been associated with mismatch negativity. Further N2 has been associated with response inhibition following a stimulus.[202] Overall, research has supported the use of P3 for concussion research, however only a few studies have incorporated the N2 ERP component following concussion.

2.8.1 Sub-concussive

ERP concussion research has shown the ability to monitor brain activity during a cognitive task and identify attentional deficits. However, ERP research on the effects of sub-concussive head impacts and brain activity is limited. One study by Wilson et al[203] found recorded ERP amplitude and latency in college football players and found no in season differences existed between controls and first year athletes. However, significantly smaller P3b amplitudes were found between third/fourth year athletes and first year athletes.[203] These effects demonstrated that following continued repeated head impacts subtle attentional difficulties may develop. This research can be used in combination with monitoring of head impacts during sport participation to outline any relationships between frequency and intensity of head impacts and brain activation pattern changes as a result.

2.8.2 Concussion Acute

Recently ERP analysis has been used to examine amplitude and latency changes acutely following sport-related concussion. Dupuis et al[34] noted a negative relationship between P3 amplitude and increased numbers of concussion symptoms in a group of college athletes 1 week to 6 months removed from concussion, however found no P3 latency differences. Additionally, Gosselin et al[204] found similar negative correlations between P3 amplitude and self-reported headaches in professional, semi-professional and collegiate ice hockey and football players. Gosselin et al[204] also showed longer P3 latency for concussed athletes compared to controls. Further, Boutin et al[205] found cortical impairments 24hours, 7 weeks, 22weeks, 32 weeks and 55 weeks post-injury in one adolescent athlete following a concussion Taken together these studies suggest cognitive function and dysfunction association with mild traumatic brain injury can be measured through ERP measurements throughout the recovery period. However, few studies

have monitored brain activity immediately following concussion and this study aims to provide evidence into concussion recovery patterns acutely following injury.

2.8.3 Concussion-Chronic

ERP research has demonstrated long-term deficits to be present following concussion. More specifically, Gaetz et al[35] studied high school ice hockey players and grouped them by concussion number and tested them 6 months post-injury. Researchers used a visual oddball task and noted that participants with three or more concussions demonstrated longer P3 latencies compared to control groups. Gaetz and Weinberg,[35] compared adults with a history of concussion and healthy controls using visual and auditory oddball paradigms. Researchers found that those with a concussion history, regardless of age, displayed longer P3 latencies during visual oddball tasks.[35] Further, Theriault et al[22] examined asymptomatic concussed high school athlete asymptomatic compared to non-concussed athletes found those who sustain a concussion within a year of testing, displayed smaller P3a amplitudes compared to individuals with no concussion. In 2009, Broglio et al[23] examined P3a and P3b components 90 collegiate and recreational athletes. The study examined individuals with and without a concussion history and found decreased N2 and P3b amplitude in individuals with a concussion history, but no P3a deficits. This study suggests that prolonged effects including cognitive dysfunction may be present up to 3 years following injury. Additionally, De Beaumont et al,[206] examined older adults 30 years removed from a concussive episode, and a group of age matched adults with no concussion history, and concluded that individuals with a concussion history showed significantly smaller P3a and P3b amplitudes, and longer peak latencies. Overall, a general decrease in cognitive function was noted 30 years post injury with attention resources, attention orientation and cognitive processing speed. Through EEG research, cognitive changes have been noted in ERP analysis. Despite the few studies talked about above, only a small group examined high school

athletes following concussion, while none examined pre-season to post-season changes in sub-concussive impacts. Since, high school athletes are at a high risk for concussion, it is important to further examine the use of EEG and ERP measurements in football athletes. ERP concussion research has the ability to identify continued deficits in brain activation following clinical recovery.

Furthermore, a novel ERP algorithm known as Brain Network Activation (BNA) seeks to identify brain activation patterns following a concussion. The BNA algorithm constructs a subject specific BNA pattern based on a phase locked evoked activity. Reches et al[40] first used the BNA algorithm to outline differences in use of donepezil treatments compared to placebo effects and found donepezil networks could outline working memory performance, and suggesting the BNA algorithm can be sensitive enough to detect cognitive performance based on drug use. Kontos et al[43], Eckner et al[207] and Broglio et al,[208] all used the BNA algorithm in association with concussion. Kontos et al[43] found post-traumatic migraine participants demonstrated reduced BNA scores compared to matched controls 3 and 4 weeks post concussion. However, while a few studies have outlined the utility of BNA and network activation, Eckner et al[207] found that the BNA score may be difficult to interpret due to the variability of the measurements and when not used in conjunction with participants own baseline score. Further, Broglio et al[208] examined post concussion time points and was unable to determine BNA performance differences between concussed and controls performance. The overall use of the BNA algorithm may have potential for clinical use. Further research is needed to determine if the BNA algorithm is able to detect subtle effects as a result of repeated head impacts and to detect deficits present during concussion recovery. In all, the use of EEG shows promise for use in sub-concussive and concussive research.

2.9 Summary of Literature Review

Contact sports participation, such as football, result in hundreds of repeated head impacts throughout a season. Previous research has suggested that repeated head impacts displayed no meaningful relationship to cognitive function. However, current research has suggested repeat head impacts may result in negative changes to brain function. In particular, it is unclear how sub-concussive impacts affect the developing brain in high school aged athletes.

During sport participation, some head impacts will lead to a concussion. Concussion management incorporates a clinical evaluation by a medical professional, supported by cognitive, balance, and symptom assessments. Since concussion clinical presentations vary by athlete, concussion diagnosis can be difficult. With a lack of sensitivity for common concussion assessment tools, concussion diagnosis and management can be difficult. Therefore, more sensitive concussion measures are needed to identify declines in cognitive function. This investigation will implement a novel evaluation of electroencephalogram (EEG) recordings, ERP analysis and standard clinical assessments in high school football athletes to evaluate concussive and sub-concussive impacts. The outcomes of this study will add to the body of literature as how sub-concussive impacts influence brain function. Therefore, this study will incorporate P3a, P3b, N2 and BNA algorithm in high school football athletes to identify concussion recovery patters and outline effects of repeated head impacts.

3.1.1 Aim 1: Sub-concussive head impacts

Aim 1: To evaluate the effect sub-concussive head impacts impose on brain activity (Brain Network Activation algorithm, Event-Related Potentials), clinical cognitive function, and symptom reporting in high school football athletes.

Hypothesis 1A: Football athletes will demonstrate a significant decline in brain network activity (BNA) following pre-season and post-season testing. Matched controls will demonstrate no changes in brain network activity performance across time-points

Hypothesis 1B: Football athletes will demonstrate a decline in P3 amplitude, and increase in P3 latency, as well as a decline N2 amplitude and an increase in N2 latency between pre-season and post-season testing, suggesting attention, cognition and allocation deficits are present following a season of high school football. Matched controls will demonstrate no changes in P3 amplitude, P3 latency, N2 amplitude, and N2 latency

Hypothesis 1C: *Hypothesis 1A*: Football athletes will not demonstrate a significant decline in the less sensitive clinical measures of cognitive function or symptom reports. Matched controls will demonstrate no changes in clinical cognitive assessment tools across time-points

Hypothesis 1D: There will be a negative relationship between the number and volume (e.g. cumulative acceleration) of head impacts recorded by the HIT System and both brain network activity (BNA) and event-related potentials (P3a, P3b, N2 amplitudes and latencies), while we do not expect a negative relationship in the less sensitive clinical measure of cognitive function or symptom reports.

Significance of Aim 1: Research has suggested that sub-concussive impacts have a negative effect on cognition.[14,44] However, it is still largely unclear how sub-concussive effect brain activity following a season of high school football.

3.2 Participants

A total of 88 participants from two Michigan high schools were included in the Aim 1. Participants are categorized into 2 groups (46 football athletes, 42 controls). The football athletes participated in high school football between the 2013, 2014, and 2015 football seasons. Controls were either athletes who participated in a non-contact sports [i.e. track/cross country (n=8), baseball (n=8), swimming (n=1), basketball (n=8), golf (n=1), bowling (n=1), tennis (n=4)], or participants who did not participate in athletics at all (n=11). Controls were recruited from two Michigan high schools. Exclusion criteria included athletes with any known neurological disorders, those with ADD/ADHD, learning disabilities, concussions within the past 6 months, history of traumatic brain injury, skull fractures, or brain bleeds. Table 1 displays demographic information for all Aim1 participants.

Table 1 Aim 1 Demographics

Group	N	Age	Height	Weight	Diagnosed Concussions
Football Athletes	N= 46	15.89 ±0.77	179.47 ±6.66	79.77±14.11	0.35±0.67
Controls	N= 42	16.02 ±1.02	177.07±7.72	66.52±11.54	0.12±0.33
Total	N=88	15.95 ±0.90	178.33 ±7.25	73.44±14.50	0.10±0.30

3.3 Testing Protocol

Following informed parent consent and child assent, varsity football athletes were enrolled and equipped with a new or refurbished Riddell Revolution Speed helmet which was embedded with the Head Impact Telemetry System (HITS) encoder that recorded all impacts during normal football participation without intervention by investigators. Football athletes were fitted with the system starting with first string varsity athletes at the greatest risk for injury.[17] HIT System data stored the location and magnitude of all impacts sustained for each football athlete and used for later analysis.

All enrolled participants were asked to complete a battery of tests at three time points: pre-season, mid-season, and post-season. The assessment battery included a demographics questionnaire that encompassed the FITBIR TBI Common Data Elements (e.g. age, height, weight, race, gender, etc.) and other variables of interest (e.g. medications, caffeine use, sleep, family history of migraines, etc.), Electroencephalography (EEG) during a three-stimulus auditory oddball cognitive task, Axon cognitive performance test, clinical reaction time task, two Health Related Quality of Life surveys (Satisfaction With Life, and Health Behavior Inventory), and symptom inventory (described below). Pre-season testing was completed through the summer months and ended prior to any pre-season practices (June to mid-August). Throughout the 9-week regular football season (September to early-November), each athlete was randomly selected (without replacement) to complete the testing procedure again. At the conclusion of the competitive season, all athletes were tested again on the assessment battery (November to December).

3.4 Instrumentation

3.4.1 Helmet Impact Telemetry (HIT) System

The Head Impact Telemetry (HIT) System (Sideline Response System, Riddell Inc, Elyria, OH) was used to measure biomechanical factors associated with head impacts from practices and games during three football seasons (2013-2015). The device consists of two units: the encoder located within the helmet and a laptop computer for data storage and processing. In addition, there was a sideline receiver that communicates with each individual player unit. The individual player encoders are composed of six thimble sized single-axis accelerometers recording at 1000Hz, one temperature sensor, a telemetry unit and data storage device, and battery pack. The memory device can record and store 100 impacts when out of range of the sideline computer. The components are sealed in waterproof plastic and retrofitted between the pads of a Riddell

Revolution Speed football helmet. Upon impact, a sideline computer receives the transmitted signals and stores the data for later analysis. The sideline computer receives impact data from up to 100 players up to 150 yards away. The data available from the software contains all pertinent impact data including: peak linear acceleration, rotational acceleration, impact duration, location, time stamp, Gadd Severity Index (GADD)[133], Head Injury Criterion (HIC),[132] and Head Injury Severity Profile (HITsp).[131] HIT System equipped helmets look and function identically to other helmets and meet National Operating Committee on Standards for Athletic Equipment (NOCSAE) safety standards. The HIT system has been deemed to be reliable for recording linear acceleration, rotational acceleration and impact location in football.[209] In addition, the accuracy of the HIT system has been significantly studied[137-139] suggesting that the HIT system is valid for monitoring head impacts when compared to Hybrid III using Anthromorphic Test Dummy's.

3.4.2 Electroencephalography (EEG)

Neuroelectric data were collected using a EGI 256 channel Ag-AgCl wet lead cap and a 300-amp amplifier (Electrical Geodesics, Inc., Eugene, OR) using standard procedures, electrode placement, and cleaning procedures outlined by the *Geodesic Sensor Net Technical Manual*.[210] Data were recorded a rate of 256 Hz. (processing described below)

3.4.2.a Oddball Task

The 3-stimulus auditory oddball task (Target, Frequent and Novel) asked participants to respond as quickly and accurately as possible using a hand push-button, which was only to be pressed when an infrequent (target) stimulus was presented, while ignoring all other auditory stimuli (frequent high tone and novel miscellaneous noises). The auditory oddball task had sections of 300 trials each. The target stimuli was a 1000 Hz tone presented with a probability of 10% (estimated 60 times), and Frequent, non-target stimuli was a 2000 Hz tone presented with a

80% probability (estimated 480 times). In addition to the target and non-target stimuli, a novel stimuli (e.g. phone ring, knock on door, misc. noises, etc.) occurred with a probability of 10% (estimated 60 times). Trials were presented using a headset over a total duration of 16 minutes.

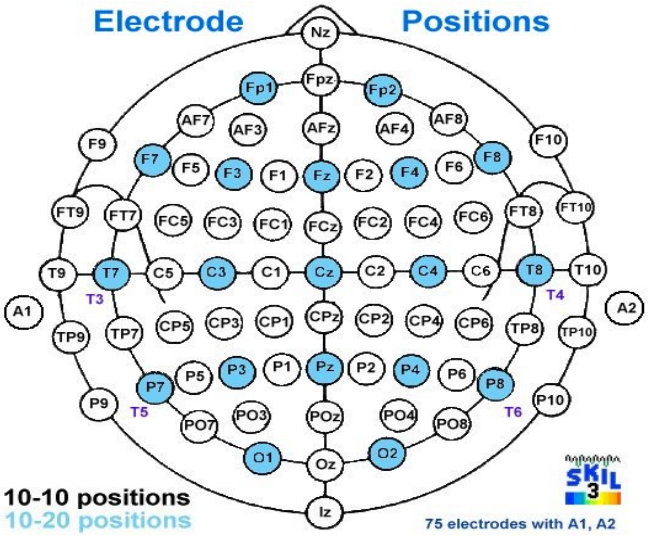


Figure 1 Electrode placement map

3.4.2.b Event Related Potentials

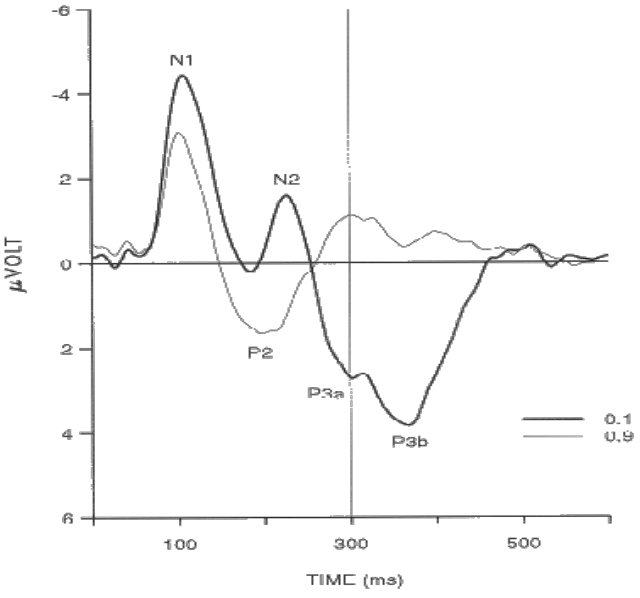
A sub-component of EEG is Event Related Potentials (ERP), which represents neural activity patterns associated with auditory or visual stimuli. Data were processed in a MatLab (Mathworks, Natick, MA) using a custom program called EEGlab developed by (UC San Diego; Swartz Center for Computational Neuroscience). Raw EEG data were referenced to average mastoid electrodes. Bad channels were identified for removal using the channel rejection tool boxes in EEGLAB (Kurtosis, Z scores threshold max 5). Rejected channels were then interpolated using Spherical Method in EEGLAB. Data were reduced from 256 to 68 channels by using a 10-20 map to identify channels. Data were then band pass filtered (0.1-30 Hz). The filtered data were epoched (-100 to 200 ms). Epochs with eye blinks or bad data were rejected. Epochs were baseline corrected using the 100-ms of EEG signal prior to the evoking stimulus.

Target epochs were extracted separately and included in analysis. Analyses were performed with data from midline electrodes (FCZ, FZ, CPZ, PZ). Figure 1 demonstrates location of midline electrodes. For P3a the electrodes FCZ and CPZ were identified due to the largest frontal and parietal distribution found, while for P3b we used electrodes CPZ and PZ for

the primary temporal and parietal amplifications. For N2, electrodes FCZ and FZ were identified because N2 is identified to be largest in the frontal or anterior scalp regions.

Three ERP components (P3a, P3b and N2), amplitude (μv) and latency (ms) were used for interpretation. The P3 component reflects allocation of attentional resources. More specifically the P3a component is generated when sufficient attentional focus is engaged during stimuli, while P3b is generated when attentional resources activate working memory.[192] The N2 components were used to identify stimulus-response conflict. The P3 component was identified by the mean amplitude within 50ms of the largest positive peak within 300-700 ms latency, which has been used in other research studies.[32] The largest negative peak between 200-350 ms was used to identify the N2 component. The time point associated with the peak amplitude for P3 and N2 defined peak latency. Figure 2 below demonstrates example ERP components.

Figure 2 ERP components



3.4.2.c ElMindA Brain Network Activation (BNA):

The BNA is a novel analysis technique that can be applied to standard EEG measures. The BNA score uses a proprietary algorithm and analysis is completed in two processing stages.

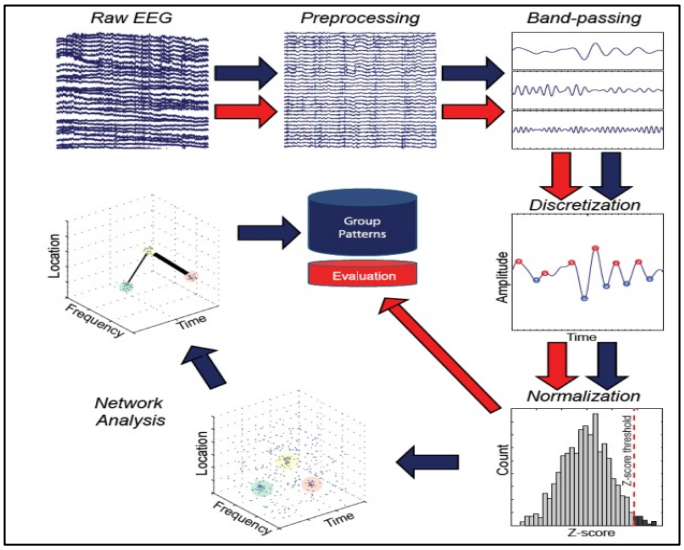


Figure 3 The process by which standard EEG signals are processed to determine brain networks associated with a given task

Figure 3 demonstrates the analysis patterns with blue arrows representing the process of analyzing group patterns and red arrows representing the process of evaluating individual participant data. In the group pattern analysis stage, raw EEG undergoes 5 steps of analysis – (1) Data preprocessing, (2) Band-passing, (3) Discretization, (4) Normalization, and (5) Network Analysis forming a set of patterns that characterize the group.[40,42] In the individual participants evaluation stage, raw EEG undergoes 5 steps of evaluation: steps (1)-(4) as performed in the group analysis stage and (5) evaluation based on a set of patterns collected during the group analysis stage.[42] The individual patterns are then compared to group patterns derived from the patient's pre-injury assessment and a BNA similarity score is generated between 0 and 100.[39-42] A low BNA score suggests the individuals scores deviates from normative values. For the purposes of this investigation, only one cognitive task was implemented to evaluate multiple aspects of brain function and connectivity: Auditory Oddball.

The task yields four unique BNA scores (Amplitude, Synchronization, Timing, and Connectivity) per stimulus (Frequent, Target, Novel) for each participant, for a total of 12 BNA scores. The BNA scores are said to represent the functional networks of the brain during a cognitive. Participants were asked to sit comfortably in a quiet room during testing. A low dim light was turned on during testing. During the testing session, participants were asked to perform the Auditory Oddball Task. Participants were instructed to minimize blinking during testing, affix their gaze on a centered location on the testing screen, and avoid excessive eye, facial and body movements.

3.4.3 Axon Sport

The Axon Sports Computerized Cognitive Assessment Tool is a concussion clinical assessment technique that has been shown to display a high sensitivity (71%) to identifying cognitive impairments following concussion.[115] Axon measures speed and accuracy of different aspects of thinking: Processing Speed, Attention, and Learning and Working Memory. Each computerized assessment displays four tasks that use playing cards and takes <15min to complete. The test was administered 3 time points: pre-season, mid-season, and post-season for aim 1 and two additional for aim 2 (72-hour post-concussion, asymptomatic).

3.4.4 Clinical Reaction Time

The clinical reaction time assessment tool is a stick drop clinical reaction time task. The clinical reaction time tool assesses cognitive and motor abilities. The tool is comprised of a 1.3 meter rod with marking every centimeter increments as well as a disk to stabilize the bottom of the stick. During testing, participants were given direction to catch the stick as quickly as possible upon release of the stick. The stick is dropped from above, parallel to the participants' hand. This assesses the participants' ability to respond to and catch the stick from a dropped

position. The participants were given two practice tests followed by eight recorded trials. The distances marked on the side of stick were recorded as the distance in centimeters. The test was administered at three time points: pre-season, mid-season and post-season. The clinical reaction time task has been deemed a valid clinical utility to measure reaction time in male football players. [122] Research has suggested clinical reaction time has a marginal test-retest reliability (ICC=0.61 and 0.69). Further studies have suggested a combined sensitivity of 75% and specificity of 68% with a 65% confidence interval to detect changes.[123]

3.4.5 Health Related Quality of Life

3.4.5.a Satisfaction with Life Scale:

The Satisfaction with Life Scale (SWL) is a 5-item Likert scale survey that assesses patients' current overall satisfaction with life based. The Likert scale ranges from strongly agree, agree, slightly agree, neither agrees nor disagree, slightly disagree, disagree, strongly disagree. The Likert scale is converted to a numerical scale ranging from 1-7 with strongly agree having a value of 7. The higher the SWL scores, the better Health Related Quality of Life the participants demonstrates. SWL has consistently been found to have a high internal reliability.[211] Lastly, SWL has been deemed valid[211,212] and highly correlated to health[213] and self esteem.

3.4.5.b Health Behavior Inventory

The Health Behavioral Inventory (HBI) is a 20-item survey assessing various personal health beliefs. There are two summation questions 1) referring to total of cognitive items and 2) referring to the total of somatic items. The survey ranges in score from 0-3. The scale uses answers of never, rarely, sometimes and often to assess behavior. The higher the score the lower the Health Related Quality Of Life the participants perceives. The HBI survey is commonly used in research and has been validated for use.[175,214]

3.4.6 Symptom Inventory

The SCAT3 Graded Symptom Checklist [26] was implemented to monitor the presence/absence of concussion related symptoms during assessment time points.[215] The symptom inventory asked the athlete if he currently had any of the 22 common concussion symptoms (e.g. headache, confusion, dizziness, etc.), and graded them on a severity scale ranging from 0-6 (none to severe). The values were summed for a total symptom score and total severity score. The higher the symptoms score the greater the number of symptoms the participant reported. In addition, if the participant was symptomatic, follow up questions were asked, to gauge if symptoms worsened with physical or mental activity, and asked for a reason for symptom presentation. The graded symptom checklist has a sensitivity of 82% and a specificity of 100%[216] and is widely used in concussion management and clinical practice. However, sensitivity of the graded symptom checklist decreases over injury timeline.[217] A graded symptom checklist is recommended in current consensus guidelines.[24-26,46]

3.5 Aim 1 Statistical Analysis

Statistical analyses was completed using SPSS version 21 (SPSS Inc, Chicago, Illinois, USA) and significance noted when $p < 0.05$. Prior to analysis, any athlete sustaining a concussion during football participation was removed from the Aim 1 analysis and moved into the Aim 2 dataset (n=18) (see below).

Primary analysis includes a mixed measures analysis of variance (ANOVA), with time as a repeated measures and group (football-athletes and control) as a between subjects factor was completed for Axon performance, clinical reaction time, Health Related Quality of life (SWL and HBI), Symptom Inventory and BNA scores generated from the Auditory Oddball cognitive task. Violations of sphericity were corrected using Greenhouse Geisser corrections. Further

significant findings warranted post-hoc analyses using Tukey's honestly significant difference (HSD) tests and Bonferroni correction. Further a mixed model analysis of variance was performed with time (pre-season and post-season) as a repeated measure and group (Football-athletes and controls) as a between subjects factor for Target and Frequent peak amplitude and latency for P3a, P3b, N2 in the following electrodes FCZ, FZ, CPZ, PZ. In addition, a mixed model ANOVA was used to analyze Auditory Oddball Task performance Reaction Time and response accuracy for group (Football-athletes, controls) and time points (pre-season and post-season). Significant findings warranted post-hoc analysis using Tukey's honestly significant difference (HSD) tests. A total of 8 football athletes and 6 control subjects were removed from analysis due to incomplete data sets and missing data points for a total of 38 football athletes and 36 control subjects.

A secondary analysis was completed using a stepwise regression analysis will be performed to predict BNA score, Event related potential amplitude and latency, and clinical assessment differences from pre-season and post-season assessment points based on impact data captured by the HIT System summarized up to the point of testing (Total season impacts, Cumulative linear acceleration, Cumulative Rotational acceleration). A step-wise regression was used for analysis in order to sequence the predictor variables by starting with no variables in the model, then adding in each variable into the model, and continuing to add variables that improve the model and best predicts the variables.

3.6 Aim 1 Results

3.6.1 Impact Data

A total of 30,425 head impacts were recorded for football athletes during a single season of football (2013season: n= 13,603; 2014season: n= 6,288; 2015season: n = 10,534). Football athletes sustained an average of 482.94 head impacts per season (2013 season = 680.15; 2014

season = 349.33; 2015 season = 421.36). Football athletes sustained an average linear acceleration of 27.41g and a median linear acceleration of 22.3g per impact. Football athletes sustained an average rotational acceleration of 1,214.24 rad/s^2, a median rotational acceleration of 1,052.85 rad/s^2. Football athletes also sustained an average HITsp of 16.41, median HITsp of 14.7. Further head impact measures are displayed in Table 2 and Table 3 by season and football positions.

Table 2 Aim 1 Head impacts per season

	Totals	**2013 Season (n=19)**	**2014 Season (n=15)**	**2015 Season (n=12)**
Total cumulative impacts	30,425	13,603	6,288	10,534
Average season impacts	482.94	680.15	349.33	421.36
Practice impacts	17,739	8,099	3,254	6,386
Game impacts	12,686	5,504	3,034	4,148
Mean Linear acceleration (g)	27.41	27.20	26.83	28.02
Mean Rotational acceleration (rad/s^2)	1,214.24	1,203.37	1,218.03	1,226.00
Mean HITsp	16.41	16.21	16.86	16.40
Mean HIC	13.78	13.35	13.13	14.73
Mean GSI	24.25	20.12	33.66	29.97

Table 3 Aim 1 Head impacts by football position

	Linemen (n=13)	**QB (n=1)**	**WR/S/Corners (n=13)**	**RB/TE/LB (n=19)**
Practice impacts	8,882	176	2,315	6,366
Game impacts	5,172	279	2,050	5,185
Total impacts	14,054	455	4,365	11,551
Mean linear acceleration	27.05g	29.36g	26.11g	27.46g
Mean rotational acceleration	1,183.70 rad/s^2	1,337.38 rad/s^2	1,205.73 rad/s^2	1,249.76 rad/s^2
Mean HITsp	16.19	17.42	16.04	16.79
Mean HIC	13.49	18.68	13.07	14.22
Mean GSI	21.89	26.39	19.37	28.89

3.6.2 Mixed Measures Analysis of Variance: Primary analysis

3.6.2.1 BNA Scores

3.6.2.1.a Frequent Amplitude BNA

Mixed model ANOVA was used to determine differences in Frequent Amplitude BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated no assumptions of sphericity had been violated for Frequent Amplitude BNA (p=0.83). No significant main effect for time was found for Frequent Amplitude [F (2,144 =2.00, p=0.14]. In addition, no interaction was found between group and time [F (2,144)=0.11,p=0.90], and no significant group effect was found for Frequent Amplitude [F (1,72)= 0.20, p=0.66]. Mean Frequent Amplitude BNA by group scores are presented in Table 4.

3.6.2.1.b Frequent Synchronization BNA

Mixed model ANOVA was used to determine differences in Frequent Synchronization BNA score across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated no assumptions of sphericity had been violated for Frequent Synchronization BNA (p=0.18). A significant main effect for time was found for Frequent Synchronization [F(2,144)= 7.07, p=0.01], with post-hoc analysis indicating significantly higher Frequent Synchronization scores at post-season (80.09 ±14.10) compared to pre-season (74.04 ±18.86). In addition, post-hoc analysis indicated significantly (p=0.03) higher post-season scores (80.09± 14.10) for Frequent Synchronization compared to mid-season Frequent Synchronization (75.43± 17.76). No interaction was found between group and time [F(2,144)=1.48, p=0.23]. Lastly, no significant group effects were found for Frequent Synchronization [F (1,72)=0.31,p=0.58]. Mean Frequent Synchronization BNA by group scores are presented in Table 4.

3.6.2.1.c Frequent Timing BNA

Mixed model ANOVA was used to determine differences in Frequent Timing BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated no assumptions of sphericity had been violated for Frequent Timing BNA ($p=0.09$). A significant main effect for time was found for Frequent Timing [$F(2,144)= 4.24$, $p=0.02$], with post-hoc analysis indicating significantly ($p<0.01$) higher BNA Frequent Timing scores at post-season (72.80± 20.24) compared to pre-season (66.34 ±26.76). No interaction was found between group and time [$F(2,144)= 1.07$, $p=0.35$). Lastly, no significant group effects were found for Frequent Timing [$F(1,72)=1.42$, $p=0.23$]. Mean Frequent Timing BNA by group scores are presented in Table 4.

3.6.2.1.d Frequent Connectivity BNA

Mixed model ANOVA was used to determine differences in Frequent Connectivity BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated no assumptions of sphericity had been violated for Frequent Connectivity BNA ($p=0.43$). A significant main effect for time was found for Frequent Connectivity [$F(2,144)= 3.53$, $p=0.03$], with post-hoc analysis indicating significant ($p=0.04$) higher Frequent Connectivity post-season scores (73.57± 11.42) compared to pre-season (70.22± 16.07) . No interaction was found between group and time [$(2,144)=1.07$,$p=0.33$]), and lastly, no significant group effects were found for Frequent Timing [$F(1,72)=1.44$,$p=0.23$]. Mean Frequent Connectivity BNA by group scores are present in Table 4.

3.6.2.1.e Target Amplitude BNA

Mixed model ANOVA was used to determine differences in Target amplitude BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated a violation of sphericity was present for Target Amplitude ($p<0.01$, $W(2)=0.82$), Therefore, a Greenhouse Geisser correction was used. A significant main effect for time was present for Target Amplitude [$F(1.70,122.38)= 3.34$, $p=0.05$], with post-hoc analysis indicating significant ($p<0.01$) decrements were present between post-season Target Amplitude (52.50 ± 32.86) and pre-season (61.31± 25.83). In addition, post-hoc analysis revealed significant ($p=0.04$) decrements in Target Amplitude BNA scores between pre-season (61.31± 25.83) and mid-season (52.50 ±32.86). No significant interactions [$F(1.70,122.38)=0.05$, $p=0.93$] or group effects [$F(1,72)=3.26$,$p=0.08$] were present for Target Amplitude. Mean Target Amplitude BNA by group scores are presented in Table 4.

3.6.2.1.f Target Synchronization

Mixed model ANOVA was used to determine differences in Target Synchronization BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated a violation of sphericity was present for Target Synchronization ($p=0.30$). No significant main effect for time was noted for Target Synchronization [$F(2,144)=0.45$, $p=0.64$]. In addition, no interaction [$F(2,144)=0.38$,$p=0.69$) or group effect [$F(1,72)=2.67$, $p=0.11$] was present for Target Synchronization. Mean Target Synchronization BNA by group scores are presented in Table 4.

3.6.2.1.g Target Timing

Mixed model ANOVA was used to determine differences in Target Timing BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated a violation of sphericity was present for Target Timing (p=0.07). No significant main effect for time was noted for Target Timing [F(2,144)=0.20 p=0.82]. In addition, no interaction [F(2,144)=1.23 p=0.30] or group effect [F(1,72)=1.44, p=0.23] was present for Target Timing. Mean Target Timing BNA by group scores are presented in Table 4.

3.6.2.1.h Target Connectivity

Mixed model ANOVA was used to determine differences in Target amplitude BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated a violation of sphericity was present for Target Connectivity (p<0.01). Therefore, a Greenhouse Geisser correction was used. No significant main effect for time was present for Target Connectivity [F(1.73,124.56)=0.51, p=0.60] No interaction [F(1.73,124.56)=0.53, p=0.57] or group effect [F(1,72)=3.41, p=0.07] was found for Target Connectivity. Mean Target Connectivity BNA by group scores are presented in Table 4.

3.6.2.1.i Novel Amplitude BNA

Mixed model ANOVA was used to determine differences in Novel Amplitude BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated a violation of sphericity was not present for Novel Amplitude (p=0.81). No significant main effect for time was found for Novel Amplitude [F(2,144)=2.93, p=0.06). No significant interaction

[F(2,144)=0.27,p=0.77], or group effect [F(1,72)=0.06,p=0.81] was present for Novel Amplitude. Mean Novel Amplitude BNA by group scores are presented in Table 4.

3.6.2.1.j Novel Synchronization

Mixed model ANOVA was used to determine differences in Novel Amplitude BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated a violation of sphericity was not present for Novel Synchronization (p=0.65). A significant main effect for time was found for Novel Synchronization [F(2,144)= 5.51, p=0.01], with post-hoc analysis indicating significantly larger Novel Synchronization scores at post-season (67.81 ± 24.87) compared to pre-season (57.67 ± 29.62). Additionally, post-hoc analysis indicated significantly higher scores at post-season (67.81 ± 24.87) Novel Synchronization compared to mid-season (60.43 ±33.73). No significant interactions [F(2,144)=0.78, p=0.46), or group effects [F(1,72)=2.96, p=0.09] were present for Novel Synchronization. Mean Novel Synchronization BNA by group scores are presented in Table 4.

3.6.2.1.k Novel Timing

Mixed model ANOVA was used to determine differences in Novel Amplitude BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated a violation of sphericity was present for Novel Timing (p=0.01,W (2)=0.86). Therefore, a Greenhouse Geisser correction was used. No main effect for time was found for Novel Timing [F(1.76,126.77)=,p=0.07). No significant interaction [F(1.76, 126.77)=0.29,p=0.72], or group effect [F(1,72=0.06,p=0.81] was present for Novel Timing. Mean Novel Timing BNA by group scores are presented in Table 4.

3.6.2.1.l Novel Connectivity

Mixed model ANOVA was used to determine differences in Novel Connectivity BNA scores across the three time points (pre-season, mid-season and post-season) as well as in comparison between football and control groups. Mauchleys test indicated a violation of sphericity was not present for Novel Connectivity ($p=0.22$). A significant main effect for time was found for Novel Connectivity [$F(2,144)= 5.32$, $p=0.01$], with post-hoc analysis indicating significantly higher Novel Connectivity performance at postseason (68.47 ± 21.32) compared to pre-season (59.65 ± 28.18). No interaction [$F(2,144)=0.58$,$p=0.56$] or group effects were present for Novel Connectivity [$F(1,72)=0.61$, $p=0.44$]. Mean Novel Connectivity BNA by group scores are presented in Table 4.

Table 4 Aim 1 BNA output scores means and standard deviations

Group	Pre-season	Mid-season	Post-season
Frequent Amplitude	(Mean± STD)	(Mean ±STD)	(Mean ±STD)
Football Athletes	71.15 ± 22.60	66.26 ± 26.62	68.26 ± 27.67
Controls	69.41 ± 18.53	62.68 ± 27.69	67.37 ± 23.56
Total	70.30 ± 20.60	64.52 ± 27.02	67.83 ± 25.57
Frequent Synchronization			
Football Athletes	71.72 ± 19.04	75.93 ± 17.45	79.10 ± 15.03
Controls	76.48 ± 16.63	74.91 ± 18.32	81.13 ± 13.18
Total	**74.04 ± 18.86***	**75.43 ± 17.76***	**80.09 ± 14.10***
Frequent Timing			
Football Athletes	67.62 ± 28.54	73.56 ± 23.55	75.65 ± 18.83
Controls	64.98 ± 25.08	64.44 ± 24.55	69.79 ± 23.17
Total	**66.34 ± 26.76***	**69.13 ± 24.32**	**72.80 ± 20.24***
Frequent Connectivity			
Football Athletes	70.16 ± 17.17	71.92 ± 15.05	74.33 ± 12.17
Controls	70.29 ± 15.08	67.32 ± 15.35	72.76 ± 10.69
Total	**70.22 ± 16.07***	**69.69 ± 15.27**	**73.57 ± 11.42***
Target Amplitude			
Football Athletes	65.36 ± 29.96	57.54 ± 30.24	56.99 ± 33.09
Controls	57.04 ± 25.36	46.78 ± 31.71	47.77 ± 32.39
Total	**61.31 ± 25.83***	**52.31 ± 31.22***	**52.50 ± 32.86***
Target Synchronization			
Football Athletes	59.83 ± 28.00	66.89 ± 30.02	60.34 ± 29.61
Controls	53.40 ± 31.91	53.60 ± 36.43	53.22 ± 35.28
Total	56.70 ± 29.93	60.23 ± 33.73	56.88 ± 32.47
Target Timing			
Football Athletes	67.21 ± 29.62	70.46 ± 32.35	67.79 ± 32.62
Controls	64.48 ± 29.73	56.73 ± 32.73	61.44 ± 37.38
Total	65.88 ± 29.50	63.78 ± 33.04	64.70 ± 34.92
Target Connectivity			
Football Athletes	64.13 ± 23.60	64.96 ± 25.79	61.71 ± 25.62
Controls	58.31 ± 25.54	52.37 ± 27.63	54.15 ± 29.79
Total	61.30 ± 24.57	58.84 ± 27.26	58.03 ± 27.80
Novel Amplitude			
Football Athletes	64.14 ± 30.84	63.96 ± 27.63	71.43 ± 23.31
Controls	60.74 ± 33.81	65.32 ± 32.68	69.30 ± 28.20
Total	62.49 ± 32.14	64.62 ± 29.99	70.39 ± 25.65
Novel Synchronization			
Football Athletes	63.99 ± 26.92	62.38 ± 25.42	71.88 ± 20.79
Controls	51.00 ± 31.22	57.41 ± 29.49	63.51 ± 28.21
Total	**59.67 ± 29.62***	**59.96 ± 27.40***	**67.81 ± 24.87***
Novel Timing			

Football Athletes	60.94 ± 34.09	61.85 ± 32.25	67.61 ± 31.02
Controls	56.58 ± 33.35	62.73 ± 30.75	66.76 ± 27.10
Total	**58.82 ± 33.57***	**62.28 ± 31.32**	**67.20 ± 28.98***
Novel Connectivity			
Football Athletes	63.02 ± 26.91	62.73 ± 24.05	70.31 ± 19.59
Controls	56.11 ± 29.42	61.82 ± 28.59	66.52 ± 23.12
Total	**59.66 ± 28.18***	**62.29 ± 26.18**	**68.47 ± 21.32***
Bold signifies p<0.05 * Denotes significance across time points + Signifies group differences			

3.6.2.2Event-Related Potentials

3.6.2.2.a The Target P3a component

Group-averaged Target P3a ERP amplitudes and latencies are reported in Table 5. Mixed model ANOVA was used to determine differences in P3a scores across the two time points (pre-season, and post-season) as well between football and control groups by electrodes FCZ and CPZ. Mauchleys test indicated that assumptions of sphericity had not been violated for either FCZ or CPZ electrodes (p's>0.05). A significant main effect for time was present for FCZ electrode for the Target P3a amplitude [F(1,74)=4.19, p=0.04], with post-hoc analysis indicating larger post-season P3a amplitudes (4.59 ± 6.18μv) present compared to pre-season P3a amplitude (2.94 ± 3.91μv) . No significant main effect for time was present for P3a Target FCZ latency [F(1,74)=0.24, p=0.62]. No significant main effect for time was present for Target P3a amplitude CPZ electrode component [F(1,74)=0.12,p=0.73], or CPZ latency [F(1,74)=0.28,p=0.60]. A significant interaction was present for FCZ Target P3a amplitude [F(1,74)=4.00, p=0.05]. No interaction was present for FCZ Target P3a latency [F(1,74)2.62, p=0.11]. Additionally, no interaction was present for CPZ P3a Target amplitude [F(1,744)=1.60, p=0.21] or CPZ latency [F(1,74)=1.68, p=0.20]. No significant group effect was present for FCZ P3a amplitude [F(1,74)=0.85, p=0.36]. A significant group effect was found for FCZ P3a latency [F(1,74)=4.24,p=0.04], with post-hoc analysis indicating group differences present between

football-athletes and controls at pre-season P3a latency with football-athletes (440.71 ±120.98 ms) demonstrated faster latencies than controls (529.50±143.19ms). No significant group effect was present for CPZ P3a Target amplitude [F(1,74)=0.04, p=0.84] or latency [F(1,74)=0.15, p=0.70]. Figures 4 and 5 displays FCZ and CPZ amplitudes and latency over time between groups.

Table 5 Aim 1 Target P3a ERP means and standard deviations

Group	Pre-season	Post-season
FCZ P3a Amplitude	**(Mean± Std)**	**(Mean± Std)**
Football Athletes	2.75 ±4.10	5.52 ±4.81
Controls	3.23 ±3.67	3.25± 7.65
Total	**2.94 ±3.91***	**4.60 ±6.18***
CPZ P3a Amplitude		
Football Athletes	8.79 ±5.07	9.82 ±5.79
Controls	9.38±4.01	8.80±6.01
Total	9.03 ±4.65	9.41 ±5.87
FCZ P3a latency		
Football Athletes	**440.71 ±120.98^{+}**	484.80 ±140.05
Controls	**524.65±142.86^{+}**	501.16 ±150.03
Total	474.95 ±135.92	491.47 ±143.44
CPZ P3a latency		
Football Athletes	414.13 ±91.61	432.11± 89.79
Controls	436.52 ±107.04	415.10± 91.09
Total	423.26 ±98.13	419.84 ±89.81
BOLD signifies p<0.05 *** Denotes significance across time points** **+ Signifies group differences**		

Figure 4 Aim 1 Pre-season and post-season football-athletes vs. controls comparisons for FCZ average ERP

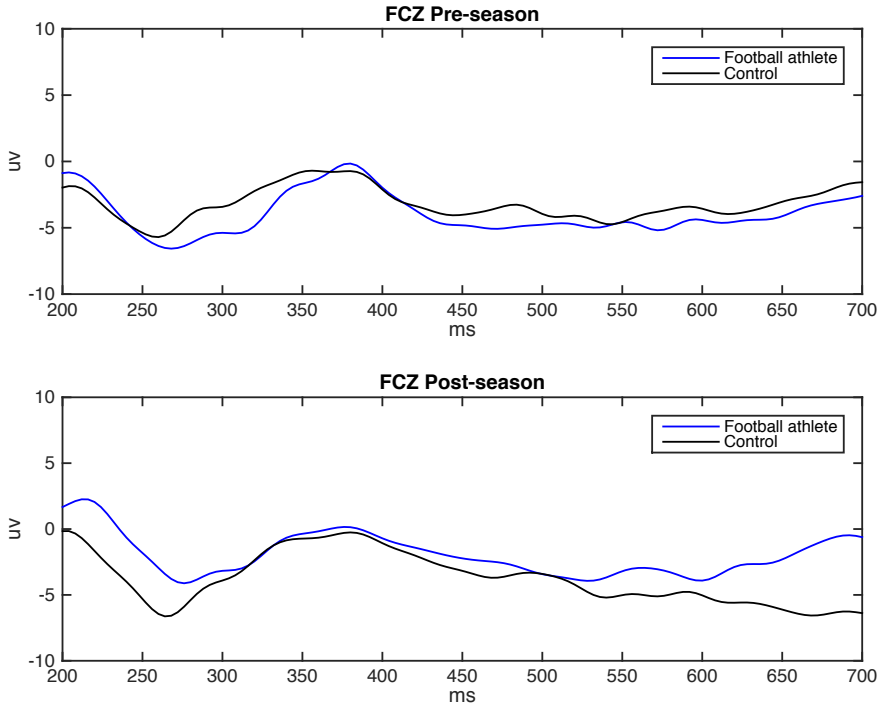
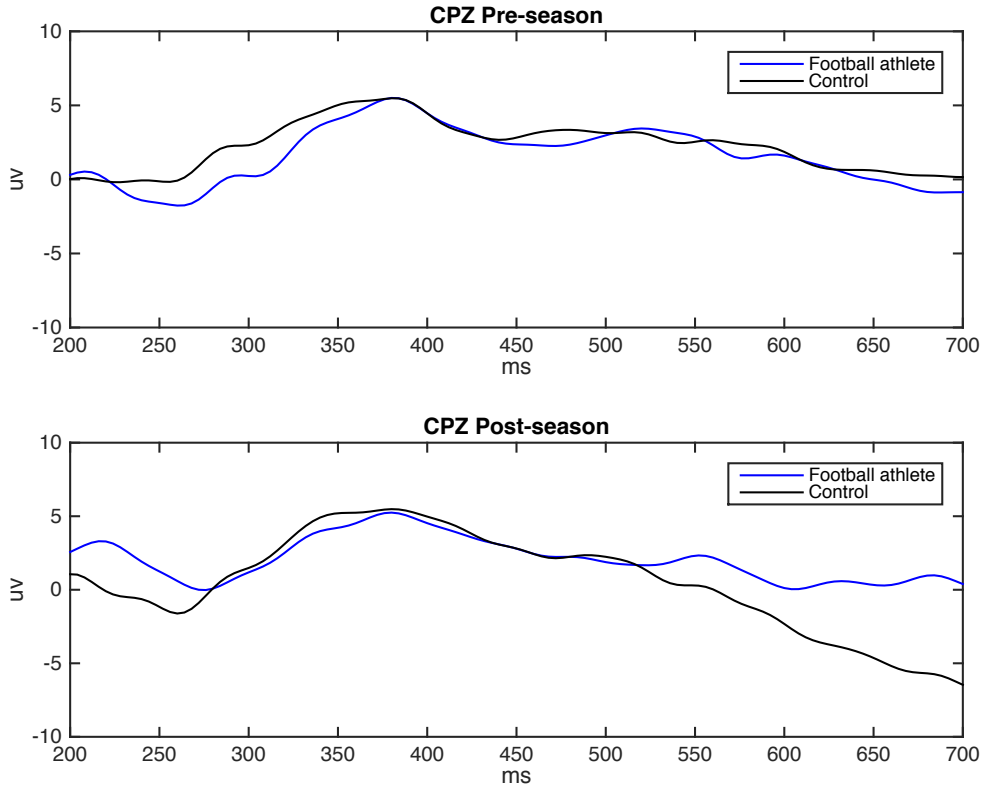


Figure 5 Aim 1 Pre-season and post-season football-athletes vs. controls comparisons for CPZ average ERP (P3a waves between 300-700ms)



3.6.2.2.b The Target P3b component

Group-average Target P3b ERP amplitudes and latencies are reported in Table 6.

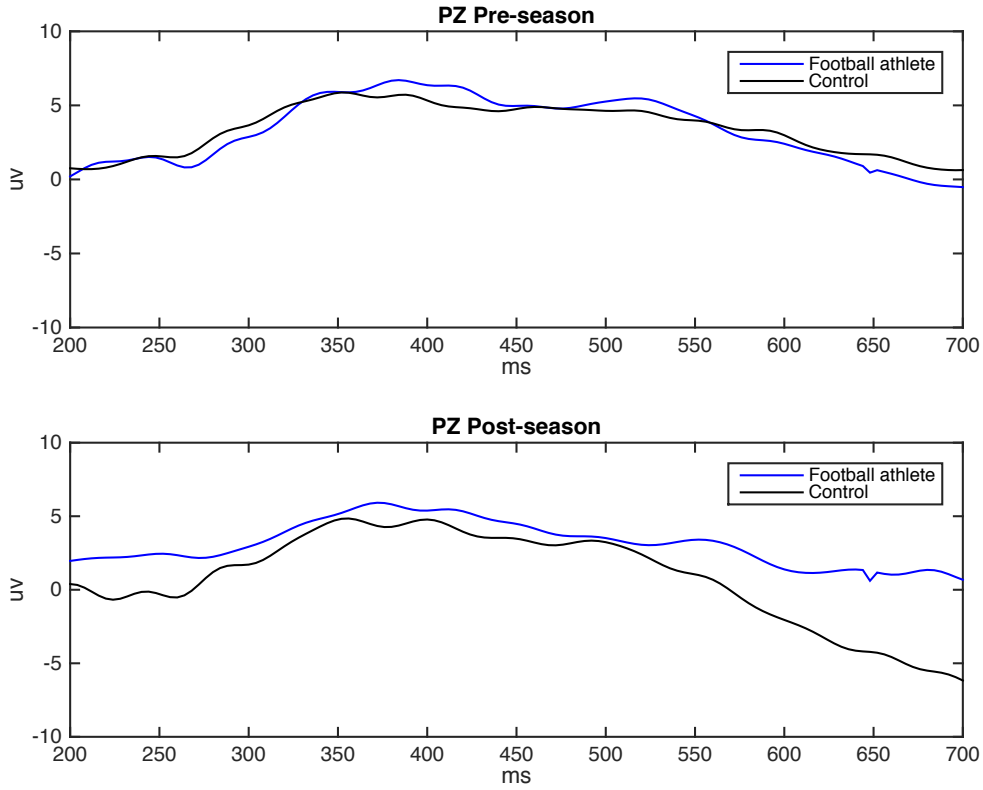
Following a Mixed model ANOVA, Mauchleys test indicated that assumptions of sphericity had not been violated for either CPZ or PZ electrodes amplitude or latency (p's>0.05). No significant main effect for time was present for CPZ target P3b amplitude [F(1,74)= 0.12, p=0.73] or latency [F(1,74)=0.28, p=0.60]. No significant main effect for time was present for PZ target P3b amplitude [F(1,74)=1.08, p=0.30], or latency [F(1,74)=0.59, p=0.44]. Additionally, no interaction between time and group was present for CPZ Target P3b amplitude [F(1,74)=1.60, p=0.21] or latency [F(1,74)=1.68, p=0.20], or between PZ P3b amplitude [F(1,74)=0.12, p=0.73]

and latency [F(1,74)= 0.09, p=0.76]. No significant group effect was present for CPZ target amplitude [F(1,74)= 0.04p=0.84], CPZ Target P3b latency [F(1,74)= 0.15, p=0.70], PZ target P3b amplitude [F(1,74)=1.56, p=0.22], or PZ target P3b latency [F(1,74)=0.85, p=0.36]. Figures 5 and 6 display CPZ and PZ amplitudes and latency over time between groups.

Table 6 Aim 1 Target P3b ERP means and standard deviations

Group	Pre-season	Post-season
CPZ P3b Amplitude	**(Mean± Std)**	**(Mean± Std)**
Football Athletes	8.79 ±5.07	9.82 ±5.79
Controls	9.38±4.01	8.80±6.01
Total	9.03 ±4.65	9.41 ±5.87
PZ P3b Amplitude		
Football Athletes	10.15 ±5.78	9.78± 5.38
Controls	9.02± 3.56	8.27± 4.83
Total	9.69± 5.00	9.16± 5.18
CPZ P3b Latency		
Football Athletes	414.13 ±91.61	432.11± 89.79
Controls	436.52 ±107.04	415.10± 91.09
Total	423.26 ±98.13	419.84 ±89.81
PZ P3b latency		
Football Athletes	418.04± 66.70	431.64± 90.34
Controls	435.87 ±95.29	441.81 ±88.33
Total	425.32 ±79.48	435.79 ±89.07
BOLD signifies p<0.05 *** Denotes significance across time points** **+ Signifies group differences**		

Figure 6 Aim 1 Pre-season and post-season football-athletes vs. controls comparisons for PZ average ERP (P3b waves between 300-700ms)



3.6.2.2.c The Target N2 component

Group-average Target N2 ERP amplitudes and latencies are reported in Table 7.

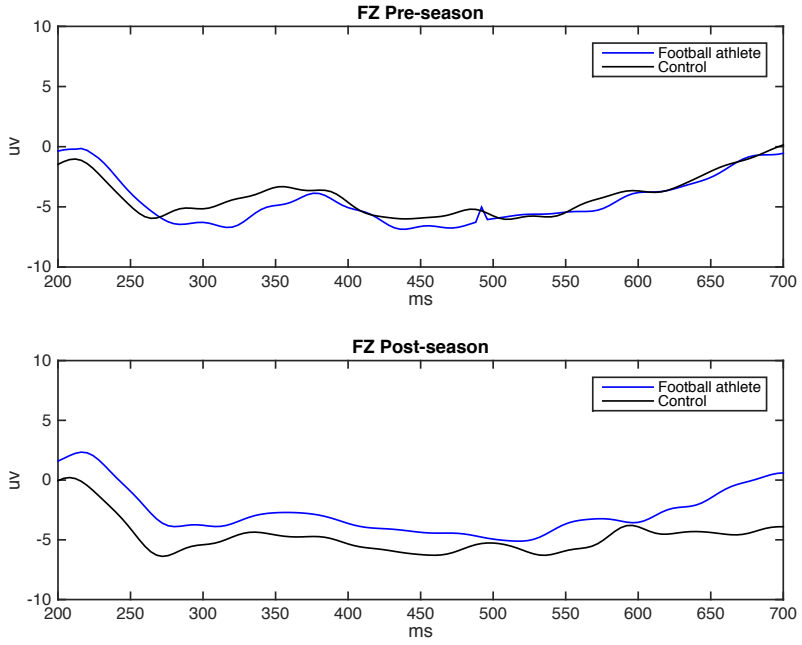
Following Mixed model ANOVA, Mauchleys test indicated that assumptions of sphericity had not been violated for either FCZ or FZ electrodes N2 amplitude or N2 latency (p's>0.05). No significant main effect for time was present for FCZ electrode during N2 amplitude [F(1,74)=0.06,p=0.82], FCZ N2 latency [F(1,74)=0.19,p=0.66], or FZ N2 amplitude [F(1,74)=0.00,p=0.99]. A significant main effect for time was present for FZ Target N2 latency

[F(1,72)= 6.76, p=0.01], with post-hoc analysis indicating longer FZ Target N2 latencies at post-season (298.86 ±37.26 ms) compared to pre-season N2 latency (284.76 ± 36.47 ms). Additionally, no interaction between time and groups was present for FCZ N2 amplitude F(1,74)=2.18, p=0.14] or FCZ N2 latency F(1,74)=0.56,p=0.46], or FZ N2 amplitude [F(1,74)=3.54,p=0.06], FZ N2 latency [F(1,74)=0.13,p=0.72]. No significant group effect was present FCZ N2 amplitude [F(1,75)=0.00,p=0.95], FCZ N2 latency [F(1,74)=2.74,p=0.10], FZ N2 amplitude [F(1,74)=0.12,p=0.74], or FZ N2 latency [F(1,74)=3.02,p=0.09]. Figures 4 and 7 display FCZ and FZ amplitudes and latency over time between groups.

Table 7 Target N2 ERP means and standard deviations

Group	Pre-season	Post-season
FCZ N2 Amplitude	**(Mean± Std)**	**(Mean± Std)**
Football Athletes	-8.85 ± 3.69	-7.72 ± 6.10
Controls	-7.57 ± 4.17	-9.14 ±10.03
Total	-8.34 ± 3.92	-8.30 ± 7.91
FZ N2 Amplitude		
Football Athletes	-9.18 ± 4.24	-7.10 ± 4.92
Controls	-7.51 ± 4.13	-9.56 ± 11.99
Total	-8.50 ± 4.25	-8.10 ± 8.54
FCZ N2 latency		
Football Athletes	278.74 ± 28.23	277.24 ± 37.24
Controls	265.29 ± 39.54	271.48±27.97
Total	273.32 ± 33.73	274.89 ± 33.69
FZ N2 latency		
Football Athletes	290.27 ± 32.40	302.72 ± 35.80
Controls	276.67 ± 40.97	293.20± 39.24
Total	**284.76 ± 36.47***	**298.86 ± 37.26***
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences		

Figure 7 Aim 1 Pre-season and post-season football-athletes vs. controls comparisons for FZ average ERP (N2 waves between 200-350 ms)



3.6.2.3 Auditory Oddball Performance Data

Following Mixed model ANOVA for auditory oddball behavior data by time (pre-season and post-season) and by group (football athletes and controls), a significant main effect for time was present for the average number of errant tones participants acknowledged as the target tone [$F(1,75)=6.11$, $p=0.02$], post-hoc analysis indicating significant ($p=0.01$) more average errant tones (1.74 ± 4.20) during pre-season compared to during post-season testing (0.82 ± 1.51). These results suggest that following multiple tests, participants were able to more accurately identify the target tone. No significant main effect was present for average target tone reaction time [$F(1,75)=0.29$, $p=0.59$], or average percent correct [$F(1,75)=2.05$, $p=0.16$]. No interaction between time and group, was present for average reaction time [$F(1,75)=0.14$, $p=0.71$], average

errant tones [F(1,75)=1.07, p=0.30], or average response accuracy [F(1,75)=1.61,p=0.21]. Additionally, no group effects were present for average reaction time [F(1,75)=0.35), or errant tone [F(1,75)=0.31, p=0.58]. However a group difference was present for average percent correct [F(1,75)=5.63, p=0.02]. Table 8 displays means and standard deviations for groups and times.

Table 8 Aim 1 Average Auditory Oddball behavior data means and standard deviations

	Pre-season	Post-season
	(Mean ±std)	(Mean ±std)
Average Reaction Time		
Football-athletes	353.42 ±72.59	351.99 ±79.57
Controls	342.78 ±77.77	334.90 ±67.87
Totals	348.31 ±74.82	343.78± 74.19
Average Accuracy (%)		
Football-athletes	96.13± 8.92	98.38± 4.18
Controls	99.10± 1.28	99.23 ±1.08
Totals	97.55± 6.62	98.79 ±3.11
Average number Errant tones identified		
Football-athletes	2.09 ±3.27	0.80 ±1.01
Controls	1.36 ±4.97	0.84 ±1.92
Totals	**1.74 ±4.16***	**0.82 ±1.51***
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences		

When the behavioral data were analyzed by each section (Block 1=first 300 trials before break, and Block 2= second 300 trials following break), a significant main effect for time was present for response accuracy Block 1 [F(1,75)=4.35, p= 0.04], with post-hoc analysis indicating improved Block 1 response accuracy at post-season (99.39%) compared to pre-season accuracy (96.67 %). No significant interaction effect was present for Block 1 response accuracy [F(1,75)=3.24, p=0.08]. Further no group effect was present for Block 1 response accuracy [F(1,75)=3.18, p=0.08]

A significant main effect for time was found for Block 1 number of errant tones [F(1,75)=6.91, p=0.01] with post-hoc analysis indicating participants improperly identified 2.47

± 5.63 errant tones tone during pre-season testing, while only incorrectly identifying 1.01 ± 2.57 errant tones during post-season testing. A significant interaction was present between time and groups for Block 1 number of errant tones [F(1,75)=4.52, p=0.04]. No significant group effect as present for Block 1 errant tones [F(1,75)=0.81, p=0.37].

No significant main effect for time was found for Block 1 reaction time [F(1,75)= 2.87, p=0.09], Block 2 reaction time [F(1,75)=0.36, p=0.55], Block 2 response accuracy [F(1,75)=0.09,=0.77] or Block 2 errant tone [F(1,75)=0.86, p=0.36]. Additionally no significant interactions were found for Block 1 reaction time [F(1,75)=0.05, p=0.82], Block 2 reaction time[F(1,75)=0.17, p=0.68], Block 2 response accuracy [F(1,75)=0.04, p=0.85]or Block 2 errant tones [F(1,75)=0.76, p=0.39]. No significant group effects were present for Block 1 reaction time [F(1,75)=0.32, p=0.57], Block 2 reaction time[F(1,75)=1.45, p=0.23], Block 2 response accuracy [F(1,75)=3.23, p=0.08]or Block 2 errant tones [F(1,75)=0.02, p=0.89].Table 9 displays means and standard deviation for auditory oddball behavior data by blocks.

Table 9 Aim 1 Auditory Oddball Behavior data by blocks; means and standard deviations

	Pre-season	Post-season
	(Mean ±std)	(Mean ±std)
Block 1 Reaction Time		
Football-athletes	343.75 ±71.97	330.33 ±85.94
Controls	337.67 ±79.15	320.00 ±61.42
Totals	340.82 ±75.07	325.37± 74.86
Block 2 Reaction Time		
Football-athletes	363.10 ±87.59	373.5± 85.51
Controls	347.90 ±84.91	349.80± 79.27
Totals	355.79 ±86.09	362.19 ±82.90
Block 1 Accuracy (%)		
Football-athletes	94.50 ±15.05	99.42 ±1.49
Controls	99.01 ±1.90	99.37 ±1.54
Totals	**96.67 ±11.10***	**99.39 ±1.50***
Block 2 Accuracy (%)		
Football-athletes	97.75± 7.02	97.33 ±7.71
Controls	99.19± 1.65	99.19 ±1.65
Totals	98.44 ±5.20	99.39 ±1.50
Block 1 Errant tones		
Football-athletes	3.38± 6.12	0.83 ±0.90
Controls	1.49± 4.93	1.22± 3.61
Totals	**2.47 ±5.63***	**1.01 ±2.57***
Block 2 Errant tones		
Football-athletes	0.80 ±1.16	0.78 ±1.87
Controls	1.24± 5.07	0.46 ±0.69
Totals	1.01 ±3.59	0.62 ±1.43
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences		

3.6.2.4 Axon

3.6.2.4.a Axon Processing Speed

Mixed model ANOVA was used to determine differences in Axon processing speed scores across the three time points (pre-season, mid-season and post-season) as well between football and control groups. Mauchleys test indicated that assumptions of sphericity had not been violated (p=0.07). No main effect for time was present for Axon Processing Speed [F(2,144)=0.63,p=0.54]. No interaction between time and groups was present [F(2,144)=1.36,

p=0.26]. However, a significant group effect was present [F(1,72)=11.21, p<0.01], with post-hoc analysis indicating differences between football and controls at pre-season processing speed with controls performing better than football athletes [(103.13± 5.95) vs. (106.80± 5.95)]. Additionally, post-hoc analysis indicated during post-season testing, control participants performed better than football athletes in Processing Speed [(102.52 ±6.21) vs. (106.63± 5.86)]. Table 10 displays means and standard deviation for Axon composite scores.

3.6.2.4.b Axon Attention

Mixed model ANOVA was used to determine differences in Axon Attention scores across the three time points (pre-season, mid-season and post-season) as well between football and control groups. Mauchleys test indicated that assumptions of sphericity had been violated (W(2)=0.21; p<0.01). Therefore, a Greenhouse Geisser Correction was used. However, no main effect for time was present for Axon Attention [F(1.12, 80.64)=2.40, p=0.12]. No significant interactions were found between time and groups [F(1.12, 80.64)=1.84, p=0.18]. In addition no significant group effect was present for Axon Attention [F(1,72)=0.34, p=0.56].

3.6.2.4.c Axon Learning

Mixed model ANOVA was used to determine differences in Axon Learning scores across the three time points (pre-season, mid-season and post-season) as well between football and control groups. Mauchleys test indicated that assumptions of sphericity had not been violated (p=0.24). A significant main effect for time was found for Axon Learning [F(2,144)=21.39, p<0.01], with post-hoc analysis indicating significant improvements were present at post-season (108.95 ±10.32) compared to pre-season (102.60 ± 7.86). No interaction was present between time and groups [F(2,144)=0.35,p=0.71]. However, a significant group effect was found for axon learning [F(1,72)=5.10, p=0.03], but post-hoc analysis indicating no significant differences were present (p=0.71).

3.6.2.4.d Axon Working Memory Speed

Mixed model ANOVA was used to determine differences in Axon Working Memory Speed scores across the three time points (pre-season, mid-season and post-season) as well between football and control groups. Mauchleys test indicated that assumptions of sphericity had not been violated (p=0.62). A significant main effect for time was found for Working Memory Speed [F(2,144)=9.54, p<0.01], with post-hoc analysis indicating significant improvements during post-season (106.12 ± 6.24) compared to pre-season (103.47 ± 6.67). Additionally, post-hoc analysis indicated significant improvements between pre-season (103.47 ± 6.67) and mid-season testing (105.32 ± 6.37). No interaction was present [F(2,144)=2.36,p=0.10], but a significant group effect was present [F(1,72)=4.96, p=0.03]. However, following post-hoc analysis no significant group differences were noted (p=0.10)

3.6.2.4.e Axon Working Memory Accuracy

Mixed model ANOVA was used to determine differences in Axon Working Memory Accuracy scores across the three time points (pre-season, mid-season and post-season) as well between football and control groups. Mauchleys test indicated that assumptions of sphericity had not been violated (p=0.29). No main effect for time was present for Axon Working Memory Accuracy [F(2,144)=2.22,p=0.11]. No significant interaction was present between time and groups [F(2,144)=2.11,p=0.13]. Lastly, no significant main effect for group was present [F(1,72)=0.17,p=0.68].

Table 10 Aim1 Axon composite scores means and standard deviations

Group	Pre-season	Mid-season	Post-season
Processing Speed	(Mean± STD)	(Mean± STD)	(Mean± STD)
Football Athletes	**103.21 ± 4.62^{+}**	103.53 ± 5.32	**103.26 ± 5.22^{+}**
Controls	**107.04 ± 5.53^{+}**	105.28 ± 5.57	**106.62 ± 3.83^{+}**
Total	105.07 ± 5.40	104.38 ± 5.47	104.89 ± 4.87
Attention			
Football Athletes	105.45 ± 4.20	105.37 ± 4.52	106.22 ± 4.31
Controls	108.78 ± 4.45	102.73 ± 22.79	107.98 ± 4.08
Total	107.07 ± 4.61	104.09 ± 16.16	107.07 ± 4.27
Learning			
Football Athletes	101.15 ± 6.55	104.98 ± 7.51	106.91 ± 9.64
Controls	104.12 ± 8.87	109.56 ± 10.03	111.10 ± 10.71
Total	**102.60 ± 7.86***	**107.21 ± 9.06***	**108.95± 10.32***
Working Memory Speed			
Football Athletes	101.60 ± 5.74	103.68 ± 5.86	105.47 ± 5.69
Controls	**105.44 ± 7.09**	**107.05 ± 6.52**	**106.80 ± 6.79**
Total	**103.47 ± 6.67***	**105.32 ± 6.38***	**106.12 ± 6.24***
Working Memory Accuracy			
Football Athletes	100.62 ± 7.97	103.82 ± 8.39	103.75 ± 8.51
Controls	102.09 ± 7.09	101.23 ± 6.91	103.10 ± 7.94
Total	101.33 ± 7.54	102.56 ± 7.76	103.44 ± 8.19
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

3.6.2.5 Clinical Reaction Time

Mixed model ANOVA was used to determine differences in CRT across the three time points (pre-season, mid-season and post-season) as well between football and control groups. Mauchleys test indicated that assumptions of sphericity had not been violated (p=0.08). No significant main effect for time was present [F(2,144)=0.93, p=0.40], nor were any significant interactions [F(2,144)=0.33,p=0.72] or group effects [F(1,72)=0.21,p=0.65] present. Table 11 displays the means for clinical reaction time across time points and groups.

Table 11 Aim 1 Clinical Reaction Time means and standard deviations

Group	Pre-season	Mid-season	Post-season
CRT	**(Mean± Std)**	**(Mean± Std)**	**(Mean± Std)**
Football Athletes	210.01 ± 22.57	205.45 ± 20.89	204.92 ± 20.09
Controls	210.27 ± 26.01	206.55 ± 31.23	209.90 ± 27.93
Total	210.14 ± 24.14	205.97 ± 26.19	207.34 ± 24.18
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

3.6.2.6 Health Related Quality of Life: Satisfaction with Life and Health Behavior Inventory

Mixed model ANOVA was used to determine differences in HRQOL (SWL and HBI) across the three time points (pre-season, mid-season and post-season) as well between football and control groups. Mauchleys test indicated that assumptions of sphericity had not been violated for SWL (p=0.84), HBI Cognitive (p=0.08) or HBI Somatic (p=0.22). No significant main effects for time were present for SWL [F(2,144)=2.35, p=1=0.10]), or HBI cognitive [F(2,144)=0.79, p=0.46]. A significant main effect for time was present for HBI somatic [F(2,144)=3.65, p=0.03], with post-hoc analysis indicating pre-season HBI somatic scores (3.69± 2.91) were higher than post-season HBI Somatic scores (2.82 ±3.31). No significant interactions were present for SWL [F(2.144)=1.36, p=0.29), or HBI Cognitive [F(2,144)=2.13, p=0.12]. A significant interaction between group and time was present for HBI somatic [F(2,144)=3.38,p=0.04]. No significant group effects were present for SWL [F(1,72)=3.95, p>0.05], HBI Cognitive [F(1,72)=0.17, p=0.65] or HBI Somatic [F(1,72)=0.12, p=0.74].Table 12 displays means for Health Related Quality of Life scores across time and groups.

Table 12 Aim 1 Health Relation Quality of Life (SWL, HBI) means and standard deviations

Group	Pre-season	Mid-season	Post-season
SWL	**(Mean± Std)**	**(Mean± Std)**	**(Mean± Std)**
Football Athletes	30.95 ± 2.62	30.53 ± 2.98	30.61 ± 2.66
Controls	29.25 ± 4.39	28.56 ±4.87	29.53 ± 4.24
Total	30.12 ± 3.67	29.57 ± 4.11	30.08 ± 3.53
HBI Cognitive			
Football Athletes	10.13 ± 4.75	9.11 ± 5.21	8.39 ± 4.61
Controls	9.44 ± 4.57	9.44 ± 4.91	9.92 ± 5.10
Total	9.79 ± 4.64	9.27 ± 5.04	9.14± 4.88
HBI Somatic			
Football Athletes	3.13 ± 2.67	3.61 ± 3.33	2.82 ± 3.45
Controls	4.28 ± 3.08	3.08 ± 3.16	2.83 ± 3.21
Total	**3.69 ± 2.91***	3.35 ± 3.24	**2.82 ± 3.31***
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

3.6.2.7 Symptom Inventory

A Mixed model ANOVA was used to determine if there were differences in Symptom number and symptom severity across the three time points (pre-season, mid-season and post-season) as well between football and control groups. Mauchleys test indicated that assumptions of sphericity had not been violated (p's>0.05). No significant main effects for time were present for symptom number [F(2,144)=0.70, p=0.50] or symptom inventory [F(2,144)=0.33,p=0.72]. Additionally, no significant interaction was present between group and time for symptom number [F(2,144)=0.44, p=0.65] or symptom severity [F(2,144)=0.55, p=0.58]. No significant group effect was present for symptom number [F(1,72)=1.47, p=0.23] or symptom severity [F(1,72)=1.76, p=0.19]. Table 13 displays means across time-points and groups for symptom inventory.

Table 13 Symptom inventory means and standard deviations

Group	Pre-season	Mid-season	Post-season
Symptom Number	**(Mean± Std)**	**(Mean± Std)**	**(Mean± Std)**
Football Athletes	0.74 ± 1.16	0.66 ± 1.70	0.92 ± 1.82
Controls	0.61 ± 1.15	0.36 ± 0.83	0.47 ± 1.06
Total	0.68 ± 1.15	0.51 ± 1.35	0.70 ± 1.51
Symptom Severity			
Football Athletes	1.52 ± 2.28	1.32 ± 3.05	1.79 ± 3.97
Controls	0.75 ± 1.27	0.97 ± 2.50	0.78 ± 1.57
Total	1.03 ± 1.85	1.15 ± 2.78	1.30 ± 3.07
BOLD signifies p<0.05 *Denotes significance across time points +Signifies group differences			

3.6.3 Stepwise Regression Analysis:

3.6.3.a BNA Output Scores

A secondary analysis of a stepwise regression analysis was used to predict whether impact variables (total season impacts, cumulative rotational acceleration, cumulative linear acceleration and cumulative HITsp) were predictive of Pre-to post-season BNA change scores. The stepwise regression did not identify any impact variables as predictive ($p>0.05$) to any of BNA output change scores (ie Frequent Amplitude, Frequent Synchronization, Frequent Timing, Frequent Connectivity, Target Amplitude, Target Synchronization, Target Timing, Target Connectivity, Novel Amplitude, Novel Synchronization, Novel Timing, Novel Connectivity).

3.6.3.b Event-Related Potentials

A stepwise regression analysis was used to predict whether impact variables (total season impacts, cumulative rotational acceleration, cumulative linear acceleration and cumulative HITsp) were necessary to predict pre-to post-season ERP Target P3a, P3b and N2 amplitude and latency change scores, The stepwise regression did not identify any impact variables as predictive (p's>0.05) to any of ERP component scores (ie P3a amplitude, P3a latency, P3b amplitude, P3b latency, N2 amplitude, N2 latency).

3.6.3.c Clinical Assessments: Axon

A stepwise regression analysis was used to predict whether impact variables (total season impacts, cumulative rotational acceleration, cumulative linear acceleration and cumulative HITsp) were able to predict pre-to post-season clinical assessment change scores. The stepwise regression identified cumulative rotational acceleration as a predictor [$F(1,43)=4.69, p=0.04$] to Axon Processing Speed pre-to-post-season change scores. The correlation coefficient was positively correlated (0.32), indicating 10% of the variance of Axon Processing speed could be accounted for cumulative rotational acceleration, meaning greater rotational acceleration resulted in better Axon processing speed performance. The stepwise regression did not identify any impact variables as predictive (p's>0.05) to Axon Attention, Axon Learning, Axon Working Memory Speed and Axon Working Memory Accuracy, SWL, HBI, CRT and Symptom Inventory pre-post-season change scores (p's>0.05).

3.7 Discussion

The purpose of this investigation was to examine the effects of repeated head impacts on cognitive function in high school football athletes. The most significant finding was that football athletes did not demonstrate significant declines in cognitive function across a football season, and head impact exposure was not indicative of performance decrements on cognitive assessment tools. Indeed, when differences were noted data suggested improvements on multiple cognitive assessments. These findings deviate from our proposed hypotheses and from previous research that outline a negative relationship between sub-concussive head impacts and functional and structural brain changes.[14,44,74,218] Two proposed theories may contribute to the overall study findings. First, decrements in cognition may be present following a football season, but benefits from physical activity may reduce any negative effects associated with repeated

head impacts. Secondly, participation in one season of high school football does not result in immediate cognitive function decrements.

Previous research has suggested repeated head impacts are associated with changes to the brain.[14,44,74,218] These particular studies used advanced imaging techniques such as functional Magnetic Resonance Imaging (fMRI), and Diffusion Tensor imaging (DTI) to demonstrate a relationship between changes in brain function and sub-concussive head impacts.[74,218] In an investigation by Bazarian et al[218] participants underwent DTI testing at pre-season and then follow-up testing at the end of the sport season. The researchers found a 1% change in pre-to post-season fractional anisotropy in sub-concussed athletes, while controls displayed a white matter change difference of 0.5%. Furthermore, McAllister et al[74] found structural brain changes in white matter resulting from sub-concussive head impacts, with group differences present in mean diffusivity (MD) in the corpus callosum. Overall, DTI studies have found structural white matter changes to be associated with repeated head impacts. Despite the evidence from previous research, the current study did not find negative changes associated with cognitive function in a football season. More importantly, this study did not investigate structural changes, but rather investigated functional changes associated with cognition.

Research on functional sub-concussive head impact has demonstrated relationship between repeated head impact exposure and brain activation changes at testing time points during sports participation.[14,44] An investigation by Talavage et al[14] explored the effects of repeated head impacts in high school football athletes using fMRI. Their results found four sub-concussed participants displayed consistent fMRI scans across the season, while four sub-concussed participants displayed decreased fMRI activation in the dorsolateral prefrontal cortex and cerebellum. This study supports the theory that head impact exposure may be related to

decreased brain activation, however, not all sport participants display activation changes as a result of head impact exposure. Breedlove et al[44] also studied high school football players (n=24) over two seasons using fMRI to measure cognitive function, and found repeated head impact exposure was correlated to neurophysiological brain changes in areas associated with working memory. These findings provide evidence that sub-concussive head impacts may lead to functional neurophysiological changes.

Although previous research has suggested a negative relationship is present following multiple head impacts, the current study findings differ from the literature. Instead, no negative relationship was present between cognitive performance and head impact exposure. Additionally, when changes were noted improvements were present. Consistent with study findings, current research suggests participation in physical activity is associated with greater cognitive function.[219,220] More specifically, the current study displayed larger P3a amplitudes at post-season testing, which is consistent with literature findings of larger P3 amplitudes and improvement on cognitive tasks following physical activity performance.[221,222] Pontifex et[221] al found participants who performed a single bout of exercise prior to testing, demonstrated either consistent or improved attentional processing, compared to attentional processing decrements found in participants who were sitting and not participating in exertion. Additionally, Hillman et al[223] and Pontifex et al[221] both analyzed P3 amplitudes in youth following physical activity participation and found those with more physical activity participation demonstrated larger P3 amplitudes, while lower physical activity participants demonstrated smaller P3 amplitudes. Increased attentional resource allocation, and improve cognitive performance is associated with greater physical activity participation,[224,225 221] therefore supporting our current study findings.

Furthermore, research has found youth involved in exercise intervention programs displayed overall improvements in cognitive performance and cognitive control.[2,223,226] Cognition encompasses working memory processing and attentional abilities.[2] Therefore, the implementation of physical activity enhances overall cognitive performance and improvements on processing abilities. Likewise, the current study demonstrated increased learning and working memory speed. Therefore, study improvements displayed over time are similar to other research findings that monitor cognitive control and cognitive function.[2,223,226] Specifically, following a 9-month physical activity intervention program, those with more physical activity demonstrated enhanced cognitive performance, enhanced brain function, executive control and improved working memory compared to controls.[2,223,226] Lastly, youth who participated in physical activity demonstrated similar anterior frontal brain activation patterns and similar incorrect response accuracy compared to young-adult subjects.[226] These findings suggest physical activity improves overall cognitive function. Overall, an increase in physical activity has been shown to improve cognitive control, and larger early allocation for selective attentional resources.[2,223,227,228] The benefits of physical activity have been shown to have greater effects on cognition in youth and young adults, contributing to reducing any negative effects resulting from repeated head impacts. An increase in number of head impacts may be indicative that the athletes were more physically active, thus alluding to the idea that physical activity may contribute to increase in cognitive performance, and weaken from any effects of repeated head contacts.

Findings from this study can additionally be supported by the theory that cognitive decrements are not present as a result of repeated head impacts sustained during a football season. Current study findings found no in-season changes present in six out of twelve BNA output scores, P3b amplitude, P3a latency, P3b latency, N2 amplitude, axon processing speed,

axon attention and axon working memory accuracy performance, clinical reaction time, symptom number and severity. Specifically, 50% of the BNA performance scores suggest no brain networks changes were associated with testing time. Additionally, no in-season amplitude or latency changes for the current study suggest that contact athletes are using the same amount of attentional resources during the cognitive task to perform the stimulus at both pre-season and post-season. Both football athletes and control participants were able to remain consistent in appropriately identifying the target stimulus similarly during each testing time point. Current findings are consistent with Wilson et al[203] who found no differences in P3b amplitude between first year football athletes and control participants during one season. However, when further analyzing the data, Wilson et al[203] found third and fourth year players to display smaller P3b amplitudes than first year players and controls. These findings suggest multiple years of subsequent head impacts may result in decreased P3b amplitude and decreased attentional resources, but less impact exposure may not display electrophysiological changes.

Negative effects associated with repeated head impact exposure and Axon performance were not present following one season of football. Results from this study are similar to Miller et al,[229] who found no significant differences across pre-season, mid-season and post-season testing in athletes without a concussion using Axon as a clinical measurement tool. Similarly, despite using a different neurocognitive test (ANAM), Gysland et al[69] found no neurocognitive changes were present following a college football season. Talavage et al,[14] found no significant football season decrements in brain activity using ImPACT computerized neurocognitive testing. Overall, negligible findings suggest decrements in neurocognitive performance may not be present in one season football.

Clinical reaction time is another assessment tool able to measure cognitive declines with poor performance representing slower reaction time. The current study, did not find slower reaction time performance across testing time points, and did not detect any subtle changes that may be present due to repeated head impacts. These findings suggest clinical reaction time decrements may not be present following a season of contact sport participation.

Furthermore, the current study found a significant decrement in HBI somatic scores at post-season testing compared to pre-season. These changes found lower HBI somatic scores, which result in a better perception of HRQOL. Despite these results being statistically significant, the change was less than a 1 point difference suggesting there may not be a clinical meaningful change across the season. Further, the statistical findings were across time and had no effect on group comparison, so repeated head impact exposure was not a likely factor contributing to changes in HBI somatic scores at post-season as the change was present in all participants.

To additionally lend support to the proposed theory that cognitive decrements are not present following one season of football, Montenigro et al[230] worked to establish a head impact threshold between 2,723- 6,480 cumulative head impacts needed prior to the presentation of cognitive impairments. Results from this research can contribute as to why contact athletes in the current study did not demonstrate significant cognitive changes over a course of one season, as they may not have reached the proposed head impact count threshold. In this study, football athletes sustained an average of 482 head impacts per player per season. According to the above minimum number of head impacts need for a change in cognitive impairment, even seniors who may have sustained an estimated 482 head impacts per year in high school may still have not reached this threshold number (estimated 1,928 head impacts over 4 years of high school). The

average number of head impacts sustained in the current study are consistent with current literature of 413-652 head impacts per player per year.[7-9]

Overall, study results did not demonstrate significant decrements in cognitive function in one season of high school football. The current study cannot draw conclusions about structural brain changes following sub-concussive head impacts or long-term effects associated with repeated head impacts, but can conclude that no cognitive decrements, nor electrophysiological changes were identified across a single season of football in high school athletes.

3.8 Limitations

This study is not without limitations. Despite reliability and validity studies, the HIT System has limitations. The HIT system calculates linear acceleration, and only estimates rotational acceleration. Therefore, caution should be taken when drawing conclusions about rotational acceleration. Additionally, the HIT system is embedded into the helmet and as a result assumes the brain moves with the helmet, while there may be uncoupling between the two present. However, poor helmet fit can result in increased error and therefore inaccurate measures of head motion.

Secondly, the Axon neurocognitive test is a computerized testing that is has only been validated to display cognitive deficit following concussive injury. Axon is most sensitive within 24 hours of concussive injury.[110] Therefore, when assessing across time with individuals who do not have a clinical concussion diagnosis, Axon may not accurately depict deficits in neurocognitive function. Thirdly, the current sample size was too small and underpowered, which may limit our ability to draw conclusions regarding the majority of assessment measures. Following statistical findings and effect size calculations, only Axon learning and Axon Working memory speed demonstrated a large effect with the current sample size. Therefore, reproducing study findings with a larger sample size of 120 football athletes and 120 controls would be strong

enough to identify findings with a power of 0.80. Table 14 displays effect size and power analysis for Aim 1. Lastly, further research is needed to validate the BNA algorithm and other measurement tools, as they may not be sensitive enough to identify cognitive decrements throughout a season of football.

Table 14 Effect sizes for clinical assessments

Measure	Cohen's d	Effect
SWL	0.37	Small effect
HBI Cognitive	0.22	Small effect
HBI Somatic	0.46	Medium effect
CRT	0.23	Small effect
SCAT Score	0.20	Small effect
SCAT Severity	0.13	Negligible effect
Frequent Amplitude	0.33	Small effect
Frequent Synchronization	0.63	Medium effect
Frequent Timing	0.49	Medium effect
Frequent Connectivity	0.44	Medium effect
Target Amplitude	0.43	Medium effect
Target Synchronization	0.16	Small effect
Target Timing	0.11	Negligible effect
Target Connectivity	0.17	Small effect
Novel Amplitude	0.40	Medium effect
Novel Synchronization	0.55	Medium effect
Novel Timing	0.40	Medium effect
Novel Connectivity	0.54	Medium effect
Axon Processing Speed	0.19	Small effect
Axon Attention	0.37	Small effect
Axon Learning	1.09	Large effect
Axon Working Memory Speed	0.73	Medium effect
Axon Working Memory Accuracy	0.35	Small effect
N2 Amplitude	0.01-0.08	Negligible effect
N2 Latency	0.07-0.61	Negligible/Medium effect
P3a Amplitude	0.14-0.56	Small/ Medium effect
P3a Latency	0.08-0.19	Negligible/Small effect
P3b Amplitude	0.14-0.24	Small effect
P3b Latency	0.08-0.20	Negligible/Small effect
Relative size of Cohen's d[231]: Negligible effect (>=-0.15 and <.15) Small effect (>=0.15 and <.40) Medium effect (>=.40 and <.75) Large effect (>=.75 and <1.10) Very large effect (>=1.10 and <1.45) Huge effect (>1.45)		

3.9 Conclusion

In conclusion, despite research suggesting head impact exposure is negatively correlated with brain changes, current findings suggest that one season of repeated head impact exposure during football participation was not overtly associated with cognitive function declines. Additionally, when changes were noted, the majority of changes were associated with improvements at post-season. Physical activity and sports participation may improve cognitive function performance. Despite the lack of negative relationship cognitive function and repeated head impacts, continued reduction to the number of cumulative head impacts sustained is recommended to reduce any negative effects associated with cumulative head impacts.

Chapter 4 Aim 2

4.1.1 Aim 2 Effects of cognitive function following concussive injury: To evaluate the effects sport-related concussions impose on brain activity (BNA, ERP), cognitive function, and symptom reporting within 72 hours of injury, when asymptomatic and at the conclusion of the season.

Hypothesis 2A: Concussed athletes will demonstrate significant declines in brain network activity (BNA), cognitive performance, and increased symptom reporting within 72 hours of injury compared to their own baseline evaluation and control athletes.

Hypothesis 2B: Concussed athletes will demonstrate restored cognitive function following asymptomatic and post-season, but continued brain network activity (BNA) impairments compared to their baseline evaluation and controls.

Hypothesis 2C: Concussed athletes will demonstrate significant declines in P3 amplitude, increased P3 latency, and decreased N2 amplitude and increased N2 latency within 72 hours of injury compared to their own baseline evaluation and control athletes.

Hypothesis 2D: Concussed athletes will continue to demonstrate a decline P3 amplitude, increased P3 latency, decline in N2 amplitude, and an increase N2 latency following Asymptomatic and post-season testing time points compared to concussed athletes baseline evaluation.

Significance of Aim 2: Current research has suggested that despite athletes reporting symptom recovery, lingering cognitive impairments may still be present. Aim 2 is outlined to capture

cognitive impairments and electrophysiological changes following concussion symptom resolution that may not be regularly detected on clinical assessment measures.

4.2 Participants

Participants were removed from Aim 1 and enrolled into Aim 2 after a physician confirmed a concussion diagnosis. A total of 18 athletes (N= 9 concussed, N=9 controls) were enrolled in this investigation and were only enrolled in Aim 2. Controls were matched to concussed athletes based on age and position. Control participants were contact football players participating on the same football team as the concussed athletes. Healthy control participants continued participating in football related activities during testing. A total of 18 participants from a Michigan High School were included in the analysis. Participants are categorized into 2 groups (9 concussed, 9 controls). Both the concussed and controls participated in high school football between the 2013 and 2015 football seasons from the high school varsity football team (concussed: 16.56 ± 0.53 yrs. old, 179.78±6.45, 87.14±19.62 kg, controls: 16.56 ± 0.53 yrs. old, 180.34±6.72 cm, 82.55 ±15.31kg). Concussed subjects had a diagnosed concussion history of 0.67±0.71 concussions, and controls had a diagnosed concussion history of 0.33±0.71 concussions. The average number of days between post-injury and asymptomatic testing time points was 6 days, and an average of 49.3 days was between post-injury and post-season testing. Due to timing of concussion and/or subjects being asymptomatic less than 72 hours after concussion, only 8 subjects had complete data sets for the 72-hour post-concussion time point (4 concussed and 4 controls). However, 14 participants (7 concussed and 7 controls) had complete data sets for the asymptomatic testing point and 13 participants (6 concussed and 7 controls) had complete post-season follow-up data sets. Therefore, 72-hour post-concussion time point will not be included in analysis and only interpreted for trends. Table 34 displays 72hour post-concussion

means and standard deviations for the 4 concussed and 4 controls. Table 15 displays demographic information for all of Aim 2.

Table 15 Aim 2 Demographics

Group	N	Age	Height	Weight	Diagnosed Concussion History
Concussed	N= 9	16.56 ± 0.53	179.78 ± 6.45	87.14 ±19.62	0.67 ± 0.71
Controls	N=9	16.56 ± 0.53	180.34 ± 6.72	82.55 ± 15.31	0.33 ± 0.71
Total	N=18	16.56 ± 0.53	180.06 ± 6.40	84.84 ± 17.23	0.50 ± 0.71

4.3 Testing protocol

Consistent with Aim 1, all enrolled athletes were asked to complete a battery of tests prior to the competitive season. Pre-season testing was completed through the summer months and ended prior to any pre-season practices (June to mid-August). All athletes participated in their sport without interference from the investigative team. In the event the athlete sustained a concussion, he was asked to return for electroencephalography testing, and clinical concussion assessment tools (described in Aim1) within 72 hours of injury. In addition to the concussed athletes, an age, gender and position matched control was also tested at a similar time point. Once the concussed athlete no longer reported concussion related symptoms (asymptomatic) and within range of athletes' own pre-season score, both athletes (concussed and control) were re-tested on all measures. Following the conclusion of the football season all aim 2 participants were tested one final time (post-season).

Should an athlete have sustained a physician-diagnosed concussion as a result of sport participation, they were enrolled in Aim 2 of the study and completed three additional time points (72-hour-post-concussion, asymptomatic, and post-season) Matched controls were found for concussed athletes based on age and position. All participants received $50 for pre-season testing, $60 for mid-season testing, and $70 for post-season testing sessions as compensation for

their participation in the study. An additional $50 was provided for each additional concussion testing session (if applicable).

Concussion was defined as a "complex pathophysiological process affecting the brain, induced by biomechanical forces."[25] The initial injury assessment was made by the athletic trainer and confirmed by a neurologist or by the athletes' choice of physician.

4.4 Aim 2 Statistical analyses

Statistical analysis was completed using SPSS version 21 (SPSS Inc, Chicago, Illinois, USA) and significance noted when $p < 0.05$. The primary analyses used for Aim 2 included a mixed model ANOVA with time as repeated measure and group (concussed and control) as a between subjects factor was completed for Axon performance, clinical reaction time, Health Related Quality of life, Symptom Inventory and BNA scores generated from the Auditory Oddball cognitive task and FCZ, FZ, CPZ, PZ electrodes. Further, significant findings warranted post-hoc analyses using Tukey's honestly significant difference (HSD) tests.

4.5 Aim 2 Results

4.5.1 Head Impact Data

A total of 7,005 head impacts were recorded for a season of play upon sustaining a concussion combining both concussed (3,555) and controls (3,450). Specific concussive head impact details could only be recognized for seven concussed athletes. The remaining two concussed subjects either reported their symptoms days afterwards (n=1), or one specific concussive event could not be recognized (n=1). During a concussive episode, concussed athletes sustained a mean linear acceleration of 77.24g, and a median linear acceleration of 70.7g. The average rotational acceleration for a concussive episode was 3,518.73 rad/s^2, and a median rotational acceleration of 3,347.01rad/s^2. The average concussive HITsp was 38.97, and a median HITsp of 35.5. Table 16 displays the head impact means per group, while Table 17 displays

concussive head impacts and Tables 18 identifies top 5% and top 1% values for concussive impacts sustained.

Table 16 Aim 2 Total season head impacts

	Concussed	Control
Total impacts	3,555	3,450
Average impacts per player	395	383.33
Mean Linear acceleration (g)	28.35	26.95
Cumulative linear acceleration (g)	100,799.7	92,961.7
Mean Rotational acceleration (rad/s^2)	1,179.90	1,221.51
Cumulative rotational acceleration (rad/s^2)	4,194,555.82	4,214,220.04
Mean HITsp	15.90	16.37
Cumulative HITsp	56,516.6	56,463.1
Total Game impacts	1,944	1,276
Total Practice impacts	1,611	2,176
Front Impacts	1,469	1,758
Top Impacts	630	381
Back impacts	906	761
Right Impacts	253	259
Left Impacts	297	291

Table 17 Aim 2 Concussion head impact descriptives

	Linear Acceleration (g)	Rotational Acceleration (rad/s^2)	HIC15	GSI	HITsp	Location
Concussed 1	70.3	2,198.58	72.7	134.8	20.7	Top
Concussed 2	77.7	3,347.01	74.1	133.2	29.3	Back
Concussed 3	87.7	4,495.31	266.5	316.1	50.1	Back
Concussed 4	69.9	3,284.47	76.6	99.3	41.4	Front
Concussed 5	106.3	5,376.87	172.1	311	73.6	Front
Concussed 6	70.7	2,416.13	85.4	156.3	22.2	Back
Concussed 7	58.1	3,512.77	49.8	85	35.5	Front

Table 18 Aim 2 Top 5% and Top 1% concussive impact values

	Top 5% Linear Acceleration	Top 1% Linear Acceleration	Top 5% Rotational Acceleration (rad/s^2)	Top 1% Rotational Acceleration (rad/s^2)	Top 5% HITsp	Top 1% HITsp
Totals	100.72	105.18	5,112.40	5,323.98	66.55	72.19

4.5.2 Mixed Measures Analysis of Variance

As a result of missing data points a total of 6 concussed and 7 controls were included in analysis for pre-season, asymptomatic and post-season time points for all clinical measures and BNA performance.

4.5.2.1 Brain Network Activity

A mixed model ANOVA was used to determine differences in BNA scores across the time points (pre-season, asymptomatic and post-season) as well as in comparison between concussed-athletes and control athletes. Mauchley's test of Sphericity indication that the assumptions of sphericity had been violated for Novel Connectivity ($p=0.03, W(2)=0.48$). Therefore, a Greenhouse Geisser correction was used. However, no other BNA output scores indicated assumptions of sphericity had been violated ($p's>0.05$). No significant main effect for time was found for Frequent Amplitude [$F(2,22)=1.27, p=0.30$]or Frequent Timing [$F(2, 22)=1.78, p=0.19$], but a significant main effect was present for Frequent Synchronization [$F(2,22)=2.61, p=0.02$] and Frequent Connectivity [$F(2,22)=3.73, p=0.04$]. However, post-hoc analysis did not indicate significant differences in testing time were present for either Frequent Synchronization or Frequent Connectivity ($p's>0.05$).

A significant main effect for time was found for Target Amplitude [$F(2,22)=6.22, p=0.01$], with post-hoc analysis indicating significant improvements at post-season BNA Target Amplitude (66.17 ± 25.34), compared to both pre-season (39.88 ± 32.53) and asymptomatic (35.43 ± 30.00) ($p's<0.05$, cohens $d=0.26$). No significant main effects for time were found for Target Synchronization [$F(2,22)=0.53, p=0.60$], Target Timing[$F(2,22)=0.50, p=0.61$], or Target Connectivity [$F(2,22)=1.69, p=0.21$]. Additionally, no significant main effects for time were present for Novel Amplitude [$F(2,22)=0.54, p=0.59$], Novel Synchronization [$F(2,22)=1.74, p=0.20$], Novel Timing [$F(2,22)=0.69, p=0.43$] or Novel Connectivity [$F(2,22)=0.40, p=0.68$].

No significant interactions or group effects were present for any of the twelve BNA output scores (p's>0.05). Table 19 displays means and standard deviation for all BNA output scores by group and time.

Table 19 Aim 2 BNA output scores means and standard deviations

Group	Pre-season	Asymptomatic	Post-season
Frequent Amplitude	(Mean± STD)	(Mean ±STD)	(Mean ±STD)
Concussed	64.89±24.86	78.33± 22.50	87.16± 8.15
Control	68.34± 32.49	62.74 ±27.68	68.97± 20.70
Total	66.75± 28.08	69.93 ±25.68	77.36 ±18.19
Frequent Synchronization			
Concussed	69.72± 25.33	76.93± 15.63	77.19 ±21.80
Control	67.12 ±27.79	76.45 ±26.71	82.76 ±11.31
Total	68.32± 25.60	76.67 ±21.42	80.19 ±16.44
Frequent Timing			
Concussed	70.34 ±21.60	80.83 1±5.55	86.31 ±12.61
Control	65.31± 31.22	71.60 ±26.53	64.01± 20.06
Total	67.63 ±26.24	75.72 ±21.78	74.30± 19.96
Frequent Connectivity			
Contact	68.31± 19.88	78.60 ±14.88	83.55 ±11.47
Control	66.92± 28.55	70.26 ±22.63	71.91 ±13.32
Total	67.57± 23.94	74.11 ±19.16	77.28 ±13.41
Target Amplitude			
Concussed	41.08± 31.06	41.19 42.21	68.53 ±19.44
Control	38.86 ±36.19	30.50 18.33	64.15 ±30.97
Total	**39.88 ±32.53***	**35.43 60.38***	**66.17 ±25.34***
Target Synchronization			
Concussed	36.80 ±39.12	42.71 ±44.51	53.30 ±26.30
Control	50.12± 44.53	59.25 ±40.75	54.74 ±35.21
Total	43.97± 40.95	51.61 ±41.59	54.08 ±30.15
Target Timing			
Concussed	32.71± 33.53	32.17± 34.86	35.34 ±26.71
Control	60.08± 4.23	44.06 ±33.97	58.22± 35.47
Total	47.45± 41.70	38.57 ±33.48	47.66 ±32.67
Target Connectivity			
Concussed	36.86 ±32.74	38.69 ±38.46	52.39 ±20.47
Control	49.69 ±40.92	44.60 ±22.14	59.04 ±29.66
Total	43.77 ±36.45	41.87 ±29.51	55.97 ±25.03
Novel Amplitude			
Contact	63.01 ±29.52	68.66 ±30.52	69.32± 22.81
Control	59.61 ±28.26	58.74 ±20.84	64.74 ±24.76
Total	61.18 ±27.67	63.32± 25.13	66.85 ±23.00
Novel Synchronization			
Concussed	62.10 ±13.50	60.72 ±21.16	68.71± 17.30
Control	55.01± 25.24	50.54 ±28.52	61.79± 22.08
Total	58.28 ±20.20	55.24 ±24.92	64.98±19.53
Novel Timing			
Concussed	67.33 23.64	63.64 ±23.78	51.71± 34.74
Control	61.60 39.03	50.52± 34.91	61.66 ±32.71
Total	64.25 31.67	56.57± 29.56	57.07 ±32.62
Novel Connectivity			

Concussed	64.14 ±19.65	61.34± 22.25	63.25± 19.18
Control	58.74 ±27.68	53.27 ±21.86	62.73± 22.66
Total	61.23± 23.49	58.38 ±21.87	62.97±20.25
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

4.5.2.2 Event- related potentials

4.5.2.2.a Target P3a component

Group-average Target P3a FCZ and CPZ P3a amplitudes and latencies are reported in Table 20. Following a mixed model ANOVA, Mauchleys test indicated that assumptions of sphericity had not been violated for either FCZ or CPZ P3a amplitude or latency (p's>0.05). No significant main effects for time were present for FCZ Target P3a amplitude [F(2,28)=0.67, p=0.52], CPZ P3a amplitude [F(1,26)=0.35, p=0.71], or CPZ P3a latency [F(2,26)=0.13, p=0.88]. However, FCZ P3a latency was found to have a significant main effect for time [F(2,28)=7.98, p<0.01, d=0.81], with post-hoc analysis indicating longer latencies were present at post-season testing (578.50 ± 150.62ms) compared to both pre-season testing (452.50 ± 144.63ms) and asymptomatic testing (441.75 ± 139.81ms). Additionally, no interactions between time and group were present for FCZ Target P3a amplitude [F(2,28)=1.10, p=0.35], CPZ P3a amplitude [F(2,28)=0.02,p=0.0.98], or CPZ P3a latency [F(2,28)=1.76, p=0.19]. However, a significant interaction was present for FCZ P3a latency [F(2,28)=3.53, p=0.04, d=1.01]. No significant group effects were present for FCZ Target P3a latency [F(1,14)=0.74, p=0.40], CPZ P3a Target amplitude [F(1,13)=1.46, p=0.25] or CPZ P3a latency [F(1,13)=0.13, p=0.72]. However, a significant group effect was present for FCZ P3a amplitude [F(1,14)= 5.44, p=0.04], with post-hoc analysis indicating concussed athletes displayed significantly smaller post-season P3a amplitudes (0.73 ± 1.28 μv) compared to control athletes (4.96 ± 2.83 μv). Figures 8 and 9 display FCZ and CPZ amplitudes and latency over time between groups.

Table 20 Aim 2 Target P3a ERP means and standard deviations

Group	Pre-season	Asymptomatic	Post-season
FCZ P3a Amplitude (μv)	**(Mean± Std)**	**(Mean± Std)**	**(Mean± Std)**
Football Athletes	0.54 ±2.87	2.55 ±4.08	**0.73 ±1.26^{+}**
Controls	3.17 ±2.80	3.54 ±4.82	**4.96 ±2.83^{+}**
Total	2.02 ±3.05	3.11 ±4.40	3.11 ±3.10
CPZ P3a Amplitude (μv)			
Football Athletes	5.61± 3.12	6.41± 4.18	5.75 ±3.33
Controls	7.52 ±3.20	8.35± 4.59	8.05 ±4.78
Total	6.63 ±3.20	7.45± 4.36	6.97± 4.18
FCZ P3a latency (ms)			
Football Athletes	495.29± 179.72	400.00 ±134.90	655.43 ±92.56
Controls	420.00 ±110.83	474.22 ±142.45	518.67 ±164.02
Total	**452.50 ±144.63***	**441.75 ±139.81***	**578.50± 150.62***
CPZ P3a latency (ms)			
Football Athletes	405.71 ±57.58	425.71 ±98.38	370.29± 50.06
Controls	389.00± 36.14	399.00 ±91.16	444.00 ±130.39
Total	396.80± 46.41	411.47±92.16	406.60 ±104.99
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

Figure 8 Aim 2 Pre-season, asymptomatic post-season concussed vs. controls comparisons for FCZ average ERP (P3a waves between 300-700 ms)

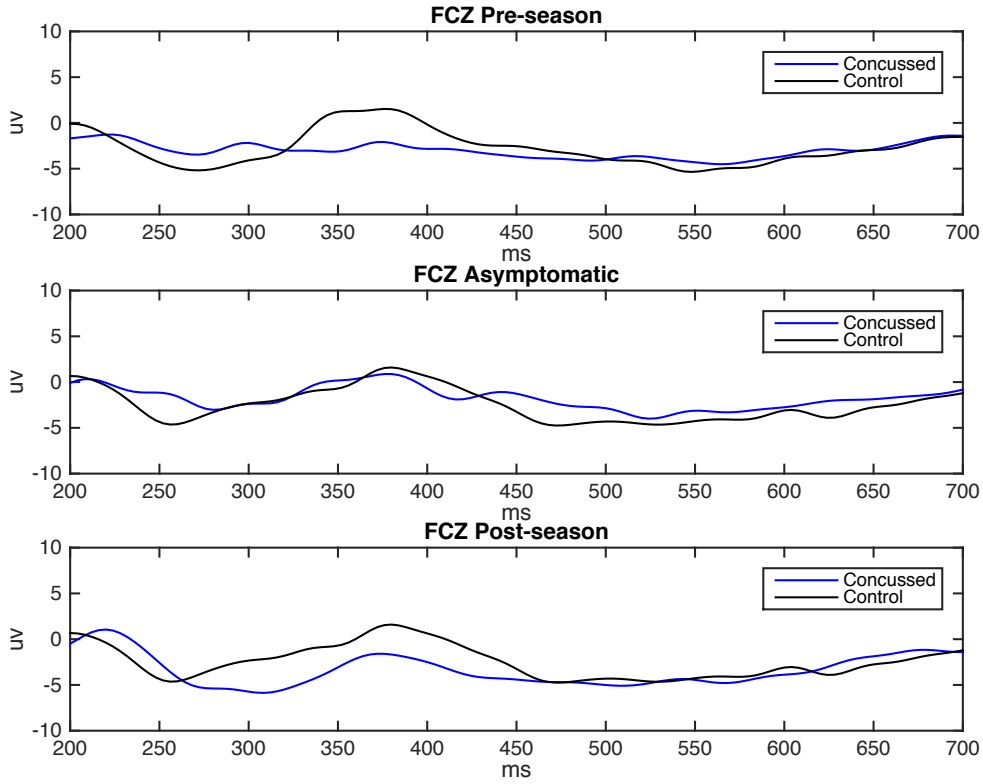
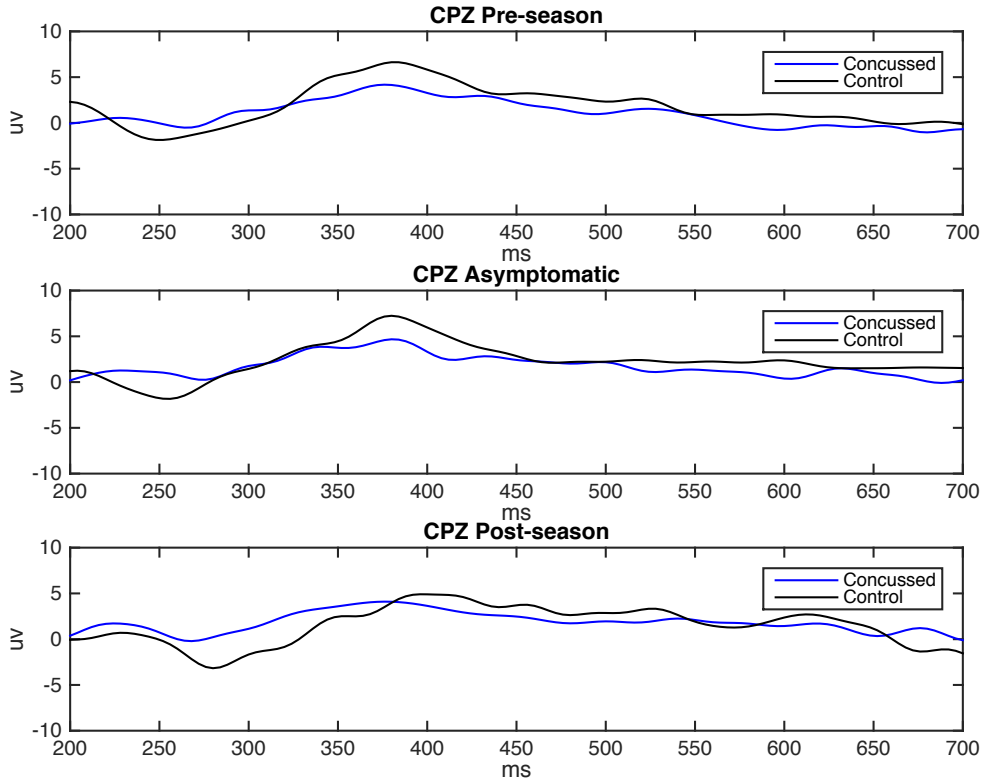


Figure 9 Aim 2 Pre-season, asymptomatic post-season concussed vs. controls comparisons for CPZ average ERP (P3a waves between 300-700 ms)



4.5.2.2.b Target P3b component.

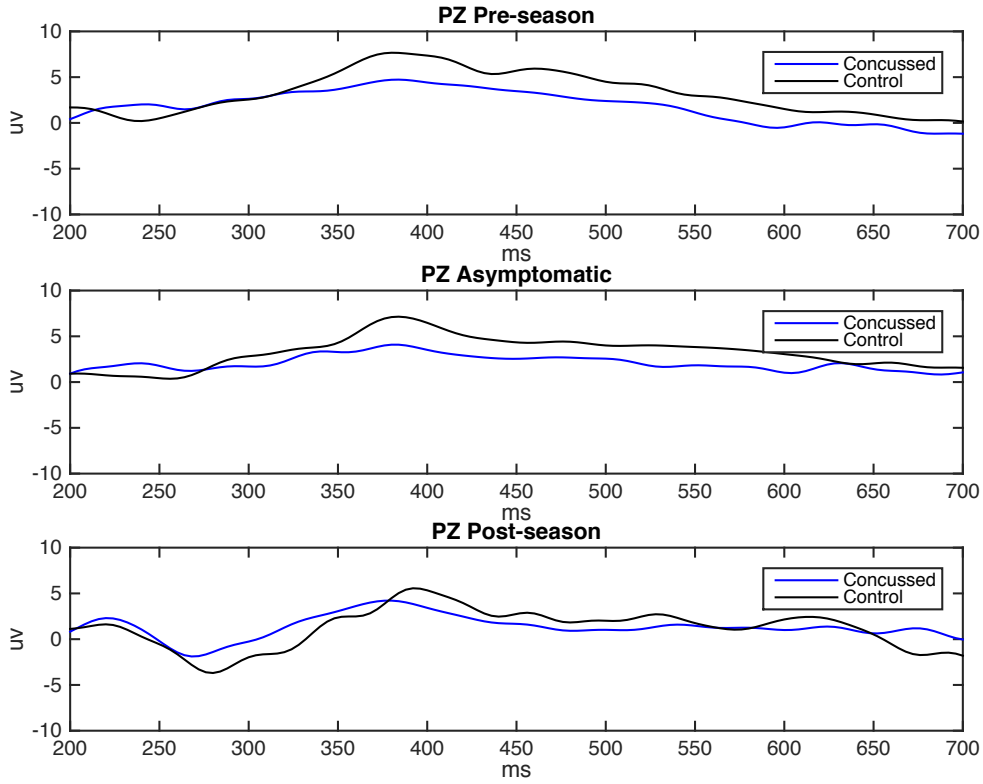
Group-average Target P3b CPZ and PZ amplitudes and latencies are reported in Table 21. Following a mixed model ANOVA, Mauchleys test indicated that assumptions of sphericity had not been violated for CPZ P3b amplitude (p=0.56), CPZ P3b latency (p=0.91) or PZ P3b latency (p=0.68). However, assumptions of sphericity had been violated of PZ P3b amplitude (W(2)=0.58, p=0.04). Therefore, a Greenhouse Geisser correction was used for PZ P3b amplitude. No significant main effects for time were present for CPZ Target P3b amplitude [F(1,26)=0.35, p=0.71], CPZ P3a latency [F(2,26)=0.13, p=0.88], PZ Target P3b amplitude [F(2,26)=1.34, p=0.28], or PZ Target P3b latency [F(2,26)=1.59, p=0.22]. Additionally, no

interactions between time and groups were present for CPZ P3a amplitude [F(2,28)=0.02,p=0.0.98], CPZ P3a latency [F(2,28)=1.76, p=0.19], PZ Target P3b amplitude [F(2,26)=0.05, p=0.95] and PZ Target P3b latency [F(2,26)=0.07, p=0.93]. No significant group effects were present for CPZ P3a Target amplitude [F(1,13)=1.46, p=0.25], CPZ P3a latency [F(1,13)=0.13, p=0.72], PZ Target P3b amplitude [F(1,13)=4.17, p=0.06], or PZ Target P3b latency [F(1,13)=0.09, p=0.77]. Figures 9 and 10 display CPZ and PZ amplitudes and latency over time between groups.

Table 21 Aim 2 Target P3b ERP means and standard deviations

Group	Pre-season	Asymptomatic	Post-season
CPZ P3b Amplitude (µv)	**(Mean± Std)**	**(Mean± Std)**	**(Mean± Std)**
Football Athletes	5.61 ±3.12	6.41 ±4.18	5.75± 3.33
Controls	7.52 ±3.20	8.35± 4.59	8.05 ±4.78
Total	6.63 ±3.20	7.45±4.36	6.97 ±4.18
PZ P3b Amplitude (µv)			
Football Athletes	5.83 ±2.17	5.66 ±1.82	4.40± 1.80
Controls	8.72 ±4.37	8.30 ±3.68	7.55± 3.45
Total	7.57 ±3.84	7.25± 3.27	6.29 ±3.24
CPZ P3b Latency (ms)			
Football Athletes	405.71± 57.58	425.71± 98.38	370.29 ±50.06
Controls	389.00± 36.14	399.00 ±91.16	444.00 ±130.39
Total	396.80± 46.41	411.47 ±92.16	406.60 ±104.99
PZ P3b latency (ms)			
Football Athletes	300.67± 75.57	337.33 ±131.64	342.67± 83.05
Controls	300.89 ±4.74	344.44± 84.39	366.22± 126.51
Total	300.80 ±55.53	341.60 ±101.35	356.80± 108.40
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

Figure 10 Aim 2 Pre-season, asymptomatic post-season concussed vs. controls comparisons for PZ average ERP (P3b waves between 300-700ms)



4.5.2.2.c *Target N2 Component*

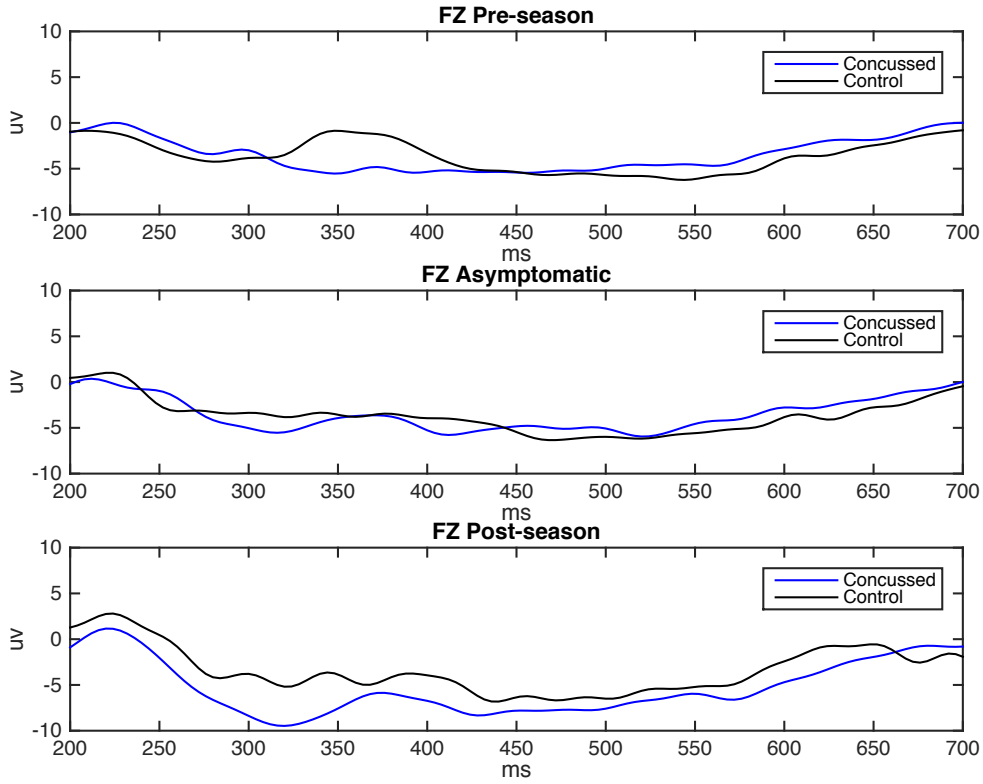
Group-average Target N2 FCZ and FZ amplitudes and latencies are reported in Table 22. Following a mixed model ANOVA, Mauchleys test indicated that assumptions of sphericity had been violated of FCZ N2 amplitude (W(2)=2.56, p=0.02), FZ N2 amplitude (W(2)=2.52, p=0.02) and FZ N2 latency (W(2)=0.57, p=<0.05). Therefore, a Greenhouse Geisser correction was used. However, Mauchleys test did not indicate assumptions of sphericity had been violated for FCZ Target N2 latency (p=0.85). No significant main effect for time was present for FCZ Target N2 amplitude [F(1.95,20.76)=0.70, p=0.46], FZ Target N2 amplitude [F(1.37,17.76)=1.44, p=0.26], or FZ Target N2 latency [F(1.40, 18.14)=2.09, p=0.16]. A significant main effect was present for

time for FCZ Target N2 latency [F(2,28)=3.74, p=0.04], however following post-hoc analysis, no significance differences were present (p=0.11). Additionally, no interactions between time and group were present for FCZ Target N2 amplitude [F(1.38, 20.76)=0.19, p=0.74], FCZ Target N2 latency [F(2,30)=0.58, p=0.57], FZ Target N2 amplitude [F(1.37, 17.76)=0.81, p=0.42], or FZ Target N2 latency [F(1.40,18.14)=2.37, p=0.13]. No significant group effects were present for FCZ Target N2 amplitude [F(1,15)=1.09, p=0.31], FCZ Target N2 latency [F(1,15)=2.08, p=0.17], FZ Target N2 amplitude [F(1,13)=0.57, p=0.47] or FZ Target N2 latency [F(1,13)=1.47, p=0.25]. Figures 8 and 11 display FCZ and FZ amplitudes and latency over time between groups.

Table 22 Aim 2 Target N2 ERP means and standard deviations

Group	Pre-season	Asymptomatic	Post-season
FCZ N2 Amplitude (μv)	**(Mean± Std)**	**(Mean± Std)**	**(Mean± Std)**
Football Athletes	-4.85±2.04	-4.69 ±5.65	-7.21 ±6.98
Controls	-7.63 ±3.10	-7.05 ±3.99	-8.12 ±8.05
Total	-6.48 ±2.99	-6.08± 4.73	-7.74 ±7.41
FZ N2 Amplitude (μv)			
Football Athletes	-6.93 ±1.97	-6.44 ±4.50	-11.36± 8.90
Controls	-6.65± 3.17	-6.14 ±4.86	-7.03± 7.93
Total	-6.76 ±2.67	-6.26± 4.56	-8.76 ±8.30
FCZ N2 latency (ms)			
Football Athletes	316.57±38.40	278.86 ±57.44	310.29 ±19.16
Controls	282.80 ±28.10	268.00 ±44.94	285.60 ±47.07
Total	296.71 ±35.92	272.47± 49.03	295.76 ±39.25
FZ N2 latency (ms)			
Football Athletes	322.00± 36.73	307.33 ±24.32	308.67 ±29.44
Controls	285.78 ±37.79	271.56± 50.77	312.44 ±55.08
Total	300.27 ±40.44	285.87 ±44.87	310.93 ±45.24
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

Figure 11 Aim 2 Pre-season, asymptomatic post-season concussed vs. controls comparisons for FZ average ERP (N2 waves between 200-350ms)



4.5.2.3 Auditory Oddball Behavioral data

Mixed model ANOVA was used to determine differences behavioral data reaction time, response accuracy and number of errant tones, across the time-points (pre-season, asymptomatic and post-season) as well as in comparison between concussed-athletes and control athletes. Mauchleys test indicated an assumption of sphericity had been violation for average errant tones ($p=0.04$), average reaction time ($p=0.01$) and average response accuracy percent ($p>0.01$).

Therefore, Greenhouse Geisser correction was used. No significant main effects for time were noted for average errant tones [F(1.39,16.73)=0.65, p=0.53], average reaction time [F(1.24, 14.87)=1.35, p=0.27] and average response accuracy percentage [F(1.10, 13.14)=0.77, p=0.41]. Additionally, no significant interactions or group effects were present for any behavioral data (p's>0.05). Lastly, when analyzing behavioral performance based on block 1 (First 300 trials) and block 2 (second 300 trials), no significant main effects for time, interactions, or groups effects were present for any of the behavioral tasks and individual blocks (p's>0.05). Table 23 and 24 displays means and standard deviations for auditory oddball behavior data.

Table 23 Aim 2 Average Auditory Oddball behavior data means and standard deviations

	Pre-season	Asymptomatic	Post-season
	(Mean ±std)	**(Mean± Std)**	**(Mean± Std)**
Average Reaction Time			
Football-athletes	344.64± 75.23	377.82 ±104.78	406.88 ±139.45
Controls	338.48 ±59.58	347.14 ±69.01	334.16 ±50.04
Totals	341.56 ±65.27	362.48± 86.71	370.52 ±107.49
Average Accuracy (%)			
Football-athletes	99.76± 0.63	99.05 ±1.31	99.05 ±1.31
Controls	98.57± 2.62	92.38 ±18.70	98.10 ±3.11
Totals	99.17± 1.93	95.71± 13.20	98.57 ±2.34
Average number Errant tones identified			
Football-athletes	1.07 ±1.81	0.29 ±0.39	0.36±0.56
Controls	0.79 ±1.25	0.57 ± 0.53	1.00± 1.85
Totals	0.93 ± 1.50	0.43± 0.47	0.68± 1.35

BOLD signifies p<0.05
* Denotes significance across time points
+ Signifies group differences

Table 24 Aim 2 Auditory Oddball Behavior data by blocks; means and standard deviations

	Pre-season	Asymptomatic	Post-season
	(Mean ± Std)	**(Mean± Std)**	**(Mean± Std)**
Block 1 Reaction Time			
Football-athletes	328.47 ± 76.27	361.42 ± 94.15	387.62 ± 142.76
Controls	328.55 ± 58.55	284.65 ± 139.10	313.52 ± 60.44
Totals	328.51 ± 65.32	323.03 ± 120.86	350.57 ± 112.12
Block 2 Reaction Time			
Football-athletes	360.81 ± 83.52	384.22 ± 117.02	426.14 ± 140.52
Controls	348.41 ± 62.75	357.92 ± 80.93	354.80 ± 45.36
Totals	654.61 ± 71.26	376.07 ± 98.48	390.47 ± 106.92
Block 1 Accuracy (%)			
Football-athletes	100.00 ± 0.00	98.57 ± 1.78	99.52 ± 1.26
Controls	98.10 ± 3.78	84.76 ± 37.41	98.57 ± 2.62
Totals	99.05 ± 2.04	91.67 ± 26.43	99.05 ± 2.04
Block 2 Accuracy (%)			
Football-athletes	99.52 ± 1.26	99.52 ±1.26	98.57 ± 1.78
Controls	99.05 ± 1.63	100.00 ± 0.00	97.62 ± 4.99
Totals	99.29 ± 1.42	99.76 ± 0.89	98.10 ± 3.63
Block 1 Errant tones			
Football-athletes	0.43 ± 1.13	0.43± 0.79	0.29 ± 0.49
Controls	1.43 ± 2.15	0.43 ± 0.53	0.71 ± 1.25
Totals	0.93 ± 1.73	0.43 ± 0.65	0.50 ± 0.94
Block 2 Errant tones			
Football-athletes	1.71 ± 3.68	0.14 ± 0.38	0.43 ± 1.13
Controls	0.14 ± 0.38	0.71 ± 0.76	1.29 ± 2.98
Totals	0.93 ± 2.64	0.43 ± 0.65	0.86 ± 2.21

BOLD signifies $p<0.05$
* Denotes significance across time points
+ Signifies group differences

4.5.2.4 Axon

Mixed model ANOVA was used to determine differences in Axon scores across the time-points (pre-season, asymptomatic and post-season) as well as in comparison between concussed-athletes and control athletes. Mauchleys test indicated a violation of assumption of sphericity was present for Axon processing speed ($p=0.03$). Therefore a Greenhouse Geisser correction was used for Axon Processing speed. However, Mauchleys test indicated no other violations of assumptions of sphericity for Axon Attention, Learning, Working Memory Speed and Working

Memory Accuracy (p's>0.05). No significant main effect for time was present for Axon Processing speed [F(1.32, 14.53)=0.17, p=0.76]. A significant main effect was present for time for Axon Learning [F(2,22)=3.78, p=0.04, cohens d=0.10]. However, following post-hoc analysis no significant differences were present between time points (p>0.05). No significant main effect for time was found Axon Attention [F(2,22)=0.95, p=0.40], Axon Working Memory Speed [F(2,22)=1.44, p=0.26], and Working Memory Accuracy [F(2,22)=2.56, p=0.10].

No interactions were present between groups and time for Axon Processing speed [F(1.32, 14.53)=1.32, p=0.28], Attention [F(2,22)=0.69, p=0.51], Learning [F(2,22)=0.42, p=0.67], Working Memory Speed [F(2,22)=0.05,p=0.96] or Working Memory Accuracy [F(2,22)=0.34, p=0.72]. Lastly, no significant group effects were present for Axon processing speed [F(1,11)=2.61, p=0.13], Attention [F(1,11)=0.28, p=0.61], Learning [F(1,11)=0.03, p=0.88], Working Memory Speed [F(1,11)=0.55, p=0.47], and Working memory Accuracy [F(1,11)=0.03, p=0.87]. Table 25 displays means and standard deviation for all Axon output scores by group and time.

Table 25 Aim 2 Axon composite scores means and standard deviations

Group	Pre-season	Asymptomatic	Post-season
Processing Speed	(Mean± STD)	(Mean ±STD)	(Mean ±STD)
Concussed	103.77± 4.59	101.47 ±5.60	102.47± 5.60
Control	104.49± 7.37	106.56± 4.19	106.99 ±4.54
Total	104.15 ±6.01	104.07 ±4.34	104.90 ±5.37
Attention			
Concussed	104.53± 5.42	106.25 ±0.95	105.63 ±3.35
Control	106.77± 4.54	107.64 ±3.97	105.03 ±5.56
Total	105.74 ±4.89	107.00 ±2.96	105.31± 4.49
Learning			
Concussed	110.82 ±7.74	113.05 ±7.06	119.90 ±8.31
Control	112.07± 10.07	113.33 ±8.54	116.67 ±8.11
Total	111.49 ±8.72	113.20±7.57	118.16± 8.03
Working Memory Speed			
Concussed	104.78 ±4.75	105.63 ±2.48	106.92± 5.01
Control	105.77 ±7.40	107.16± 4.36	108.84± 3.56
Total	105.32± 5.90	106.45 ±3.56	107.95 ±4.22
Working Memory Accuracy			
Concussed	104.40 ±4.02	105.63 ±2.48	106.92 ±5.01
Control	105.71 ±8.91	107.16 ±4.36	108.84 ±3.56
Total	105.11± 6.84	106.45± 3.56	107.95± 4.22
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

4.5.2.5 Clinical Reaction Time

Mixed model ANOVA was used to determine differences in clinical reaction time across the time-points (pre-season, asymptomatic and post-season) as well as in comparison between concussed-athletes and control athletes. Mauchleys test indicated a violation of sphericity was not present for clinical reaction time (p=0.06). No significant main effect for time was present for clinical reaction time [F(2,22)=0.01,p=0.99]. Additionally, no significant interaction [F(2,22)=0.84, p=0.44] or group effects [F(1,11)=0.26, p=0.62] were present. Table 26 displays means and standard deviation for all CRT scores by group and time.

Table 26 Aim 2 Clinical reaction time means and standard deviations

Group	Pre-season	Asymptomatic	Post-season
CRT			
Concussed	195.64 ±39.83	197.16 ±24.88	202.94 ±30.00
Control	207.84 ±27.03	207.57 ±16.93	200.60 ±20.02
Total	202.21 ±32.66	202.77 ±20.75	201.58 ±24.02
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

4.5.2.6 Health Related Quality of Life

Mixed model ANOVA was used to determine differences in SWL, HBI Cognitive, and HBI Somatic across the time-points (pre-season, asymptomatic and post-season) as well as in comparison between concussed-athletes and control athletes. Mauchleys test indicated no violation of sphericity was present for SWL, HBI cognitive, or HBI Somatic (p's>0.05). No significant main effects for time were noted for SWL [F(2,22)=1.72, p=0.20], HBI Cognitive [F(2,22)=2.37 p=0.12] or HBI Somatic [F(2,22)=0.19, p=0.83].No significant interactions were present for SWL [F(2,22)=1.62, p=0.22], HBI Cognitive [F(2,22)=0.34, p=0.72] or HBI Somatic [F(2,22)=3.14, p=0.06]. Additionally, no group effects were present for SWL [F(1,11)=0.21, p=0.58], HBI Cognitive [F(1,11)=1.98, p=0.19] and HBI somatic [F(1,11)=0.73, p=0.41]. Table 27 displays means and standard deviation for HRQOL scores by group and time.

Table 27 Aim 2 Health Related Quality of Life means and standard deviations

Group	Pre-season	Asymptomatic	Post-season
SWL	(Mean± STD)	(Mean ±STD)	(Mean ±STD)
Concussed	32.17 ±3.06	30.17± 3.49	31.00 ±3.74
Control	30.00 ±3.61	30.00± 4.43	29.71 ±5.12
Total	31.00 ±3.42	30.08± 3.86	30.31± 4.40
HBI Cognitive			
Concussed	8.67 ±4.13	8.83 ± 5.11	6.83± 5.53
Control	6.57 ±3.55	4.86 ±5.15	3.43± 4.64
Total	7.54 ±3.82	6.69± 5.33	5.00± 5.16
HBI somatic			
Concussed	4.33 ±3.67	3.00± 3.79	2.17± 3.92
Control	1.14± 2.04	1.57 ±1.81	2.71 ±3.82
Total	2.46± 3.71	2.23± 2.86	2.46± 3.71
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

4.5.2.7 Symptom Inventory

Mixed model ANOVA was used to determine differences in symptom number and symptom severity across the time-points (pre-season, asymptomatic and post-season) as well as in comparison between concussed-athletes and control athletes. Mauchleys test indicated a violation of sphericity was present for symptom number ($W(2)=0.18$, $p<0.01$), but was not present for symptom severity ($p=0.07$). Therefore, a Greenhouse Geisser correction was made for symptom number. No significant main effect for time for symptom number [$F(1.10,12.07)=2.00, p=0.18$] or symptom severity [$F(2,22)=2.75$, $p=0.09$]. Additionally, no significant interactions were present between group and time for symptom number [$F(1.10, 12.07) = 1.23$, $p=0.30$] or for symptom severity [$F(2,22)= 1.44$, $p=0.26$]. No significant group effects were present for symptom number [$F(1,11)=4.11$, $p=0.07$] or symptom severity

[F(1,11)=1.58, p=0.24]. Table 28 displays means and standard deviation for Symptom Inventory scores by group and time.

Table 28 Aim 2 symptoms means and standard deviations

Group	Pre-season	Asymptomatic	Post-season
Symptom Number	(Mean± STD)	(Mean ±STD)	(Mean ±STD)
Concussed	2.33 ± 3.93	1.00 ± 1.10	0.00 ± 0.00
Control	0.29 ± 0.49	0.14 ± 0.38	0.00 ± 0.00
Total	1.23 ± 2.77	0.54 ± 0.88	0.00 ± 0.00
Symptom Severity			
Concussed	1.50 ± 3.21	1.83 ± 2.40	0.00 ± 0.00
Control	0.57 ± 0.98	0.14 ± 0.38	0.00 ± 0.00
Total	1.00 ± 2.24	0.92 ± 1.80	0.00 ± 0.00
BOLD signifies p<0.05 * Denotes significance across time points + Signifies group differences			

4.5.3 Case Series:

Four complete concussed cases were examined at length and included pre-season, 72-hour post-concussion, asymptomatic and post-season testing performance scores for BNA output scores, ERP P3a, P3b and N2 amplitudes and latencies, Axon scores, clinical reaction time, and Symptom inventory. The case series was conducted due to the lack of complete concussed data sets in order to identify any 72-hour post-concussion deficits, as this time point was removed from earlier analysis. Table 29 displays 72-hour post-concussion means and standard deviations.

Table 29 Post-concussion means and standard deviations (n=4 concussed, n=4 controls)

	Concussed	Control	Total
	Mean ±Std.	**Mean ±Std.**	**Mean ±Std.**
SWL	6.50 ± 0.58	5.75± 1.26	6.13 ± 0.99
HBI cognitive	8.5 ± 3.00	7.75± 9.07	8.13 ± 6.27
HBI somatic	7.50 ±4.04	4.00 ±7.35	5.75 ± 5.80
Frequent Amplitude	58.50 ±31.74	73.32±27.41	65.91± 28.57
Frequent Synchronization	76.87 ±18.06	86.06±6.45	81.47 ± 13.48
Frequent Timing	82.87 ±11.02	66.85±20.57	74.86 ± 17.51
Frequent Connectivity	72.75± 11.54	75.41±2.337	74.08 ± 7.835
Target Amplitude	34.20 ±40.64	48.58±46.92	41.39 ± 41.36
Target Synchronization	38.86± 40.64	85.04±6.01	61.95 ± 36.26
Target Timing	42.96± 48.19	86.07±9.93	64.52 ± 39.06
Target Connectivity	42.48± 42.72	78.63±15.69	60.55 ± 34.97
Novel Amplitude	54.76± 40.18	50.24±20.52	52.50 ± 29.63
Novel Synchronization	55.00± 39.84	57.47±29.74	56.23 ± 32.57
Novel Timing	56.84± 49.30	51.58±27.40	54.21 ± 37.03
Novel Connectivity	55.53± 41.99	53.10±21.79	54.31 ± 31.00
Axon Processing Speed	103.3± 5.68	104.88±2.84	104.09 ± 4.24
Axon Attention	104.73± 2.54	105.93±2.29	105.33 ± 2.33
Axon Learning	109.9± 4.97	112.75±9.41	111.33 ± 7.13
Axon Working Memory Speed	106.13± 2.46	105.05±4.84	105.59 ± 3.60
Axon Working Memory Accuracy	97.40± 5.87	104.18±9.00	100.79 ± 7.91
CRT ms	216.35± 35.16	200.42±10.03	208.38 ± 25.40
Symptom number	7.25 ± 3.30	0.00±0.00	3.63 ± 4.44
Symptom Severity	13.25± 10.50	0.00±0.00	6.63 ± 9.87

4.5.3.a Case #1

Case # 1 is a high school senior who sustained a concussion during practice. However, case #1 continued to practice that day and reported symptoms halfway through the following days practice. No specific linear acceleration, rotational acceleration or HITsp could be localized for the concussive impact. Case #1 plays both sides of the football field (offensive lineman and

defensive lineman). The asymptomatic testing time was 4 days post-injury, and post-season testing was conducted 53 days post-injury. No Frequent BNA deficits were noted during 72-hour post concussion, or asymptomatic testing. However, improvements were noted during post-season testing for Frequent BNA scores compared to pre-season, post-concussion and asymptomatic. During Target Timing BNA performance, case #1 demonstrated deficits at post-concussion (33.82), and asymptomatic (38.21), compared to preseason (68.95), while improving at postseason (92.68). These changes did not fall outside of normative data and therefore do not pose any clinical implications. No other deficits were noted for any other BNA output scores, or Axon composite score. During post-concussion clinical reaction time a slightly slower reaction time score was present at post-concussion (174.82ms) and asymptomatic (185.65ms) compared to pre-season (152.54 ms). Furthermore, smaller FCZ P3 amplitudes present at post-season (0.35 μv) compared to preseason (2.74 μv), post-concussion (5.21 μv) and asymptomatic (9.95 μv). Additionally, smaller amplitudes were found during post-season CPZ Target P3b electrode (4.36 μv), PZ Target P3b electrode (4.56 μv) compared to pre-season testing. Further, smaller Target N2 amplitudes were noted during asymptomatic testing (FCZ=1.02μv, FZ=0.42 μv) compared to preseason N2 amplitudes (FCZ= -1.88 μv, FZ =-4.98 μv). An increase in FCZ Target P3a latency was noted during post-season (700ms) compared to pre-season (300ms). No other latency changes were present. Lastly, case #1 displayed more symptoms and greater symptom severity scores at post-concussion (symptoms= 8, severity= 13) compared to all other time points. Table 30 displays performance scores for case # 1 at all four time points.

Table 30 Means for Case #1 over testing time points (pre-season, 72hour post-concussion, asymptomatic, post-season)

	Pre-season	72hour Post-concussion	Asymptomatic	Post-season
Frequent Amplitude	22.52	29.01	32.25	90.65
Frequent Synchronization	77.45	82.81	71.16	79.71
Frequent Timing	47.51	85.03	62.97	84.93
Frequent Connectivity	49.16	65.61	56.46	85.10
Target Amplitude	53.79	56.65	88.44	79.97
Target Synchronization	29.29	35.52	85.34	86.66
Target Timing	68.95	33.82	38.21	92.68
Target Connectivity	50.67	42.00	70.66	76.44
Novel Amplitude	77.88	65.33	88.30	60.37
Novel Synchronization	64.57	84.47	87.52	65.11
Novel Timing	94.85	98.31	97.83	93.73
Novel Connectivity	79.10	82.71	91.21	73.07
Processing Speed	110.40	105.50	104.40	107.10
Attention	109.80	107.60	107.10	107.50
Learning	110.10	115.40	112.50	108.10
Working Memory Speed	109.30	108.60	109.60	113.30
Working Memory Accuracy	106.10	106.10	101.70	106.10
CRT ms	152.54	174.82	185.65	163.62
Symptom Number	0.00	8.00	0.00	0.00
Symptom Severity	0.00	13.00	0.00	0.00
FCZ P3a amplitude(μv)	2.74	5.21	9.95	0.35
CPZ amplitude(μv)	9.00	7.92	11.19	4.36
PZ P3b amplitude(μv)	8.08	7.08	7.70	4.56
FCZ N2 amplitude(μv)	-1.77	-2.73	1.02	-2.41
FZ N2 amplitude(μv)	-4.98	-4.65	0.42	-4.25
FCZ P3a latency (ms)	300	396	432	700
CPZ latency (ms)	392	380	400	380
PZ P3b latency(ms)	388	376	376	388
FCZ N2 latency(ms)	352	320	200	316
FZ N2 latency(ms)	352	328	320	348
***denotes scores are not similar to normative data**				

4.5.3.b Case #2

Case #2 is a junior in high school and plays both linebacker and fullback. Case #2 sustained a concussion during a game and linear acceleration was recorded to be 70.3g, rotational

acceleration to be 2,198.58 rad/s^2, and HITsp to be 20.7. The asymptomatic testing time was 4 days post-injury, and contributed to missing 1 season game. Further, post-season testing was performed 54 days post-injury. Case #2 did not demonstrate any deficits at 72 hours post-concussion on any of the Frequent or Target BNA output scores. However, a BNA performance deficit was found during the 72hour post-concussion for Novel Timing (31.77) compared to pre-season Novel Timing performance score (73.11). Furthermore, during asymptomatic and post season testing, Novel Timing BNA output scores remained lower than pre-season (56.93, 32.89). Similarly Novel Connectivity, followed the same pattern with deficits at post-concussion (46.63), asymptomatic (50.40) and postseason (49.32) compared to pre-season (62.55) suggesting following injury with deficits in BNA performance were present. However, it is unclear if these deficits are clinically significant. No deficits were present for Axon Processing Speed, Attention, Learning or Working Memory Speed. However a slight deficit was present for Axon Working Memory Accuracy at 72hours post-concussion (95.80) compared to pre-season (105.90). No deficits were preset for any of the ERP amplitudes. However, for CPZ P3 latency, longer 72hour post-concussion (692 ms) and asymptomatic latencies (700 ms) were noted compared pre-season (360 ms) and post-season (300 ms). Lastly, symptom reporting during post-concussion testing was only slightly greater than during pre-season, asymptomatic or post-season testing (symptoms= 3, severity =4). Table 31 displays performance scores for case # 2 at all four time points.

Table 31 Means for Case #2 over testing time points (pre-season, 72hour post-concussion, asymptomatic, post-season)

	Pre-season	72hour Post-concussion	Asymptomatic	Post-season
Frequent Amplitude	59.78	88.85	94.04	94.66
Frequent Synchronization	90.03	88.20	91.02	92.31
Frequent Timing	82.64	92.77	96.70	92.63
Frequent Connectivity	77.48	89.94	93.92	94.20
Target Amplitude	67.99	80.16	93.68	58.04
Target Synchronization	86.58	81.08	73.82	37.51
Target Timing	68.58	95.07	90.74	68.42
Target Connectivity	74.38	95.43	86.08	54.66
Novel Amplitude	62.68	57.42	59.07	68.52
Novel Synchronization	51.85	51.29	35.20	46.54
Novel Timing	73.11	31.77	56.93	32.89
Novel Connectivity	62.55	46.63	50.40	49.32
Processing Speed	98.40	105.40	102.80	103.40
Attention	103.4	102.90	107.40	105.40
Learning	97.90	105.40	103.60	118.60
Working Memory Speed	102.20	107.10	105.30	102.90
Working Memory Accuracy	105.90	95.80	101.90	101.70
CRT ms	244.43	260.83	238.69	241.38
Symptom Number	0.00	3.00	2.00	0.00
Symptom Severity	0.00	4.00	2.00	0.00
FCZ P3a amplitude(μv)	-1.37	0.47	-1.85	-0.18
CPZ amplitude(μv)	1.21	2.48	1.93	1.78
PZ P3b amplitude(μv)	2.85	2.34	2.75	1.56
FCZ N2 amplitude(μv)	-5.47	-3.26	-5.06	-3.48
FZ N2 amplitude(μv)	-6.84	-4.86	-4.57	n/a
FCZ P3a latency (ms)	660	304	300	660
CPZ latency (ms)	360	692	700	300
PZ P3b latency(ms)	300	440	544	680
FCZ N2 latency(ms)	316	352	352	344
FZ N2 latency(ms)	316	352	352	n/a
***denotes scores are not similar to normative data**				

4.5.3.c Case #3

Case # 3 was a senior linebacker who sustained a concussion during a game. The concussive linear acceleration recorded was 87.7g, rotational acceleration was 4,495.31 rad/s^2 and HITsp was 30.1. Case # 3 missed one game, the asymptomatic testing visit was 9 days

following injury, and post-season testing was conducted 59 days post-injury. Case #3 did not demonstrate any Frequent BNA deficits at 72hour post-concussion or asymptomatic testing time points. During Target and Novel BNA output scores, case #3 recorded scores of 0 for the post-concussion testing time point. These findings show that case #3 did not register a similarity score to the provided network base. Further, for the asymptomatic period, Target BNA output scores continued to demonstrate a BNA similarity score of 0, while returning back to or above pre-season performance at postseason testing. These findings fall below the normative data suggesting that the BNA output scores for case #3 were not similar to normative data. Therefore, case # 3 could have demonstrated worse performance. Axon composite score and clinical reaction time did not show post-injury deficits at either 72-hour post-concussion or asymptomatic. Further, FCZ P3a amplitude was smaller post-injury and continued throughout post-season testing. However latency for FCZ remained consistent across testing time points. No other amplitude or latency ERP components demonstrated deficits post-injury. Table 32 displays performance scores for case # 3 at all four time points.

Table 32 Means for Case #3 over testing time points (pre-season, 72hour post-concussion, asymptomatic, post-season)

	Pre-season	72hour Post-concussion	Asymptomatic	Post-season
Frequent Amplitude	59.76	92.87	77.51	95.61
Frequent Synchronization	24.18	49.99	50.19	35.63
Frequent Timing	42.00	67.12	63.40	63.77
Frequent Connectivity	41.97	66.56	63.70	61.67
Target Amplitude	7.69	**0.00***	**0.00***	54.53
Target Synchronization	0.00	0.00	0.00	17.01
Target Timing	4.98	**0.00***	**0.00***	3.44
Target Connectivity	4.22	**0.00***	**0.00***	25.00
Novel Amplitude	22.75	**0.00***	13.72	43.88
Novel Synchronization	62.34	**0.00***	45.32	83.55
Novel Timing	32.16	**0.00***	37.51	11.86
Novel Connectivity	39.08	**0.00***	32.18	46.43
Processing Speed	104.70	107.40	99.30	99.10
Attention	96.30	106.10	105.30	105.8
Learning	112.50	112.80	111.20	119.00
Working Memory Speed	101.80	106.00	103.40	104.5
Working Memory Accuracy	96.20	93.70	95.90	93.70
CRT ms	246.31	215.07	200.50	234.85
Symptom Number	0.00	11.00	2.00	0.00
Symptom Severity	0.00	28.00	3.00	0.00
FCZ P3a amplitude(μv)	4.33	2.90	3.82	0.95
CPZ amplitude(μv)	6.77	5.11	4.23	4.16
PZ P3b amplitude(μv)	5.38	6.48	4.50	3.42
FCZ N2 amplitude(μv)	-7.62	-7.82	-10.04	-9.52
FZ N2 amplitude(μv)	-5.16	-8.31	-9.73	-9.82
FCZ P3a latency (ms)	408	412	376	448
CPZ latency (ms)	524	468	476	452
PZ P3b latency(ms)	524	504	508	488
FCZ N2 latency(ms)	272	200	236	280
FZ N2 latency(ms)	276	200	300	284
***denotes scores are not similar to normative data**				

4.5.3.d Case #4

Case #4 was a senior wide receiver that sustained a concussion during a game. The concussive linear acceleration was 70.7g, rotational acceleration was 2,416.13 rad/s^2 and HITsp

was 22.2. Case # 4 did not miss a game as a result of the concussion, and the asymptomatic testing visit was 5 days post injury. The post-season testing session was conducted 46 days post-injury. Frequent BNA output scores deficit was present for 72 hour post-concussion Frequent Amplitude (33.26) compared to pre-season (53.89). Frequent Amplitude BNA performance slightly improved at asymptomatic testing (48.27) and post-season (47.86) but remained slightly below pre-season Frequent Amplitude performance score. It is unclear how slight deficit in Frequent Amplitude are clinically relevant. Target BNA output scores did not generate output scores for post-concussion or asymptomatic. This might have been due to a lack of similarity between network scores, or issues with the testing session, as we were not provided any output scores. Axon Processing Speed decreased at 72hour post-concussion (94.90) compared to pre-season (103.90). Axon Processing Speed returned back to pre-season levels during asymptomatic testing session. Axon Attention showed a slight deficit as 72 hour post-concussion (102.30) compared to pre-season (109.80), and slightly improved at asymptomatic (104.10). Finally at post-season, Axon attention returned back to pre-season testing levels (109.90). Clinical reaction time was slightly slower at 72-hour post-concussion (214.66 ms) compared to pre-season (176.95ms), and then improved during asymptomatic testing (176.29 ms). However during post-season testing, the clinical reaction time score slower again (215.86 ms). No ERP amplitude or latency deficits were present at any of the testing time points. Pre-season CPZ and PZ and Asymptomatic PZ amplitudes and latencies were unavailable. Table 33 displays performance scores for case # 4 at all four time points.

Table 33 Means for Case #4 over testing time points (pre-season, 72hour post-concussion, asymptomatic, post-season)

	Pre-season	72hour Post-concussion	Asymptomatic	Post-season
Frequent Amplitude	53.89	33.26	48.27	47.86
Frequent Synchronization	76.32	86.50	91.27	92.26
Frequent Timing	89.18	86.58	76.72	67.40
Frequent Connectivity	73.13	68.78	72.09	69.17
Target Amplitude	93.61	**0.00***	n/a	48.75
Target Synchronization	75.97	n/a	n/a	82.20
Target Timing	78.90	n/a	n/a	95.04
Target Connectivity	82.83	n/a	n/a	75.33
Novel Amplitude	73.20	96.29	70.38	77.26
Novel Synchronization	88.31	84.23	72.19	83.37
Novel Timing	79.21	97.86	95.58	78.93
Novel Connectivity	80.24	92.79	79.38	79.85
Processing Speed	103.90	94.90	104.00	101.90
Attention	109.80	102.30	104.10	109.90
Learning	110.30	106.00	110.30	115.70
Working Memory Speed	104.00	102.80	107.60	109.60
Working Memory Accuracy	101.70	94.00	93.70	117.10
CRT ms	176.95	214.66	176.29	215.86
Symptom Number	0.00	7.00	0.00	0.00
Symptom Severity	0.00	8.00	0.00	0.00
FCZ P3a amplitude(μv)	-0.51	1.68	4.50	0.63
CPZ amplitude(μv)	n/a	6.47	n/a	5.90
PZ P3b amplitude(μv)	n/a	6.30	5.06	5.84
FCZ N2 amplitude(μv)	-6.80	-4.63	-6.35	-6.08
FZ N2 amplitude(μv)	-6.29	-7.38	-4.99	-8.15
FCZ P3a latency (ms)	700	564	688	700
CPZ latency (ms)	n/a	508	n/a	512
PZ P3b latency(ms)	n/a	436	396	436
FCZ N2 latency(ms)	352	264	312	312
FZ N2 latency(ms)	352	332	332	328
***denotes scores are not similar to normative data**				

4.6 Discussion

This investigation aimed to monitor the recovery period in high school football athletes following a sports-related concussion. We hypothesized that despite being asymptomatic, concussed athletes would continue to show decrements on sensitive electroencephalogram testing, while returning back to pre-season testing scores on traditional clinical sensitive cognitive measures.

Research suggests following a concussion, a neurometabolic cascade ensues.[61,62] This neurometabolic cascade causes neuronal dysfunctions,[61,62] which consists of changes in cellular functioning, ionic shifts, metabolic changes and impaired neurotransmission.[61,62] Animal models have demonstrated that increased glucose consumption and hyperglycolysis lasts 7-10 days post-concussive injury,[68] with models conducted in human research showing continued metabolic deficits up to 30 days post-injury.[232,233] These studies suggest metabolic recovery takes weeks to fully resolve. Interestingly, further concussion research suggests the typical clinical concussion recovery period to last between 7-10 days for college athletes[28] and slightly longer for high school athletes.[19,20] Due to the differences in clinical and metabolic recovery time frames, there is concern that despite patients showing clinical concussion resolution, metabolic recovery may continue and athletes may be returning back to play before metabolic recovery is completed. Therefore, this study aimed to examine the effects of cognitive recovery following concussion, using measures of brain activity that would identify continued deficits despite symptom resolution or clinical recovery.

Current concussion consensus suggests implementation of a multifaceted approach to concussion management, including symptom inventory, cognitive function, and motor control.[24-

[26] Individual concussion clinical assessment techniques are not meant as main diagnostic tools, but are implemented to aide in measuring the degree of cognitive functioning post-injury.[24-26] The sensitivity of clinical assessment tools diminishes as time from concussive injury lengthens. [234]As such, Axon neurocognitive testing is most sensitive within 24 hours of injury,[110] and declines in ability to detect cognitive deficits thereafter.[110 88,234]

Results from the current study did not identify changes in axon neurocognitive performance (Processing Speed, Attention, Learning, Working Memory Speed or Working Memory Accuracy) or differences amongst concussed and controls at the post-injury time points. The asymptomatic testing session was performed on average 6 days post-injury, and based on previous research high school athletes display cognitive recovery between 4 and 14 days post injury.[19,20,94,114,116,235] More specifically, Iverson et al[73,235] found the majority of athletes displayed cognitive recovery 5 days post injury, followed by all participants demonstrating cognitive recovery at 10 days post-injury.[235] Similarly, McCrea et al[94] found cognitive function resolution 5-7 days post injury, with research largely supporting cognitive function recovery 3-10 days post injury. Overall, computerized neurocognitive testing at the asymptomatic time point may not have been able to detect subtle deficits in cognitive functioning and more sensitive measures may be needed to detect those deficits.

Additionally, there were no HRQOL differences found for any of the time points or between groups for either SWL or HBI surveys. These findings differ from HRQOL literature following injury, with research suggesting diminished HRQOL is present following injury. Further, Valovich McLeod[236] found negative changes associated with quality of life following concussions. A lower quality of life was found on day 3 post-injury and was found to be short-lived with returning back at day 10 and day 30 post-injury. The current study first assessed

HRQOL within 72 hours post-concussion; however, limited data resulted in this time point being removed. Further upon testing at the asymptomatic time point, no changes were noted. A more thorough, comprehensive and age appropriate HRQOL outcome measurement tools may be more appropriate following concussion. Despite the lack of statistical significance, continuing to use and develop injury specific outcome measurement tools is vital for clinical practice and can enhance patient care.

Furthermore, symptom resolution has been shown to take up to 15 days post-concussion in high school athletes, with some researchers reporting symptom resolution 7-8 days post injury.[20] The current study found no significant differences in symptom reporting between pre-season, asymptomatic, and post-season testing time points. However, despite small sample size and an inability to analyze 72-hour post concussion, trends suggest concussed athletes displayed more post-concussion symptoms and greater symptom severity scores compared to controls within 72 hours post-injury. This finding is consistent with the literature suggesting immediately post-injury, symptom presentation is highest, with gradual resolution back to baseline symptom state.[19] Due to lack of complete data for the 72-hour post concussion time symptom grouping analysis was unable to be run. The relationship between symptom severity, cognitive performance and attentional resources is not clearly defined. However, following a concussion cognitive impairments are present, as such these impairments pose difficulties with attention, concentration, processing speed, learning and executive function.[237] Therefore, one can conclude that as common concussion symptoms are present such as headache, difficulty concentrating, and difficulty remembering, athletes have inherent difficulties on cognitive tasks. However, further analysis with a larger sample size is needed to determine the greater effects of symptoms on cognition.

Furthermore, researchers have used advanced imaging techniques to identify brain function deficits following a concussion. The current study used the BNA algorithm to identify if brain activity changes were present following concussion. Current study findings found no deficits in brain activity over the course of testing time points (pre-season, asymptomatic and post-season) for all BNA output scores. However, Target Amplitude did demonstrate significant improvements for all participants at post-season testing compared to pre-season and asymptomatic testing. These results suggest that the BNA algorithm was unable to detect deficits or differences between concussed and control participants during varying testing time points. The findings deviated from our proposed hypothesis and from previous literature that continued deficits would be present at asymptomatic and post-season following a concussion. Previous research has concluded that continued deficits might be present despite symptom resolution. Specifically, Lovell et al[238] monitored brain activation patterns using fMRI throughout concussion recovery in older teens and found patients with an initial increase in brain activation following a concussion had prolonged recovery. While, McAllister et al[74] found abnormal increased in BOLD activation in mTBI patients following injury during working memory processing and smaller brain activation during higher order processing. Magnetic resonance spectroscopy has shown continued metabolic changes and researchers have found metabolic dysfunctions present in concussed athletes.[232,233] These more sensitive measures of brain function are able to detect concussive deficits throughout the recovery period, while less sensitive measures such as Axon neurocognitive testing, symptom inventory and reaction time are not able to detect subtle changes present outside immediate recovery days. It is unclear as to why BNA performance did not demonstrate significant deficits at asymptomatic and post-injury. A larger sample size may contribute to further significant findings. Further, the BNA algorithm is a novel

tool that is still in its infancy and may not be sensitive enough to detect changes greater than 6 days post-injury.

Furthermore, when looking at the trends of the post-concussion data for concussed participants and comparing it to Eckner et al[207] reliable change index scores, only two out of the nine concussed individuals had a performance scores that fell negatively outside of the 95% confidence interval for Target Connectivity between pre-season and asymptomatic change scores. This is an interesting finding as the Eckner et al[207] paper developed scores for performance in healthy controls and we would have anticipated no deficits were present during asymptomatic time point. No other time point difference scores were identified to deviate from the proposed change index. The BNA tool algorithm may not be sensitive enough to capture post-concussive deficits. Broglio et al[208] supported the current study using the BNA algorithm on 24 concussed athletes and 21 controls. No detectable group level BNA changes were present between concussed and controls following concussive injury.[208] The BNA algorithm has been used in other medical studies and able to identify changes to brain activity. Reches et al[40] used the BNA algorithm in patients with Donepezil administration and found increases in working memory performance in those with Donepezil use. While in another study by Reches et al[39] increased reaction time and decreased response accuracy was identified in patients with Scopolamine use. Both reported that the BNA algorithm can identify working memory and reaction time differences in patient populations. Recently, Kontos et al[43] was able to distinguish group performance in individuals with post-traumatic migraine following concussion with post-traumatic migraine patients demonstrating poorer BNA performance. Despite, these limited studies suggesting the BNA algorithm has clinical utility for various medical conditions, currently the use of BNA for sport-related concussions does not provide greater insight into the

recovery than using ERP analysis, nor does the test provide greater feasibility or sensitivity than clinical concussion assessment techniques. The differing results suggest that subtle changes in cognitive function may not be easily detectable with clinical assessment tools and more sensitive measures are needed to capture these changes.

Electroencephalography has been used in a variety of settings to examine electrical activity in the brain.[188] One component of using EEG is the ability to recover event related potentials (ERP). ERPs allow for brain activity to be recorded while subsequently monitoring performance on cognitive tasks. The P3 component of ERPs demonstrates decision-making processes.[192] Specifically, the P3a component demonstrates an electrophysiological response to an infrequent and unexpected event, while P3b shows an expected but infrequent event.[192] Recently ERP analysis has been used to examine amplitude and latency changes following sport-related concussion.[21-23,38] Results from the current study found longer P3a latencies during post-season testing compared to pre-season and asymptomatic testing time points. In addition, concussed athletes displayed smaller post-season P3a amplitude compared to control participants. These results suggest that following concussion recovery, no deficits were present immediately following injury or at asymptomatic but deficits in attentional resource allocation developed at post-season testing. These findings are different than the proposed hypothesis that continued deficits would be present at asymptomatic and post-season. Although, this study did not detect deficits during the asymptomatic time point, there were deficits present on average 53 days post-injury during post-season testing. The post-season deficits may be a result of environmental factors of having completed the final game of the season and therefore a lack of interest in participating in testing. However, further psychological and environmental monitoring is needed to confirm this hypothesis. Furthermore, the development of post-season deficits may

be a result of continued sports participation following a concussion and sustaining multiple repeated head contacts throughout the remainder of the season. Howell et al[239] examined adolescent athletes and found persistent attentional deficits and lack of execute function 2 months post concussion. Smaller P3 amplitudes suggest that the participants are uncertain or having greater difficulty identifying the difference between the target and nontarget stimuli. These findings are consistent with research that suggests smaller amplitudes and longer latencies are present in individuals with a history of concussion.[22,38,206]

Furthermore, research has suggested that following a concussion, prolonged deficits may occur and appear later in life. Gaetz and Weinberg[35], researched young adults (18-34 years old) and older adults (35-55 years old) with and without a concussion history and found that those with a concussion history, regardless of age, displayed longer P3 latency during visual oddball tasks. Theriault et al[22] found subjects who had a recent concussion history (within the previous year) demonstrated smaller P3a amplitude compared to subjects with no concussion history. In 2009, Broglio et al[23] found decreased P3b amplitude in individuals with a concussion history compared to controls. Similarly, De Beaumont et al[206] examined a group of older adults who sustained their last concussion 30 years prior to testing and concluded that individuals with a concussion history showed significantly smaller P3a and P3b amplitude as well as a longer peak latency than the comparison group. The above findings are similar to the current study in which group differences were present with smaller P3a amplitude at post-season in concussed athletes compared to controls. Overall, EEG research shows strong support to detect changes in neuronal response following a concussion. Further research with a larger sample size is needed to outline deficits 72hours post-concussion and through the recovery period. Monitoring more time points

throughout the recovery period will further identify where deficits are present following concussive injury.

Further, average concussive linear acceleration was 77.24g, rotational acceleration was 3,518.73 rad/s^2 and HITsp was 38.9. Although there is no established concussion threshold, the recorded linear acceleration was similar to prior research, while the rotational acceleration concussive values are slightly lower than established high school research, but similar to establish college research. More specifically, concussive literature has found between 74g and 146g of linear acceleration and between 5,582 rad/s^2 and 9,515 rad/s^2 of rotational acceleration at the high school level.[140,142,148,165,169] With more 72hour post-concussive data, a thorough analysis could be conducted to determine if symptom presentation, and cognitive performance was associated with greater linear and rotational acceleration.

Lastly, the use of the BNA algorithm or ERP analysis does not provide more information than already available with common concussion assessment tools. Clinically, using the current validated concussion assessment tools recommended provides a multifaceted approach to concussion management. Further research is needed to validate the use of the BNA or ERP analysis as concussion diagnosis and management tools. Overall, continuing to follow best practices for concussion management is recommended.

4.7 Limitations

This study is not without limitations. For an effect size of 0.20, power of 0.80 and alpha of 0.05, 36 participants are required to reach significance. Table 34 displays effect sizes and power analysis for Aim2. However, the current study only had full data on 4 concussed and 4 controls for all four of the time points and therefore, the 72hour post-concussion time point was not included in statistical analysis and only referenced in the case studies. Additional limitations include the testing time points. Concussed participants were required to have a diagnosed

concussion from a physician prior to 72-hour post-concussion testing session. However, due to the nature of when football games are played (majority Saturdays), obtaining physician diagnosis within 72 hours can be logistically difficult and therefore some participants were lost for the 72 hour time point.

Table 34 Aim 2 Effect sizes for clinical assessments

Measure	Cohen's d	Effect
SWL	0.34	Small effect
HBI Cognitive	0.85	Large effect
HBI Somatic	0.52	Medium effect
CRT	0.31	Small effect
SCAT Score	1.21	Large effect
SCAT Severity	0.76	Negligible effect
Frequent Amplitude	0.58	Medium effect
Frequent Synchronization	0.04	Negligible effect
Frequent Timing	0.65	Medium effect
Frequent Connectivity	0.43	Medium effect
Target Amplitude	0.26	Small effect
Target Synchronization	0.35	Small effect
Target Timing	0.76	Large effect
Target Connectivity	0.35	Small effect
Novel Amplitude	0.27	Small effect
Novel Synchronization	0.45	Medium effect
Novel Timing	0.11	Negligible effect
Novel Connectivity	0.30	Small effect
Axon Processing Speed	0.92	Large effect
Axon Attention	0.32	Small effect
Axon Learning	0.10	Negligible effect
Axon Working Memory Speed	0.45	Medium effect
Axon Working Memory Accuracy	0.10	Negligible effect
Average number of errant tones	0.31	Small effect
Average percent accuracy	0.71	Medium effect
Average reaction time	0.50	Medium effect
FCZ P3a amplitude	1.26	Very Large effect
CPZ P3a amplitude	0.65	Medium effect
CPZ P3b amplitude	0.65	Medium effect
PZ P3b amplitude	1.11	Very Large effect
FCZ N2 amplitude	0.57	Medium effect
FZ N2 amplitude	0.41	Medium effect
FCZ P3a latency	0.46	Medium effect
CPZ P3a latency	0.20	Small effect
CPZ P3b latency	0.20	Small effect
PZ P3b latency	0.16	Small effect
FCZ N2 latency	0.78	Large effect
FZ N2 latency	0.66	Medium effect
Relative size of Cohen's d[231]: Negligible effect (>=-0.15 and <0.15) Small effect (>=0.15 and <0.40) Medium effect (>=0.40 and <0.75) Large effect (>=0.75 and <1.10) Very large effect (>=1.10 and <1.45) Huge effect (>1.45)		

4.8 Conclusion

In conclusion, concussed high school football athletes did not differ negatively from their pre-season assessments during any of the post-concussion clinical assessments. However, concussed athletes demonstrated smaller P3a amplitudes during post-season testing, suggesting that the participants did not display initial deficits following concussion, but upon returning back to participation and at the conclusion of football deficits were present with difficulty differing between stimuli and deficits in resource allocation. Furthermore, all participants demonstrated a prolonged P3a latency at post-season suggesting deficits were present to stimulus categorization. Lastly, the lack of significance to clinical assessments may be likely due to lack of power and small sample size. Further analysis will include a larger sample size and additionally incorporate symptom severity correlations.

Chapter 5 Conclusion and Future Directions

5.1 Conclusion

In conclusion, the purpose of these studies was to monitor brain activity following repeated head impacts associated with a season of high school football and furthermore to monitor recovery patterns following a subsequent concussion. In all, participation in one season of high school football did not demonstrate negative brain activity patterns and cognitive function declines. Further, when differences were noted, significant improvements were found throughout the testing time points. These improvements are theorized to be associated with benefits of physical activity and sport participation, and outweigh any negative effects of repeated head trauma. Despite, the lack of negative effects associated with repeated head impacts in one season of football, cumulative effects following multiple years of head impact exposure is unknown and reducing the overall number of head impacts may diminish late life cognitive impairments.

Furthermore, recovery patterns following a concussion did not differ from pre-season clinical assessments. These results suggest that once a concussed athlete was asymptomatic, no deficits were found compared to pre-season testing scores. Further, post-season deficits were present, suggesting that upon returning back to participation following a concussion, attentional deficits were found during post-season. This suggests that although the concussed athlete may be recovered following a concussion, continued exposure to repeated head impacts may present post-season cognitive deficits at the conclusion of the season. In all, further research is needed to

monitor concussion recovery patterns immediately post-injury and continue throughout the remainder of a football season to track cognitive function.

5.2 Future Directions

Future research will incorporate monitoring the effects cumulative head impacts impose on cognitive function from the beginning of a playing career. Starting monitoring at a young age will allow researchers to calculate the number of head impacts sustained throughout a playing career and how those impacts affect cognition. More specifically, analyzing current data based on academic year, may demonstrate deficits as athletes progress through playing careers and increase playing time. Further, a longitudinal study will allow researchers to map how cognitive function changes as a result of past sport participation while controlling for head impact exposure. Research has shown cognitive deficits in athletes with a concussion history, therefore, further analyzing the study based on concussion history exposure, may eliminate any factors as a result of a previous concussion and focus on the effects sub-concussive head impacts impose on cognitive function. Lastly, using a more difficult task or dual task during testing may highlight further deficits that may be present as a result of head impact exposure. Further research will continue to monitor the effects repeated head impacts impose of brain health and monitor neurophysiological changes that are present during sport participation. Further understanding brain development through adolescents will help enhance the effects associated with repeated head impacts.

Future research will continue to monitor recovery patterns following a concussive injury. Monitoring recovery patterns during a more specific window (24 hours, 72 hours, 5 days, asymptomatic, 1 month, 6 months and 1 year post injury) may further outline the recovery pattern following concussion and gain a better understanding into brain activity during recovery. Furthermore, monitoring metabolic recovery through blood draws or magnetic resonance

spectroscopy while monitoring brain activity through ERP, and common clinical assessment measures will be able to enhance the ability to monitor concussion recovery and make appropriate RTP decisions. Lastly, future research will analyze current data based on concussion history, and replicate with a larger sample size to include 72-hour post concussion time points.

Appendix A

GUID_____ Subject Number_____ | 1

VISIT 1: BASELINE TESTING

Informed Consent

Specify the date the subject visited for baseline testing prior to start of season (MM/DD/YYYY)
_____/_____/_____

Specify the date on which the participant/subject (or the legal representative on behalf of the participant/subject) agrees to participate in a protocol, treatment, or other activity by signing an informed consent document
_____/_____/_____

Specify the type of informed assent/consent that was obtained ☐ Written ☐ Electronic ☐ Other

Did the subject provide informed assent (if <18 years) or consent (if >17)? ☐ Yes ☐ No ☐ Not applicable

If the subject is a minor (<18 years), was written informed parental consent obtained?
☐ Yes ☐ No

If applicable, what was the date of obtained assent? _____/_____/_____

Inclusion Criteria

Is the subject aged 14-26? ☐ Yes ☐ No

Is the subject currently symptomatic? ☐ Yes ☐ No

Does the subject express willingness to participate and is he/she able to give informed assent (child) and/or consent (parent for minors or adult 18+ of age for self)? ☐ Yes ☐ No

Is the subject a member of an organized athletic team or do they regularly train for and participate in independent athletic contests during at least one sports season? ☐ Yes ☐ No

Is the subject currently enrolled in a high school or college? ☐ Yes ☐ No

Exclusion Criteria

Is the subject bald or do they have dread locks/long, thick hair which precludes the appropriate scalp electrode fit?
☐ Yes ☐ No

What is the value for the subject's age, calculated as elapsed time since the birth of the participant/subject
_____

Does the subject currently have ADHD or have a history of ADHD? ☐ Yes ☐ No

Does the subject have an active head lice infection, open scalp wound, deafness or/and blindness?
☐ Yes ☐ No

Does the subject currently have or ever had a history of moderate or severe TBI (i.e., Glasgow Coma Scale <13), any brain injury with positive neuroimaging findings, or brain surgery? ☐ Yes ☐ No

Has the subject sustained a diagnosed concussion within the previous six months?
☐ Yes ☐ No

Demographics

Date the participant/subject was born _____/_____/_____

Specify the subject's natural sex ☐ Male ☐ Female

What is the subject's city of birth? _____

What is the subject's country of birth? ☐ United States ☐ Other _____

What is the subject's self-reported height in cm? _____

What is the subject's self-reported weight in kg? _____

What is the subject's laterality? ☐ Right-handed ☐ Left-handed

Category of race(s) the participant/ subject most closely identifies with

- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White
- ☐ Unknown
- ☐ Not reported
- ☐ Other_____

Category of ethnicity the participant/subject most closely identifies with

- ☐ Hispanic or Latino
- ☐ Not Hispanic or Latino
- ☐ Unknown
- ☐ Not reported

Text for the language the participant/subject speaks most often _____

Status of employment of participant/subject

- ☐ Working now
- ☐ Only temporarily laid off
- ☐ Sick leave or maternity leave
- ☐ Looking for work, unemployed
- ☐ Retired
- ☐ Disabled, permanently or temporarily
- ☐ Keeping house
- ☐ Student
- ☐ Unknown
- ☐ Other_____

Highest grade or level of school the participant's/subject's primary caregiver has completed or the highest degree he/she has received

- ☐ Never attended/Kindergarten only
- ☐ 1st grade
- ☐ 2nd grade
- ☐ 3rd grade
- ☐ 4th grade
- ☐ 5th grade
- ☐ 6th grade
- ☐ 7th grade
- ☐ 8th grade
- ☐ 9th grade
- ☐ 10th grade
- ☐ 11th grade
- ☐ 12th grade, no diploma
- ☐ High school diploma
- ☐ GED or equivalent
- ☐ Some college, no degree
- ☐ Associate degree: occupational, technical, or vocational program
- ☐ Associate degree: academic program
- ☐ Bachelor's degree (e.g., BA, AB, BS, BBA)
- ☐ Master's degree (e.g., MA, MS, MEng, MEd, MBA)
- ☐ Professional school degree (e.g., MD, DDS, DVM, JD)
- ☐ Doctoral degree (e.g., PhD, EdD)
- ☐ Unknown

Number of years of education the subject has completed _____

Status of participant's/subject's participation in school

- ☐ Going to school
- ☐ On vacation from school (between grades)
- ☐ Neither
- ☐ Unknown

Specify whether the subject is enrolled in high school or college

- ☐ High school
- ☐ College
- ☐ Other, please specify _____

What is the name of the institution the subject is enrolled in? _____

Has the subject ever repeated a year of school? ☐ Yes ☐ No

Has the subject ever skipped a year of school? ☐ Yes ☐ No

Has the subject ever received academic assistance? ☐ Yes ☐ No

High School Sport History

Did the subject play sports in high school (Grades 9-12)? ☐ Yes No

What sport did the subject participate in? (List primary sport first)
_____

How many years did the subject play? ☐ 1 ☐ 2 ☐ 3 ☐ 4

List all other sports and specify number of years played in high school (choose only 1-4 years)

Junior High School Sport History

Did the subject play sports in high school (Grades 6-8)? ☐ Yes No

What sport did the subject participate in? (List primary sport first) _____

How many years did the subject play? ☐ 1 ☐ 2 ☐ 3

List all other sports and specify number of years played in high school (choose only 1-3 years)

Elementary School Sport History

Did the subject play sports in high school (Grades 1-5)? ☐ Yes No

What sport did the subject participate in? (List primary sport first)

_____

How many years did the subject play? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

List all other sports and specify number of years played in high school (choose only 1-4 years)

Medical Screening

Condition	Yes	No	If "Yes," please specify	Year of diagnosis	Status Active	Status Inactive
Experience migraines						
Alcohol Abuse			Frequency (drinks/week):			
Drug Abuse			Drug type: Frequency (times/week):			
Regular medication use			Medication name: Frequency:			
Family history of migraine headache in a first degree (eg mother, father, sibling) relative?			Whom: Year of diagnosis for each relative:			
Been under general anesthesia			Number of times			
Takes non-prescription stimulants (e.g., caffeine, red bull, monster, etc.)			Frequency (times/day):			

Have you had one or more headaches in the last 3 months?	**Yes**	**No**
Has your migraine limited your ability to work, study, or do what you wanted to do?	**Yes**	**No**
If yes, has light bothered you while experiencing a headache or migraine?	**Yes**	**No**
If yes, has a migraine or headache resulted in nauseas or getting sick to your stomach?	**Yes**	**No**

Concussion History

Number of prior concussions	_____
The reliability of the reported injury date	☐ Verified ☐ Estimated ☐ Unknown
The point in time estimated as injury date and time ☐ Time that the participant/subject became symptomatic ☐ Time of first trauma activation	☐ Time of presentation to emergency department
Date (and time, if applicable and known) reported for onset of participant's/subject's symptoms	_____/_____/_____
Date (and time, if applicable and known) of arrival at the first hospital, if the participant/subject was transferred to the study center from another hospital	_____/_____/_____

Diagnosed Concussion

Number of times subject has been diagnosed with a concussion by a medical provider (i.e. MD, ATC, EMT, PA, Nurse, etc.,) in the past (not including current concussion). Injury may or may not have been sport related (e.g. auto accident)

	Specify the date the concussion was sustained	Approximate age at time of injury	Did the concussion result in loss of consciousness?	Specify the duration of unconsciousness (minutes)	Did the concussion result in post-traumatic amnesia?	Specify amnesia duration (min)	Duration of symptoms (days)
Injury #1			Yes No		Yes No		
Injury #2			Yes No		Yes No		
Injury #3			Yes No		Yes No		
Injury #4			Yes No		Yes No		
Injury #5			Yes No		Yes No		

Undiagnosed Concussion

Please use the following definition of concussion to answer the questions below

Definition of concussion: A concussion is a blow to your head that causes a variety of symptoms that may last for a short period of time, such as a few plays or minutes of a game, or a longer period of time. These symptoms may include any of the following:

- Headache
- Difficulty concentrating or focusing
- Feeling slowed down
- Dizziness or balance problems
- Nausea
- Fatigue / lack of energy
- Feeling like you're in a fog
- Irritable
- Drowsiness
- Forgetting things (before or after the injury)
- Sensitivity to light
- Loss of balance
- Sensitivity to noise
- Blurred vision

IMPORTANT: A) you can have a concussion without being "knocked out" or unconscious

B) Getting your "bell rung" and "clearing the cobwebs" is a concussion

Following a blow to the head, have the subject ever experienced any of the symptoms listed below or had a concussion that was not evaluated by a medical professional (eg Doctor, Athletic Trainer, EMT)

☐ **Yes** ☐ **No**

	Specify the date the concussion was sustained	Approximate age at time of injury	Did the concussion result in loss of consciousness?	Specify the duration of unconsciousness (minutes)	Did the concussion result in post-traumatic amnesia?	Specify amnesia duration (min)	Duration of symptoms (days)
Injury #1			Yes No		Yes No		
Injury #2			Yes No		Yes No		
Injury #3			Yes No		Yes No		
Injury #4			Yes No		Yes No		
Injury #5			Yes No		Yes No		

Satisfaction with Life Survey

	Strongly Agree	Agree	Slightly Agree	Neither agree nor Disagree	Slightly Disagree	Disagree	Strongly Disagree
In most ways my life is close to my ideal	7	6	5	4	3	2	1
The conditions of my life are excellent	7	6	5	4	3	2	1
I am satisfied with my life	7	6	5	4	3	2	1
So far I have gotten the important things I want in life	7	6	5	4	3	2	1
If I could live my life over, I would change almost nothing	7	6	5	4	3	2	1
Total sum of the responses to the five items							

Health Behavior Inventory

	Never	Rarely	Sometimes	Often
I have trouble paying attention	0	1	2	3
I get distracted easily	0	1	2	3
I have a hard time concentrating	0	1	2	3
I have problems remembering what people tell me	0	1	2	3
I have problems following directions	0	1	2	3
I daydream too much	0	1	2	3
I get confused	0	1	2	3
I forget things	0	1	2	3
I have problems finishing things	0	1	2	3
I have trouble figuring things out	0	1	2	3
It's hard for me to learn new things	0	1	2	3
I have headaches	0	1	2	3
I feel dizzy	0	1	2	3
I feel like the room is spinning	0	1	2	3
I feel like I'm going to faint	0	1	2	3
Things are blurry when I look at them	0	1	2	3
I see double	0	1	2	3
I feel sick to my stomach	0	1	2	3
I get tired a lot	0	1	2	3
I get tired easily	0	1	2	3
Sum of cognitive items 1-11 (0-33)				
Sum of somatic items 12-20 (0-27)				

Head Impact Monitoring

What is the helmet make? ☐ Riddell ☐ Other_____

What is the helmet's model? ☐ Revolution Speed ☐ Other_____

How many seasons has the subject's helmet been in use? _____

What is the size of the subject's helmet?

☐ Small ☐ Large
☐ Medium ☐ Extra-Large

EEG/ERP

Were EEG/ERP measurements recorded? ☐ Yes ☐ No

What is the test session number: _____

What is the value for circumference of the subject's head (cm): _____

What EEG Net size was used? ☐ Small ☐ Medium ☐ Large

Specify the time the EEG recording started and ended (hh:mm) Start: End:

What was the order the ERP tasks were conducted in? ☐ Oddball-GoNoGo ☐ GoNoGo-Oddball

Indicate level of Oddball task completion: ☐ Completed ☐ Started but incomplete ☐ Not Done

BNA Scores	Synchronization	Timing	Connectivity
Auditory Odd-Ball Task			
Go-NoGo Task - Go			
Go-NoGo Task - NoGo			

Axon Results

Specify the date and time axon evaluation was completed: _____/_____/_____, _____:_____ AM PM

#	Composite Scores	Score	Reaction Time (minutes)
1	Processing Speed		
2	Attention		
3	Learning		
4	Working Memory Speed		
5	Working Memory Accuracy		

Clinical Reaction Time

Specify the date and time CRT evaluation was completed: _____/_____/_____, _____:_____ AM PM

Trial #	Fall distance (cm)	Clinical Reaction Time (ms)
1	☐☐.☐ cm	
2	☐☐.☐ cm	
3	☐☐.☐ cm	
4	☐☐.☐ cm	
5	☐☐.☐ cm	
6	☐☐.☐ cm	
7	☐☐.☐ cm	
8	☐☐.☐ cm	

SCAT-3: Symptoms

	None	Mild		Moderate		Severe	
Headache:	0	1	2	3	4	5	6
"Pressure in head:"	0	1	2	3	4	5	6
Neck pain:	0	1	2	3	4	5	6
Nausea or vomiting:	0	1	2	3	4	5	6
Dizziness:	0	1	2	3	4	5	6
Blurred vision:	0	1	2	3	4	5	6
Balance problems:	0	1	2	3	4	5	6
Sensitivity to light:	0	1	2	3	4	5	6
Sensitivity to noise:	0	1	2	3	4	5	6
Feeling slowed down:	0	1	2	3	4	5	6
Feeling like "in a fog:"	0	1	2	3	4	5	6
"Don't feel right:"	0	1	2	3	4	5	6
Difficulty concentrating:	0	1	2	3	4	5	6
Difficulty remembering:	0	1	2	3	4	5	6
Fatigue or low energy:	0	1	2	3	4	5	6
Confusion:	0	1	2	3	4	5	6
Drowsiness:	0	1	2	3	4	5	6
Trouble falling asleep:	0	1	2	3	4	5	6
More emotional:	0	1	2	3	4	5	6
Irritability:	0	1	2	3	4	5	6
Sadness:	0	1	2	3	4	5	6
Nervous or anxious:	0	1	2	3	4	5	6

Total number of symptoms reported:	**Total symptom score:**
Do the symptoms get worse with physical activity?	☐ Yes ☐ No
Do the symptoms get worse with mental activity?	☐ Yes ☐ No
Cause of symptoms:	

Adverse Events

#	Adverse Event diagnosis, if known, or Signs/Symptoms (One sign/symptom per line)	Serious	Start date (mm/dd/yyyy)	Stop date or specify if ongoing (mm/dd/yyyy)	Severity	Relation to study procedure	Action taken	Outcome
1		Yes No						
2		Yes No						
3		Yes No						
4		Yes No						
5		Yes No						
6		Yes No						
7		Yes No						
8		Yes No						
9		Yes No						
10		Yes No						
					1-Mild 2-Moderate 3-Severe	1-Unrelated 2-Unlikely related 3-Possibly related 4-Probably related 5-Definitely related	1-None 2-Drug therapy 3-Study discontinued 4-Other (specify on comment box)	1-Resolved 2-Improved 3-Unchanged 4-Worsened

Protocol Deviations

Have any protocol deviations occurred? ☐ Yes ☐ No

#	Date of Deviation	CRF Page	Specify	Outcome
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Concomitant Medication/Treatment

Is the subject currently taking any medication/treatment? ☐ Yes ☐ No

#	Drug Name (generic name if possible)	Dose	Units	Frequency	Route	Indication	Therapy Start Date	Therapy End Date	Therapy Ongoing
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									

Frequency		Route	
QD = Every day	QID = Four Times a Day	PO = Oral	SC = Subcutaneous
QOD = Every other day	SID = Five Times a Day	TOP = Topical	INH = Inhalation
BID = Twice a Day	PRN = as needed	IV = Intravenous	PR = Per Rectum

TID = Three Times a Day	Other (Specify)	IM = Intramuscular	Other (Specify

Comments Page

Are there any comments to this form?

☐ Yes
☐ No

Page Number	Comment

VISIT 2: MID-SEASON EVALUATION

Specify the date the subject visited for testing (MM/DD/YYYY)	_____/_____/_____
What was the date of the first game?	_____/_____/_____
What was the date the season started?	_____/_____/_____

Adverse Events and Concomitant Medications

Did the subject experience any adverse events since the last visit?	☐ Yes ☐ No
Has the subject had any change in medications since the last visit?	☐ Yes ☐ No

Head Impact Monitoring

Head Impact System used (if applicable)		☐ HIT-System ☐ Estimation	
Number of practices	_____	Number of practice impacts	_____
Number of games	_____	Number of game impacts	_____
Total number of practices and games	_____	Total number of impacts	_____

Satisfaction with Life Survey

	Strongly Agree	Agree	Slightly Agree	Neither agree nor Disagree	Slightly Disagree	Disagree	Strongly Disagree
In most ways my life is close to my ideal	7	6	5	4	3	2	1
The conditions of my life are excellent	7	6	5	4	3	2	1
I am satisfied with my life	7	6	5	4	3	2	1
So far I have gotten the important things I want in life	7	6	5	4	3	2	1
If I could live my life over, I would change almost nothing	7	6	5	4	3	2	1
Total sum of the responses to the five items							

Health Behavior Inventory

	Never	Rarely	Sometimes	Often
I have trouble paying attention	0	1	2	3
I get distracted easily	0	1	2	3
I have a hard time concentrating	0	1	2	3
I have problems remembering what people tell me	0	1	2	3
I have problems following directions	0	1	2	3
I daydream too much	0	1	2	3
I get confused	0	1	2	3
I forget things	0	1	2	3
I have problems finishing things	0	1	2	3
I have trouble figuring things out	0	1	2	3
It's hard for me to learn new things	0	1	2	3
I have headaches	0	1	2	3
I feel dizzy	0	1	2	3
I feel like the room is spinning	0	1	2	3
I feel like I'm going to faint	0	1	2	3
Things are blurry when I look at them	0	1	2	3
I see double	0	1	2	3
I feel sick to my stomach	0	1	2	3
I get tired a lot	0	1	2	3
I get tired easily	0	1	2	3
Sum of cognitive items 1-11 (0-33)				
Sum of somatic items 12-20 (0-27)				

EEG/ERP

Were EEG/ERP measurements recorded?	☐ Yes ☐ No
What is the test session number:	_____
What is the value for circumference of the subject's head (cm):	_____
What EEG Net size was used?	☐ Small ☐ Medium ☐ Large
Specify the time the EEG recording started and ended (hh:mm)	Start: End:
What was the order the ERP tasks were conducted in?	☐ Oddball-GoNoGo ☐ GoNoGo-Oddball
Indicate level of Oddball task completion:	☐ Completed ☐ Started but incomplete ☐ Not Done

BNA Scores	Synchronization	Timing	Connectivity
Auditory Odd-Ball Task			
Go-NoGo Task - Go			
Go-NoGo Task - NoGo			

Axon Results

Specify the date and time axon evaluation was completed: _____/_____/_____, _____:_____ AM PM

#	Composite Scores	Score	
1	Processing Speed		
2	Attention		
3	Learning		
4	Working Memory Speed		
5	Working Memory Accuracy		

Clinical Reaction Time

Specify the date and time CRT evaluation was completed: _____/_____/_____, _____:_____ AM PM

Trial #	Fall distance (cm)	Clinical Reaction Time (ms)
1	□□.□ cm	
2	□□.□ cm	
3	□□.□ cm	
4	□□.□ cm	
5	□□.□ cm	
6	□□.□ cm	
7	□□.□ cm	
8	□□.□ cm	

SCAT-3: Symptoms

	None	Mild		Moderate		Severe	
Headache:	0	1	2	3	4	5	6
"Pressure in head:"	0	1	2	3	4	5	6
Neck pain:	0	1	2	3	4	5	6
Nausea or vomiting:	0	1	2	3	4	5	6
Dizziness:	0	1	2	3	4	5	6
Blurred vision:	0	1	2	3	4	5	6
Balance problems:	0	1	2	3	4	5	6
Sensitivity to light:	0	1	2	3	4	5	6
Sensitivity to noise:	0	1	2	3	4	5	6
Feeling slowed down:	0	1	2	3	4	5	6
Feeling like "in a fog:"	0	1	2	3	4	5	6
"Don't feel right:"	0	1	2	3	4	5	6
Difficulty concentrating:	0	1	2	3	4	5	6
Difficulty remembering:	0	1	2	3	4	5	6
Fatigue or low energy:	0	1	2	3	4	5	6
Confusion:	0	1	2	3	4	5	6
Drowsiness:	0	1	2	3	4	5	6
Trouble falling asleep:	0	1	2	3	4	5	6
More emotional:	0	1	2	3	4	5	6
Irritability:	0	1	2	3	4	5	6
Sadness:	0	1	2	3	4	5	6
Nervous or anxious:	0	1	2	3	4	5	6

Total number of symptoms reported:	**Total symptom score:**
Do the symptoms get worse with physical activity?	☐ Yes ☐ No
Do the symptoms get worse with mental activity?	☐ Yes ☐ No
Cause of symptoms:	

Adverse Events

#	Adverse Event diagnosis, if known, or Signs/Symptoms (One sign/symptom per line)	Serious	Start date (mm/dd/yyyy)	Stop date or specify if ongoing (mm/dd/yyyy)	Severity	Relation to study procedure	Action taken	Outcome
1		Yes No						
2		Yes No						
3		Yes No						
4		Yes No						
5		Yes No						
6		Yes No						
7		Yes No						
8		Yes No						
9		Yes No						
10		Yes No						
					1-Mild 2-Moderate 3-Severe	1-Unrelated 2-Unlikely related 3-Possibly related 4-Probably related 5-Definitely related	1-None 2-Drug therapy 3-Study discontinued 4-Other (specify on comment box)	1-Resolved 2-Improved 3-Unchanged 4-Worsened

Protocol Deviations

Have any protocol deviations occurred? ☐ Yes ☐ No

#	Date of Deviation	CRF Page	Specify	Outcome
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Concomitant Medication/Treatment

Is the subject currently taking any medication/treatment? ☐ Yes ☐ No

#	Drug Name (generic name if possible)	Dose	Units	Frequency	Route	Indication	Therapy Start Date	Therapy End Date	Therapy Ongoing
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									

Frequency		Route	
QD = Every day	QID = Four Times a Day	PO = Oral	SC = Subcutaneous
QOD = Every other day	SID = Five Times a Day	TOP = Topical	INH = Inhalation
BID = Twice a Day	PRN = as needed	IV = Intravenous	PR = Per Rectum

TID = Three Times a Day	Other (Specify)	IM = Intramuscular	Other (Specify

Comments Page

Are there any comments to this form?

☐ Yes
☐ No

Page Number	Comment

VISIT 3: POST-SEASON EVALUATION

Specify the date the subject visited for testing (MM/DD/YYYY)	_____/_____/_____
What was the date of the first game?	_____/_____/_____
What was the date the season started?	_____/_____/_____

Adverse Events and Concomitant Medications

Did the subject experience any adverse events since the last visit?	☐ Yes ☐ No
Has the subject had any change in medications since the last visit?	☐ Yes ☐ No

Head Impact Monitoring

Head Impact System used (if applicable)		☐ HIT-System ☐ Estimation	
Number of practices	_____	Number of practice impacts	_____
Number of games	_____	Number of game impacts	_____
Total number of practices and games	_____	Total number of impacts	_____

Satisfaction with Life Survey

	Strongly Agree	Agree	Slightly Agree	Neither agree nor Disagree	Slightly Disagree	Disagree	Strongly Disagree
In most ways my life is close to my ideal	7	6	5	4	3	2	1
The conditions of my life are excellent	7	6	5	4	3	2	1
I am satisfied with my life	7	6	5	4	3	2	1
So far I have gotten the important things I want in life	7	6	5	4	3	2	1
If I could live my life over, I would change almost nothing	7	6	5	4	3	2	1
Total sum of the responses to the five items							

Health Behavior Inventory

	Never	Rarely	Sometimes	Often
I have trouble paying attention	0	1	2	3
I get distracted easily	0	1	2	3
I have a hard time concentrating	0	1	2	3
I have problems remembering what people tell me	0	1	2	3
I have problems following directions	0	1	2	3
I daydream too much	0	1	2	3
I get confused	0	1	2	3
I forget things	0	1	2	3
I have problems finishing things	0	1	2	3
I have trouble figuring things out	0	1	2	3
It's hard for me to learn new things	0	1	2	3
I have headaches	0	1	2	3
I feel dizzy	0	1	2	3
I feel like the room is spinning	0	1	2	3
I feel like I'm going to faint	0	1	2	3
Things are blurry when I look at them	0	1	2	3
I see double	0	1	2	3
I feel sick to my stomach	0	1	2	3
I get tired a lot	0	1	2	3
I get tired easily	0	1	2	3
Sum of cognitive items 1-11 (0-33)				
Sum of somatic items 12-20 (0-27)				

EEG/ERP

Were EEG/ERP measurements recorded?	☐ Yes ☐ No
What is the test session number:	_____
What is the value for circumference of the subject's head (cm):	_____
What EEG Net size was used?	☐ Small ☐ Medium ☐ Large
Specify the time the EEG recording started and ended (hh:mm)	Start: End:
What was the order the ERP tasks were conducted in?	☐ Oddball-GoNoGo ☐ GoNoGo-Oddball
Indicate level of Oddball task completion:	☐ Completed ☐ Started but incomplete ☐ Not Done

BNA Scores	Synchronization	Timing	Connectivity
Auditory Odd-Ball Task			
Go-NoGo Task - Go			
Go-NoGo Task - NoGo			

Axon Results

Specify the date and time axon evaluation was completed: _____/_____/_____, _____:_____ AM PM

#	Composite Scores	Score	
1	Processing Speed		
2	Attention		
3	Learning		
4	Working Memory Speed		
5	Working Memory Accuracy		

Clinical Reaction Time

Specify the date and time CRT evaluation was completed: _____/_____/_____, _____:_____ AM PM

Trial #	Fall distance (cm)	Clinical Reaction Time (ms)
1	☐☐.☐ cm	
2	☐☐.☐ cm	
3	☐☐.☐ cm	
4	☐☐.☐ cm	
5	☐☐.☐ cm	
6	☐☐.☐ cm	
7	☐☐.☐ cm	
8	☐☐.☐ cm	

SCAT-3: Symptoms

	None	Mild		Moderate		Severe	
Headache:	0	1	2	3	4	5	6
"Pressure in head:"	0	1	2	3	4	5	6
Neck pain:	0	1	2	3	4	5	6
Nausea or vomiting:	0	1	2	3	4	5	6
Dizziness:	0	1	2	3	4	5	6
Blurred vision:	0	1	2	3	4	5	6
Balance problems:	0	1	2	3	4	5	6
Sensitivity to light:	0	1	2	3	4	5	6
Sensitivity to noise:	0	1	2	3	4	5	6
Feeling slowed down:	0	1	2	3	4	5	6
Feeling like "in a fog:"	0	1	2	3	4	5	6
"Don't feel right:"	0	1	2	3	4	5	6
Difficulty concentrating:	0	1	2	3	4	5	6
Difficulty remembering:	0	1	2	3	4	5	6
Fatigue or low energy:	0	1	2	3	4	5	6
Confusion:	0	1	2	3	4	5	6
Drowsiness:	0	1	2	3	4	5	6
Trouble falling asleep:	0	1	2	3	4	5	6
More emotional:	0	1	2	3	4	5	6
Irritability:	0	1	2	3	4	5	6
Sadness:	0	1	2	3	4	5	6
Nervous or anxious:	0	1	2	3	4	5	6

Total number of symptoms reported:	**Total symptom score:**
Do the symptoms get worse with physical activity?	☐ Yes ☐ No
Do the symptoms get worse with mental activity?	☐ Yes ☐ No
Cause of symptoms:	

Adverse Events

#	Adverse Event diagnosis, if known, or Signs/Symptoms (One sign/symptom per line)	Serious	Start date (mm/dd/yyyy)	Stop date or specify if ongoing (mm/dd/yyyy)	Severity	Relation to study procedure	Action taken	Outcome
1		Yes No						
2		Yes No						
3		Yes No						
4		Yes No						
5		Yes No						
6		Yes No						
7		Yes No						
8		Yes No						
9		Yes No						
10		Yes No						
					1-Mild 2-Moderate 3-Severe	1-Unrelated 2-Unlikely related 3-Possibly related 4-Probably related 5-Definitely related	1-None 2-Drug therapy 3-Study discontinued 4-Other (specify on comment box)	1-Resolved 2-Improved 3-Unchanged 4-Worsened

Protocol Deviations

Have any protocol deviations occurred? ☐ Yes ☐ No

#	Date of Deviation	CRF Page	Specify	Outcome
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Concomitant Medication/Treatment

Is the subject currently taking any medication/treatment? ☐ Yes ☐ No

#	Drug Name (generic name if possible)	Dose	Units	Frequency	Route	Indication	Therapy Start Date	Therapy End Date	Therapy Ongoing
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									

Frequency		Route	
QD = Every day	QID = Four Times a Day	PO = Oral	SC = Subcutaneous
QOD = Every other day	SID = Five Times a Day	TOP = Topical	INH = Inhalation
BID = Twice a Day	PRN = as needed	IV = Intravenous	PR = Per Rectum

TID = Three Times a Day	Other (Specify)	IM = Intramuscular	Other (Specify

Comments Page

Are there any comments to this form?

- ☐ Yes
- ☐ No

Page Number	Comment

POST-CONCUSSION VIST: WITHIN 72 HOURS

Visit Details

Specify the date the subject visited for testing (MM/DD/YYYY)	_____/_____/_____
What was the date of the first game?	_____/_____/_____
What was the date the season started?	_____/_____/_____

Adverse Events and Concomitant Medications

Did the subject experience any adverse events since the last visit?	☐ Yes ☐ No
Has the subject had any change in medications since the last visit?	☐ Yes ☐ No

Concussion Event Details

Date of concussion	_____/_____/_____
Description of concussion event	
Type of injury	☐ Direct impact ☐ Indirect impact
If direct impact, specify	☐ Front ☐ Top ☐ Back ☐ Left ☐ Right ☐ Unknown
Was subject taken to E.R.?	☐ Yes ☐ No
Was neuroimaging performed?	☐ Yes ☐ No
If yes, were there positive findings?	☐ Yes ☐ No
Has subject received any medications after the event?	☐ Yes ☐ No
Has the subject suffered from any of the following symptoms?	☐ Loss of consciousness ☐ Retrograde amnesia ☐ Anterograde amnesia
If the subject was unconscious, specify the length of time (minutes)	_____

Medical History

Abusive head trauma likelihood type
To what extent abusive head trauma is determined to be likely

☐ No concern ☐ Possible abuse
☐ Probable abuse ☐ Definite abuse

TBI mechanism type
Type of mechanism/forces causing the traumatic brain injury

- ☐ Direct impact: blow to head
- ☐ Direct impact: head against object
- ☐ Crush
- ☐ Blast
- ☐ Ground level fall
- ☐ Fall from height > 1 meter (3 ft)
- ☐ Gunshot wound
- ☐ Fragment (incl. shell/shrapnel)
- ☐ Other penetrating brain injury
- ☐ Acceleration/Deceleration

Subarachnoid hemorrhage indicator
Indicator of macroscopic blood located between the brain surface and the arachnoid membrane. On CT and MR, the blood in this location will follow the contour of the sulci and cisterns. Acute SAH is hyperdense on CT and hyperintense on FLAIR MR imaging. Subacute SAH may be invisible on CT, although the presence of subtle sulcal effacement may occasionally be seen. Chronic SAH, or hemosiderosis may be seen on MR as hypointense linear areas of cortical staining on GRE and SW-imaging.

☐ Present ☐ Absent ☐ Indeterminate

Seizure indicator
Indicator of seizure activity

☐ Yes ☐ No ☐ Suspected ☐ Unknown

Seizure presentation type
Type of seizure activity as convulsive or non-convulsive (diagnosed on EEG only, no motor manifestations)

☐ Convulsive ☐ Non-convulsive

Definitive clinical care post trauma location type
Indicates type of location where patient received definitive clinical care after the injury

- ☐ None
- ☐ Physicians office
- ☐ Outpatient/Urgent Care Clinic
- ☐ Emergency Department-Trauma Center
- ☐ Emergency Department-Non-trauma Center
- ☐ Other

GCS confounders type
Type of confounders influencing participant's/subject's Glasgow Coma Scale (GCS) score

- ☐ GCS Accurate
- ☐ Alcohol/drugs of abuse
- ☐ C-spine injury
- ☐ Hypoxia/hypotension
- ☐ Hypothermia
- ☐ Sedation
- ☐ Paralytic
- ☐ Unknown

Loss of consciousness indicator
Indicator of whether the participant/subject experienced any period of loss of or a decreased level of consciousness

- ☐ Yes
- ☐ No
- ☐ Suspected
- ☐ Unknown

Loss of consciousness reporter type
How the period of loss of consciousness (LOC) was verified

- ☐ Self-report
- ☐ Witness
- ☐ Clinical interview
- ☐ Medical chart
- ☐ Not available

Post traumatic amnesia indicator
"Indicator of whether the participant/subject experienced a period of post traumatic amnesia, defined as any loss of memory for events immediately before (retrograde amnesia) or after the injury"

- ☐ Yes
- ☐ No
- ☐ Suspected
- ☐ Unknown

Post traumatic amnesia reporter type
How the period of post traumatic amnesia (PTA) was verified

- ☐ Self-report
- ☐ Witness
- ☐ Clinical interview
- ☐ Medical chart
- ☐ Not available

Alteration of consciousness indicator
Indicator of whether the participant/subject experienced a period of time with an alteration of consciousness (AOC), defined as any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.), not including loss of consciousness (LOC) or post traumatic amnesia (PTA).

- ☐ Yes
- ☐ No
- ☐ Suspected
- ☐ Unknown

TBI symptom or sign type
TBI physical symptom or sign exhibited by the participant/subject

- ☐ Headache
- ☐ Nausea
- ☐ Vomiting
- ☐ Balance problems
- ☐ Fatigue
- ☐ Sensitive to light
- ☐ Sensitive to noise
- ☐ Numbness/tingling
- ☐ Drowsiness
- ☐ Sleeping less than usual
- ☐ Sleeping more than usual
- ☐ Difficulty falling asleep
- ☐ Feeling mentally foggy
- ☐ Feeling slowed down
- ☐ Difficulty concentrating
- ☐ Difficulty remembering
- ☐ Emotional: Irritability
- ☐ Sadness
- ☐ More emotional
- ☐ Nervousness
- ☐ Other, specify

TBI symptom or sign indicator
Indicator of whether the participant/subject exhibited the specific TBI physical symptom/sign

- ☐ Yes
- ☐ No
- ☐ Unknown

Imaging study date and time
Date (and time, if applicable and known) the radiologic study was obtained.

_____/_____/_____

Imaging modality type
Type of radiologic study performed on the participant/subject

- ☐ Non-contrast CT
- ☐ Contrast CT
- ☐ CT Angiography
- ☐ X-Ray Angiography
- ☐ MRI
- ☐ MRA

Imaging scanner strength value
Value of magnetic field strength of scanner used in Tesla

- ☐ 1.5T ☐ 3.0T ☐ 4.0T ☐ 7.0T
- ☐ Other, specify _____

Imaging scanner manufacturer name
Name of manufacturer of imaging scanner
Carestream

☐ Agfa
☐
☐ GE
☐ Hitachi
☐ Hologic
☐ Konica Minolta
☐ Philips
☐ Siemens
☐ Toshiba
☐ Other, specify

Imaging scanner model name
Name of model of imaging scanner
_____

Imaging scanner software version number
Number of software version used by imaging scanner
_____

Imaging sequence type
Type of imaging sequence used

☐ T1-weighted
☐ T2-weighted
☐ FLAIR
☐ DWI
☐ **GRE**
☐ SWI
☐ DTI
☐ MRSI
☐ PWI
☐ Other, specify
_____

Skull fracture indicator
Indicator of a break in the normal integrity of the skull, which may be partial or full thickness, caused by presumed mechanical force.
☐ Present ☐ Absent ☐ Indeterminate

Epidural hematoma indicator
Indicator of a collection of blood between the skull and dura. On CT, the EDH typically (though not always) has a biconvex shape, an adjacent skull fracture/scalp injury, and classically does not cross sutural margins. (In patients with skull fractures, especially those in children involving the sutures, this rule may not always apply.) The acute EDH is hyperdense, but may contain hypodense areas representing unclotted blood. As the EDH evolves, it gradually loses its hyperdensity and may appear iso/hypodense. On MRI, the acute EDH is hypo/isointense on T1 and very hypointense on T2, GRE, and SW-imaging. The inwardly displaced dura should be directly visualized on MR as a thin dark line on all pulse sequences.
☐ Present ☐ Absent ☐ Indeterminate

Extraaxial hematoma indicator
Indicator of a collection of blood between the brain surface and the skull which may be subarachnoid, subdural, or epidural, but for which the exact site cannot be determined with certainty, and is not already classified as a more specific entity elsewhere in the data set. These are typically small in volume. (This entity may be seen particularly in young children with contact injuries.)
☐ Present ☐ Absent ☐ Indeterminate

Subdural hematoma acute indicator
Indicator of a collection of acute blood between the arachnoid and the dura, typically (though not always) hyperdense with a crescent shape on CT. Mixed density may be seen if the collection contains unclotted blood, CSF admixture, and/or active extravasation. On MRI, the acute SDH is iso/hypointense on T1 and very hypointense on T2, GRE, and SW-imaging. Note: Please see additional categories below for subacute, chronic, and mixed collections if these better describe the lesion, or if the chronicity/timing is uncertain.
☐ Present ☐ Absent ☐ Indeterminate

Subdural hematoma subacute or chronic indicator
Indicator of a collection of non-acute blood between the arachnoid and the dura, typically (though not always) with a crescent shape. On CT, a subacute or chronic SDH will be predominantly iso- or hypodense. On MRI, a subacute SDH will be hyperintense on T1 and will have varying signal intensity on T2. The chronic SDH is slightly hyperintense compared to CSF on both T1 and T2-weighted imaging. FLAIR imaging increases the conspicuity. If rebleeding has occurred in the collection (i.e., "chronic recurrent SDH"), the signal may be a variable combination of hypo/iso/hyper-intensity/density on CT and all MR sequences. Internal loculations and septations may be seen on both CT and MRI and these are more conspicuous following intravenous contrast enhancement.

☐ Present ☐ Absent ☐ Indeterminate

Subdural hematoma mixed density or CSF-like collection indicator

Indicator of a collection of inhomogeneous blood products between the arachnoid and the dura, typically (though not always) with a crescent shape, in which timing (e.g., acute vs. chronic or subacute) is indeterminate. On CT and MRI, mixed collections may have hyper, iso, or hypodense/intense components. This classification is used for those collections in which the exact nature of the collection or its chronicity cannot be determined by the characteristics noted in the definitions of subdural hematomas in the two prior sections. In addition to mixed collections, more homogeneous CSF-density/intensity collections also may be seen after known trauma in which low density/intensity collections occur over time on serial images, presumably from arachnoid tears, decreased CSF absorption, increased CSF protein, or other mechanisms. This definition does NOT apply to CSF-intensity collections or prominent spaces seen on a single image, which may represent entities other than trauma.

☐ Present ☐ Absent ☐ Indeterminate

Subarachnoid hemorrhage indicator

Indicator of macroscopic blood located between the brain surface and the arachnoid membrane. On CT and MR, the blood in this location will follow the contour of the sulci and cisterns. Acute SAH is hyperdense on CT and hyperintense on FLAIR MR imaging. Subacute SAH may be invisible on CT, although the presence of subtle sulcal effacement may occasionally be seen. Chronic SAH, or hemosiderosis may be seen on MR as hypointense linear areas of cortical staining on GRE and SW-imaging.

☐ Present ☐ Absent ☐ Indeterminate

Vascular dissection indicator

Indicator of an incomplete disruption of one or more inner layers of an artery, which may be traumatic or spontaneous. CTA and MR/MRA may show an abnormally small or irregular caliber of the injured artery. A crescent sign may be seen on axial MR (and less well with CTA), and is best identified on T1-weighted Fat-Saturation images. If the caliber of the lumen is unaffected, conventional catheter angiography may miss the vascular dissection, and the diagnosis may be visualized only with CTA/MR.

☐ Present ☐ Absent ☐ Indeterminate

Traumatic aneurysm indicator

Indicator of false aneurysmal outpouching of an artery due to mechanical disruption of the entire vessel wall with extravasation of blood into a confined soft-tissue space. CTA, MR/MRA, and catheter angiography reveal focal dilation of the vessel lumen. In contrast to non-traumatic aneurysms, the dilated wall of a pseudoaneurysm may have an irregular surface, and the lesion is not located in typical berry aneurysm locations. Intraluminal thrombus of varying ages can appear as laminated rings of varying signal intensity on MRI. Phase artifact, indicative of pulsation within the lesion, may be seen on MRI. Peripheral wall calcification may be seen in older pseudoaneurysms and is best visualized with CT or, in some cases, conventional angiography.

☐ Present ☐ Absent ☐ Indeterminate

Venous sinus injury indicator

Indicator of compression (>50%), occlusion, or laceration of a dural venous sinus due to trauma.

☐ Present ☐ Absent ☐ Indeterminate

Midline shift supratentorial indicator

Displacement of the supratentorial midline structures, particularly the septum pellucidum, 2 mm or more due to mass effect of a focal traumatic lesion or brain swelling. ☐ Present ☐ Absent ☐ Indeterminate

Cisternal compression indicator

Indicator of asymmetry or obliteration of the normal configuration of the perimesencephalic, suprasellar, prepontine, or superior cerebellar cistern, and/or cisterna magna due to mass effect and/or brain swelling in the setting of trauma.

☐ Present ☐ Absent ☐ Indeterminate

Ventricle - fourth shift or effacement indicator

Indicator of displacement or effacement of the fourth ventricle 2 mm or more due to adjacent mass lesions or brain swelling.

☐ Present ☐ Absent ☐ Indeterminate

Contusion indicator

Indicator of a focal area of brain parenchymal disruption due to acute mechanical deformation. Contusions typically occur in the cortex and may extend into subcortical region. Contusions may show grossly visible hemorrhage or minimal/absent hemorrhage. Acute contusions typically have a mottled, inhomogeneous appearance due to stippling of blood along the brain surface. As such, their size is difficult to measure. In addition, CT streak artifact limits visualization of the cortical surface, so contusions are best seen with MRI, particularly on the FLAIR sequence. For purposes of categorization, contusions are differentiated from "intracerebral hematomas" by a containing a mixture of hemorrhagic and non-hemorrhagic tissue, or by having no grossly visible hemorrhage ("bland contusion"), while an "intracerebral hematoma" is predominantly a uniform collection of blood alone. The term "contusion" should not be used for hemorrhagic lesions which fit better in other categories, such as small hemorrhages associated with the pattern of diffuse axonal injury, lesions which in context are more likely to represent infarction or other primary vascular lesion, or isolated SAH. Contusions can, however, be associated with other lesions which commonly co-occur, such as brain laceration, adjacent SAH, and depressed skull fractures. Contusions which are questionable, such as those in an area of beam hardening on CT scan, should be noted as "indeterminate". Note: areas of delayed hypodensity or signal change around a traumatic lesion should not necessarily be classified as contusions. Contusions in which the hemorrhagic component enlarges over time should not be re-classified on subsequent images as "intraparenchymal hemorrhage" ☐ Present ☐ Absent ☐ Indeterminate

Contusion findings type.
Further describes the contusion

- ☐ Hemorrhagic
- ☐ Non-hemorrhagic
- ☐ Cortical
- ☐ Subcortical
- ☐ Deep brain structures
- ☐ Probable brain laceration (linear hemorrhagic or non-hemorrhagic pattern, often associated with overlying skull fracture)

Intracerebral hemorrhage indicator

Indicator of a collection of confluent, relatively homogeneous blood within the brain parenchyma. Intracerebral hemorrhage can occur in the setting of brain laceration, diffuse axonal injury, and other brain injury types, and there is some overlap with other entities. In general, lesions characterized by mixed blood and tissue are generally classified as contusions. In most instances, the term "intracerebral hemorrhage" is used to refer to larger collections of blood (typically, more than about 5 mm). Hemorrhages can have a surrounding region of non-hemorrhagic (e.g., hypointense) signal abnormality that may represent edema or clot retraction. Very small collections more often occur in the setting of contusion or, when scattered throughout the brain, may represent diffuse axonal injury/traumatic axonal injury (sometimes called "microhemorrhages"). Note: Hemorrhages in the context of other injury types such as contusion, or small hemorrhages (e.g. < 5 mm) in the setting of DAI or TAI, should be classified in those categories only. ☐ Present ☐ Absent ☐ Indeterminate

Intraventricular hemorrhage indicator

Indicator of acute-appearing blood within the ventricles. ☐ Present ☐ Absent ☐ Indeterminate

Diffuse axonal injury indicator

Indicator of a widespread distribution of lesions, including the subcortical white matter in more than one lobe or hemisphere, along with lesions in the corpus callosum, and may include the dorsomedial midbrain and other brainstem and cerebellar regions. For purposes of this database, DAI includes more than 3 foci of signal abnormality.

☐ Present ☐ Absent ☐ Indeterminate

Traumatic axonal injury indicator

Indicator of multiple, scattered, small hemorrhagic and/or non-hemorrhagic lesions in a more confined white matter distribution. For purposes of this database, TAI includes 1-3 foci of signal abnormality.

☐ Present ☐ Absent ☐ Indeterminate

Diffuse axonal injury and traumatic axonal injury anatomic site

Anatomic site of the diffuse axonal injury (DAI) and/or traumatic axonal injury (TAI)

- ☐ Frontal - R
- ☐ Frontal - L
- ☐ Parietal - R
- ☐ Parietal - L
- ☐ Temporal - R
- ☐ Temporal - L
- ☐ Occipital - R
- ☐ Occipital - L
- ☐ Thalamus/Basal ganglia - R
- ☐ Thalamus/Basal ganglia - L
- ☐ Midbrain - R
- ☐ Midbrain – L
- ☐ Pons - R
- ☐ Pons - L
- ☐ Medulla - R
- ☐ Medulla -L
- ☐ Cerebellum - R
- ☐ Cerebellum - L
- ☐ Corpus Callosum: Genu - R
- ☐ Corpus Callosum: Genu - L
- ☐ Corpus Callosum: Body - R
- ☐ Corpus Callosum: Body - L
- ☐ Corpus Callosum: Splenium - R
- ☐ Corpus Callosum: Splenium - L
- ☐ Subcortical White matter: Frontal - R
- ☐ Subcortical White matter: Frontal - L
- ☐ Subcortical White matter: Parietal - R
- ☐ Subcortical White matter: Parietal - L
- ☐ Subcortical White matter: Temporal - R
- ☐ Subcortical White matter: Temporal - L
- ☐ Subcortical White matter: Occipital - R
- ☐ Subcortical White matter: Occipital - L
- ☐ Internal Capsule: Anterior limb - R
- ☐ Internal Capsule: Anterior limb - L
- ☐ Internal Capsule: Posterior limb -R
- ☐ Internal Capsule: Posterior limb -L
- ☐ Brainstem: Dorsolateral rostral - R
- ☐ Brainstem: Dorsolateral rostral - L
- ☐ Brainstem: other - R
- ☐ Brainstem: other - L
- ☐ Cerebellar Peduncles - R
- ☐ Cerebellar Peduncles - L

Penetrating injury brain indicator

Indicator of injuries caused by traumatic forces which penetrate any of the normal layers of the head, including scalp, skull, dura, and brain (excluding superficial scalp injuries). ☐ Present ☐ Absent ☐ Indeterminate

Gunshot wound caliber number

The caliber of the gun used

_____

Cervicomedullary junction or brainstem injury indicator

Indicator of injuries typically occurring in the setting of crush or distraction forces which cause disruption in the brainstem and/or cervicomedullary junction. In the acute phase, these are usually areas of low density with or without blood on CT, and high signal on T2 and FLAIR with or without blood on MRI. ☐ Present ☐ Absent ☐ Indeterminate

Cervicomedullary junction or brainstem injury anatomic site

Anatomic site of the cervicomedullary junction/ brainstem injury. ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cervical

Edema indicator

Indicator of an abnormal accumulation of water in the intracellular and/or extracellular spaces of the brain. It can be divided into 4 types (recognizing that there are a number of types and schemes described by various authors): cytotoxic, vasogenic, interstitial, and osmotic. In "cytotoxic" edema, the blood-brain barrier (BBB) remains intact and the excess fluid is due to a derangement in cellular metabolism resulting in cellular retention of sodium and water, and the abnormal fluid is seen within the gray matter on CT and MR. In "vasogenic" edema, there is a breakdown of the BBB and the excess fluid is typically located in the white matter. "Interstitial" edema is found in obstructive hydrocephalus and the fluid is located within the extracellular space of the periventricular white matter. In "osmotic" cerebral edema, plasma osmolality is slightly greater than brain tissue, such as during hyponatremia or rapid drops in glucose. The abnormal pressure gradient will trigger water to flow into the brain, causing cerebral edema. In all types of edema, the abnormal fluid is hypodense on CT and hyperintense on T2-weighted and FLAIR MR.

☐ Present ☐ Absent ☐ Indeterminate

Brain swelling indicator

Indicator of brain swelling. Brain swelling is an all-inclusive term that refers to a non-specific increase in brain tissue mass. It can result from increased water as described above in the various types of cerebral "edema", but it can also result from "hyperemia" (i.e., increased intravascular blood volume). The latter situation is typically found in venous hypertension in which the tissue is engorged due to outflow obstruction. Cerebral hyperemia can also be found in the dysautoregulated brain when the systemic blood pressure is elevated, and in some hypermetabolic states in which the tissue is hyperperfused. For radiologic purposes, cerebral hyperemia appears as focal or diffuse mass effect (i.e. sulcal/cisternal effacement) with preservation of the gray-white differentiation (GWD). Cerebral edema also appears as focal or diffuse mass effect, but the increased water results in obscuration of the GWD.

For the present purposes, brain swelling refers to increased brain mass which does not otherwise fit into the definitions included under "Edema" in the prior section, or for which these pathophysiologies are felt to be operational in the findings noted.

☐ Present ☐ Absent ☐ Indeterminate

Brain swelling extent type

Extent of the brain swelling.

- ☐ Focal (Involves less than half of one lobe)
- ☐ Lobar (Involves more than half of one lobe)
- ☐ Multilobar (Involves multiple lobes)
- ☐ Hemispheric (Involves an entire supratentorial hemisphere)
- ☐ Bihemispheric (Involves both hemispheres)
- ☐ Posterior fossa (Involves the cerebellum and/or brainstem)
- ☐ Global (Involves the entire brain)

Ischemia or infarction or hypoxic-ischemic injury indicator

Indicator of findings in tissue which sustains, for a variety of reasons, a deficit between substrate demand and delivery. This may be reversible or irreversible. Examples of specific etiologies include arterial occlusion, embolic infarction, lacunar infarction, watershed infarction, venous infarction, and changes from global insults such as hypoxia, hypotension, status epilepticus, and others.

☐ Present ☐ Absent ☐ Indeterminate

Brain atrophy or encephalomalacia result

Result of assessment of brain atrophy or encephalomalacia, defined as loss of tissue volume over time due to cell death or shrinkage. When strictly defined, a change should be seen over serial images to confirm that the changes are due to a specific traumatic event, rather than being preexisting. In some cases, atrophy can be inferred at a single time point due to patterns of brain appearance (for example, a smaller size and increased signal of one hippocampus compared to the other). It should be noted that enlargement of the subarachnoid spaces does not in itself confirm atrophy, as it may represent primary problems with CSF hydrodynamics (for instance, in infancy or early after traumatic subarachnoid hemorrhage).

☐ Present ☐ Absent ☐ Indeterminate

Satisfaction with Life Survey

	Strongly Agree	Agree	Slightly Agree	Neither agree nor Disagree	Slightly Disagree	Disagree	Strongly Disagree
In most ways my life is close to my ideal	7	6	5	4	3	2	1
The conditions of my life are excellent	7	6	5	4	3	2	1
I am satisfied with my life	7	6	5	4	3	2	1
So far I have gotten the important things I want in life	7	6	5	4	3	2	1
If I could live my life over, I would change almost nothing	7	6	5	4	3	2	1
Total sum of the responses to the five items							

Health Behavior Inventory

	Never	Rarely	Sometimes	Often
I have trouble paying attention	0	1	2	3
I get distracted easily	0	1	2	3
I have a hard time concentrating	0	1	2	3
I have problems remembering what people tell me	0	1	2	3
I have problems following directions	0	1	2	3
I daydream too much	0	1	2	3
I get confused	0	1	2	3
I forget things	0	1	2	3
I have problems finishing things	0	1	2	3
I have trouble figuring things out	0	1	2	3
It's hard for me to learn new things	0	1	2	3
I have headaches	0	1	2	3
I feel dizzy	0	1	2	3
I feel like the room is spinning	0	1	2	3
I feel like I'm going to faint	0	1	2	3
Things are blurry when I look at them	0	1	2	3
I see double	0	1	2	3
I feel sick to my stomach	0	1	2	3
I get tired a lot	0	1	2	3
I get tired easily	0	1	2	3
Sum of cognitive items 1-11 (0-33)				
Sum of somatic items 12-20 (0-27)				

Head Impact Monitoring

Head Impact System used (if applicable) ☐ HIT-System ☐ Estimation

Number of practices _____ Number of practice impacts _____

Number of games _____ Number of game impacts _____

Total number of practices and games_____ Total number of impacts _____

Concussive Linear Acceleration (g)_____ Concussive Rotational Acceleration (rad/s/s)_____

Concussive Impact Location_____

EEG/ERP

Were EEG/ERP measurements recorded? ☐ Yes ☐ No

What is the test session number: _____

What is the value for circumference of the subject's head (cm): _____

What EEG Net size was used? ☐ Small ☐ Medium ☐ Large

Specify the time the EEG recording started and ended (hh:mm) Start: End:

What was the order the ERP tasks were conducted in? ☐ Oddball-GoNoGo ☐ GoNoGo-Oddball

Indicate level of Oddball task completion: ☐ Completed ☐ Started but incomplete ☐ Not Done

BNA Scores	Synchronization	Timing	Connectivity
Auditory Odd-Ball Task			
Go-NoGo Task - Go			
Go-NoGo Task - NoGo			

Axon Results

Specify the date and time axon evaluation was completed: _____/_____/_____, _____:_____ AM PM

#	Composite Scores	Score	
1	Processing Speed		
2	Attention		
3	Learning		
4	Working Memory Speed		
5	Working Memory Accuracy		

Clinical Reaction Time

Specify the date and time CRT evaluation was completed: _____/_____/_____, _____:_____ AM PM

Trial #	Fall distance (cm)	Clinical Reaction Time (ms)
1	☐☐.☐ cm	
2	☐☐.☐ cm	
3	☐☐.☐ cm	
4	☐☐.☐ cm	
5	☐☐.☐ cm	
6	☐☐.☐ cm	
7	☐☐.☐ cm	
8	☐☐.☐ cm	

SCAT-3: Symptoms

	None	Mild		Moderate		Severe	
Headache:	0	1	2	3	4	5	6
"Pressure in head:"	0	1	2	3	4	5	6
Neck pain:	0	1	2	3	4	5	6
Nausea or vomiting:	0	1	2	3	4	5	6
Dizziness:	0	1	2	3	4	5	6
Blurred vision:	0	1	2	3	4	5	6
Balance problems:	0	1	2	3	4	5	6
Sensitivity to light:	0	1	2	3	4	5	6
Sensitivity to noise:	0	1	2	3	4	5	6
Feeling slowed down:	0	1	2	3	4	5	6
Feeling like "in a fog:"	0	1	2	3	4	5	6
"Don't feel right:"	0	1	2	3	4	5	6
Difficulty concentrating:	0	1	2	3	4	5	6
Difficulty remembering:	0	1	2	3	4	5	6
Fatigue or low energy:	0	1	2	3	4	5	6
Confusion:	0	1	2	3	4	5	6
Drowsiness:	0	1	2	3	4	5	6
Trouble falling asleep:	0	1	2	3	4	5	6
More emotional:	0	1	2	3	4	5	6
Irritability:	0	1	2	3	4	5	6
Sadness:	0	1	2	3	4	5	6
Nervous or anxious:	0	1	2	3	4	5	6

Total number of symptoms reported:	**Total symptom score:**
Do the symptoms get worse with physical activity?	☐ Yes ☐ No
Do the symptoms get worse with mental activity?	☐ Yes ☐ No
Cause of symptoms:	

Adverse Events

#	Adverse Event diagnosis, if known, or Signs/Symptoms (One sign/symptom per line)	Serious	Start date (mm/dd/yyyy)	Stop date or specify if ongoing (mm/dd/yyyy)	Severity	Relation to study procedure	Action taken	Outcome
1		Yes No						
2		Yes No						
3		Yes No						
4		Yes No						
5		Yes No						
6		Yes No						
7		Yes No						
8		Yes No						
9		Yes No						
10		Yes No						
					1-Mild 2-Moderate 3-Severe	1-Unrelated 2-Unlikely related 3-Possibly related 4-Probably related 5-Definitely related	1-None 2-Drug therapy 3-Study discontinued 4-Other (specify on comment box)	1-Resolved 2-Improved 3-Unchanged 4-Worsened

Protocol Deviations

Have any protocol deviations occurred? ☐ Yes ☐ No

#	Date of Deviation	CRF Page	Specify	Outcome
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Concomitant Medication/Treatment

Is the subject currently taking any medication/treatment? ☐ Yes ☐ No

#	Drug Name (generic name if possible)	Dose	Units	Frequency	Route	Indication	Therapy Start Date	Therapy End Date	Therapy Ongoing
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									

Frequency		Route	
QD = Every day	QID = Four Times a Day	PO = Oral	SC = Subcutaneous
QOD = Every other day	SID = Five Times a Day	TOP = Topical	INH = Inhalation
BID = Twice a Day	PRN = as needed	IV = Intravenous	PR = Per Rectum

TID = Three Times a Day	Other (Specify)	IM = Intramuscular	Other (Specify

Comments Page

Are there any comments to this form?

☐ Yes
☐ No

Page Number	Comment

POST-CONCUSSION VIST: Asymptomatic
Visit Details

Specify the date the subject visited for testing (MM/DD/YYYY)	_____/_____/_____
What was the date of the first game?	_____/_____/_____
What was the date the season started?	_____/_____/_____
Date of concussion	_____/_____/_____
Days since concussion	_____

Adverse Events and Concomitant Medications

Did the subject experience any adverse events since the last visit?	☐ Yes ☐ No
Has the subject had any change in medications since the last visit?	☐ Yes ☐ No

Concussion Event Details

Date of concussion	_____/_____/_____
Description of concussion event	
Type of injury	☐ Direct impact ☐ Indirect impact
If direct impact, specify	☐ Front ☐ Top ☐ Back ☐ Left ☐ Right ☐ Unknown
Was subject taken to E.R.?	☐ Yes ☐ No
Was neuroimaging performed?	☐ Yes ☐ No
If yes, were there positive findings?	☐ Yes ☐ No
Has subject received any medications after the event?	☐ Yes ☐ No
Has the subject suffered from any of the following symptoms?	☐ Loss of consciousness ☐ Retrograde amnesia ☐ Anterograde amnesia
If the subject was unconscious, specify the length of time (minutes)	_____

Medical History

Abusive head trauma likelihood type
To what extent abusive head trauma is determined to be likely

☐ No concern ☐ Possible abuse
☐ Probable abuse ☐ Definite abuse

TBI mechanism type
Type of mechanism/forces causing the traumatic brain injury

- ☐ Direct impact: blow to head
- ☐ Direct impact: head against object
- ☐ Crush
- ☐ Blast
- ☐ Ground level fall
- ☐ Fall from height > 1 meter (3 ft)
- ☐ Gunshot wound
- ☐ Fragment (incl. shell/shrapnel)
- ☐ Other penetrating brain injury
- ☐ Acceleration/Deceleration

Subarachnoid hemorrhage indicator
Indicator of macroscopic blood located between the brain surface and the arachnoid membrane. On CT and MR, the blood in this location will follow the contour of the sulci and cisterns. Acute SAH is hyperdense on CT and hyperintense on FLAIR MR imaging. Subacute SAH may be invisible on CT, although the presence of subtle sulcal effacement may occasionally be seen. Chronic SAH, or hemosiderosis may be seen on MR as hypointense linear areas of cortical staining on GRE and SW-imaging.

☐ Present ☐ Absent ☐ Indeterminate

Seizure indicator
Indicator of seizure activity

☐ Yes ☐ No ☐ Suspected ☐ Unknown

Seizure presentation type
Type of seizure activity as convulsive or non-convulsive (diagnosed on EEG only, no motor manifestations)

☐ Convulsive ☐ Non-convulsive

Definitive clinical care post trauma location type
Indicates type of location where patient received definitive clinical care after the injury

- ☐ None
- ☐ Physicians office
- ☐ Outpatient/Urgent Care Clinic
- ☐ Emergency Department-Trauma Center
- ☐ Emergency Department-Non-trauma Center
- ☐ Other

GCS confounders type
Type of confounders influencing participant's/subject's Glasgow Coma Scale (GCS) score

- ☐ GCS Accurate
- ☐ Alcohol/drugs of abuse
- ☐ C-spine injury
- ☐ Hypoxia/hypotension
- ☐ Hypothermia
- ☐ Sedation
- ☐ Paralytic
- ☐ Unknown

Loss of consciousness indicator
Indicator of whether the participant/subject experienced any period of loss of or a decreased level of consciousness

- ☐ Yes
- ☐ No
- ☐ Suspected
- ☐ Unknown

Loss of consciousness reporter type
How the period of loss of consciousness (LOC) was verified

- ☐ Self-report
- ☐ Witness
- ☐ Clinical interview
- ☐ Medical chart
- ☐ Not available

Post traumatic amnesia indicator
"Indicator of whether the participant/subject experienced a period of post traumatic amnesia, defined as any loss of memory for events immediately before (retrograde amnesia) or after the injury"

- ☐ Yes
- ☐ No
- ☐ Suspected
- ☐ Unknown

Post traumatic amnesia reporter type
How the period of post traumatic amnesia (PTA) was verified

- ☐ Self-report
- ☐ Witness
- ☐ Clinical interview
- ☐ Medical chart
- ☐ Not available

Alteration of consciousness indicator
Indicator of whether the participant/subject experienced a period of time with an alteration of consciousness (AOC), defined as any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.), not including loss of consciousness (LOC) or post traumatic amnesia (PTA).

- ☐ Yes
- ☐ No
- ☐ Suspected
- ☐ Unknown

TBI symptom or sign type
TBI physical symptom or sign exhibited by the participant/subject

- ☐ Headache
- ☐ Nausea
- ☐ Vomiting
- ☐ Balance problems
- ☐ Fatigue
- ☐ Sensitive to light
- ☐ Sensitive to noise
- ☐ Numbness/tingling
- ☐ Drowsiness
- ☐ Sleeping less than usual
- ☐ Sleeping more than usual
- ☐ Difficulty falling asleep
- ☐ Feeling mentally foggy
- ☐ Feeling slowed down
- ☐ Difficulty concentrating
- ☐ Difficulty remembering
- ☐ Emotional: Irritability
- ☐ Sadness
- ☐ More emotional
- ☐ Nervousness
- ☐ Other, specify

TBI symptom or sign indicator
Indicator of whether the participant/subject exhibited the specific TBI physical symptom/sign

- ☐ Yes
- ☐ No
- ☐ Unknown

Imaging study date and time
Date (and time, if applicable and known) the radiologic study was obtained.

_____/_____/_____

Imaging modality type
Type of radiologic study performed on the participant/subject

- ☐ Non-contrast CT
- ☐ Contrast CT
- ☐ CT Angiography
- ☐ X-Ray Angiography
- ☐ MRI
- ☐ MRA

Imaging scanner strength value
Value of magnetic field strength of scanner used in Tesla

- ☐ 1.5T ☐ 3.0T ☐ 4.0T ☐ 7.0T
- ☐ Other, specify

_____

Imaging scanner manufacturer name
Name of manufacturer of imaging scanner

- ☐ Agfa
- ☐ Carestream
- ☐ GE
- ☐ Hitachi
- ☐ Hologic
- ☐ Konica Minolta
- ☐ Philips
- ☐ Siemens
- ☐ Toshiba
- ☐ Other, specify

Imaging scanner model name
Name of model of imaging scanner

_____

Imaging scanner software version number
Number of software version used by imaging scanner

_____

Imaging sequence type
Type of imaging sequence used

- ☐ T1-weighted
- ☐ T2-weighted
- ☐ FLAIR
- ☐ DWI
- ☐ **GRE**
- ☐ SWI
- ☐ DTI
- ☐ MRSI
- ☐ PWI
- ☐ Other, specify

_____

Skull fracture indicator
Indicator of a break in the normal integrity of the skull, which may be partial or full thickness, caused by presumed mechanical force.

☐ Present ☐ Absent ☐ Indeterminate

Epidural hematoma indicator
Indicator of a collection of blood between the skull and dura. On CT, the EDH typically (though not always) has a biconvex shape, an adjacent skull fracture/scalp injury, and classically does not cross sutural margins. (In patients with skull fractures, especially those in children involving the sutures, this rule may not always apply.) The acute EDH is hyperdense, but may contain hypodense areas representing unclotted blood. As the EDH evolves, it gradually loses its hyperdensity and may appear iso/hypodense. On MRI, the acute EDH is hypo/isointense on T1 and very hypointense on T2, GRE, and SW-imaging. The inwardly displaced dura should be directly visualized on MR as a thin dark line on all pulse sequences.

☐ Present ☐ Absent ☐ Indeterminate

Extraaxial hematoma indicator
Indicator of a collection of blood between the brain surface and the skull which may be subarachnoid, subdural, or epidural, but for which the exact site cannot be determined with certainty, and is not already classified as a more specific entity elsewhere in the data set. These are typically small in volume. (This entity may be seen particularly in young children with contact injuries.)

☐ Present ☐ Absent ☐ Indeterminate

Subdural hematoma acute indicator
Indicator of a collection of acute blood between the arachnoid and the dura, typically (though not always) hyperdense with a crescent shape on CT. Mixed density may be seen if the collection contains unclotted blood, CSF admixture, and/or active extravasation. On MRI, the acute SDH is iso/hypointense on T1 and very hypointense on T2, GRE, and SW-imaging. Note: Please see additional categories below for subacute, chronic, and mixed collections if these better describe the lesion, or if the chronicity/timing is uncertain.

☐ Present ☐ Absent ☐ Indeterminate

Subdural hematoma subacute or chronic indicator
Indicator of a collection of non-acute blood between the arachnoid and the dura, typically (though not always) with a crescent shape. On CT, a subacute or chronic SDH will be predominantly iso- or hypodense. On MRI, a subacute SDH will be hyperintense on T1 and will have varying signal intensity on T2. The chronic SDH is slightly hyperintense compared to CSF on both T1 and T2-weighted imaging. FLAIR imaging increases the conspicuity. If rebleeding has occurred in the collection (i.e., "chronic recurrent SDH"), the signal may be a variable combination of hypo/iso/hyper-intensity/density on CT and all MR sequences. Internal loculations and septations may be seen on both CT and MRI and these are more conspicuous following intravenous contrast enhancement.

☐ Present ☐ Absent ☐ Indeterminate

Subdural hematoma mixed density or CSF-like collection indicator

Indicator of a collection of inhomogeneous blood products between the arachnoid and the dura, typically (though not always) with a crescent shape, in which timing (e.g., acute vs. chronic or subacute) is indeterminate. On CT and MRI, mixed collections may have hyper, iso, or hypodense/intense components. This classification is used for those collections in which the exact nature of the collection or its chronicity cannot be determined by the characteristics noted in the definitions of subdural hematomas in the two prior sections. In addition to mixed collections, more homogeneous CSF-density/intensity collections also may be seen after known trauma in which low density/intensity collections occur over time on serial images, presumably from arachnoid tears, decreased CSF absorption, increased CSF protein, or other mechanisms. This definition does NOT apply to CSF-intensity collections or prominent spaces seen on a single image, which may represent entities other than trauma.

☐ Present ☐ Absent ☐ Indeterminate

Subarachnoid hemorrhage indicator

Indicator of macroscopic blood located between the brain surface and the arachnoid membrane. On CT and MR, the blood in this location will follow the contour of the sulci and cisterns. Acute SAH is hyperdense on CT and hyperintense on FLAIR MR imaging. Subacute SAH may be invisible on CT, although the presence of subtle sulcal effacement may occasionally be seen. Chronic SAH, or hemosiderosis may be seen on MR as hypointense linear areas of cortical staining on GRE and SW-imaging.

☐ Present ☐ Absent ☐ Indeterminate

Vascular dissection indicator

Indicator of an incomplete disruption of one or more inner layers of an artery, which may be traumatic or spontaneous. CTA and MR/MRA may show an abnormally small or irregular caliber of the injured artery. A crescent sign may be seen on axial MR (and less well with CTA), and is best identified on T1-weighted Fat-Saturation images. If the caliber of the lumen is unaffected, conventional catheter angiography may miss the vascular dissection, and the diagnosis may be visualized only with CTA/MR.

☐ Present ☐ Absent ☐ Indeterminate

Traumatic aneurysm indicator

Indicator of false aneurysmal outpouching of an artery due to mechanical disruption of the entire vessel wall with extravasation of blood into a confined soft-tissue space. CTA, MR/MRA, and catheter angiography reveal focal dilation of the vessel lumen. In contrast to non-traumatic aneurysms, the dilated wall of a pseudoaneurysm may have an irregular surface, and the lesion is not located in typical berry aneurysm locations. Intraluminal thrombus of varying ages can appear as laminated rings of varying signal intensity on MRI. Phase artifact, indicative of pulsation within the lesion, may be seen on MRI. Peripheral wall calcification may be seen in older pseudoaneurysms and is best visualized with CT or, in some cases, conventional angiography.

☐ Present ☐ Absent ☐ Indeterminate

Venous sinus injury indicator

Indicator of compression (>50%), occlusion, or laceration of a dural venous sinus due to trauma.

☐ Present ☐ Absent ☐ Indeterminate

Midline shift supratentorial indicator

Displacement of the supratentorial midline structures, particularly the septum pellucidum, 2 mm or more due to mass effect of a focal traumatic lesion or brain swelling. ☐ Present ☐ Absent ☐ Indeterminate

Cisternal compression indicator

Indicator of asymmetry or obliteration of the normal configuration of the perimesencephalic, suprasellar, prepontine, or superior cerebellar cistern, and/or cisterna magna due to mass effect and/or brain swelling in the setting of trauma.

☐ Present ☐ Absent ☐ Indeterminate

Ventricle - fourth shift or effacement indicator

Indicator of displacement or effacement of the fourth ventricle 2 mm or more due to adjacent mass lesions or brain swelling.

☐ Present ☐ Absent ☐ Indeterminate

Contusion indicator

Indicator of a focal area of brain parenchymal disruption due to acute mechanical deformation. Contusions typically occur in the cortex and may extend into subcortical region. Contusions may show grossly visible hemorrhage or minimal/absent hemorrhage. Acute contusions typically have a mottled, inhomogeneous appearance due to stippling of blood along the brain surface. As such, their size is difficult to measure. In addition, CT streak artifact limits visualization of the cortical surface, so contusions are best seen with MRI, particularly on the FLAIR sequence. For purposes of categorization, contusions are differentiated from "intracerebral hematomas" by a containing a mixture of hemorrhagic and non-hemorrhagic tissue, or by having no grossly visible hemorrhage ("bland contusion"), while an "intracerebral hematoma" is predominantly a uniform collection of blood alone. The term "contusion" should not be used for hemorrhagic lesions which fit better in other categories, such as small hemorrhages associated with the pattern of diffuse axonal injury, lesions which in context are more likely to represent infarction or other primary vascular lesion, or isolated SAH. Contusions can, however, be associated with other lesions which commonly co-occur, such as brain laceration, adjacent SAH, and depressed skull fractures. Contusions which are questionable, such as those in an area of beam hardening on CT scan, should be noted as "indeterminate". Note: areas of delayed hypodensity or signal change around a traumatic lesion should not necessarily be classified as contusions. Contusions in which the hemorrhagic component enlarges over time should not be re-classified on subsequent images as "intraparenchymal hemorrhage"

☐ Present ☐ Absent ☐ Indeterminate

Contusion findings type.
Further describes the contusion

☐ Hemorrhagic
☐ Non-hemorrhagic
☐ Cortical
☐ Subcortical
☐ Deep brain structures
☐ Probable brain laceration (linear hemorrhagic or non-hemorrhagic pattern, often associated with overlying skull fracture)

Intracerebral hemorrhage indicator

Indicator of a collection of confluent, relatively homogeneous blood within the brain parenchyma. Intracerebral hemorrhage can occur in the setting of brain laceration, diffuse axonal injury, and other brain injury types, and there is some overlap with other entities. In general, lesions characterized by mixed blood and tissue are generally classified as contusions. In most instances, the term "intracerebral hemorrhage" is used to refer to larger collections of blood (typically, more than about 5 mm). Hemorrhages can have a surrounding region of non-hemorrhagic (e.g., hypointense) signal abnormality that may represent edema or clot retraction. Very small collections more often occur in the setting of contusion or, when scattered throughout the brain, may represent diffuse axonal injury/traumatic axonal injury (sometimes called "microhemorrhages"). Note: Hemorrhages in the context of other injury types such as contusion, or small hemorrhages (e.g. < 5 mm) in the setting of DAI or TAI, should be classified in those categories only.

☐ Present ☐ Absent ☐ Indeterminate

Intraventricular hemorrhage indicator

Indicator of acute-appearing blood within the ventricles.

☐ Present ☐ Absent ☐ Indeterminate

Diffuse axonal injury indicator

Indicator of a widespread distribution of lesions, including the subcortical white matter in more than one lobe or hemisphere, along with lesions in the corpus callosum, and may include the dorsomedial midbrain and other brainstem and cerebellar regions. For purposes of this database, DAI includes more than 3 foci of signal abnormality.

☐ Present ☐ Absent ☐ Indeterminate

Traumatic axonal injury indicator

Indicator of multiple, scattered, small hemorrhagic and/or non-hemorrhagic lesions in a more confined white matter distribution. For purposes of this database, TAI includes 1-3 foci of signal abnormality.

☐ Present ☐ Absent ☐ Indeterminate

Diffuse axonal injury and traumatic axonal injury anatomic site

Anatomic site of the diffuse axonal injury (DAI) and/or traumatic axonal injury (TAI)

- ☐ Frontal - R
- ☐ Frontal - L
- ☐ Parietal - R
- ☐ Parietal - L
- ☐ Temporal - R
- ☐ Temporal - L
- ☐ Occipital - R
- ☐ Occipital - L
- ☐ Thalamus/Basal ganglia - R
- ☐ Thalamus/Basal ganglia - L
- ☐ Midbrain - R
- ☐ Midbrain – L
- ☐ Pons - R
- ☐ Pons - L
- ☐ Medulla - R
- ☐ Medulla -L
- ☐ Cerebellum - R
- ☐ Cerebellum - L
- ☐ Corpus Callosum: Genu - R
- ☐ Corpus Callosum: Genu - L
- ☐ Corpus Callosum: Body - R
- ☐ Corpus Callosum: Body - L
- ☐ Corpus Callosum: Splenium - R
- ☐ Corpus Callosum: Splenium - L
- ☐ Subcortical White matter: Frontal - R
- ☐ Subcortical White matter: Frontal - L
- ☐ Subcortical White matter: Parietal - R
- ☐ Subcortical White matter: Parietal - L
- ☐ Subcortical White matter: Temporal - R
- ☐ Subcortical White matter: Temporal - L
- ☐ Subcortical White matter: Occipital - R
- ☐ Subcortical White matter: Occipital - L
- ☐ Internal Capsule: Anterior limb - R
- ☐ Internal Capsule: Anterior limb - L
- ☐ Internal Capsule: Posterior limb -R
- ☐ Internal Capsule: Posterior limb -L
- ☐ Brainstem: Dorsolateral rostral - R
- ☐ Brainstem: Dorsolateral rostral - L
- ☐ Brainstem: other - R
- ☐ Brainstem: other - L
- ☐ Cerebellar Peduncles - R
- ☐ Cerebellar Peduncles - L

Penetrating injury brain indicator

Indicator of injuries caused by traumatic forces which penetrate any of the normal layers of the head, including scalp, skull, dura, and brain (excluding superficial scalp injuries). ☐ Present ☐ Absent ☐ Indeterminate

Gunshot wound caliber number

The caliber of the gun used

_____

Cervicomedullary junction or brainstem injury indicator

Indicator of injuries typically occurring in the setting of crush or distraction forces which cause disruption in the brainstem and/or cervicomedullary junction. In the acute phase, these are usually areas of low density with or without blood on CT, and high signal on T2 and FLAIR with or without blood on MRI. ☐ Present ☐ Absent ☐ Indeterminate

Cervicomedullary junction or brainstem injury anatomic site

Anatomic site of the cervicomedullary junction/ brainstem injury. ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cervical

Edema indicator

Indicator of an abnormal accumulation of water in the intracellular and/or extracellular spaces of the brain. It can be divided into 4 types (recognizing that there are a number of types and schemes described by various authors): cytotoxic, vasogenic, interstitial, and osmotic. In "cytotoxic" edema, the blood-brain barrier (BBB) remains intact and the excess fluid is due to a derangement in cellular metabolism resulting in cellular retention of sodium and water, and the abnormal fluid is seen within the gray matter on CT and MR. In "vasogenic" edema, there is a breakdown of the BBB and the excess fluid is typically located in the white matter. "Interstitial" edema is found in obstructive hydrocephalus and the fluid is located within the extracellular space of the periventricular white matter. In "osmotic" cerebral edema, plasma osmolality is slightly greater than brain tissue, such as during hyponatremia or rapid drops in glucose. The abnormal pressure gradient will trigger water to flow into the brain, causing cerebral edema. In all types of edema, the abnormal fluid is hypodense on CT and hyperintense on T2-weighted and FLAIR MR.

☐ Present ☐ Absent ☐ Indeterminate

Brain swelling indicator

Indicator of brain swelling. Brain swelling is an all-inclusive term that refers to a non-specific increase in brain tissue mass. It can result from increased water as described above in the various types of cerebral "edema", but it can also result from "hyperemia" (i.e., increased intravascular blood volume). The latter situation is typically found in venous hypertension in which the tissue is engorged due to outflow obstruction. Cerebral hyperemia can also be found in the dysautoregulated brain when the systemic blood pressure is elevated, and in some hypermetabolic states in which the tissue is hyperperfused. For radiologic purposes, cerebral hyperemia appears as focal or diffuse mass effect (i.e. sulcal/cisternal effacement) with preservation of the gray-white differentiation (GWD). Cerebral edema also appears as focal or diffuse mass effect, but the increased water results in obscuration of the GWD.

For the present purposes, brain swelling refers to increased brain mass which does not otherwise fit into the definitions included under "Edema" in the prior section, or for which these pathophysiologies are felt to be operational in the findings noted.

☐ Present ☐ Absent ☐ Indeterminate

Brain swelling extent type

Extent of the brain swelling.

- ☐ Focal (Involves less than half of one lobe)
- ☐ Lobar (Involves more than half of one lobe)
- ☐ Multilobar (Involves multiple lobes)
- ☐ Hemispheric (Involves an entire supratentorial hemisphere)
- ☐ Bihemispheric (Involves both hemispheres)
- ☐ Posterior fossa (Involves the cerebellum and/or brainstem)
- ☐ Global (Involves the entire brain)

Ischemia or infarction or hypoxic-ischemic injury indicator

Indicator of findings in tissue which sustains, for a variety of reasons, a deficit between substrate demand and delivery. This may be reversible or irreversible. Examples of specific etiologies include arterial occlusion, embolic infarction, lacunar infarction, watershed infarction, venous infarction, and changes from global insults such as hypoxia, hypotension, status epilepticus, and others.

☐ Present ☐ Absent ☐ Indeterminate

Brain atrophy or encephalomalacia result

Result of assessment of brain atrophy or encephalomalacia, defined as loss of tissue volume over time due to cell death or shrinkage. When strictly defined, a change should be seen over serial images to confirm that the changes are due to a specific traumatic event, rather than being preexisting. In some cases, atrophy can be inferred at a single time point due to patterns of brain appearance (for example, a smaller size and increased signal of one hippocampus compared to the other). It should be noted that enlargement of the subarachnoid spaces does not in itself confirm atrophy, as it may represent primary problems with CSF hydrodynamics (for instance, in infancy or early after traumatic subarachnoid hemorrhage).

☐ Present ☐ Absent ☐ Indeterminate

Satisfaction with Life Survey

	Strongly Agree	Agree	Slightly Agree	Neither agree nor Disagree	Slightly Disagree	Disagree	Strongly Disagree
In most ways my life is close to my ideal	7	6	5	4	3	2	1
The conditions of my life are excellent	7	6	5	4	3	2	1
I am satisfied with my life	7	6	5	4	3	2	1
So far I have gotten the important things I want in life	7	6	5	4	3	2	1
If I could live my life over, I would change almost nothing	7	6	5	4	3	2	1
Total sum of the responses to the five items							

Health Behavior Inventory

	Never	Rarely	Sometimes	Often
I have trouble paying attention	0	1	2	3
I get distracted easily	0	1	2	3
I have a hard time concentrating	0	1	2	3
I have problems remembering what people tell me	0	1	2	3
I have problems following directions	0	1	2	3
I daydream too much	0	1	2	3
I get confused	0	1	2	3
I forget things	0	1	2	3
I have problems finishing things	0	1	2	3
I have trouble figuring things out	0	1	2	3
It's hard for me to learn new things	0	1	2	3
I have headaches	0	1	2	3
I feel dizzy	0	1	2	3
I feel like the room is spinning	0	1	2	3
I feel like I'm going to faint	0	1	2	3
Things are blurry when I look at them	0	1	2	3
I see double	0	1	2	3
I feel sick to my stomach	0	1	2	3
I get tired a lot	0	1	2	3
I get tired easily	0	1	2	3
Sum of cognitive items 1-11 (0-33)				
Sum of somatic items 12-20 (0-27)				

Head Impact Monitoring

Head Impact System used (if applicable)	☐ HIT-System ☐ Estimation		
Number of practices	_____	Number of practice impacts	_____
Number of games	_____	Number of game impacts	_____
Total number of practices and games	_____	Total number of impacts	_____

EEG/ERP

Were EEG/ERP measurements recorded? ☐ Yes ☐ No

What is the test session number: _____

What is the value for circumference of the subject's head (cm): _____

What EEG Net size was used? ☐ Small ☐ Medium ☐ Large

Specify the time the EEG recording started and ended (hh:mm) Start: End:

What was the order the ERP tasks were conducted in? ☐ Oddball-GoNoGo ☐ GoNoGo-Oddball

Indicate level of Oddball task completion: ☐ Completed ☐ Started but incomplete ☐ Not Done

BNA Scores	Synchronization	Timing	Connectivity
Auditory Odd-Ball Task			
Go-NoGo Task - Go			
Go-NoGo Task - NoGo			

Axon Results

Specify the date and time axon evaluation was completed: _____/_____/_____, _____:_____ AM PM

#	Composite Scores	Score	
1	Processing Speed		
2	Attention		
3	Learning		
4	Working Memory Speed		
5	Working Memory Accuracy		

Clinical Reaction Time

Specify the date and time CRT evaluation was completed: _____/_____/_____, _____:_____ AM PM

Trial #	Fall distance (cm)	Clinical Reaction Time (ms)
1	□□.□ cm	
2	□□.□ cm	
3	□□.□ cm	
4	□□.□ cm	
5	□□.□ cm	
6	□□.□ cm	
7	□□.□ cm	
8	□□.□ cm	

SCAT-3: Symptoms

	None	Mild		Moderate		Severe	
Headache:	0	1	2	3	4	5	6
"Pressure in head:"	0	1	2	3	4	5	6
Neck pain:	0	1	2	3	4	5	6
Nausea or vomiting:	0	1	2	3	4	5	6
Dizziness:	0	1	2	3	4	5	6
Blurred vision:	0	1	2	3	4	5	6
Balance problems:	0	1	2	3	4	5	6
Sensitivity to light:	0	1	2	3	4	5	6
Sensitivity to noise:	0	1	2	3	4	5	6
Feeling slowed down:	0	1	2	3	4	5	6
Feeling like "in a fog:"	0	1	2	3	4	5	6
"Don't feel right:"	0	1	2	3	4	5	6
Difficulty concentrating:	0	1	2	3	4	5	6
Difficulty remembering:	0	1	2	3	4	5	6
Fatigue or low energy:	0	1	2	3	4	5	6
Confusion:	0	1	2	3	4	5	6
Drowsiness:	0	1	2	3	4	5	6
Trouble falling asleep:	0	1	2	3	4	5	6
More emotional:	0	1	2	3	4	5	6
Irritability:	0	1	2	3	4	5	6
Sadness:	0	1	2	3	4	5	6
Nervous or anxious:	0	1	2	3	4	5	6

Total number of symptoms reported:	**Total symptom score:**
Do the symptoms get worse with physical activity?	☐ Yes ☐ No
Do the symptoms get worse with mental activity?	☐ Yes ☐ No
Cause of symptoms:	

Adverse Events

#	Adverse Event diagnosis, if known, or Signs/Symptoms (One sign/symptom per line)	Serious	Start date (mm/dd/yyyy)	Stop date or specify if ongoing (mm/dd/yyyy)	Severity	Relation to study procedure	Action taken	Outcome
1		Yes No						
2		Yes No						
3		Yes No						
4		Yes No						
5		Yes No						
6		Yes No						
7		Yes No						
8		Yes No						
9		Yes No						
10		Yes No						
					1-Mild 2-Moderate 3-Severe	1-Unrelated 2-Unlikely related 3-Possibly related 4-Probably related 5-Definitely related	1-None 2-Drug therapy 3-Study discontinued 4-Other (specify on comment box)	1-Resolved 2-Improved 3-Unchanged 4-Worsened

Protocol Deviations

Have any protocol deviations occurred? ☐ Yes ☐ No

#	Date of Deviation	CRF Page	Specify	Outcome
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Concomitant Medication/Treatment

Is the subject currently taking any medication/treatment? ☐ Yes ☐ No

#	Drug Name (generic name if possible)	Dose	Units	Frequency	Route	Indication	Therapy Start Date	Therapy End Date	Therapy Ongoing
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									

Frequency		Route	
QD = Every day	QID = Four Times a Day	PO = Oral	SC = Subcutaneous
QOD = Every other day	SID = Five Times a Day	TOP = Topical	INH = Inhalation
BID = Twice a Day	PRN = as needed	IV = Intravenous	PR = Per Rectum

TID = Three Times a Day	Other (Specify)	IM = Intramuscular	Other (Specify

Comments Page

Are there any comments to this form?

☐ Yes
☐ No

Page Number	Comment

References

1. Gill DL, Hammond CC, Reifsteck EJ, et al. Physical activity and quality of life. *J Prev Med Public Health*. 2013;46 Suppl 1:S28-34.
2. Hillman CH, Pontifex MB, Castelli DM, et al. Effects of the FITKids randomized controlled trial on executive control and brain function. *Pediatrics*. 2014;134(4):e1063-1071.
3. Associations. NFoSHS. 2011-12 High School Athletics Participation Survey. http://www.nfhs.org/content.aspx?id=3282. Accessed May 17, 2013.
4. National Federation of High School Sports Association. 2013-14 High School Athletics Participation Survey. 2014:53-71.
5. Marar M, McIlvain NM, Fields SK, Comstock RD. Epidemiology of Concussions Among United States High School Athletes in 20 Sports. *Am J Sport Med*. 2012;40(4):747-755.
6. Broglio SP, Eckner JT, Paulson HL, Kutcher JS. Cognitive decline and aging: the role of concussive and subconcussive impacts. *Exerc Sport Sci Rev*. 2012;40(3):138-144.
7. Broglio SP, Eckner JT, Kutcher JS. Field-based measures of head impacts in high school football athletes. *Curr Opin Pediatr*. 2012;24(6):702-708.
8. Broglio SP, Eckner JT, Martini D, Sosnoff JJ, Kutcher JS, Randolph C. Cumulative Head Impact Burden in High School Football. *J Neurotrauma*. 2011;28(10):2069-2078.
9. Schnebel B, Gwin JT, Anderson S, Gatlin R. In vivo study of head impacts in football: a comparison of National Collegiate Athletic Association Division I versus high school impacts. *Neurosurgery*. 2007;60(3):490-495; discussion 495-496.
10. Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clin Sports Med*. 2011;30(1):179-188, xi.
11. Shultz SR, Bao F, Omana V, Chiu C, Brown A, Cain DP. Repeated mild lateral fluid percussion brain injury in the rat causes cumulative long-term behavioral impairments, neuroinflammation, and cortical loss in an animal model of repeated concussion. *J Neurotrauma*. 2012;29(2):281-294.
12. Shultz SR, MacFabe DF, Foley KA, Taylor R, Cain DP. Sub-concussive brain injury in the Long-Evans rat induces acute neuroinflammation in the absence of behavioral impairments. *Behav Brain Res*. 2012;229(1):145-152.
13. Parker TM, Osternig LR, van Donkelaar P, Chou LS. Balance control during gait in athletes and non-athletes following concussion. *Med Eng Phys*. 2008;30(8):959-967.
14. Talavage TM, Nauman EA, Breedlove EL, et al. Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. *J Neurotrauma*. 2014;31(4):327-338.

15. Bazarian JJ, Zhu T, Blyth B, Borrino A, Zhong J. Subject-specific changes in brain white matter on diffusion tensor imaging after sports-related concussion. *Magn Reson Imaging*. 2012;30(2):171-180.
16. Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *J Am Med Assoc*. 2003;290(19):2549-2555.
17. Guskiewicz K, Weaver N, Padua D, Garrett W. Epidemiology of concussion in collegiate and high school football players. *Am J Sport Med*. 2000 28:643-650.
18. Guskiewicz KM, Marshall SW, Bailes J, et al. Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc*. 2007;39(6):903-909.
19. Field M, Collins MW, Lovell MR, Maroon J. Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate athletes. *J Pediatr*. 2003;142(5):546-553.
20. Williams RM, Puetz TW, Giza CC, Broglio SP. Concussion recovery time among high school and collegiate athletes: a systematic review and meta-analysis. *Sports Med*. 2015;45(6):893-903.
21. De Beaumont L, Henry LC, Gosselin N. Long-term functional alterations in sports concussion. *Neurosurg Focus*. 2012;33(6):E8: 1-7.
22. Theriault M, De Beaumont L, Gosselin N, Filipinni M, Lassonde M. Electrophysiological abnormalities in well functioning multiple concussed athletes. *Brain Inj*. 2009;23(11):899-906.
23. Broglio SP, Pontifex MB, O'Connor P, Hillman CH. The persistent effects of concussion on neuroelectric indices of attention. *J Neurotrauma*. 2009;26(9):1463-1470.
24. Broglio SP, Cantu R, Gioia GA, et al. National Athletic Trainers' Association Position Statement on the Management of Sport-Related Concussion Update. *J Athl Train*. 2013;49(2):245-265.
25. McCrory P, Meeuwisse WH, Aubry M, et al. Consensus Statement On Concussion In Sport - The 4th International Conference On Concussion In Sport Held In Zurich, November 2012. *Br J Sports Med*. 2013;47(5):250-258.
26. McCrory P, Meeuwisse W, Johnston K, et al. Consensus statement on concussion in sport - The 3rd international conference on concussion in sport held in Zurich, November 2008. *J Inj Funct Rehabil*. 2009;1(5):406-420.
27. McCrory P, Johnston K, Meeuwisse W, et al. Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *Br J Sports Med*. 2005;39(4):196-204.
28. McCrea M, Guskiewicz K, Marshall S. Acute effects and recovery time following concussion in collegiate football players. *Sports Med Update*. 2004;38:369-371.
29. Moore RD, Hillman CH, Broglio SP. The persistent influence of concussive injuries on cognitive control and neuroelectric function. *J Athl Train*. 2014;49(1):24-35.
30. Guskiewicz K, McCrea M, Marshall S, Cantu R, Randolph C, Barr W. Cumulative effects associated with recurrent concussion in collegiate football players: The NCAA concussion study. *J Am Med Assoc*. 2003;290(19):2549-2555.
31. Cantu RC. Second-impact syndrome. *Clin Sports Med*. 1998;17(1):37-+.

32. Moore DR, Pindus DM, Raine LB, et al. The persistent influence of concussion on attention, executive control and neuroelectric function in preadolescent children. *Int J Psychophysiol*. 2016;99:85-95.
33. De Beaumont L, Brisson B, Lassonde M, Jolicoeur P. Long-term electrophysiological changes in athletes with a history of multiple concussions. *Brain Inj*. 2007;21(6):631-644.
34. Dupuis F, Johnston KM, Lavoie M, Lepore F, Lassonde M. Concussions in athletes produce brain dysfunction as revealed by event-related potentials. *Neuroreport*. 2000;11(18):4087-4092.
35. Gaetz M, Goodman D, Weinberg H. Electrophysiological evidence for the cumulative effects of concussion. *Brain Inj*. 2000;14(12):1077-1088.
36. Rogers JM, Donnelly J, Wilson PH. Source localization of an event-related potential marker of executive attention following mild traumatic brain injury. *Neuroreport*. 2015;26(15):903-907.
37. Baillargeon A, Lassonde M, Leclerc S, Ellemberg D. Neuropsychological and neurophysiological assessment of sport concussion in children, adolescents and adults. *Brain Inj*. 2012;26(3):211-220.
38. Gosselin N, Bottari C, Chen JK, et al. Evaluating the cognitive consequences of mild traumatic brain injury and concussion by using electrophysiology. *Neurosurg Focus*. 2012;33(6):E7: 1-7.
39. Reches A, Levy-Cooperman N, Laufer I, et al. Brain Network Activation (BNA) reveals scopolamine-induced impairment of visual working memory. *J Mol Neurosci*. 2014;54(1):59-70.
40. Reches A, Laufer I, Ziv K, et al. Network dynamics predict improvement in working memory performance following donepezil administration in healthy young adults. *NeuroImage*. 2013;88C:228-241.
41. Reches M. Thread based devices for low-cost diagnostics. *Methods Mol Biol*. 2013;949:197-205.
42. Shahaf G, Reches A, Pinchuk N, et al. Introducing a novel approach of network oriented analysis of ERPs, demonstrated on adult attention deficit hyperactivity disorder. *Clin Neurophysiol*. 2012;123(8):1568-1580.
43. Kontos AP, Reches A, Elbin RJ, et al. Preliminary evidence of reduced brain network activation in patients with post-traumatic migraine following concussion. *Brain Imaging Behav*. 2015.
44. Breedlove EL, Robinson M, Talavage TM, et al. Biomechanical correlates of symptomatic and asymptomatic neurophysiological impairment in high school football. *J Biomech*. 2012;45(7):1265-1272.
45. McCrea M, Kelly JP, Kluge J, Ackley B, Randolph C. Standardized assessment of concussion in football players. *Neurology*. 1997;48(3):586-588.
46. Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: Evaluation and management of concussion in sports: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Am Aca Neuro*. 2013.
47. Aubry M, Cantu R, Dvorak J, et al. Summary and agreement statement of the First International Conference on Concussion in Sport, Vienna 2001. Recommendations for the improvement of safety and health of athletes who may suffer concussive injuries. *Br J Sports Med*. 2002;36(1):6-10.

48. Gottschalk AW, Andrish JT. Epidemiology of Sports Injury in Pediatric Athletes. *Sports Med Arthro Review*. 2011;19(1):2-6.
49. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehab*. 2006;21(5):375-378.
50. Buzzini SR, Guskiewicz KM. Sports -related concussion in the young athlete. *Curr Opin Pediatr*. 2006;18:376-282.
51. Grindel SH, Lovell MR, MW. C. The assessment of sport-related concussion: The evidence behind neuropsychological testing and management. *Clin J Sport Med*. 2001;11(3):134-143.
52. Powell JW, Barber-Foss KD. Traumatic brain injury in high school athletes. *J Am Med Assoc*. 1999;282(10):958-963.
53. Pellman EJ, Lovell MR, Viano DC, Casson IR, Tucker AM. Concussion in professional football: neuropsychological testing--part 6. *Neurosurg*. 2004;55(6):1290-1303; discussion 1303-1295.
54. Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: summary and recommendations for injury prevention initiatives. *J Athl Train*. 2007;42(2):311-319.
55. Gessel LM, Fields SK, Collins CL, Comstock R. Concussions among United States high school and collegiate athletes. *J Athl Train*. 2007;42:495-503.
56. Covassin T, Swanik CB, Sachs ML. Sex Differences and the Incidence of Concussions Among Collegiate Athletes. *J Athl Train*. 2003;38(3):238-244.
57. Rosenthal JA, Foraker RE, Collins CL, Comstock RD. National High School Athlete Concussion Rates From 2005-2006 to 2011-2012. *Am J Sports Med*. 2014.
58. Meehan S, d'Hemecourt P, Collins C, Comstock R. Assessment and management of sport related concussion in United States high schools. *Am J Sport Med*. 2011;20:1-5.
59. Covassin T, Elbin RT, Larson E, Kontos A. Sex and age difference in depression and baseline sport-related concussion neurocognitive performance and symptoms. . *Clin J Sport Med*. 2012;22:98-104.
60. Lincoln AE, Caswell SV, Almquist JL, Dunn RE, Norris JB, Hinton RY. Trends in Concussion Incidence in High School Sports A Prospective 11-Year Study. *Am J Sport Med*. 2011;39(5):958-963.
61. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery*. 2014;75 Suppl 4:S24-33.
62. Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. *J Athl Train*. 2001;36(3):228-235.
63. Marieb E. *Essentials of Human Anatomy and Physiology*. 8th ed: Pearson; 2005.
64. Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. *Dis Model Mech*. 2013;6(6):1307-1315.
65. Meier TB, Bellgowan PS, Singh R, Kuplicki R, Polanski DW, Mayer AR. Recovery of cerebral blood flow following sports-related concussion. *JAMA Neurol*. 2015;72(5):530-538.
66. Hovda DA, Villablanca JR, Chugani HT, Phelps ME. Cerebral metabolism following neonatal or adult hemineodecortication in cats: I. Effects on glucose metabolism using [14C]2-deoxy-D-glucose autoradiography. *J Cereb Blood Flow Metab*. 1996;16(1):134-146.

67. Yoshino A, Hovda DA, Kawamata T, Katayama Y, Becker DP. Dynamic changes in local cerebral glucose utilization following cerebral conclusion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Res*. 1991;561(1):106-119.
68. Thomas S, Prins ML, Samii M, Hovda DA. Cerebral metabolic response to traumatic brain injury sustained early in development: a 2-deoxy-D-glucose autoradiographic study. *J Neurotrauma*. 2000;17(8):649-665.
69. Gysland S, Mihalik J, Register-Mihalik J, Trulock S, Shields E, Guskiewicz K. The relationship between subconcussive impacts and concussion history on clinical measures of neurologic function in collegiate football players. *Ann Biomed Eng*. 2012;40(1):14-22.
70. Miller J, Adamson G, Pink M, Sweet J. Comparison of preseason, midseason, and postseason neurocognitive scores in uninjured collegiate football players. *Am J Sports Med*. 2007;35(8):1284-1288.
71. Dashnaw ML, Petraglia AL, Bailes JE. An overview of the basic science of concussion and subconcussion: where we are and where we are going. *Neurosurg Focus*. 2012;33(6):E5: 1-9.
72. Bauer JA, Thomas TS, Cauraugh JH, Kaminski TW, Hass CJ. Impact forces and neck muscle activity in heading by collegiate female soccer players. *J Sports Sci*. 2001;19(3):171-179.
73. Talavage TM, Nauman EA, Breedlove EL, et al. Functionally- detected cogntive impairment in high school football players without clinically-daignosed concussion. *J Neurotraum*. 2012;[In Press].
74. McAllister TW, Ford JC, Flashman LA, et al. Effect of head impacts on diffusivity measures in a cohort of collegiate contact sport athletes. *Neurology*. 2014;82(1):63-69.
75. Johnson B, Neuberger T, Gay M, Hallett M, Slobounov S. Effects of subconcussive head trauma on the default mode network of the brain. *J Neurotrauma*. 2014;31(23):1907-1913.
76. Halstead M, Walter K. Clinical report Sport-related concussion in children and adolescents. *Am Acad Pediatr*. 2010;126(3):597-615.
77. Fineman I, Giza C, Nahed B, Lee S, Hovda D. Inhibition of neocortical plasticity during development by a moderate concussive brain injury. *J Neurotrauma*. 2000;17(9):739-749.
78. Giza CC, Griesbach GS, Hovda DA. Experience-dependent behavioral plasticity is disturbed following traumatic injury to the immature brain. *Behav Brain Res*. 2005;157(1):11-22.
79. Reeves TM, Phillips LL, Povlishock JT. Myelinated and unmyelinated axons of the corpus callosum differ in vulnerability and functional recovery following traumatic brain injury. *Exp Neurol*. 2005;196(1):126-137.
80. Ip E, Giza C, Griesbach G, Hovda D. Effects of enriched environment and fluid percussion injury on dendritic arborization within the cerebral cortex of the developing rat. *J Neurotrauma*. 2002;19(5):573-585.
81. Guskiewicz K, Bruce S, Cantu R, et al. National athletic trainers association position statement: management of sport related concussion. *J Athl Training*. 2004;39(3):284.
82. Bey T, Ostick B. Second impact syndrome. *West J Emerg Med*. 2009;10(1):6-10.
83. Cobb S, Battin B. Second impact syndrome. *J Sch Nurs*. 2004;20:262-267.

84. Cantu RC, Gean AD. Second-Impact Syndrome and a Small Subdural Hematoma: An Uncommon Catastrophic Result of Repetitive Head Injury with a Characteristic Imaging Appearance. *J Neurotrauma*. 2010;27(9):1557-1564.
85. Hebert O, Schlueter K, Hornsby M, Van Gorder S, Snodgrass S, Cook C. The diagnostic credibility of second impact syndrome: A systematic literature review. *J Sci Med Sport*. 2016.
86. Bruce D. Delayed deterioration of consciousness after trivial head injury in childhood. *Brit Med J*. 1984:715-716.
87. Gioia G, Schneider J, Vaughan C, Isquith P. Which symptoms assessment approaches are uniquely appropriate for pediatric concussion. *J Sports Med*. 2009:13-22.
88. Broglio SP, Macciocchi SN, Ferrara MS. Sensitivity of the concussion assessment battery. *Neurosurg*. 2007;60(6):1050-1057; discussion 1057-1058.
89. Prevention CfDCa. *Nonfatal traumatic brain injuries from sports and recreation activities- United States, 2001 to 2009*. 2011.
90. Sady M, Vaughan C, Gioia G. School and youth: recommend for concussion education and management. *Phys Med Rehabil Cli*. 2001;22:701-719.
91. Herring SA, Cantu RC, Guskiewicz KM, et al. Concussion (mild traumatic brain injury) and the team physician: a consensus statement--2011 update. *Med Sci Sports Exerc*. 2011;43(12):2412-2422.
92. Macciocchi SN, Barth JT, Alves W, Rimel RW, Jane JA. Neuropsychological functioning and recovery after mild head injury in collegiate athletes. *Neurosurgery*. 1996;39(3):510-514.
93. Ellemberg D, Leclerc S, Couture S, Daigle C. Prolonged neuropsychological impairments following a first concussion in female university soccer athletes. *Clin J Sport Med*. 2007;17(5):369-374.
94. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *J Am Med Assoc*. 2003;290(19):2556-2563.
95. Gioia G, Collins M, isquith P. Improving identification and diagnosis of mild traumatic brain injury with evidence: Psychometric support for the acute concussion evaluation. *J Head Trauma Rehab*. 2008;23:230-242.
96. Collins MW, Lovell MR, McKeag DB. Current issues in managing sports-related concussion. *J Am Med Assoc*. 1999;282(24):2283-2285.
97. Echemendia RJ, Putukian M, Mackin RS, Julian L, Shoss N. Neuropsychological test performance prior to and following sports-related mild traumatic brain injury. *Clin J Sports Med*. 2001;11(1):23-31.
98. Hinton-Bayre AD, Geffen G. Severity of sports-related concussion and neuropsychological test performance. *Neurology*. 2002;59(7):1068-1070.
99. Maddocks D, Saling M. Neuropsychological deficits following concussion. *Brain Inj*. 1996;10(2):99-103.
100. Makdissi M, Collie A, Maruff P, et al. Computerised cognitive assessment of concussed Australian Rules footballers. *Br J Sports Med*. 2001;35(5):354-360.
101. Barr WB, McCrea M. Sensitivity and specificity of standardized neurocognitive testing immediately following sports concussion. *J Int Neuropsychol Soc*. 2001;7(6):693-702.
102. Delaney JS, Lacroix VJ, Gagne C, Antoniou J. Concussions among university football and soccer players: a pilot study. *Clin J Sport Med*. 2001;11(4):234-240.

103. Guskiewicz KM, Ross SE, Marshall SW. Postural Stability and Neuropsychological Deficits After Concussion in Collegiate Athletes. *J Athl Train*. 2001;36(3):263-273.
104. Erlanger D, Kaushik T, Cantu R, et al. Symptom-based assessment of the severity of a concussion. *J Neurosurg*. 2003;98(3):477-484.
105. McCrea M, Kelly JP, Randolph C, Cisler R, Berger L. Immediate neurocognitive effects of concussion. *Neurosurgery*. 2002;50(5):1032-1040; discussion 1040-1032.
106. Warden DL, Bleiberg J, Cameron KL, et al. Persistent prolongation of simple reaction time in sports concussion. *Neurology*. 2001;57(3):524-526.
107. Matser JT, Kessels AG, Lezak MD, Troost J. A dose-response relation of headers and concussions with cognitive impairment in professional soccer players. *J Clin Exp Neuropsychol*. 2001;23(6):770-774.
108. Collie A, Maruff P, McStephen M, Darby D. Are Reliable Change (RC) calculations appropriate for determining the extent of cognitive change in concussed athletes? *Br J Sports Med*. 2003;37(4):370-372.
109. Eckner JT, Kutcher JS, Richardson JK. Effect of concussion on clinically measured reaction time in 9 NCAA division I collegiate athletes: a preliminary study. *J Inj Funct Rehabil*. 2011;3(3):212-218.
110. Louey AG, Cromer JA, Schembri AJ, et al. Detecting cognitive impairment after concussion: sensitivity of change from baseline and normative data methods using the CogSport/Axon cognitive test battery. *Arch Clin Neuropsychol*. 2014;29(5):432-441.
111. Collie A, Darby D, Maruff P. Computerised cognitive assessment of athletes with sports related head injury. *Br J Sports Med*. 2001;35(5):297-302.
112. Collie A, Maruff P. Computerised neuropsychological testing. *Br J Sports Med*. 2003;37(1):2-3.
113. Collie A, Makdissi M, Maruff P, Bennell K, McCrory P. Cognition in the days following concussion: comparison of symptomatic versus asymptomatic athletes. *J Neurol Neurosurg Psychiatry*. 2006;77(2):241-245.
114. Lovell MR, Collins MW, Iverson GL, et al. Recovery from mild concussion in high school athletes. *J Neurosurg*. 2003;98(2):296-301.
115. Makdissi M, Darby D, Maruff P, Ugoni A, Brukner P, McCrory PR. Natural history of concussion in sport: markers of severity and implications for management. *Am J Sports Med*. 2010;38(3):464-471.
116. McClincy MP, Lovell MR, Pardini J, Collins MW, Spore MK. Recovery from sports concussion in high school and collegiate athletes. *Brain Inj*. 2006;20(1):33-39.
117. Collie A, Maruff P, Makdissi M, McCrory P, McStephen M, Darby D. CogSport: reliability and correlation with conventional cognitive tests used in postconcussion medical evaluations. *Clin J Sport Med*. 2003;13(1):28-32.
118. Collie A, Maruff P, McStephen M, Darby DG. Psychometric issues associated with computerised neuropsychological assessment of concussed athletes. *Br J Sports Med*. 2003;37(6):556-559.
119. McCrea KW, Xie J, Marrs CF, Gilsdorf JR. Prevalence of genetic differences in phosphorylcholine expression between nontypeable Haemophilus influenzae and Haemophilus haemolyticus. *BMC microbiology*. 2010;10:286.
120. Erlanger D, Saliba E, Barth J, Almquist J, Webright W, Freeman J. Monitoring Resolution of Postconcussion Symptoms in Athletes: Preliminary Results of a Web-Based Neuropsychological Test Protocol. *J Athl Train*. 2001;36(3):280-287.

121. MacDonald J, Duerson D. Reliability of a Computerized Neurocognitive Test in Baseline Concussion Testing of High School Athletes. *Clin J Sport Med*. 2014.
122. Eckner JT, Kutcher JS, Richardson JK. Pilot evaluation of a novel clinical test of reaction time in national collegiate athletic association division I football players. *J Athl Train*. 2010;45(4):327-332.
123. Eckner JT, Kutcher JS, Broglio SP, Richardson JK. Effect of sport-related concussion on clinically measured simple reaction time. *Br J Sports Med*. 2014;48(2):112-118.
124. Eckner JT, Whitacre RD, Kirsch NL, Richardson JK. Evaluating a clinical measure of reaction time: an observational study. *Percept Mot Skills*. 2009;108(3):717-720.
125. Guskiewicz KM, Mihalik JP. Biomechanics of sport concussion: quest for the elusive injury threshold. *Exerc Sport Sci Rev*. 2011;39(1):4-11.
126. Zhang L, Yang KH, King AI. A proposed injury threshold for mild traumatic brain injury. *J Biomech Eng*. 2004;126(2):226-236.
127. Eckner JT, Sabin M, Kutcher JS, Broglio SP. No Evidence for a Cumulative Impact Effect on Concussion Injury Threshold. *J Neurotrauma*. 2011;28(10):2079-2090.
128. Pellman EJ, Viano DC, Tucker AM, Casson IR, Waeckerle JF. Concussion in professional football: reconstruction of game impacts and injuries. *Neurosurgery*. 2003;53(4):799-812; discussion 812-794.
129. Abbas K, Shenk TE, Poole VN, et al. Alteration of default mode network in high school football athletes due to repetitive subconcussive mild traumatic brain injury: a resting-state functional magnetic resonance imaging study. *Brain Connect*. 2015;5(2):91-101.
130. McAllister TW, Flashman LA, Maerlender A, et al. Cognitive effects of one season of head impacts in a cohort of collegiate contact sport athletes. *Neurology*. 2012;78(22):1777-1784.
131. Greenwald RM, Gwin JT, Chu JJ, Crisco JJ. Head impact severity measures for evaluating mild traumatic brain injury risk exposure. *Neurosurgery*. 2008;62(4):789-798; discussion 798.
132. Versace J. A review of the severity index. *SAE Technical Paper 710881*. 1971.
133. Gadd C. Use of a weighted-impulse criterion for estimating injury hazard. *SAE Technical Paper 660793*. 1966.
134. Moon DW, Beedle CW, Kovacic CR. Peak head acceleration of athletes during competition--football. *Med Sci Sports*. 1971;3(1):44-50.
135. Reid SE, Epstein HM, O'Dea TJ, Louis MW, Reid SE, Jr. Head protection in football. *J Sports Med*. 1974;2(2):86-92.
136. Naunheim RS, Standeven J, Richter C, Lewis LM. Comparison of impact data in hockey, football, and soccer. *J Trauma*. 2000;48(5):938-941.
137. Manoogian S, McNeely D, Duma S, Brolinson G, Greenwald R. Head acceleration is less than 10 percent of helmet acceleration in football impacts. *Biomed Sci Instrum*. 2006;42:383-388.
138. Crisco JJ, Chu JJ, Greenwald RM. An algorithm for estimating acceleration magnitude and impact location using multiple nonorthogonal single-axis accelerometers. *J Biomech Eng*. 2004;126(6):849-854.
139. Duma SM, Manoogian SJ, Bussone WR, et al. Analysis of real-time head accelerations in collegiate football players. *Clin J Sport Med*. 2005;15(1):3-8.

140. Cobb BR, Urban JE, Davenport EM, et al. Head impact exposure in youth football: elementary school ages 9-12 years and the effect of practice structure. *Ann Biomed Eng*. 2013;41(12):2463-2473.
141. Crisco JJ, Fiore R, Beckwith JG, et al. Frequency and location of head impact exposures in individual collegiate football players. *J Athl Train*. 2010;45(6):549-559.
142. Daniel RW, Rowson S, Duma SM. Head impact exposure in youth football. *Ann Biomed Eng*. 2012;40(4):976-981.
143. Duhaime AC, Beckwith JG, Maerlender AC, et al. Spectrum of acute clinical characteristics of diagnosed concussions in college athletes wearing instrumented helmets: clinical article. *J Neurosurg*. 2012;117(6):1092-1099.
144. Broglio SP, Schnebel B, Sosnoff JJ, et al. Biomechanical properties of concussions in high school football. *Med Sci Sports Exerc*. 2010;42(11):2064-2071.
145. Broglio SP, Sosnoff JJ, Shin S, He X, Alcaraz C, Zimmerman J. Head impacts during high school football: a biomechanical assessment. *J Athl Train*. 2009;44(4):342-349.
146. Pellman EJ, Lovell MR, Viano DC, Casson IR. Concussion in professional football: recovery of NFL and high school athletes assessed by computerized neuropsychological testing--Part 12. *Neurosurgery*. 2006;58(2):263-274.
147. Viano DC, Pellman EJ, Withnall C, Shewchenko N. Concussion in professional football: performance of newer helmets in reconstructed game impacts--Part 13. *Neurosurgery*. 2006;59(3):591-606; discussion 591-606.
148. Mihalik JP, Blackburn JT, Greenwald RM, Cantu RC, Marshall SW, Guskiewicz KM. Collision type and player anticipation affect head impact severity among youth ice hockey players. *Pediatrics*. 2010;125(6):e1394-1401.
149. Crisco JJ, Greenwald RM. Let's get the head further out of the game: a proposal for reducing brain injuries in helmeted contact sports. *Curr Sports Med Rep*. 2011;10(1):7-9.
150. Crisco JJ, Wilcox BJ, Beckwith JG, et al. Head impact exposure in collegiate football players. *J Biomech*. 2011;44(15):2673-2678.
151. Brolinson PG, Manoogian S, McNeely D, Goforth M, Greenwald R, Duma S. Analysis of linear head accelerations from collegiate football impacts. *Curr Sports Med Rep*. 2006;5(1):23-28.
152. Mihalik JP, Bell DR, Marshall SW, Guskiewicz KM. Measurement of head impacts in collegiate football players: an investigation of positional and event-type differences. *Neurosurgery*. 2007;61(6):1229-1235; discussion 1235.
153. Schmidt JD, Guskiewicz KM, Blackburn JT, Mihalik JP, Siegmund GP, Marshall SW. The influence of cervical muscle characteristics on head impact biomechanics in football. *Am J Sports Med*. 2014;42(9):2056-2066.
154. Schmidt JD, Guskiewicz KM, Mihalik JP, Blackburn JT, Siegmund GP, Marshall SW. Does Visual Performance Influence Head Impact Severity Among High School Football Athletes? *Clin J Sport Med*. 2014.
155. King NS. Post-concussion syndrome: clarity amid the controversy? *Br J Psychiatry*. 2003;183:276-278.
156. King D, Hume PA, Brughelli M, Gissane C. Instrumented mouthguard acceleration analyses for head impacts in amateur rugby union players over a season of matches. *Am J Sports Med*. 2015;43(3):614-624.

157. Rowson S, Goforth MW, Dietter D, Brolinson PG, Duma SM. Correlating cumulative sub-concussive head impacts in football with player performance - biomed 2009. *Biomed Sci Instrum*. 2009;45:113-118.
158. Crisco JJ, Wilcox BJ, Machan JT, et al. Magnitude of head impact exposures in individual collegiate football players. *J Appl Biomech*. 2012;28(2):174-183.
159. Broglio SP, Surma T, Ashton-Miller JA. High school and collegiate football athlete concussions: a biomechanical review. *Ann Biomed Eng*. 2012;40(1):37-46.
160. Urban JE, Davenport EM, Golman AJ, et al. Head impact exposure in youth football: high school ages 14 to 18 years and cumulative impact analysis. *Ann Biomed Eng*. 2013;41(12):2474-2487.
161. Martini D, Eckner J, Kutcher J, Broglio SP. Subconcussive Head Impact Biomechanics: Comparing Differing Offensive Schemes. *Med Sci Sports Exerc*. 2013;45(4):755-761.
162. Daniel RW, Rowson S, Duma SM. Head impact exposure in youth football: middle school ages 12-14 years. *J Biomech Eng*. 2014;136(9):291-296.
163. Young TJ, Daniel RW, Rowson S, Duma SM. Head impact exposure in youth football: elementary school ages 7-8 years and the effect of returning players. *Clin J Sport Med*. 2014;24(5):416-421.
164. Munce TA, Dorman JC, Thompson PA, Valentine VD, Bergeron MF. Head Impact Exposure and Neurologic Function of Youth Football Players. *Med Sci Sports Exerc*. 2015;47(8):1567-1576.
165. Reed N, Taha T, Keightley M, et al. Measurement of head impacts in youth ice hockey players. *Int J Sports Med*. 2010;31(11):826-833.
166. Mihalik JP, Greenwald RM, Blackburn JT, Cantu RC, Marshall SW, Guskiewicz KM. Effect of infraction type on head impact severity in youth ice hockey. *Med Sci Sports Exerc*. 2010;42(8):1431-1438.
167. Gurdjian ES, Roberts VL, Thomas LM. Tolerance curves of acceleration and intracranial pressure and protective index in experimental head injury. *J Trauma*. 1966;6(5):600-604.
168. Guskiewicz KM, Mihalik JP, Shankar V, et al. Measurement of head impacts in collegiate football players: relationship between head impact biomechanics and acute clinical outcome after concussion. *Neurosurgery*. 2007;61(6):1244-1252; discussion 1252-1243.
169. Young T, Rowson S, Duma SM. High magnitude head impacts experienced during youth football practices. *Biomed Sci Instrum*. 2014;50:100-105.
170. Barlow KM, Brooks BL, MacMaster FP, et al. A double-blind, placebo-controlled intervention trial of 3 and 10 mg sublingual melatonin for post-concussion syndrome in youths (PLAYGAME): study protocol for a randomized controlled trial. *Trials*. 2014;15:271.
171. CDC. Nonfatal traumatic brain injuries related to sports and recreation activities among persons aged < 19 years- United States 2001-2009. *MMWR*. 2011;60(39):1337-1342.
172. Barlow M, Schlabach D, Peiffer J, Cook C. Differences in change scores and the predictive validity of three commonly used measures following concussion in the middle school and high school aged population. *Int J Sports Phys Ther*. 2011;6(3):150-157.
173. Makdissi M, Davis G, Jordan B, Patricios J, Purcell L, Putukian M. Revisiting the modifiers: how should the evaluation and management of acute concussions differ in specific groups? *Br J Sports Med*. 2013;47(5):314-320.

174. Meehan W, d'Hemecourt P, Comstock R. High school concussions in the 2008-2009 academic year: mechanism, symptoms, management. *Am J Sports Med*. 2010;38:2405.
175. Yeates KO, Taylor HG, Rusin J, et al. Premorbid child and family functioning as predictors of post-concussive symptoms in children with mild traumatic brain injuries. *Int J Dev Neurosci*. 2012;30(3):231-237.
176. Piebes S, Gourley M, Valovich McLeod T. Caring for student athlete following concussion. *J Sch Nurs*. 2009;25:270-281.
177. Testa MA, DC. S. Assessment of quality-of-life outcomes. *N Engl J Med*. 1996;334:835-840.
178. Broglio SP, Puetz TW. The effect of sport concussion on neurocognitive function, self-report symptoms and postural control : a meta-analysis. *Sports Med*. 2008;38(1):53-67.
179. Valovich McLeod TC, Bay RC, Parson JT, Sauers EL, AR. S. Recent injury and HRQOL in adolescent athletes. *J Athl Train*. 2009;44:603-610.
180. Kuehl M, Snyder A, Erickson S, McLeod T. Impact of prior concussions on health-related quality of life in collegiate athletes. *Clin J Sport Med*. 2010;20(2):86-91.
181. McGuine T, Winterstein A, Carr K, Hetzel S, Scott J. Changes in self-reported knee function and health-related quality of life after knee injury in female athletes. *Clin J Sport Med*. 2012;22(4):334-340.
182. Martland HS. Punch drunk. *J Amer Med Assoc*. 1928;91:1103-1107.
183. JA M. Dementia pugilistica. *US Naval Medicine Bulletin*. 1937(35):297-303.
184. Courville CB. Punch drunk. Its pathogenesis and pathology on the basis of a verified case. *Bull Los Angel Neuro Soc*. 1962;27:160-168.
185. McKee AC, Gavett BE, Stern RA, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2010;69(9):918-929.
186. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol*. 2009;68(7):709-735.
187. Bieniek KF, Ross OA, Cormier KA, et al. Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. *Acta neuropathologica*. 2015;130(6):877-889.
188. Berger H. Electroencephalogram in humans. *Arch Psychiat Nerven*. 1929;87:527-570.
189. Davis H, Davis PA, Loomis AL, Harvey EN, Hobart G. Electrical reactions of the human brain to auditory stimulation during sleep. *J Neurophysiol*. 1939;2(6):500-514.
190. Walter WG. Contingent Negative Variation - Electrocortical Sign of Significant Association in Human Brain. *Science*. 1964;146(364):434-&.
191. Sutton S, Braren M, Zubin J, John ER. Evoked-potential correlates of stimulus uncertainty. *Science*. 1965;150(3700):1187-1188.
192. Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol*. 2007;118(10):2128-2148.
193. Kutas M, Mccarthy G, Donchin E. Measuring Erp Amplitudes Despite Latency Jitter. *Psychophysiology*. 1977;14(1):95-95.
194. Magliero A, Bashore TR, Coles MG, Donchin E. On the dependence of P300 latency on stimulus evaluation processes. *Psychophysiology*. 1984;21(2):171-186.
195. Kok A. On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology*. 2001;38(3):557-577.

196. Polich J. Response mode and P300 from auditory stimuli. *Biol Psychol*. 1987;25(1):61-71.
197. Emmerson RY, Dustman RE, Shearer DE, Turner CW. P3 latency and symbol digit performance correlations in aging. *Experimental aging research*. 1989;15(3-4):151-159.
198. Polich J, Howard L, Starr A. P300 Latency Correlates with Digit Span. *Psychophysiology*. 1983;20(6):665-669.
199. Fabiani M, Karis D, Donchin E. Effects of mnemonic strategy manipulation in a Von Restorff paradigm. *Electroencephalogr Clin Neurophysiol*. 1990;75(2):22-35.
200. Segalowitz SJ, Barnes KL. The Reliability of Erp Components in the Auditory Oddball Paradigm. *Psychophysiology*. 1993;30(5):451-459.
201. Walhovd KB, Fjell AM. One-year test-retest reliability of auditory ERPs in young and old adults. *Int J Psychophysiol*. 2002;46(1):29-40.
202. Patel SH, Azzam PN. Characterization of N200 and P300: selected studies of the Event-Related Potential. *Int J Med Sci*. 2005;2(4):147-154.
203. Wilson MJ, Harkrider AW, King KA. Effect of Repetitive, Subconcussive Impacts on Electrophysiological Measures of Attention. *South Med J*. 2015;108(9):559-566.
204. Gosselin N, Theriault M, Leclerc S, Montplaisir J, Lassonde M. Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. *Neurosurgery*. 2006;58(6):1151-1161; discussion 1151-1161.
205. Boutin D, Lassonde M, Robert M, Vanassing P, Ellemberg D. Neurophysiological assessment prior to and following sports-related concussion during childhood: a case study. *Neurocase*. 2008;14(3):239-248.
206. De Beaumont L, Theoret H, Mongeon D, et al. Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain*. 2009;132(Pt 3):695-708.
207. Eckner JT RA, Narisetty N, Greer J, Moore B, Brimacombe S, He X, Broglio SP. . Stability of an ERP-based measure of Brain Network Activation (BNA) in athletes: A new electrophysiological assessment tool for concussion. *Clin J Sports Med*. 2016;In press.
208. Broglio SP. Investigating a novel measure of brain networking following sport concussion. *Int J Sports Med*. 2016;In Press.
209. Beckwith JG, Greenwald RM, Chu JJ. Measuring head kinematics in football: correlation between the head impact telemetry system and Hybrid III headform. *Ann Biomed Eng*. 2012;40(1):237-248.
210. Electrical Geodesics I. Net Station Acquisition Technical Manual. Eugene, OR2003.
211. Pavot W, Diener E. Review of the Satisfaction with life scale. *Psychol Assess*. 1993;5(2):164-172.
212. Pavot W, Diener E, Colvin CR, Sandvik E. Further validation of the Satisfaction with Life Scale: evidence for the cross-method convergence of well-being measures. *J Pers Assess*. 1991;57(1):149-161.
213. Arrindell WA, Meeuwesen L, Huyse FJ. The Satisfaction with Life Scale (Swls) - Psychometric Properties in a Nonpsychiatric Medical Outpatients Sample. *Pers Indiv Differ*. 1991;12(2):117-123.
214. Ayr LK, Yeates KO, Taylor HG, Browne M. Dimensions of postconcussive symptoms in children with mild traumatic brain injuries. *J Int Neuropsychol Soc*. 2009;15(1):19-30.

215. Guskiewicz KM, Register-Mihalik J, McCrory P, et al. Evidence-based approach to revising the SCAT2: introducing the SCAT3. *Br J Sports Med*. 2013;47(5):289-293.
216. Alla S, Sullivan SJ, Hale L, McCrory P. Self-report scales/checklists for the measurement of concussion symptoms: a systematic review. *Br J Sports Med*. 2009;43 Suppl 1:i3-12.
217. McCrea M, Barr WB, Guskiewicz K, et al. Standard regression-based methods for measuring recovery after sport-related concussion. *J Int Neuropsychol Soc*. 2005;11(1):58-69.
218. Bazarian JJ, Zhu T, Zhong J, et al. Persistent, long-term cerebral white matter changes after sports-related repetitive head impacts. *PloS one*. 2014;9(4):e94734.
219. Erickson KI, Barr LL, Weinstein AM, et al. Measuring physical activity using accelerometry in a community sample with dementia. *J Am Geriatr Soc*. 2013;61(1):158-159.
220. Hillman CH, Kamijo K, Scudder M. A review of chronic and acute physical activity participation on neuroelectric measures of brain health and cognition during childhood. *Prev Med*. 2011;52 Suppl 1:S21-28.
221. Pontifex MB, Raine LB, Johnson CR, et al. Cardiorespiratory fitness and the flexible modulation of cognitive control in preadolescent children. *J Cogn Neurosci*. 2011;23(6):1332-1345.
222. Hillman CH, Castelli DM, Buck SM. Aerobic fitness and neurocognitive function in healthy preadolescent children. *Med Sci Sports Exerc*. 2005;37(11):1967-1974.
223. Kamijo K, Pontifex MB, O'Leary KC, et al. The effects of an afterschool physical activity program on working memory in preadolescent children. *Dev Sci*. 2011;14(5):1046-1058.
224. Hillman CH, Pontifex MB, Raine LB, Castelli DM, Hall EE, Kramer AF. The effect of acute treadmill walking on cognitive control and academic achievement in preadolescent children. *Neuroscience*. 2009;159(3):1044-1054.
225. Pontifex MB, Hillman CH, Fernhall B, Thompson KM, Valentini TA. The effect of acute aerobic and resistance exercise on working memory. *Med Sci Sports Exerc*. 2009;41(4):927-934.
226. Chaddock-Heyman L, Erickson KI, Voss MW, et al. The effects of physical activity on functional MRI activation associated with cognitive control in children: a randomized controlled intervention. *Front Hum Neurosci*. 2013;7:72.
227. Erickson KI, Banducci SE, Weinstein AM, et al. The brain-derived neurotrophic factor Val66Met polymorphism moderates an effect of physical activity on working memory performance. *Psychol Sci*. 2013;24(9):1770-1779.
228. Cabeza R, Nyberg L. Neural bases of learning and memory: functional neuroimaging evidence. *Curr Opin Neurol*. 2000;13(4):415-421.
229. Miller JR, Adamson GJ, Pink MM, Sweet JC. Comparison of preseason, midseason, and postseason neurocognitive scores in uninjured collegiate football players. *Am J Sports Med*. 2007;35(8):1284-1288.
230. Montenigro PH, Alosco ML, Martin B, et al. Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players. *J Neurotrauma*. 2016.
231. Cohen J. A power primer. *Psychol Bull*. 1992;112(1):155-159.

232. Henry LC, Tremblay S, Leclerc S, et al. Metabolic changes in concussed American football players during the acute and chronic post-injury phases. *BMC Neurol*. 2011;11:105.
233. Vagnozzi R, Signoretti S, Cristofori L, et al. Assessment of metabolic brain damage and recovery following mild traumatic brain injury: a multicentre, proton magnetic resonance spectroscopic study in concussed patients. *Brain*. 2010;133(11):3232-3242.
234. McLeod TCV. The Value of Various Assessment Techniques in Detecting the Effects of Concussion on Cognition, Symptoms, and Postural Control. *J Athl Train*. 2009;44(6):663-665.
235. Iverson GL, Brooks BL, Collins MW, Lovell MR. Tracking neuropsychological recovery following concussion in sport. *Brain Inj*. 2006;20(3):245-252.
236. Valovich McLeod T, Bay R, Valier A, Lam K, Parsons J. Health-related quality of life following sport-related concussion in interscholastic athletes. 4th international conference on concussion in sport; 2013; Zurich.
237. Covassin T, Moran R, Wilhelm K. Concussion symptoms and neurocognitive performance of high school and college athletes who incur multiple concussions. *Am J Sports Med*. 2013;41(12):2885-2889.
238. Lovell MR, Iverson GL, Collins MW, et al. Measurement of symptoms following sports-related concussion: reliability and normative data for the post-concussion scale. *Appl Neuropsychol*. 2006;13(3):166-174.
239. Howell D, Osternig L, Van Donkelaar P, Mayr U, Chou LS. Effects of concussion on attention and executive function in adolescents. *Med Sci Sports Exerc*. 2013;45(6):1030-1037.