Profiling Brain Trauma in Professional American-style Football and the Implications to Developing Neurological Injury

Clara Karton

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School of Human Kinetics
Faculty of Health Sciences
University of Ottawa,
Ottawa, Canada

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Abstract

American-style football participation is associated with high risks to a spectrum of sports-related brain injury involving acute reactions and chronic manifestations. Traditional methods of identifying injury have proven ineffective at protecting athletes and mitigating risk as they rely on the presence and recognition of inconsistent symptom expression. This is, in part, due to the lack of an objective measure of quantifying exposure.

Brain trauma profiling was defined to capture a spectrum of exposure by incorporating the primary characteristics that associate with risk of neurological injury. This profile includes strain magnitude associated with impact, frequency at which impacts are experienced, time interval between impacts, over the duration of exposure. Trauma profiling methods differentiated player field position in professional American-style football where three unique trauma profiles were identified based on similarities among the characteristics of trauma. Regional strain from common head impacts showed that distribution was independent of field position regardless of variation in impact conditions. Rather, brain regions vulnerable to strains were dictated by the frequency and magnitude that govern the position profile. The extent of tissue volume involved in common head impacts was field position dependent. Skill positions tended to experience impacts involving greater tissue volumes reaching deeper white matter structures, but were infrequent. Impacts common to line positions typically involved less brain tissue of predominately superficial cortical gray matter, but were experienced at high frequency counts.

The primary findings from this research show that *brain trauma profiling* may be used as an objective measurement tool to define exposure. The results indicate that exposure is not uniform and that brain trauma and injury risk can be described using unique combinations of these characteristics. Regional areas vulnerable to strain are dictated by the frequency and magnitude of impact and therefore in order to effectively protect against brain injury, both characteristics need to be managed. Lastly, this research demonstrates that either few impacts involving high brain volume or frequent impacts with little brain volume involvement may both result in brain dysfunction.

Brain trauma profiling methods has broad application in future research. This measurement tool will be useful in identifying how injury occurs in various sports, military units, and particularly important for vulnerable populations and the developing brain. This knowledge is instrumental in establishing risk prevention strategies and public health policies for specific environments.

Preface

This dissertation is organized into five main parts with multiple sections in each.

Part I: Introduction, presents relevant background and research objectives.

Part II: Review of literature covers the area of research.

Part III: Research methods development and studies.

Part IV: Global discussion, including research implications, limitations, and future recommendations.

Part V: Complete list of references.

List of Collaborators

Clara Karton (PhD student) was involved in all aspects of this thesis, including the conception, data collection, and analysis. All writing of papers and final thesis was completed by the student.
Dr. T. Blaine Hoshizaki was the thesis supervisor and was involved in a supervisory role in all aspects of the thesis.
Dr. Jing Xian Li was involved as a committee member for this thesis.
Dr. Shawn Marshall was involved as a committee member for this thesis.
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PART I

1 Introduction

1.1 Problem Statement

There is little debate that organized sport provides individuals with a host of physical, mental and emotional benefits, while enriching one's experience through a sense of belonging and community. Unfortunately what intends as a positive experience and healthy lifestyle comes with a risk for injury, including injury to the brain. It is estimated that as many as 3.8 million concussions occur in the United States each year during competitive sports [Harmon *et al.,* 2013], the highest rates occurring during participation in sports that involve contact and collisions [Marar *et al.,* 2012; Marshall *et al.,* 2015; Gessel *et al.,* 2007], most notably is American-style football (ASF) [Pfister *et al.,* 2016; Lincoln *et al.,* 2011]. No doubt large amounts of resources have been allocated to increasing awareness, prevention, management and treatment of concussion injuries. Nonetheless, undiagnosed concussion estimates remain unacceptably high, showing that less than half are identified, either from reluctance to report, or the inability to detect the vast expression of possible signs [Meehan *et al.,* 2013; McCrea *et al.,* 2014; Harmon *et al.,* 2013; McCrory *et al.,* 2017]. What is particularly unsettling is that head impacts sustained in ASF pose a variety of risks not limited to increased concussion susceptibility, but have also been associated with mental health disorders, cognitive impairments and brain disease pathologies [McKee *et al.,* 2013; Abbas *et al.,* 2015]. Physical trauma to neurons, involving multiple low magnitude impacts, disrupts a number of processes, many with acute and chronic consequences and may not immediately express as recognizable injury [McAllister *et al.,* 2014; Lin *et al.,* 2015; Shultz *et al.,* 2012; Oliver *et al.,* 2016], and develop over time [Alosco *et al.,* 2017a; Montenigro *et al.,* 2017; Stamm *et al.,* 2015a]. As a result, only major traumatic events with associated symptoms are identified as 'injuries', whereas repetitive strain from more minor undetected head trauma events are having deleterious health effects, but are not being acknowledged with an athlete's trauma profile. With approximately 5.22 million people in the US participating in tackle football [Statista, 2019], head trauma poses a risk to quality of life with lasting consequences representing a public health concern [Finkel & Bieniek, 2018].

1.2 Background and Rationale

Neurological injuries are closely associated with activities involving direct impacts to the head, where patients who have suffered a single moderate to severe traumatic brain injury are at an increased risk of developing cognitive impairments from progressive and psychiatric disorders [Masel & DeWill, 2010]. This also holds true for neural tissues experiencing cumulative repetitive head impacts of lower magnitudes with growing evidence of the potential manifestation into progressive diseases and serious disability [Omalu, 2005; McKee *et al.,* 2009; 2013]. In 2002, Dr. Bennet Omalu [2005] discovered neurodegeneration in the brain of a retired ASF player, consistent with brain disease initially found in boxers. This brain, of Michael Lewis Webster, former lineman in the National Football League (NFL) for 16 years, would be the first, of many diagnosed with Chronic Traumatic Encephalopathy (CTE) within the modern era of contact sport [Mez *et al.,* 2018]. To date, CTE diagnoses have been predominantly in those individuals with known exposure to repetitive head impacts [Beineik *et al.,* 2015; Maroon *et al.,* 2015; Noy *et al.,* 2016; Iverson *et al.,* 2019]. This progressive disease is arguably the most severe consequence to brain trauma exposure. However, this finding provided a motive to examine the effects of brain trauma outside of the boundaries of acute clinically recognizable signs. The myriad of possible symptoms, the individualized expression of symptoms or lack thereof, and inconsistency in injury identification and reporting has stunted our ability to move forward with understanding brain trauma and its effects on function.

Currently, ASF players represent one of the highest 'at risk' populations for a spectrum of sports-related brain injury that envelop acute reactions and chronic manifestations, including symptomatic concussions [Gessel *et al.,* 2007; Marar *et al.,* 2012], functional changes [Talavage *et al.,* 2014; Bahrami *et al.,* 2016], and neurological diseases [Lehman *et al.,* 2013; Mez *et al.,* 2017]. Brain trauma is unique to field position, where athletes typically are limited to one, occasionally two positions throughout their careers. Variability in player positions is reflected in differences reported in injury rates and trauma exposure characteristics [Nathanson *et al.,* 2016; Mez *et al.,* 2017; Crisco *et al.,* 2010; 2011; 2012; Baugh *et al.,* 2015]. These players provide us with a population to examine the characteristics of brain trauma and contextually advance our understanding of the relationship between trauma and risk to acute injury and chronic mental health disorders and neurological disease from cumulative mechanisms.

Following years of cumulative brain trauma, current and former football athletes report suffering from depression, behavioral changes and neurocognitive and neurophysiological impairments [Alosco *et al.,* 2017a; Montenigro *et al.,* 2017; Strain *et al.,* 2013]. Research employing sophisticated and sensitive techniques to examine the effects of brain trauma exposure is also growing. Metabolic reactions, structural changes, and physiological responses to trauma have been detected in athletes using various imaging techniques and biomarkers of axonal injury [Shultz *et al.,* 2012; Mayinger *et al.,* 2018; Breedlove *et al.,* 2012; 2014; Amen *et al.,* 2016; Stern *et al.,* 2016]. One season of play where athletes experience repetitive impacts to the head associates with measurable brain damage [Talavage *et al.,* 2014; McAllister *et al.,* 2014; Bahrami *et al.,* 2016], with worsened outcomes at higher impact intensities [Bazarian *et al.,* 2012; Hampshire *et al.,* 2013; Oliver *et al.,* 2016], and when trauma is sustained for longer periods of time [Alosco *et al.,* 2017a; 2017b; Stern *et al.,* 2016]. These modalities demonstrate abnormalities in neuronal activity, cerebral blood flow, brain connectivity, and protein concentrations, indicating both localized and widespread dysfunction. How the characteristics of one or more traumatic events influence where brain injury distributes and to what extent brain damage occurs has not been well defined. Reports have demonstrated deficits in a number of brain regions [Amen *et al.,* 2016; Hampshire *et al.,* 2013] and have shown to be influenced by both the brain's anatomical structures and physiological systems [Bayly *et al.,* 2005; McKee *et al.,* 2016; Iliff *et al.,* 2014; Cloots *et al.,* 2011], as well as the details of the event including impact severity and head impact location [Talavage *et al.,* 2014; Bazarian *et al.,* 2012]. This work demonstrates that brain trauma is complex and multifaceted, influenced by the magnitude of an impact, the frequency at which impacts are sustained, the time interval between impacts, and the duration of overall exposure.

Traditionally biomechanical investigations have related head motion analysis and brain deformation of an event with observable outcomes. Strain based metrics have become common based on their good association with injury and usefulness in estimating injury thresholds and prediction [Zhang *et al.,* 2004; Kleiven, 2007; McAllister *et al.,* 2014]. Biomechanical assessments of brain trauma that incorporate multiple event characteristics have predominantly relied on head impact sensors to estimate exposure characteristics which have a number of drawbacks. Measurements are often inconsistent and inaccurate, and are restricted to head acceleration-based metrics which provide limited information about the brain's response to

impact [Jadischke *et al.*, 2013]. Exclusively measuring head motion limits our understanding of the injury itself and consequently provides a poor interpretation of exposure results. Video observation of game play is useful in identifying head impact event frequencies with estimated time intervals. Physical head injury reconstruction in conjunction with finite element (FE) modeling techniques allows for the determination of brain tissue deformations associated with these loading inputs [Post & Hoshizaki, 2012]. Used in combination, these approaches permit quantifying and describing brain trauma sustained from multiple head impact events.

With considerable evidence of neuronal damage sustained from head impacts [Bailes *et al.*, 2013; Kerr *et al.*, 2014; Hutchison *et al.*, 2009], brain trauma risk assessment should not be limited to macroscopic and/or symptoms-based injuries. Relying on the presence and recognition of acute symptoms to establish when brain tissue has become injured is subjective and limits our capacity to connect trauma to injury. An objective approach to quantifying physical trauma to the brain, one that captures the spectrum of head impact severities, is a plausible medium to better understand this relationship. This thesis addresses the multi-dimensional characteristics of brain trauma exposure that contribute to risk in the context of brain function, mental health and neurological disorder development.

1.3 Research Objectives

The governing objective of this research was to use biomechanical methods to measure brain trauma exposure in ASF game play. The specific aims of this dissertation include:

1. Define *brain trauma profiling* that captures a spectrum of exposure by identifying and incorporating the primary characteristics that associate with risk of neurological injury including strain magnitude, impact frequency, time interval between impacts and duration of exposure.
2. Using an objective measurement tool, describe the characteristics of brain trauma exposure specific to player field position in ASF.
3. Examine the volume and regional distribution of brain tissue strain associated with common head impacts sustained by ASF field positions.

PART II

2 Brain Structure and Function

The human brain is the most complex and impressive organ in the body. It grants the human the ability to generate higher consciousness, intelligence, physical action, memory and feelings making each individual unique and different. This complexity and individuality also grants challenges for head and brain injury research as damage to the brain consequently disrupts one or more of its processes. For protection, the brain is encased inside a hard skull. Unfortunately many challenges faced today in sport pertains to injuries caused by the motion of the brain within the skull and the integrity of axons [Bailes, 2009]. The brain is composed of billions of neurons, which communicate with each other to form circuits and share information which is interrupted from physical trauma. To improve on ways to protect the brain from axonal damage and disruption, an understanding of the human brain's structures and functions are required. Unlike differences in human personality and injury predisposition, gross anatomical structures and brain mechanics are similar among individuals and will be presented in general terms.

2.1 Brain Anatomy and Material Properties

Along with nerves and vasculature, the brain is comprised of three main regions; the brain stem, the cerebellum, and the cerebrum, which are surrounded by cerebrospinal fluid. The cerebrum is essentially, the *brain of the brain* containing two (right and left) hemispheres which are mirror images of one another, both comprised of an outside layer of gray matter surrounding the innermost portion of white matter (Fig. 2-1). The most superficial layer of the cerebrum, the cerebral cortex, is a layer of approx. 2-4 mm of gray matter. Beneath the cerebral cortex is the deeper white matter. The crests of the cortical folds are called gyri and are separated by small grooves known as sulci, and deeper grooves known as fissures (Fig. 2-2). Brain disease pathologies, including those caused by repetitive physical trauma, typically initiates in the depths of the sulcus [Omalu *et al.,* 2005; 2006; McKee *et al.,* 2013; 2016], shown as an area experiencing high strains in sporting accidents [Ghajari *et al.,* 2017]. The left and right cerebral hemispheres are separated by a longitudinal fissure which runs along the midsagittal plane, and communication between the hemispheres is made via tracts (bundles of white matter axons), the

corpus callosum being the largest. Techniques identifying microstructural damage to white matter, demonstrate the sensitivity of these measurements to the cumulative effect of trauma [Miles *et al.*, 2007; Bazarian *et al.,* 2014; Bahrami *et al.,* 2016; Mayinger *et al.,* 2018]. Often the corpus callosum is identified as an area highly influenced by trauma and may have implications to understanding why symptom expression is so vast [Oni *et al.*, 2010; McCrory *et al.*, 2017].

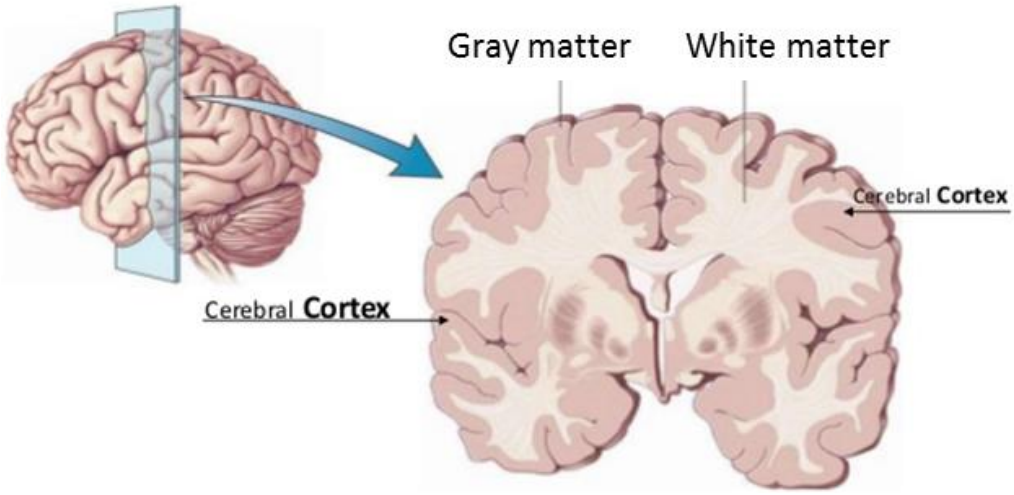

Figure 2-1: Gray and white matter distribution within the cerebrum [Martini, 2017].

Brain tissue is heterogeneous material as it is comprised of both gray and white matter. Nerve synapses mainly occur in gray matter which chiefly consists of neuronal cell bodies, dendrites, terminals, and few unmyelinated axons [Budday *et al.,* 2015]. The white matter primarily made up of myelinated ascending and descending nerve fibers that connect, relay and coordinate communication, giving white matter its highly directional orientation. Therefore, brain tissue is inhomogeneous, as gray matter is considered isotropic, whereas white matter is anisotropic material [Prange & Margulies, 2002; Prevost *et al.*, 2011, Jin *et al.*, 2013, Budday *et al.*, 2015]. Reported stiffness values of brain tissue are quite broad and different between species, individuals, and different regions within the same brain [Prange & Margulies, 2002; Elkin *et al.*, 2011; Coats & Margulies, 2006]. Stiffness comparisons have reported differing results between gray and white matter tissue, where some have reported stiffer properties of gray matter [Christ *et al.,* 2010, Zhang *et al.,* 2011], while others demonstrate the myelination of white matter results in stiffer mechanical properties [Weickenmeier *et al.,* 2016; Kruse *et al.,* 2008], and few finding equal stiffness [Nicolle *et al.,* 2004; Feng 2013]. Differences in findings may be explained by the presence of vasculature, including capillary density and blood flow [Budday *et al.,* 2017; Bilston,

2002], however these differences have been shown to be most influential in severe brain injury outcomes [Ho & Kleiven, 2007].

Direct impacts to the head cause physical trauma to the axons resulting in a number of different responses and express as various types and severities of brain injury [Viano *et al.*, 1989; King *et al.,* 2003]. One study used computer simulated impacts to examine the differential in energy absorption between gray and white matter. They demonstrated the majority of the external kinetic energy is absorbed by the external structures of the head with only about 5% reaching the internal structures [von Holst & Li, 2013]. Interestingly, this study revealed that the gray matter absorbed almost twice as much internal energy as the white matter, possibly indicative of the varying sensitivity levels to injury amongst brain tissue materials [Prange & Margulies, 2002; Elkin *et al.,* 2011; MacManus *et al.,* 2016], as many experiments have revealed a role in white matter damage in traumatic and mild head injury [Rutgers *et al.,* 2008; Nakayama *et al.,* 2006]. This could shed light on why similar energy event characteristics have the potential to result in varying severities and lengths of symptom expression. It may be that the event itself is not the long-term injury, but rather as neuronal communication is inhibited, this causes a cascade of lasting symptomology and cognitive impairment [Fakhran *et al.,* 2013]. Also consistent with these findings, is research indicating that impacts of higher force create more damage in the deeper brain regions [Ommaya & Gennarelli, 1974; King *et al.,* 2003]. Damage to gray and/or white matter axons may express through different symptoms, or be associated with, and therefore manifest, as different injuries and possible brain disease [Mayinger *et al.,* 2018; McKee *et al.,* 2013; Zetterberg et al. 2006]. Injury to an axon by the application of a stretch in *in vivo* and *in vitro* models can be observed in many forms. Stretch causes local axonal swelling, blood-barrier disruption, and altered transportation and metabolic processes [Giza & Hovda, 2014; Cherry *et al.,* 2016], and may lead to neurodegeneration [Smith *et al.,* 1999; Yuen *et al.,* 2009; Tagge *et al.,* 2018]. Neuronal injury is also measured through structural damage to protein and cytoskeletal components [Tang-Schomer *et al.,* 2010; McKee *et al.,* 2013]. These responses can also be worsened by a subsequent stretch demonstrating exacerbated ionic shifts and increased levels of toxic protein states [Yuen *et al.,* 2009; Kondo *et al.,* 2015; Alosco *et al.,* 2017b; Stern *et al.,* 2016]. Widespread damage and neuronal degeneration is observed in a diseased brain, evidenced as the lasting consequences of repetitive axonal injury [Ballatore *et al.,* 2007; Omalu *et al.,* 2006; Stern *et al.,* 2016; Bernick *et al.,* 2014].

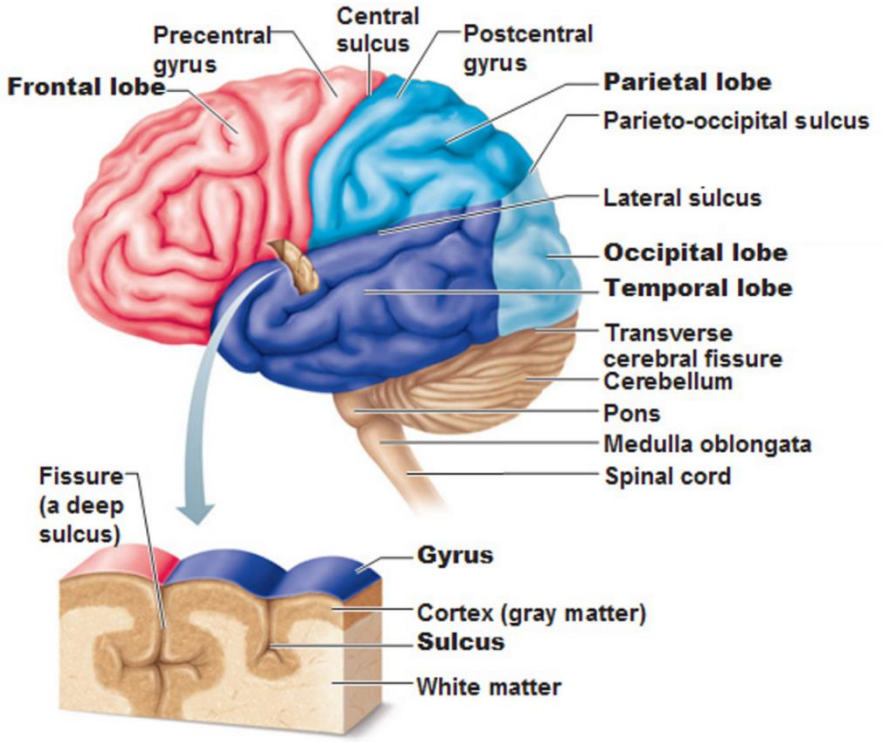

Figure 2-2: Anatomical locations of lobes, sulci and gyri of the cerebrum within the human brain [Martini, 2017].

2.2 Functional Regions

The cerebrum contains four lobes within each hemisphere; frontal, parietal, temporal and occipital which are defined by their functionalities (Fig. 2-2). The frontal lobe, located at the forehead, is involved in higher level cognitive functions including memory, cognitive flexibility, planning, inhibition, abstract reasoning, organization and regulation. This area of the brain is also involved in voluntary movement or activity and expressive (output) language [Miller & Cummings, 2006; Drubach, 2000]. Posterior the frontal lobe is the parietal lobe involved in the processing of sensory information such as touch, pressure, pain, and object identification through tactile. Together with the temporal lobe, the parietal lobe interprets language input [Drubach, 2000]. Processing auditory information and interpreting the meaning of language are functions of the temporal lobe, located near the temples. This location is involved with the formation of memories by the hippocampus (located within the temporal lobe) and has a prominent role in learning and emotional modulation [Drubach, 2000]. The most caudal part of the brain is the occipital lobe involved in processing and interpretation of all visual stimuli and information

including vertical and horizontal lines, colours, shapes, contrasts, motion of varying velocities etc. [Drubach, 2000].

Physical trauma may injure any one part of the brain where cognitive abnormalities may be indicative of regional damage. Head trauma expressing as adverse mental health disorders, motor deficiencies and cognitive impairments are dictated by the affected areas of the brain, and may be expressed short or long-term [Alosco *et al.,* 2017a; Montenigro *et al.,* 2017; Talavage *et al.,* 2014]. Cerebral blood flow and regional activation associate with neurocognitive performance and neurophysiological changes in current and former sports athletes, involving widespread areas throughout the brain [Hart *et al.,* 2013; Keightley *et al.,* 2014; Chen *et al.,* 2008; Amen *et al.,* 2016; Lipton *et al.,* 2013; Breedlove *et al.,* 2014]. More specifically, Goswami et al [2016] demonstrated that functional changes in frontotemporal lobe correlated with aggression and impulsivity in retired athletes. Altered activation within the dorsolateral prefrontal cortex has shown to associate with depression, deficits in visual working memory, and executive dysfunction [Chen *et al.,* 2008; Talavage *et al.,* 2014; Hampshire *et al.,* 2013]. Hart et al [2013] measured differences in blood flow within the temporal and parietal lobe regions which corresponded with measurable impairments in cognitive tasks associated with these areas. Memory, naming and word finding were deficient in clinically impaired football players. Changes at the cellular level have also been measured in active and retired athletes with a history of repetitive sports-related head impacts in the form of prolonged microglial activation, specifically in temporal lobe [Coughlin *et al.,* 2015; 2017]. These studies demonstrate that sports-related brain damage may be widespread and interrupt a number of its functions.

2.3 Summary

Damage to brain tissue may be localized or widespread reflective of the variation in mechanical responses and functional regions. These disparities influence the brain's response to a mechanical load and association with injury. Head motion causing anatomical tissue strain can cause disruption of brain function and/or alterations in the structural component of neuronal cells. Biomechanical methods examining head motion and relative brain response to various loading conditions is used to understand mechanisms of injury and can be used to better connect trauma to various brain regions and cumulative tissue damage.

3 Biomechanics of Head Injury

Early investigations employing cadaver and animal models examined the head's mechanical response to impact and ascertained the mechanisms associated with brain injury. The injury mechanism describes the mechanical and physical changes that result in structural or functional damage [Viano *et al.,* 1989]. As momentum and energy are transferred to the head during a direct impact, causing a change in head motion, this leads to deformation of soft tissues involving the scalp, skull and brain. Therefore head injuries include those that affect its external and internal structures and are often categorized as either focal or diffuse. An understanding of mechanisms associated with head injury outcomes is important in biomechanics research as it provides a platform for establishing the human tissue's biological response and tolerance criteria.

3.1 Mechanisms of Brain Injury

3.1.1 Focal Brain Injury

Focal type injuries are localized to a single area and typically demonstrate immediate and observable outcomes that are visible using standard imaging techniques. Focal brain injuries are present in the moderately to severely injured requiring neurosurgical intervention and intensive care. These injuries are often the result of localized in-bending of the skull, intracranial pressure gradients and relative movement of the brain compared to its encompassing skull and include skull fracture and primary vascular injuries that cause bleeding within the brain, on the surface of the brain or in the cortical gray matter such as subdural haematoma and cerebral contusion [Holbourn, 1943; Ommaya & Hirsch, 1971; King *et al.,* 2003; Meaney *et al.,* 2014]. Direct impact causing localized and rapid in-bending of the skull at the site of impact was first observed by Gurdjian et al. [1964]. Local areas of stress, bends the skull bone inward producing a 'slap' effect on the tissue beneath [Gurdjian, 1975]. Depending on the degree of bending, damage to brain tissue, cerebral blood vessels, and surrounding area may result. This mechanism is often associated with contusions at lower magnitudes where the brain makes contact with the bony protuberances inside the skull. Intracranial hematomas caused by tearing of arteries/veins are more common at higher magnitudes [Gennarelli *et al.,* 1971]. Skull deformation is transient and as it quickly regains its shape, with sufficient force, rebounding of the brain within the skull may cause separation of the dura [Gurdjian, 1975], and skull fracture results if this deformation

exceeds its critical limit [Thomas *et al.,* 1966; Yoganandan *et al.,* 1995; Yoganandan & Pintar, 2004]. Fluctuations in intracranial pressure have also been demonstrated during blunt head impacts causing local tissue damage at coup and contre-coup sites. The inertia of the brain will cause it to move independently from the skull creating pressure gradients throughout. During an impact the brain lags behind that of the skull causing an area of positive pressure at the site of impact with a corresponding negative pressure opposite the impact site [Gurdjian & Lissner, 1944; Gurdjian *et al.,* 1964]. The differential in pressure creates shear stresses on the brain resulting in tissue deformation [Gurdjian *et al.,* 1963; Gurdjian, 1975]. The injury itself results when this deformation is resisted by the skull, thus damaging the tissue. Using a physical model, and further supported by many researchers, Thomas et al. [1967] demonstrated the existence of pressure gradients and its positive association with head acceleration [Kopecky & Ripperger, 1969, Lindenburg, 1960; Edberg *et al.,* 1963]. In sport, particularly contact/collision sport where head protection is worn, focal injuries are rarely seen.

3.1.2 Diffuse Brain Injury

Diffuse brain injuries are those not localized to one area but are more widespread and distributed throughout the brain. Characterized as axonal injury at a microscopic scale affecting white matter within various brain regions, a continuum of diffuse brain injury has been documented, with diffuse axonal injury (DAI) being the most severe injury to survive [Gennarelli *et al.,* 1982; 1998; Bandak, 1994]. Early work identifying the presence of diffuse axonal damage in humans and animal models despite any long-term deficit from severe traumas, were among the first to provide evidence of this type of brain injury [Strich, 1969; Jane *et al.,* 1985]. These injuries are primarily associated with head motion causing diffuse strains to brain tissues [Ommaya & Gennarelli, 1974]. Caused primarily by the rotational component of the inertial loading, damage is produced by the centripetal progression of strains, increasing as they move from the outer surface of the brain towards its core, with more severe outcomes as the level of trauma engages more tissue [Ommaya & Gennarelli, 1974]. Research suggests that the continuum of injury severity is the result of strain magnitude, the volume of tissue affected, and vulnerable brain regions (as the strain moves inward) [LaPlaca *et al.,* 2007; Ommaya & Gennarelli, 1974]. Mild brain injuries are a form of DAI resulting in disruption of brain networks without any further sign of brain damage [Bailes, 2009]. A less understood area of research pertains to the diffuse

brain swelling that occurs secondary to the initial injury which often appears over time, and in itself may be a form of injury. Diffuse injuries affecting the integrity of axons throughout the brain are extremely common in contact/collision sport and remain a prominent category of research. When the head is impacted, the experienced acceleration is the result of the forces generated by the collision (Newman, 1993). The motion of the head has been demonstrated as a critical component in the mechanisms creating brain injury.

3.2 Head Motion and Brain Deformation

Gurdjian and colleagues attributed intracranial damage to high linear head accelerations, which caused changes in pressure gradients within the brain and/or skull deformations [Gurdjian *et al.,* 1958; 1963; Gurdjian, 1975]. Ommaya & Hirsh [1971] later reported that approximately 50% of the risk of brain injury was due to the rotational component. Translational energy produced focal injuries, such as skull fracture and contusion, but diffuse brain injury was achieved only if the head had been rotated [Gurdjian *et al.,* 1953; Gennarelli *et al.,* 1971; 1972]. This work supported the first suggestion of the potential role of rotational acceleration as a mechanism of head injury [Holbourn, 1943]. The principal mechanism of injury involving linear accelerations was attributed to pressure gradients, whereas rotational accelerations caused shear stress within the neural tissue from differential motion between the skull and brain [Ommaya, 1968; Unterharnscheidt, 1971]. Current head injury research suggests that the combination of linear and rotational accelerations caused by an impact lead to physical brain tissue deformations and a cascade of physiologic responses [Meaney & Smith, 2011; Post & Hoshizaki, 2012]. Head acceleration's involvement in the subsequent strain placed on tissues has deemed it one of the primary targets in biomechanical head injury research.

3.2.1 Linear/Translational Acceleration

Translational or linear motion of the head has been predominantly associated with focal injuries that are more severe in nature caused from high magnitude, shorter duration loading, resulting from pressure gradients throughout the brain and/or skull deformation (Holbourn, 1943; Gurdjian *et al.,* 1964; Gennarelli *et al.,* 1972; King *et al.,* 2003). As linear head acceleration and deceleration was found to be highly related to the internal pressure changes, this became a preferred measure of injury due to its feasibility [Thomas *et al.,* 1967; Nuscholtz *et al.,* 1987].

Linear acceleration is a measure of the rate of change in translational head velocity caused by an applied load, measured as a unit of gravity g, (9.81 m/s^2). More current impact reconstruction methods have been employed to establish tolerance thresholds using linear acceleration and linear acceleration based metrics, where estimated thresholds and results are variable among researcher [Zhang *et al.,* 2004; Pellman *et al.,* 2003a; Viano *et al.,* 2007; Fréchède & McIntosh, 2009; Funk *et al.,* 2007]. One of the more complete analyses was performed by Zhang et al. [2004] who used risk curves to establish injury probability estimates. They report a 25%, 50% and 80% probability of sustaining mild head injury at 66g, 82g, and 106g, respectively. The success of linear acceleration as an injury metric is demonstrated in the mitigation ability of head protection and the reduction of life-threatening injuries within collision sport [Hoshizaki & Brien, 2004].

3.2.2 Rotational/Angular Acceleration

Impacts creating rotational head motion have been demonstrated to be closely associated with mild and diffuse brain injuries **[**Holbourn, 1943; Gennarelli *et al.,* 1982]**.** However a number of studies report a relationship between head rotation and both focal and diffuse injury, and declare that linear acceleration has little effect on injury mechanisms [Holbourn, 1943; Unterharnscheidt & Higgins, 1969; Gennarelli, *et al.,* 1972; Gennarelli *et al.,* 1979]. Holbourn [1943] suggested that shear strains within the brain are the main cause of injury, and because linear acceleration forces produce compressional strains, they don't have an injurious effect. He demonstrated this theory by comparing the skull/brain interaction with an image of a sudden rotation to a flask full of water. The water tends to stay in place as the glass flask rotates around it. However, the water attached to the inner surface of the flask will rotate with the flask, separating it from the other water particles, thus producing large shear strains. Concluding that rotation has a far greater influence than translation and only shear stresses and strains were responsible for injury due to the nearly incompressibility of neural tissue [Holbourn, 1943]. Many researchers later demonstrated this theory, showing that controlled rotational, or angular acceleration, was the primary source of shear strain and brain displacement which was capable of producing a range of injuries severities including cerebral haematoma and concussion [Unterharnscheidt & Higgins, 1969; Gennarelli *et al.,* 1972; 1979; Hodgson & Thomas, 1979; Adams *et al.,* 1981). Rotational head acceleration is measured in radians/$second^2$ and describes the time rate of change of angular

velocity of the head. Similarly, head injury tolerance criteria, particularly for sustaining mild head injury, have been estimated for rotational head acceleration, with a fairly large range in reports [Ommaya & Hirsch, 1971; Willinger & Baumgartner, 2003; Funk *et al.,* 2007; Viano *et al.,* 2007]. Zhang et al.'s [2004] estimates for a 25%, 50% and 80% probability of sustaining mild head injury was reported at 4600 rad/s^2, 5900 rad/s^2 and 7900 rad/s^2, respectively. The increasing rates of mild head injury in collision/contact sport has initiated on-going research that utilizes tissue/cell cultures to link various levels of head motion to localized axonal stretch that disrupt the structure and function of cell membranes [Barkhoudarian *et al.,* 2011; LaPlaca *et al.,* 2007].

3.2.3 Strain

To better understand brain injury, anatomical evaluation of applying a dynamic stretch, or strain, to the tissue is performed to examine the neurons injury threshold. Various axonal responses have been observed from an applied strain, including swelling, electrophysiological impairment, morphological responses, cytoskeleton disassociation and axotomy [Smith *et al.,* 1999; Bain & Meaney, 2000; Tang-Schomer *et al.,* 2010]. Response values are influenced by the type of cultures used, the methods of dynamic stretch applied, and stretch rates [Geddes *et al.,* 2003]. However, these studies demonstrate the brain's biological response to mechanical loading, specifically strain as a measure of injury. A summary of strain values associated in both functional and structural changes to the axon are presented in Table 3-1. These responses may be acute and transient however may also initiate chronic cellular dysfunction and death. Axonal failure can occur in two ways; the primary mode is mechanical rupture and the secondary mode is gradual failure via progressive degradation [McKee *et al.,* 2009]. Mechanical tissue strain has been linked to neurodegeneration in *in vitro* TBI models [Smith *et al.,* 1999; Tang-Schomer *et al.,* 2010; Morrison *et al.,* 2003; Elkin & Morrison, 2007]. When an axon is stretched below the strain necessary for primary axotomy, axons develop morphological changes, wave like appearances called undulations caused by the immediate breakage and buckling of microtubules, at periodic points along their length. Smith et al. [1999] demonstrated primary axotomy at 65% dynamic stretch, however distortions along the axon were observed under all the strains that were tested (58-77%). Although axons will gradually recover their original pre-stretch straight orientation, the axons develop swellings similar to that found in brain injured humans [Smith *et*

al., 1999]. In addition, the physical damage caused by the direct mechanical failure triggers a progressive disassembly of microtubules around the breakage sites [Tang-Schomer *et al.*, 2010].

Table 3-1: Strain levels associated with functional and structural changes to an axon under dynamic stretch. [1]Yuen *et al.*, 2009; [2]Maxwell *et al.*, 1997; [3]Ahmadzadeh *et al.*, 2015; [4]Singh *et al.*, 2006; [5]Bain & Meaney, 2000; [6]Galbraith *et al.*, 1993; [7]Elkin & Morrison, 2007; [8]Morrison *et al.*, 2003; [9]Geddes *et al.*, 2003; [10]Tang-Schomer *et al.*, 2010; [11]Smith *et al.*, 1999.

<table>
<tr><th></th><th>0.05</th><th>0.1</th><th>0.15</th><th>0.2</th><th>0.25</th><th>0.3</th><th>0.35+</th></tr>
<tr><td rowspan="5">FUNCTIONAL</td><td rowspan="2">Calcuim influx[1]</td><td rowspan="3">Mitochondrial swelling; axolemma functional change[2]</td><td rowspan="3"></td><td colspan="3">Permanent membrane potential injury[6]</td><td></td></tr>
<tr><td colspan="2"></td><td colspan="2">Disruption of the plasma membrane[9]</td></tr>
<tr><td rowspan="2">Transient depolarization[2]</td><td colspan="3" rowspan="2"></td><td colspan="3" rowspan="2"></td></tr>
<tr><td colspan="2">Nerve conduction loss[4]</td></tr>
<tr><td></td><td colspan="2">Electrophysical impairment[5,6]</td><td colspan="3"></td></tr>
<tr><td rowspan="5">STRUCTURAL</td><td>Morphological injury[1]</td><td>Axolemma structural change; loss of microtubules [2]</td><td>Loss of axonal transport[2]</td><td>Axonal degeneration[2]</td><td>Structural failure[6]</td><td colspan="2">Mechanical failure, microtubule disorganization[10]</td></tr>
<tr><td rowspan="2">Disrupted tau-tau, tau-microtubule bonding[3]</td><td rowspan="2"></td><td colspan="2">Morphological injury 8</td><td colspan="2"></td><td rowspan="3">Morphological response and primary axotomy[11]</td></tr>
<tr><td colspan="2">Cell death[7]</td><td colspan="3"></td></tr>
<tr><td></td><td colspan="3">Morphological injury to neurofilament[5]</td><td colspan="2"></td></tr>
<tr><td colspan="3">Vascular injury, axotomy, impaired axoplasmic transport[4]</td><td colspan="4"></td></tr>
</table>

At lower levels of strain, cellular homeostasis is disrupted effecting neuronal function. Strain levels as low as 5-15% has been associated with functional impairment of signal transmission in the absence of structural damage [Singh *et al.*, 2006; Bain & Meaney, 2000; Galbraith *et al.*, 1993]. Bain and Meaney [2000] conducted experiments by dynamically stretching the optic nerve of guinea pig *in vivo*. They reported a conservative threshold of electrophysiological impairment at 0.09-0.18, and that morphological injury was estimated at 0.14-0.34 strain. Similarly, Galbraith et al [1993] used giant squid axons to show transient impairment of the membrane potential below a 20% strain however axons did not recover their resting state at elongations above this threshold. Structural failure occurred above a 25% stretch. Yuen and colleagues [2009] used cell cultures to demonstrate that a 5% strain was the minimum level of

injury required to observe minor undulations and induce a calcium influx. Further, when two sub-threshold injuries were repeated within 24hrs, a significant increase in calcium was observed. In addition, Ahmadzadeh et al [2015] have shown how macroscopic strains, as low 5% can cause microscopic changes in the form of protein unfolding resulting in disruption of both tau-tau bonding and tau-microtubule connections. Under dynamic loading conditions of rapid axon stretch, tau proteins behave more stiffly resulting in primary breaking of microtubules [Ahmadzadeh *et al.,* 2015], which has been shown to lead to subsequent disassembly of microtubules and axon degeneration [Tang-Schomer *et al.,* 2010]. Head impact research commonly employs physical reconstructions and computational analysis to evaluate head injury risk and prediction.

3.3 Physical Reconstructions

Injury biomechanics employs a number of methods to measure head response during mechanical loading including animal, cadaver, and instrumented anthropometric test devices (ATD), each with their own advantages and disadvantages. Animal subjects provide a direct assessment of the physiological response of live tissue, but is limited by unknown scaling factors [Gennarelli, 1994; Ueno *et al.,* 1995]. While human head geometry and weight distribution is much more concise with cadavers, tissue preservation can be difficult and result in inconsistent responses [van Dommelen *et al.,* 2009]. ATD represent the mass distribution and geometry of the human head and were developed to provide a robust and replicable response in a simplified model [Patrick, 1973], the trade-off being the lack of true biofidelity. However, ATD have become a useful tool in describing the mechanical forces associated with human head injury [Pellman *et al.,* 2003a; Viano *et al.,* 2005], and when coupled with FE models, provides an assessment of subsequent brain tissue response [Zhang *et al.,* 2004; Rousseau, 2014; Post *et al.,* 2014a; 2018].

3.3.1 Head and Brain Injury Surrogate Models

Made of steel and rubber, these models are durable allowing for repeatability during impact testing. A common group of ATD are the Hybrid III head forms. Hybrid III head forms are currently the most widely used and advanced human surrogate and represents human impact characteristics in terms of the essential biomechanical responses [Deng, 1989; Hubbard & McLeod, 1974]. Hybrid III head forms were originally designed for car crash testing to evaluate

passenger safety and was validated against cadaveric frontal head impacts using peak linear acceleration [Mertz, 1985]. For adult impact reconstructions, the 50th percentile adult male Hybrid III head form is used (4.54±0.01 kg; 58 cm circumference) (Fig. 3-1). Biomechanical variables, such as linear and rotational acceleration, are measured by inserting sensors inside the head form. Nine single-axis Endevco 7264C-2KTZ-2-300 accelerometers placed orthogonally in a 3-2-2-2 array measures linear acceleration, (Fig. 3-1) and calculates rotational acceleration using the following equations [Padgaonkar *et al.*, 1975];

$$\vec{\alpha_x} = \frac{\vec{a_{zS}} - \vec{a_{zC}}}{2S} - \frac{\vec{a_{yT}} - \vec{a_{yC}}}{2T} \quad (1)$$

$$\vec{\alpha_y} = \frac{\vec{a_{xT}} - \vec{a_{xC}}}{2T} - \frac{\vec{a_{zF}} - \vec{a_{zC}}}{2F} \quad (2)$$

$$\vec{\alpha_z} = \frac{\vec{a_{yF}} - \vec{a_{yC}}}{2F} - \frac{\vec{a_{xS}} - \vec{a_{xC}}}{2S} \quad (3)$$

Where α_i is the angular acceleration for the component *i* (*x*, *y*, *z*) and a_{ij} is for the linear acceleration for component *i* (*x*, *y*, *z*) along the orthogonal arm *j* (S, T, F). The right-hand rule is used to define the coordinate system for the head form. The positive axis is directed anteriorly towards the left ear, and superiorly for the *x*, *y* and *z*, respectively [Walsh *et al.*, 2011].

Figure 3-1: Adult male 50th percentile Hybrid III head form (left) with 3-2-2-2 accelerometer array (middle), and unbiased neck form (right) with rear, front, and side view.

This head form is typically attached to a standard Hybrid III neck form. A directional bias within the sagittal plane is built into its design containing partial slits in the front of the neck [Deng, 1989]. This design is appropriate during whiplash at high energy in car crash scenarios, offering increased neck extension and limiting neck flexion. The appropriateness of this bias under direct contact loading in sporting impact scenarios is unknown. An unbiased neck was designed to perform similarly with matched mass and dimensions of the Hybrid III neck form, but eliminate

the directional bias [Walsh & Hoshizaki, 2012; Walsh *et al.,* 2018]. Its construction consists of four centred and unarticulated rubber butyl disks (radius 68.0 mm; height 21.5 mm) which are slightly recessed (3.2 mm) inside four aluminium disks (radius 85.6 mm; height 12.8 mm) (Fig. 3-1). The same braided steel cable used in the Hybrid III neck form passes through the center of all the discs in the unbiased neck form and is tensioned to 1.10 Nm as prescribed for the Hybrid III neck form. The top and bottom aluminum discs attach to the Hybrid III head form and load cell.

3.4 Finite Element Modeling

Sophisticated computational modeling of the human brain awards an opportunity to examine the tissues deformation response under varying impact loading conditions. Researcher proposes using FE analysis of the three-dimensional motion of the head to determine stress and strain on brain tissue is a more comprehensive representation of brain trauma than using peak head accelerations alone [Thibault *et al.,* 1990; Galbraith *et al.,* 1993; Bain & Meaney, 2000; Morrison *et al.,* 2003; Willinger & Baumgartner, 2003; Zhang *et al.,* 2004]. FE modeling is an important and useful tool for measuring brain tissue response demonstrating the relationship between local mechanical deformation and brain injury associated with head motion from direct impacts. FE modeling is used to estimate risk probabilities of specific head and brain injury outcomes by calculating logistic regression curves from combined injury and 'no' injury data sets, however many studies report average values associated with impact. Commonly, strain, specifically maximum principal strain (MPS) is reported as a deformation metric to describe brain response [Patton *et al.,* 2013; Viano *et al.,* 2005]. Cumulative strain damage measure (CSDM) has also been used to identify a volume of brain tissue that exceeds a predetermined strain threshold [Bandak & Eppinger, 1995; DiMasi *et al.,* 1995; Takhounts *et al.,* 2003; Giordano & Kleiven, 2014]. Both metrics have been used as predictors of concussion and DAI.

3.4.1 Maximum Principal Strain

The most frequent brain deformation metric used in the analysis of brain injury prediction and risks is MPS as it is in close agreement with anatomic failure testing, and measurement of brain function [Zou *et al.,* 2007, Post *et al.,* 2013a; Hoshizaki *et al.,* 2014; McAllister *et al.,* 2012].

MPS has been used to measure the elongation of brain tissue from impact [Zhang et al. 2004; Kleiven, 2007]. It is described by tissue elongation relative to its original length. This elongation occurs in the tissue along one of the principal axes [Silva, 2006]. This dependent variable was first established as a brain injury metric as a result of its correlation to mechanical failure in anatomical testing. MPS is calculated as follows;

$$\varepsilon 1,2 = \frac{\varepsilon_x + \varepsilon_y + \varepsilon_z}{3} \pm \frac{\sqrt{2}}{3}\sqrt{(\varepsilon_x - \varepsilon_y)^2 + (\varepsilon_y - \varepsilon_z)^2 + (\varepsilon_z - \varepsilon_x)^2} \quad (4)$$

where, εx, εy and εz = strains measured along corresponding axes.

FE analysis has described how trauma/tissue strains are associated with injury severity. Injury reconstructions have reported 50% risk of sustaining a concussion using MPS values of approximately 19-30% found in gray and white matter in the cerebrum [Kleiven, 2007; Zhang *et al.,* 2004; Patton *et al.,* 2013; Rousseau, 2014]. Although a reasonable assumption can be made regarding strain levels associated with cumulative injury, a gap exists within research in distinguishing and interpreting implications for risks on the playing field. Reconstructions of front head impacts with no reported symptoms experienced by American football linemen during game play reported an average of 12% MPS [Zanetti *et al.,* 2013], corresponding to roughly 20-30g head accelerations. Linemen experience around 15 impacts per game and possibly over 1,000 impacts during a season [Crisco *et al.,* 2010; 2011; Hoshizaki et al. unpublished data]. In contrast, Kendo, a Japanese martial art involving a very high frequency of head strikes using a bamboo sword, does not report brain injury or abnormal rates of neurologic disorders among practitioners. Kendo sword strikes to multiple head locations using a Hybird III head form elicited a 5-7% MPS response [Karton *et al.,* 2016].

A summary of strain values associated with risk of head injury is presented in Table 3-2. The variation reported among researchers is reflective of different sporting environments, injury severities and differences between FE models that were used in the analysis, and therefore comparing results should be limited [Ji *et al.,* 2014]. A general severity scale can be observed from this research and should be represented in head impact exposure measurements (Table 3-2). Low strain values are documented from reconstructions of impacts that demonstrated 'no' identifiable or reported injury [Karton *et al.,* 2016; Zanetti *et al.,* 2013]. Strain levels calculated as a 50% risk probability of sustaining a concussion typically are reported within a range lower than average estimates [Kleiven, 2007; Rousseau, 2014]. The highest strains associate with a risk

of loss of consciousness and longer lasting post-concussion symptoms [Post *et al.*, 2015; Cournoyer & Hoshizaki, 2019].

3.4.2 Cumulative Strain Damage Measure

CSDM has been used to examine the predictive ability for concussion and diffuse brain injury [Bandak & Eppinger, 1995; DiMasi *et al.*, 1995; Takhounts *et al.*, 2003]. Takhounts et al. [2003] estimated 0.55 of the brain needs to experience a strain of 15% for a 50% probability of concussion. Similarly, using CSDM of 10%, Giordano & Kleiven [2014] reported a range of 0.09-0.23 brain volume for a 50% injury probability within various brain locations. To date, CDSM has been used to predict injury with immediately observable outcomes. However, as this measures an accumulative volume of brain tissue enduring strain, this metric may provide some usefulness in contact sports providing insight in to the brain's cumulative response to trauma from repetitive impacts that are potentially leading to microscopic neuronal changes.

Table 3-2: Severity scale from physical reconstructions of head impacts using MPS as an indicator of magnitude.

Author(s)	Sport	Injury	Brain Region	Strain Value	Severity Scale
Karton et al 2016	Kendo	'no' injury (range)	cerebrum	0.05-0.07	very low
Giordano & Kleiven 2014	American football	mTBI (50% risk)	midbrain	0.11	
Zanetti et al 2013	American football (lineman)	unreported	cerebrum	0.12	
Patton et al 2013	Rugby	mTBI (50% risk)	corpus callosum	0.15	low
Zhang et al 2004	American football	mTBI (50% risk)	-	0.19	
Giordano & Kleiven 2014	American football	mTBI (50% risk)	white matter	0.19	
Kleiven 2007	American football	mTBI (50% risk)	corpus callosum	0.21	
Kleiven 2007	American football	mTBI (50% risk)	gray matter	0.26	moderate
Patton et al 2013	Rugby	mTBI (50% risk)	white matter	0.26	
Patton et al 2013	Rugby	mTBI (50% risk)	gray matter	0.27	
McAllister et al 2012	American football/Ice hockey	mTBI (ave.)	corpus callosum	0.28	
Rousseau 2014	Ice hockey	mTBI (ave.)	gray matter	0.3	
Deck & Willinger 2008	Mixed	mDAI (50% risk)	-	0.31	high
Viano et al 2005	American football	mTBI (ave.)	cerebrum	0.32	
Viano et al 2005	American football	mTBI (ave.)	midbrain	0.34	
Post et al 2014	Pedestrian	PCS (ave.)	white matter	0.38	
Cournoyer & Hoshizaki 2019	American football	LOC (50% risk)	white matter	0.39	
Oeur et al 2015	Pedestrian	PCS (ave.)	cerebrum	0.45	very high
Cournoyer & Hoshizaki 2019	American football	LOC (50% risk)	cerebral cortex	0.45	
Post et al 2014	Pedestrian	PCS (ave.)	gray matter	0.48	

3.4.3 University College Dublin Brain Trauma Model

The University College Dublin Brain Trauma Model (UCDTBM) was developed by Horgan and Gilchrist [2003; 2004] using head geometry from CT and MRI and sliced coloured photographs of an adult male cadaver. The model components include; scalp, 3-layered skull (cortical and trabecular bone), dura, cerebrospinal fluid, pia, falx, tentorium, cerebral hemispheres (gray and white matter), cerebellum and the brain stem [Horgan & Gilchrist, 2003; 2004]. Material characteristics of the model were established from earlier research presented in Tables 3-3 & 3-4 [Zhang *et al.*, 2001; Kleiven and von Holst, 2002; Ruan, 1994; Willinger *et al.*, 1995; Zhou *et al.*, 1995]. The tissues of the brain are modelled as linearly viscoelastic. The behaviour of the tissue is characterized as linear viscoelastic in shear with a deviatoric stress rate dependent on the shear relaxation modulus [Horgan & Gilchrist, 2003]. The compression of the brain tissue is defined as elastic. The interaction between the cerebrospinal fluid (CSF) and the brain represents the brain/skull interface and is modeled with solid elements with a high bulk modulus and low shear modulus to allow for sliding behavior similar to fluid. This interface used a friction coefficient of 0.2 and the contact interaction specified no separation [Horgan, 2005]. The shear modulus characteristics of the brain tissue, modeled as viscoelastic is expressed by:

$$G(t) = G_\infty + (G_0 - G_\infty)e^{-\beta t} \qquad (5)$$

where G_∞, is the long term shear modulus, G_0, is the short term shear modulus, and β is the decay factor [Horgan & Gilchrist, 2003]. Overall, the brain was composed of approximately 26,000 hexahedral elements [Horgan & Gilchrist, 2003; 2004]. The response of the UCDBTM was partially validated by comparing simulation responses from cadaveric testing measurements of intracranial pressure [Nahum *et al.*, 1977], relative brain skull motion [Hardy *et al.*, 2001], and brain acceleration [Trosseille *et al.*, 1992]. Comparisons to real world reconstructions of traumatic brain injury incidents were also conducted as a further validation [Doorly & Gilchrist, 2006; Post, 2013].

3.5 Summary

Head impacts that transfer mechanical energy to the skull that result in brain injuries have unique dynamic responses and brain tissue trauma characteristics. The magnitude of the impact energy and how it is applied creates three-dimensional linear and rotational accelerations of the head,

resulting in unique strains on brain tissue. Biomechanical investigations of head injuries in contact sports have historically focused on attenuating energy transfer to the skull and brain. Typically, severe life-threatening events are caused by high-energy impact events that result in immediate anatomic damage. Protective equipment attenuates energy transmission to neural tissues to decrease the risk of structural damage. In addition to reducing risk of skull fracture, helmets work by increasing impact compliance, to decrease the magnitude of the head's dynamic response and increase the duration of the event. This strategy helps prevent severe traumatic brain injuries and shifts the risk to concussion and repetitive head impact exposure.

Table 3-3: Material properties used for the UCDBTM components.

Material	Poisson's Ratio	Density (kg/m^3)	Young's Modulus (MPa)
Scalp	0.42	1000	16.7
Grey Matter	0.49	1060	30
White Matter	0.49	1060	37.5
Cortical Bone	0.22	2000	15,000
Trabecular Bone	0.24	1300	1000
Dura	0.45	1130	31.5
Pia	0.45	1130	11.5
Falx and Tentorium	0.45	1140	31.5
CSF	0.50	1000	-

Table 3-4: UCDBTM brain tissue material characteristics.

Material	Shear Modulus (kPa)		Decay Constant (s^{-1})	Bulk Modulus (GPa)
	G_0	G_∞		
Cerebellum	10	2	80	2.19
Brain Stem	22.5	4.5	80	2.19
White Matter	12.5	2.5	80	2.19
Grey Matter	10	2	80	2.19

4 Repetitive Brain Trauma

It was commonly believed that mild brain injuries with transient symptoms or even low energy impacts to the head are minor events with no injury implications. Growing evidence suggests that although many minor head impacts and sub-concussive events show no immediate consequences, over time these impacts have the potential to cause mental health disorders, neurocognitive deficiencies, and may manifest into a progressive injury that causes serious disability [Omalu, 2005; McKee *et al.,* 2009; 2013]. Although a link has been made between head impact and long-term disability, the amount of energy that is required to cause an injury is very much still unknown. As our knowledge surrounding trauma exposure continues to grow, so will the definition of what is considered a tissue 'injury' [Bailes *et al.,* 2013]. As it currently stands, only major traumatic events with associated concussive symptoms are identified as 'injuries', whereas repetitive strain from more minor undetected head trauma events associated with deleterious health effects are not captured in an athlete's trauma profile nor are they considered in traditional symptom based diagnostic assessments. It has been proposed that a progressive cognitive decline may be associated with repeated trauma to the nervous tissues over time. Each impact, although low energy, has a cumulative effect. Repeated mechanical loading to neural tissues leads to cognitive impairments. Further, in severe cases, repeat impact is associated with an abnormal accumulation of pathogenic toxic proteins in a similar fashion to that of a single severe load, leading to degeneration that manifests itself through progressive decline [Kondo *et al.,* 2015; Mckee *et al.,* 2013].

4.1 Cumulative Brain Injury

There is increasing evidence that support the conception that repetitive head impact exposure common to contact/collision sports carry risks of neurologic injury from cumulative trauma. This is demonstrated through the increased risk of neurologic disease and mental health disorders such as depression among American football players and contact/collision sport participants [Guskiewicz *et al.,* 2004; Chen *et al.,* 2008; Lehman, 2013]. Further, neurodegenerative diseases have been described in athletes who participated in contact/collision sports [McKee *et al.,* 2013; Bieniek *et al.,* 2015; Tagge *et al.,* 2018]. Many athletes experience hundreds of unrecognized impacts to the head throughout the season, where they continue to participate seemingly

unharmed. The frequency of head impacts has been associated with microstructural changes within the brain and functional impairments measured by neuropsychological testing in athletes playing various sports. Sports considered 'high' contact such as football and wrestling have shown significantly greater neurophysiological deficits in athletes compared to their 'moderate' and 'low' contact sport comparisons [Tsushima *et al.,* 2016]. Cumulative exposure to repetitive head impacts results in both acute and chronic injury [Montenigro *et al.*, 2017; Alosco *et al.*, 2017a; Stamm *et al.,* 2015a; McAllister *et al.,* 2014; Lin *et al.,* 2015; Bailes *et al.,* 2013; Kerr *et al.,* 2012], and presents as changes in brain function, connectivity, activation and cognition. Alterations in 'non-concussed' athletes are measured using imaging techniques and protein biomarkers of axonal injury. Deviations from normal functioning reflect the presence of tissue injury [Hulkower *et al.,* 2013; McDonald *et al.,* 2012; Zetterberg *et al.,* 2013], and participation at younger ages has been associated with greater deviation [Stamm *et al.,* 2015a]. Athletes receiving repetitive asymptomatic head impacts during contact sport suffer measurable changes within the brain [Breedlove *et al.,* 2012; 2014; Talavage *et al.,* 2014; Bahrami *et al.,* 2016; Abbas *et al.,* 2015; Davenport *et al.,* 2014], which have been detected in adolescent rugby participants as early as two hours following a match in the form of blood brain barrier disruption, and was dependent on the level of exposure [O'Keeffe *et al.,* 2019]. Contact/collision sport participation at young age associates with a higher deficit in a number of cognitive, behavioural and neuropsychiatric outcomes including depression, apathy, and executive dysfunction later in life [Montenigro *et al.,* 2017; Alosco *et al.,* 2017a]. This group of researchers developed a predictor metric by drawing relationships between a history of repeated head impact exposure and degree of cognitive impairment in former football athletes (Fig. 4-1). They identified a conversion point at which the baseline risk of playing football changes to a dose-response relationship above which a higher exposure to head impacts can lead to a higher risk of impairment. Specifically, they found that the risk of impairment increases steadily for every 1000 impacts above the baseline change point, which was estimated as approximately 2 seasons of play [Montenigro *et al.,* 2017]. These findings were consistent for all impairments tested. The cumulative effects of repeated low-level trauma disrupt the integrity of the axon and expresses as impaired cognitive function from deficits in neurotransmission, decreased cerebral blood flow and structural damage to neurons. The most severe consequences of repeated exposure to trauma

are changes to the molecular structure of brain cells leading neurodegeneration observed in former athletes [McKee *et al.*, 2013; Mez *et al.*, 2017].

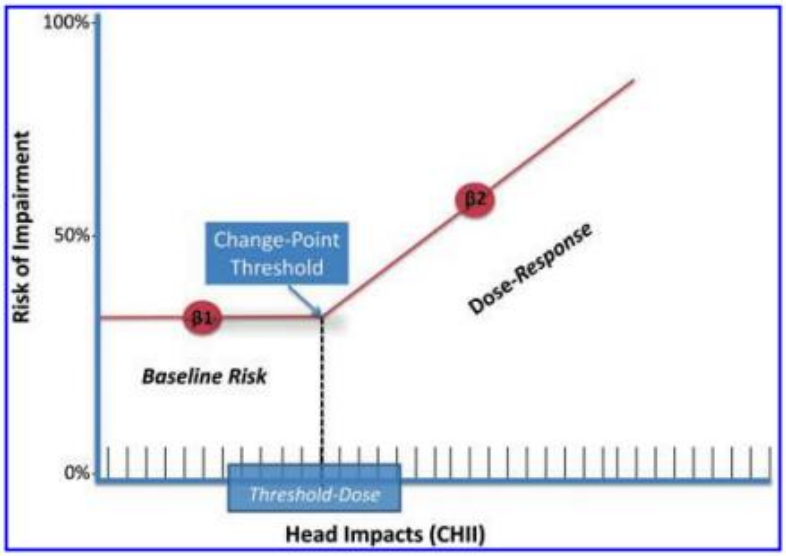

Figure 4-1: Dose-response model for the relationship between cumulative head impact exposure and risk of later-life impairment from participating in American-style football [Montenigro *et al.*, 2017].

4.2 Trauma Induced Neurological Disorder

Impacts that do not present with conventional signs and symptoms may be contributing to trauma induced protein changes, which have the potential to lead to chronic injury and degeneration of neurons [Omalu *et al.*, 2005; McKee *et al.*, 2009; 2013; Mez *et al.*, 2017]. Changes to the neuronal cytoskeleton are common with neurological disorders. A microtubule-associated protein called tau is important in microtubule stabilization for regulating the structural integrity of the cytoskeleton. In a healthy adult human brain, phosphorylation of tau protein regulates its function and promotes the proper stabilization of microtubules [Ballatore *et al.*, 2007; Shahani & Brandt, 2002]. However, pathological hyper-phosphorylated tau reduces its affinity to binding to microtubules, destabilizing their structure [Cowan *et al.*, 2010] (Fig. 4-2). Furthermore, under particular conditions, unstable proteins 'misfold' or unfold preventing them from forming into their biochemically functional native form [Uversky & Fink, 2006]. These toxic formations have the ability to form aggregates of neurofibrillary tangles and neuropil threads leading to neural cell degeneration [Stefani & Dobson, 2003; McKee *et al.*, 2013]. Further amplifying the process, these toxic configurations have the ability to interact with nearby native proteins, which catalyzes their transition into a similar toxic state [Prusiner, 2013a; 2013b]. Pathologies leading

to these neurodegenerative pathways are collectively known as ‘tauopathies’. Consequences of repetitive head injury presenting as neuronal cytoskeletal changes in the form of neurofibrillary tangles [Geddes *et al.*, 1999], essentially categorizes Chronic Traumatic Encephalopathy as a trauma induced tauopathy.

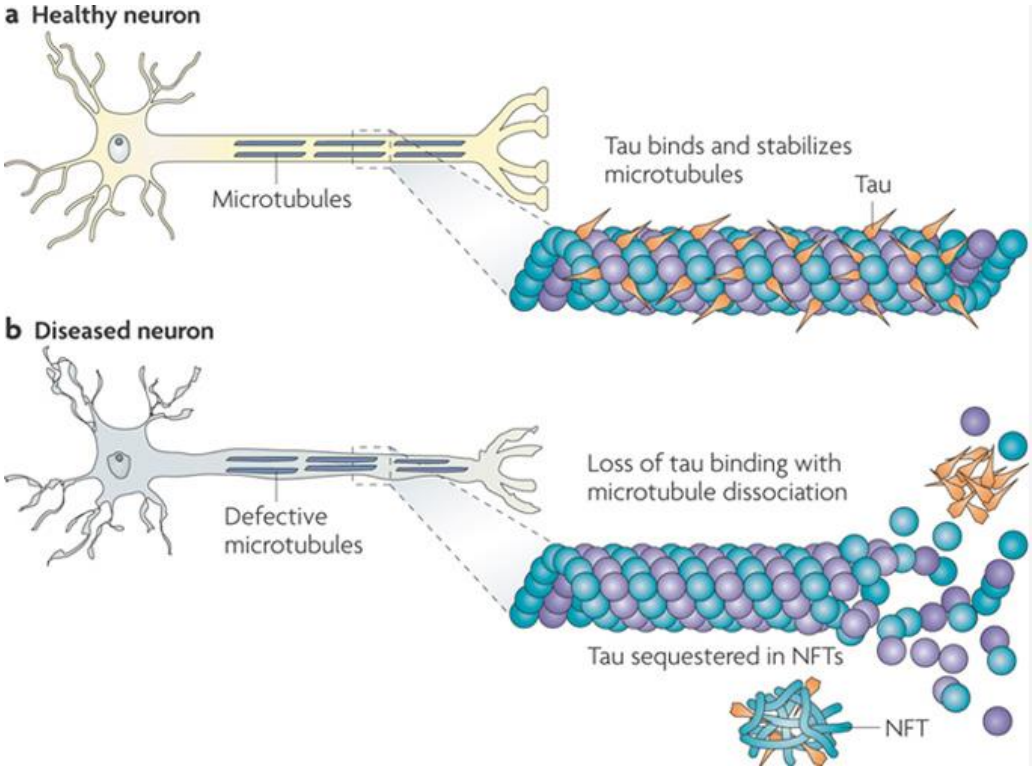

Figure 4-2: Depicting tau binding to microtubule in a) healthy neuron with stabilizing properties, and b) diseased neuron de-stabilizing microtubules and forming aggregates [Brunden *et al.*, 2009]

4.3 Neuropathology of Chronic Traumatic Encephalopathy

Initially declared ‘punch drunk’ by Martland in 1928 was a way to describe the abnormal neurological symptoms seen in boxers who suffered repeated blows to the head [Martland, 1928]. Symptoms included confusion, tremors, slowed speech and gait. Millspaugh [1937] then introduced the term ‘dementia pugilistica’ to describe the symptoms, followed by ‘psychopathic deterioration of pugilists’ by Courville [1962]. Introduced by Critchley [1949] in his report on ‘punch-drunk syndromes’, CTE is now the term that is most widely used to describe this brain injury. Brandenburg and Hallervorden, who demonstrated Alzheimer’s disease-like changes in a 51 years-old boxer, made the first published neuropathological report on CTE in 1954. CTE is characterized by marked tau-immunoreactive neurofibrillary tangles (NFT) and neuropil threads

(NT). There are four identified stages of progression including focal perivascular epicenters of hyperphosphorylated tau (p-tau) initiating in the dorsolateral prefrontal cortices typically in clusters within sulcal depths, to profound tauopathy in some cases involving all regions of the brain [Omalu *et al.*, 2006; McKee *et al.*, 2013; 2016] (Fig. 4-3). In advanced CTE there is an overall decrease in brain volume; gross neuropathological characteristics include ventriculomegaly of lateral and third ventricles, cavum septum pellucidum, and scarring of cerebellar tonsils [Corsellis *et al.*, 1973]. Microscopically, there is cell loss in the hippocampus, substantia nigra, and cerebral cortex, with advance cases also showing cell loss in the subcallosal and insular cortices, and frontal and temporal cortices [McKee *et al.*, 2009]. The pathology of CTE is one that is similar to other neurodegenerative diseases such as Alzheimer's disease, however there are distinctive features of CTE [McKee *et al.*, 2009; Tokuda *et al.*, 1991]. It is the accumulation of abnormally structured tau that no longer stabilize the cytoskeleton of neuronal cells that leads to behavioural symptoms and eventually neuro-cognitive decline. The diagnosis of CTE is dependent on the presence of four criteria [Corsellis *et al.*, 1973; Hof *et al.*, 1991; Geddes *et al.*, 1999; Omalu *et al.*, 2005; 2006; 2010; McKee *et al.*, 2009; 2010; Goldstein *et al.*, 2012;Saing *et al.*, 2012]: 1) perivascular foci of p-tau immunoreactive astrocytic tangles and neurofibrillary tangles; 2) irregular cortical distribution of p-tau immunoreactive neurofibrillary tangles and astrocytic tangles with a predilection for the depth of cerebral sulci; 3) clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia and brainstem; and 4) neurofibrillary tangles in the cerebral cortex located preferentially in the superficial layers.

4.3.1 Clinical Presentation of CTE

Research involving the clinic-pathological presentation of CTE has predominantly been determined through neurological investigations and pathological studies either involving boxers or retired football players from where clinical information was gathered retrospectively from interviews with family members [Mez *et al.*, 2017; McKee *et al.*, 2009; 2013; Corsellis *et al.*, 1973; Omalu *et al.*, 2005; 2006; 2011; Stern *et al.*, 2013]. Often the first signs of CTE are characterized as behaviour and mood changes, which are then followed by more severe cognitive decline [Stern *et al.*, 2013]. Mood changes such as euphoria and hypomania have been reported in early stages [Guterman & Smith, 1987]. Impulsiveness has been a commonly reported

component to neurological disorders of boxers [Mendez, 1995]. More recently, Banks et al. [2014] discovered an association between increased impulsiveness scores from boxers who had greater fight exposure. Fight exposure was associated with a reduction in brain volume for certain brain structures, particularly those fighters with more than 5 years' experience [Banks *et al.*, 2014]. As the disease progresses, disinhibition, paranoia, irritability and violent outbursts are reported symptoms [Lehman *et al.*, 2012]. Depression and/or having had suicidal ideation are often reported as symptoms [McKee *et al.* 2013; Guskiewicz *et al.*, 2005; 2007; Kerr *et al.*, 2012], and suicide, overdose, and drug overdose have been listed as causes of death among CTE sufferers. Cognitive deterioration has been reported to be a later stage of CTE [Stern *et al.*, 2013]. These symptoms appear to be similar to those experienced by patients suffering from Alzheimer's disease including memory impairment, executive dysfunction, decreased attention and concentration, language impairment, and visuo-spatial difficulties [Lakhan & Kirchgessner, 2012, Mendez, 1995]. An interesting finding by Stern et al. [2013] who further analyzed a subset of individuals from McKee et al.'s [2013] work, found two patterns of behavior emerged; findings indicated a younger onset of behavioural dysfunction and an older onset of cognitive dysfunction.

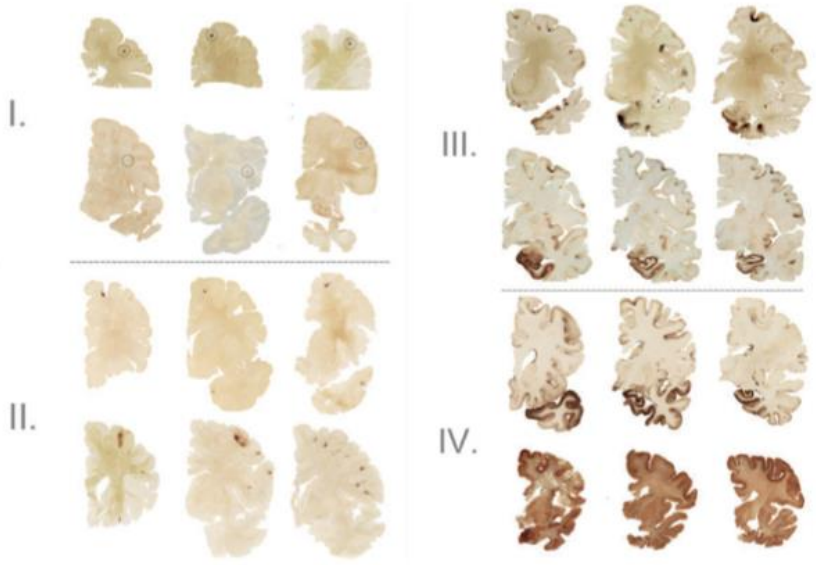

Figure 4-3: Four stages of CTE showing microscopic localized p-tau pathology in stage 1 and becoming widespread throughout all brain regions by stage IV with accompanied brain atrophy [McKee *et al.*, 2013].

4.3.2 Potential Risk Factors to CTE Development

Disease incidence, prevalence and contributors are all important issues to be examined. As there are limited human data sets, fundamental questions regarding specific biological and non-biological risk factors remain. It has been established that one of the most prevailing risk factors associated with CTE development is exposure to repetitive brain trauma [McKee *et al.,* 2013; Bieniek *et al.,* 2015; Mez *et al.,* 2017]. To date, CTE diagnoses have predominantly involved individuals with a history of some level of head trauma, however it is clear that not all those exposed to trauma will develop brain disease [McKee *et al.,* 2013; Bieniek *et al.,* 2015; Mez *et al.,* 2017; Iverson *et al.,* 2019; Noy *et al.,* 2016]. This suggests that although trauma exposure may be an essential ingredient, it alone, may not be sufficient for its development. Figure 4-4 illustrates three broad interacting categories with a non-exhaustive list of factors that may influence the neuropathological and clinical outcomes of CTE. Apart from brain trauma exposure, genetic predisposition and environment/lifestyle encompass a number of confounding risk factors that may contribute to one's susceptibility and/or disease progression.

Head trauma in the context of repeated head impact has shown to have the most dominant association to CTE diagnosis [Maroon *et al.,* 2015; Bieniek *et al.,* 2015; Mez *et al.,* 2017], however, a single moderate to severe traumatic brain injury event is also connected to a later onset of dementia [Fleminger *et al.,* 2003; Plassman *et al.,* 2000; Graves *et al.,* 1990], which may include CTE risk [Kondo *et al.,* 2015]. In addition, head trauma from pressure waves has caused CTE in military veterans exposed to blast [Goldstein *et al.,* 2012; Tagge *et al.,* 2018; Kondo *et al.,* 2015; McKee *et al.,* 2013]. A blast wave cause head motion similar to that observed during a direct head impact potentially being the primary source of disease pathology [Tagge *et al.,* 2018]. Head trauma from impacts cause forces to the head and brain either through direct or indirect contact. During a direct blow, where the head is struck or strikes another object, energy is transferred from one object to the other occurring in less than 200ms [Bailes & Hudson, 2001; Meaney & Smith, 2011]. During indirect contact, described as the absence of direct contact such as collision with another part of the body or during whiplash conditions, energy transfers over a longer duration as it travels through the body towards the head and brain [Bailes & Hudson, 2001]. Energy transfer in contact sports is often the result of direct head hits however players may experience head motions resulting from body to body contact. CTE-like neuropathology has been diagnosed in a number of individuals exposed to repeated impacts from non-sport related

scenarios including physical abuse and autistic head banging tendencies [Hof *et al.*, 1991; Roberts *et al.*, 1990]. A number of impact characteristics influence long-term head and brain injury outcomes. The frequency of impact, the strain magnitude, the time interval between impacts and the duration of exposure characterize head trauma and their associations with risk are discussed in more details later and in this thesis.

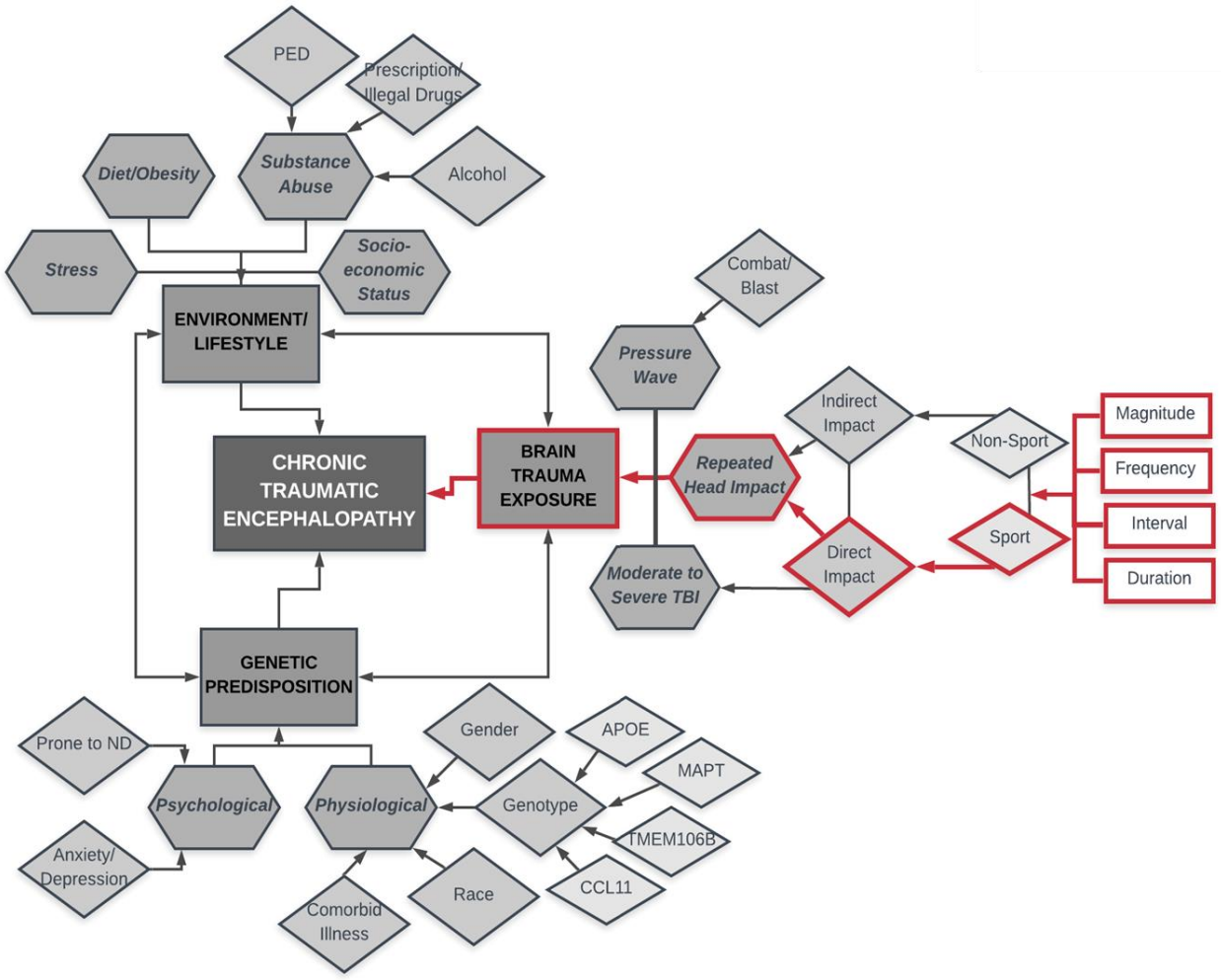

Figure 4-4: Conceptual model of risk factors associated with the development of CTE. Red lines indicate the flow of interest pertaining to this dissertation.

Genetic predisposition could be expressed physiologically such as one's genotype, gender and/or race, or psychologically such as family history or vulnerability to neurodegenerative disorders, and susceptibility to anxiety/depressive disorder. Mez et al. [2017] reported that half of the brains examined had pathology indicating purely CTE, the other half also showing signs of Alzheimer's disease and Lewy body dementia, among others [Mez *et al.*, 2017]. The prevalence

of suicide and accidental deaths is higher amongst those with CTE compared with the general population [Hoyert & Xu, 2012], suggestive of one's psychological stability which may manifest through anxiety and depressive disorder, however a direct link has yet to be established between suicide and contact sport participation [Iverson, 2014]. As many neurodegenerative diseases have hereditary or genetic influence, research on CTE has begun to examine genotype and clinical presentation, predominantly those found to influence similar diseases such as Alzheimer's. Specifically, it has been suggested that Apolipoprotein E ε4 (*ApoE* ε4) genotype increases one's susceptibility to CTE, and trends towards an overexpression among boxers with CTE have been reported [Gandy & DeKosky, 2012; Jordan *et al.,* 1997], however no concrete relationships have been established [Bieniek *et al.,* 2015; Maroon *et al.,* 2015]. Additionally, analysis on variants in *MAPT* and *TMEM1006B* have been explored, where a slight increase in *MAPT* H1 haplotype, and a trend for fewer homozygous carriers of the protective *TMEM1006B* rs3173615 minor allele was observed in those with a history of sports participation and CTE positive [Bieniek *et al.,* 2015].

Influencing environmental/lifestyle factors may include family socioeconomic status, substance abuse, diet and physical health/fitness, and stress levels. Socioeconomic background has historically been associated with poorer cognitive development, mood, learning disabilities and an increased likelihood of developing anxiety and depression in adulthood [Asken *et al.,* 2016], which could influence the functioning of athletes and the expression of neurodegenerative disorders in adulthood [Asken *et al.,* 2016; Borenstein *et al.,* 2006]. Additional lifestyle factors including substance abuse in the form of alcohol, performance enhancing, illegal and/or prescription drugs, as well as a stressful lifestyle, diet, and body fat may influence risk but have not been empirically verified. An important variable of one's lifestyle, particularly among professional athletes is substance abuse. The physical and psychological adverse effects of performance enhancing drugs (PED) have been well documented [Trenton & Currier, 2005; Cotlar, 2001; Thiblin & Pärlklo, 1999] and include mood swings and poor impulse control such as violence, aggression, mania and suicide, and cognitive symptoms such as attention, memory and psychosis [Trenton & Currier, 2005; Lester & Gunn, 2013]. Aside from PEDs the use of prescription and illegal drugs such as opioids are prevalent among football players [Cottler *et al.,* 2011] and have been shown to significantly contribute to psychiatric disorders [Ilyuk *et al.,* 2013]. While it is clear that there are numerous variables that may confound CTE risk and

further investigation is required, it is beyond the scope of this thesis. Modeling and examining the biomechanical characteristics of repeated brain trauma experienced in contact/collision sport is the main focus.

4.3.3 Prevalence of CTE

Initially found in boxers, CTE prevalence in this population was estimated at 20% in retired professionals by Roberts in 1969. More recently, out of a cohort of 30 Olympic boxers, >80% demonstrated increases in CSF biomarkers suggestive of cumulative nervous tissue injuries. Until a little over a decade ago, CTE was believed to be a rare disease found only in boxers but is now discussed as a consequence of head trauma seen in a number of different sports, positions, and levels of play. Mez et al. [2017] reported that 87% of the examined brains of former football players were found positive for CTE from a sample of brains that were donated for research. Further when level of play was considered, 99% of those who played in National Football League were positive for CTE. Acknowledged by the authors, this resulted in a biased sample, which overestimates the actual incidence of CTE in football players, which cannot be established until more randomized neuropathological studies are conducted. This report does however, provide us with an opportunity to begin to understand cumulative brain trauma and provide a guide to safer sport. Bieniek et al. [2015] attempted to estimate the prevalence of CTE in the general population by retrospectively analyzing brains that were banked for neurodegenerative diseases research. They reported that 32% of brains derived from those with a history of contact sport had cortical tau pathology consistent with CTE. Although this study is not without limitation, if larger unbiased studies confirm similar findings, the implications can be extensive. It is clear that there is an association between exposure to repetitive head trauma and the development of cumulative injury, however the dose-response relationship between the traumatic event(s) and outcome of injury has not been fully described.

4.4 Cumulative Trauma Exposure

Studies investigating the cumulative effect of repetitive impact exposure, predominantly in American football, have used helmet impact sensors where few have developed a metric to quantify the effects. A cumulative head impact index (CHII) was used to retrospectively

determine the repeated head impact exposure experienced by former professional football players. This metric was derived from self-reported history on a number of measures including the number of seasons played, position played, level of play, and impact frequencies based on helmet sensor accelerometer estimates. CHII positively correlated with plasma-tau levels and the degree of neurocognitive deficits in former athletes [Alosco *et al.,* 2017b; Montenigro *et al.*, 2017]. Risk weighted cumulative exposure (RWE) is a metric developed using concussion injury risk curves based on linear and rotational acceleration [Urban *et al.,* 2013]. The RWE was used to measure impact exposure in high school football and statistically significant linear relationships were found with RWE score and decreased fractional anisotropy in white matter tracts after one season of play [Bahrami *et al.*, 2016]. Munce et al. [2014] measured the cumulative head impact exposure (HIE) defined as impact frequency (#) x impact magnitude of linear acceleration based on HIT system sensor data in youth football. Individual clinical measures of balance, oculomotor performance, reaction time and self-reported symptoms of neurologic function were not correlated to this cumulative metric [Munce *et al.,* 2014].

4.5 Summary

Brain trauma is not fully described by the magnitude of a head impact and limits the understanding of neurological origins of injury. There is increasing documentation expressing the importance not to ignore impacts of lower magnitudes sustained at higher frequencies and at shorter time intervals. Head impacts sustained during contact/collision sport participation that do not exhibit signs or symptoms indicating neurocognitive dysfunction still present risk for neurological injury. This demonstrates that not only do high energy impacts lead to psychiatric disorders, but repetitive low magnitude impacts result in changes to the molecular structures within brain tissue presenting a risk for cognitive deficits. It has been assumed in the past that as an arbitrary level of head trauma is surpassed, symptoms are presented that we associate with mild head injuries diagnosed as concussions; however, as our understanding of the physiological response and changes in molecular structures of protein cells following even low level tissue strains, our appreciation of the risks associated with all levels of brain trauma is revealed. Metabolic, cellular, and physiologic responses characterize cumulative brain trauma. These responses, when caused by physical trauma, are the precursor to suffering neurocognitive deficits consistent with neurological injury.

5 Physiologic Responses and Indicators of Brain Injury

When the human body endures a physical stress there is a response. One could argue that this stress or trauma is, in some circumstances, similar to an 'injury'. For example, exercise and sport can result in injury to the skeletal muscle if the stress placed on the muscle exceeds its contractile elements beyond its habitual requirements. Microscopic tears in muscle fibers induce inflammation that can both help and hinder the injury. Fortunately muscle cells regenerate via rebuilding and repair, however this system is not as efficient in human brain cells. Brain cells do not possess the same capacity to regenerate and are seemingly ill equipped to manage stressful or traumatic environments. This is observed through a number of responses and processes, including microglia activation, ionic disturbances and structural disruption that occur from being exposed to trauma, in some cases of various magnitudes. These responses often occur simultaneously and most likely interact. Brain injury produces both acute responses and more chronic consequences that may lend in permanent disabilities. This area of research has demonstrated the progressive nature of the initial traumatic event and the involvement of many secondary pathophysiological mechanisms. Initially these mechanisms have been observed and studied in single, mild, moderate and severe TBI, however there is growing evidence of their potential role in repetitive insult trauma profiles.

5.1 Neuro-metabolism

The functioning of a neuronal cell is altered from stretching and shearing of axonal and cell membranes during mild head trauma [Katayama *et al.,* 1990; Giza & Hovda, 2001]. This temporary neuronal dysfunction expresses in the form of ionic shifts, altered metabolism, impaired connectivity, and/or changes in neurotransmission [Giza & Hovda, 2001]. Experimental research involving animal models shows an immediate flux of ions through formerly regulated channels following an insult [Farkas *et al.,* 2006; Katayama *et al.,* 1990; 1992]. Due to ionic disequilibrium, there is an indiscriminate presynaptic release of excitatory neurotransmitter, namely glutamate, which activates postsynaptic receptors [Katayama *et al.,* 1990; Takahashi *et al.,* 1981; Hubschmann & Korhauser, 1983; Julian & Goldman, 1962]. Caused by the axonal stretching, opening of the voltage-dependent K^+ channels leads to an efflux and abnormal accumulation of extracellular K^+ [Katayama *et al.,* 1990; Takahashi *et al.,* 1981].

In efforts to restore equilibrium, the Na^+/K^+ pumps work in overdrive, increasing the demand for adenosine triphosphate. This leads to a dramatic increase in glucose metabolism, which triggers a cellular energy crisis [Giza & Hovda, 2001]. Over activation of receptors causes a large influx of Ca^{2+} accumulation in the mitochondria, hindering glucose metabolism [Xiong *et al.,* 1997; Babikian *et al.,* 2012]. This state of hyperglycolysis occurs in the acute phase after trauma, which is followed by a more prolonged phase of hypoglycolysis and reduced cerebral blood flow due to the discrepancy between glucose supply vs demand [Martin *et al.,* 1997; Yoshino *et al.,* 1991]. In the period of depressed metabolism the brain is in a state of heightened vulnerability to repeat injury [Giza & Hovda, 2014]. Subsequent insults during this time are often more severe, take longer to recover from, and the brain is less tolerable to impacts of lower severity [Guskiewicz *et al.,* 2003; Prins *et al.,* 2013; Vagnozzi *et al.,* 2008; Effgen & Morrison, 2017]. Chronic consequences could lead to potential exitotoxic processes, as neurons have been shown to be particularly vulnerable to glutamate receptor activation [McDonald *et al.,* 1998, Algattas & Huang, 2013; Katayama *et al.,* 1990; Palmer *et al.,* 1993], and higher levels of glutamate is measured in athletes with a history of repetitive brain trauma [Lin *et al.,* 2015]. Moreover a state of oxidative stress may lead to irreversible damage to neuronal membranes shown to result in secondary injury pathophysiological mechanisms leading to chronic neurological deficits and cell death [Buczek *et al.,* 2002; Rodrigues- Rodrigues, 2014; Cornelius *et al.,* 2013].

5.2 Inflammation

In response to traumatic trauma, the brain's immune response involves a number of processes, predominately with the activation of microglia and reactive astrocytes, where this response can be both beneficial and detrimental. Microglia immune responses produce anti-inflammatory mediators that promote neurologic recovery. However, they also have the ability to produce proinflammatory mediators in excess that may hinder repair, neurologic recovery and potentially exacerbate brain damage [Loane & Kumar, 2016]. In an injured brain, there is evidence of increased levels of proinflammatory mediators coupled with a reduced level of anti-inflammatory cytokines, which have the ability to counteract and downregulate inflammatory and cytotoxic reactions [Loane & Kumar, 2016; Hellewell *et al.,* 2016; Finnie, 2013; Kumar & Loane, 2012; Stoll *et al.,* 2002; Ziebell & Morganti-Kossmann, 2010; Cederberg & Siesjo, 2010; Dheen *et al.,* 2007]. Dysfunction of astrocytes, which play a key role in regulating homeostasis

[Vasile *et al.,* 2017], may contribute to neuronal disturbances and death [Rivetti di Val Cervo *et al.,* 2017; Liddelow *et al.,* 2017], as they also possess pro-inflammatory and anti-inflammatory mechanisms [Sofroniew, 2015; Okada *et al.,* 2006]. An important role of astrocytes is to form borders that separate neural from non-neural tissue that create functional barriers and form scarring during the repair process following TBI [Bush *et al.,* 1999; Faulkner *et al.,* 2004]. These barriers perform immune and inflammatory cell trafficking and thus play an important role in regulating the entry of inflammatory cells into the CNS following brain injury [Wilson *et al.,* 2010; Engelhardt & Coisne, 2011], by restricting the spread of leukocytes and microbial pathogens [Wanner *et al.,* 2013; Faulkner *et al.,* 2004; Li *et al.,* 2008; Voskuhl *et al.,* 2009]. When astrocytes are rendered dysfunctional, cytotoxic inflammation is free to spread throughout healthy parenchyma [Zamanian *et al.,* 2012; Hamby *et al.,* 2012; John *et al.,* 2005]. Persistent pro-inflammation, manifested by extensive activation of microglial and astroglial, associates with the on-set of depression [Fenn *et al.,* 2014], and has been shown to be an important contributor to post-traumatic neurodegeneration [Xiong *et al.,* 2018; Li *et al.,* 2019]. Prolonged microglial activation is measured in active and retired athletes with a history of repetitive sports-related head impacts [Coughlin *et al.,* 2015; 2017], and worsens brain disease pathology [Simon *et al.,* 2017; Hernandez-Ontiveros *et al.,* 2013]. The neuroinflammatory response to physical trauma has been shown to contribute to p-tau pathology, specifically in the dorsolateral prefrontal cortex within the brain of subjects diagnosed with CTE, where the degree of neuroinflammation present is associated with a longer duration of exposure to repeated head impacts [Cherry *et al.,* 2016]. The chronic inflammatory events that occur following brain trauma may contribute to, or be exacerbated by degenerative brain disease pathology.

5.3 Blood-brain Barrier Disruption

Dysfunction of the blood brain barrier (BBB) is strongly evident in patients who have sustained severe traumatic brain injuries as reported in numerous studies [Alluri *et al.,* 2015; Price *et al.,* 2016]. The integrity of the BBB is also compromised in mild TBI [Johnson *et al.,* 2018]. As the breakdown of BBB components influences the time course and extent of neuronal recovery, this deficit may persist and have implications in those who have experienced repetitive brain trauma [Hay *et al.,* 2015; Doherty *et al.,* 2016]. BBB disruption is found at gray-white matter boundary, perivascular regions and within regions of axonal pathology in the white matter [Johnson *et al.,*

2018; Doherty *et al.*, 2016]. This not only allows peripheral immune cells to infiltrate into the brain which leads to further complications of long lasting inflammation but it allows for the extravasation of plasma proteins into the brain [Corps *et al.*, 2015; Yu *et al.*, 2010]. Research on repetitive brain trauma has shown that the extravasation of these systemic components are specifically found in regions of associated with distinct areas of perivascular p-Tau deposition in CTE patients [Doherty *et al.*, 2016; Farrell *et al.*, 2019], which shows similarities to the disease course involved in other tauopathies [Marques *et al.*, 2013; Bartels *et al.*, 2008; Garbuzova-Davis *et al.*, 2012]. Interestingly, Blair et al. [2015] demonstrated in an animal model that perivascular p-Tau deposition was sufficient to cause BBB dysfunction and when tau buildup was suppressed, the BBB integrity is recovered. In clinical studies, elevated serum S100B concentrations, a biomarker of BBB dysfunction [Blyth *et al.*, 2008], are detected in athletes exposed to repeated head impacts of sub-concussive levels including boxers and football players [Graham *et al.*, 2011; Puvenna *et al.*, 2014; Rogatzki *et al.*, 2016]. Specifically, Marchi et al. [2013] studied a cohort of 67 college football athletes and found serum S100B levels were highest in athletes who received the most sub-concussive head impacts, and serum S100B antibodies predicted lasting changes in mean brain white matter diffusivity using DTI scans.

5.4 Brain Imaging

Neuro-imaging measures are used as research tools to identify subtle structural and/or functional abnormalities following head trauma. Specifically, diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) are becoming common techniques for detecting changes in brain function and activity. Methodologies involving DTI, typically a modality that is used to detect axonal injury by measuring changes in directionality of water diffusion, show sensitivity in detecting microstructural damage via axonal mean diffusivity (MD) and fractional anisotropy (FA) in white matter integrity and gray-white matter junction after diagnosed mild brain injury, and repetitive asymptomatic head impacts [Bazarian *et al.*, 2007; Cubon *et al.*, 2011; Fakhran *et al.*, 2013; Bahrami *et al.*, 2016]. Changes in FA and MD are reported within major fiber tracts, often involving the corpus callosum [Lipton *et al.*, 2008; Chamard *et al.*, 2016; McAllister et al. 2014; Mayinger *et al.*, 2018]. Connectivity disruption is variable and widespread, as altered diffusion has been shown in a number of regions including but not limited to the fornix-stria terminalis, hippocampus amygdala, white-gray matter junction and thalamus [Kuzminski *et al.*,

2018; McAllister *et al.,* 2014; Bahrami *et al.,* 2016]. Changes within the microenvironment and axonal structure may contribute to long-term progressive changes and functional disturbances. Local demyelination associates with changes to white matter [Smith *et al.,* 1997; Adnan *et al.,* 2013; Kumar *et al.,* 2009]. Research regarding long-term effects of repetitive trauma on white matter damage is still young, however repeated mild head injury causes white matter thinning and reductions in myelin in an animal model corpus callosum [Briggs *et al.,* 2016]. Further, experiencing trauma during periods of neurodevelopment may affect multiple processing including myelination showing altered corpus callosum microstructure later in life [Stamm *et al.,* 2015b]. Although less common to DTI, neuroimaging assessments using fMRI measure changes in blood oxygen levels associated with neuronal activity and have been used to show changes in humans following head trauma based on the execution of specific cognitive tasks often involving working memory using auditory, visual, verbal and motor performance [McAllister *et al.,* 2001; 2006; Smits *et al.,* 2009; Scheibel *et al.,* 2012; Mayer et al. 2009]. This modality is used to show altered executive functioning patterns and possibly prolonged injury recovery [Lovell *et al.,* 2007]. Neurophysiological fluctuations from baseline and post season whole brain and region of interest brain activation have been shown in athletes sustaining multiple head impacts [Breedlove *et al.,* 2014; Talavage *et al.,* 2014]. Hypoconnectivity during resting state and hyperactivation of brain regions during cognitive tasks has also been measured in retired athletes with pronounced deficits.

5.5 Cytoskeletal Disconnection

Following axonal stretch from trauma, the structural integrity of the cell can become compromised through microtubule and neurofilament disruption. The process of phosphorylation causes the collapse of proteins that maintain the backbone of the cytoskeleton [Pettus *et al.,* 1994; Lovestone *et al.,* 1996]. A highly phosphorylated state of protein, specifically tau, has been shown to affect its microtubule-binding properties [Drechsel *et al.,* 1992; Mandelkow *et al.,* 1995; Trinczek *et al.,* 1999]. Athletes exposed to greater head trauma have shown higher levels of biological markers within the blood and CSF, indicative of axonal integrity interference [Oliver *et al.,* 2016]. Various biomarkers have been association with injury in severe and mild TBI patients [Peskind *et al.,* 2015; Zetterberg *et al.,* 2013], and athletes following both symptomatic and asymptomatic head impacts [Oliver *et al.,* 2016; Shahim *et al.,* 2016].

Neurofilament light polypeptide (NF-L) and total tau (T-tau) have been found predominantly to associate with chronic consequences of repeated head trauma [Zetterberg *et al.,* 2006; Neselius *et al.,* 2012; Shahim *et al.,* 2016]. High levels of plasma total tau and exosomal tau are found in retired American football players with long term exposure to repetitive head impact [Alosco *et al.,* 2017b; Stern *et al.,* 2016], which are carried from traumatized brain parenchyma to peripheral blood vis lymphatic vessels [Plog *et al.,* 2015]. In extreme cases of neurodegenerative brain disease, neurofibrillary tangles are found throughout the brain tissue indicative of disrupted microtubules and neurofilaments [Omalu *et al.,* 2005; McKee *et al.,* 2013]. In a hyperphosphorylated state tau will engage in pathogenic interaction with endogenous normal tau and withdraw it from microtubules [Cowan *et al.,* 2010].

5.6 Cerebrospinal and Interstitial Fluid Exchange

Irrespective of whether through bulk flow [Cserr *et al.,* 1977; 1986; Iliff *et al.,* 2012; Nedergaard, 2013], or diffusion [Asgari *et al.,* 2016; Holter *et al.,* 2017; Pizzo *et al.,* 2017] there is exchange between CSF and interstitial fluid (ISF) which facilitates metabolite and waste clearance through fluid drainage pathways. This system is affected by physical trauma [Iliff *et al.,* 2014], potentially leading to secondary pathophysiological mechanisms effecting brain cells [Iliff *et al.,* 2012; 2013; Jessen *et al.,* 2015]. CSF inflow to brain parenchyma through cervical lymphatics, sweeps along harmful metabolic products and soluble proteins that are sitting between the cells, before interstitial fluid clearance via the venous system. When this naturally occurring pathway breaks down or malfunctions, the deposition and accumulation of amyloid beta results, which is the hallmark of Alzheimer's disease [Iliff *et al.,* 2012; 2013; Jessen *et al.,* 2015; Peng *et al.,* 2016], and may have implications for the development of other neuroinflammatory and neurodegenerative diseases associated with immune system dysfunction [Louveau *et al.,* 2015]. Subarachnoid cerebral spinal fluid enters the parenchyma by way of perivascular spaces surrounding the penetrating arteries, where exchanges are made with the interstitial fluid. Iliff et al. [2014] demonstrated that lymphatic pathway function is reduced following head trauma, which persists for at least 1 month after injury, and renders the brain vulnerable to tau aggregation. This could be in part due to re-localization of astroglial water channel aquaporin-4 highly involved in waste removal [Iliff *et al.,* 2012], although the precise role that AQP4 water channels play in tracer distribution is debated and still under investigation

[Smith *et al.,* 2017]. In CTE, ptau deposition is initially found around perivascular spaces and along interstitial pathways that relate to the low-resistance pathways associated with CSF and ISF exchange [McKee *et al.,* 2013; Puvenna *et al.,* 2016]. Brain-fluid flow is influenced by the extracellular matrix [Syková & Nicholson, 2008], where exchange is limited by many factors including an aggregation state [Abbott *et al.,* 2018]. As levels of pathogenic tau proteins remain elevated within a chronic state, potentially from repetitive trauma, and accumulation of perivascular tau takes place, blood brain barrier dysfunction results, potentially exacerbating pathology [Blair *et al.,* 2015]. Further, impediment of the CSF and ISF flow and drainage might play a role in the prion-like spread of abnormal phosphorylated tau [Abbott *et al.,* 2018].

5.7 Prion Propagation

Prusiner's [2013a; 2013b] work with bigenic mice identified a disease progression from a self-propagating process of tau prions, suggesting that trauma to the brain can cause a prion-like spread of pathogenic protein leading to neuro-degeneration, similar to what had been previously shown in other neurodegenerative disease pathologies [Prusiner, 1982; Collinge, 2001]. The aggregating tau polymerizes inside the neurons, and as it travels towards the synapse it then leaves one cell and enters another, thereby infecting the new healthy cell [Prusiner, 2013a; 2013b]. The misfolded tau protein cause structural disruption of near-by native tau proteins eventually inhibiting cell-to-cell communication. This propagation of tau has been shown in a number of studies using animal models [Clavaguera *et al.,* 2009; Goedert, 2015; Woerman *et al.,* 2016; Sanders *et al.,* 2014; Reilly *et al.,* 2017]. The movement of self-propagating proteins is a slow process, explaining why even the most aggressive cases of disease, only expresses decades after the insult [McKee *et al.,* 2013; Stern *et al.,* 2016].

5.8 Summary

Indications of trauma induced axonal injury have been detected via numerous pathologies including but not limited to neuroinflammation, blood brain barrier disruption and antibody autoimmune responses [Cherry *et al.,* 2016; Banks *et al.,* 2017; Blair *et al.,* 2015; Ferrerosa *et al.,* 2013; McKee *et al.,* 2013; Bazarian *et al.,* 2014]. Structural and physiological responses occur within the brain due to trauma and may present immediately following trauma, or over

time. Likely there is an interaction that occurs between multiple responses and one may lead to the other, meaning a physiological response may lead to structural changes and vice versa. These responses are complex and multi-dimensional involving acute processes that may resolve or lead to secondary pathophysiological mechanisms potentially resulting in chronic neuronal dysfunction, impairment and degeneration. Neurological injury investigations demonstrate that the mechanisms for neurodegeneration are a compound and dynamic process and these interactions are not fully understood. How these responses lead to, create, or put one at risk of cumulative injury from repetitive trauma is not well defined. Understanding how trauma is created, and the characteristics of that trauma in various environments, coupled with an injury outcome could however, help to further understand the brain's various responses and how they may lend a hand in ultimately expressing as acute and chronic brain damage. Many of the responses regarding repetitive brain trauma in humans have been detected in ASF football athletes. This environment creates risk to a variety of head and brain trauma characteristics and injury outcomes.

6 Brain Injury in American-style Football

Head contact in ASF is common practice during game play. Distinct to ASF is the variation in player field positions, field roles and required physical skills. Each position has a unique experience during play due to the well-defined player roles on the football field. This influences the type of head impact events each experience, and subsequently injury risk profiles. Different positions may be exposed to various levels of trauma based on and characterized by multiple factors including; number of impacts, magnitude of the impact, and the conditions of the event. Epidemiology studies have investigated the risks of head impact and injury outcomes specific to position. Moreover, reports on CTE diagnosis have published player field position details from their former ASF athlete cohort. There have been a number of studies that have collected on field hit count data using helmet sensor technology in ASF practice and game play. While this information provides useful insight as to the frequency of impact it provides limited information concerning risk of brain trauma or the mechanism of injury [Jadishke *et al.*, 2013, Rowson *et al.*, 2011].

6.1 Player Field Positions

In ASF, each team will have 11 players on the field at any one time. Teams are composed of 3 sub teams based on their role; offense, defense, and special teams. Although some variation in the starting arrangement, the number of players on the field per position, and play formation exist, the following describes the standard positions and designated roles (Fig. 6-1).

The offensive team consists of backs and receivers; quarterback (QB), running backs (RB); fullback and halfback, wide receiver (WR), tight end (TE), and offensive line (OL) players; center, offensive guard, and offensive tackle [Bass, 2004]. The QB is responsible for receiving the ball from the center OL and executing the play. RB are those who line-up behind the OL in a position ready to execute a rushing or 'running' play either from a hand off or short pass from the QB. This position may also line up closer to the line and act as a blocker to protect the QB as he executes the play. Occasionally RB may catch passes, typically from shorter distances. WR is a highly skilled position that requires the physical speed, timing, and ability to catch the ball from long distances. Their primary role is to provide the QB with a pass route and run the ball into the end zone. The TE position has a dual role on the field, as either a receiver, or lineman.

As a receiver, this position will typical catch passes from shorter distances than the WR. On the line, they are much like an OL player. OL is responsible for protecting the QB while be finds a pass opportunity, thus there goal is to block the defensive line players from reaching the QB [Bass, 2004]. This positon requires high levels of strength.

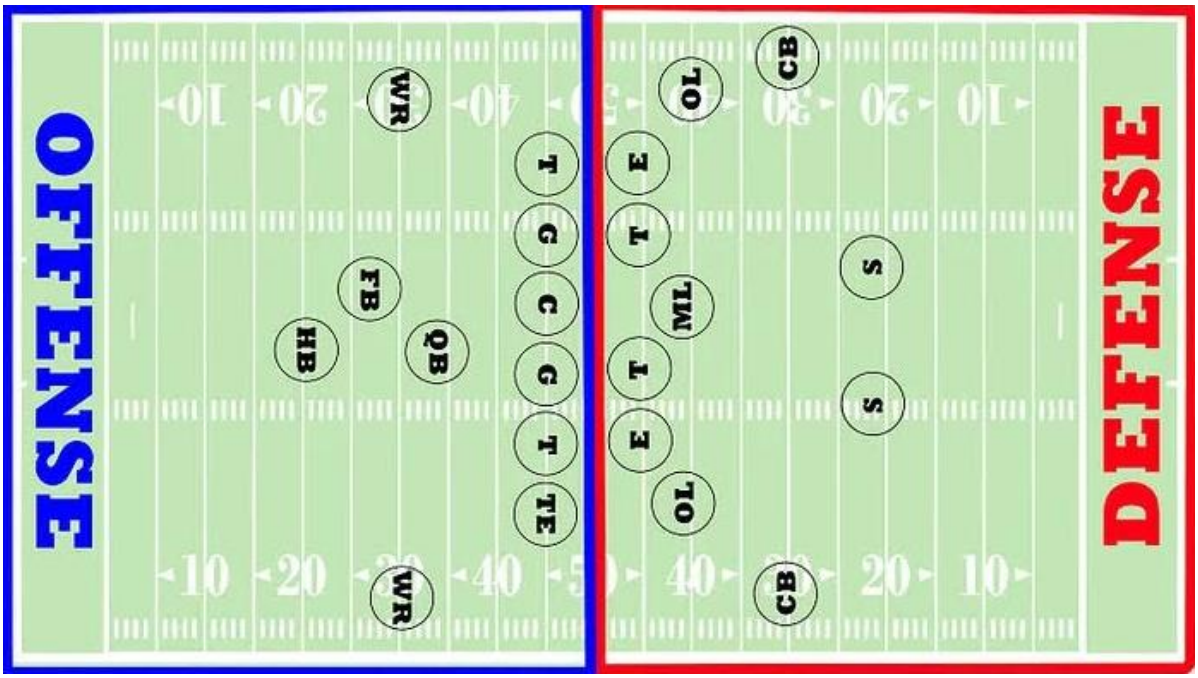

Figure 6-1: Standard starting formation of field positions in ASF [wikihow.com/Play-American-Football].

Defense team is divided into defensive line (DL); defensive tackle and defensive end, linebackers (LB); middle and outside, and finally defensive backs (DB); cornerback and safety [Bass, 2004]. The goal of the DL is to defeat the OL in order to tackle the QB before they have an opportunity to pass the ball. Much like the OL, this position requires a lot of physical strength. LB positions are the second line of defense, stand behind the line of scrimmage, and are more often required to run and tackle the ball carrier or stop a running play. Lastly, DB players are responsible for stopping a touch-down, either through a tackle or pass interception [Bass, 2004]. This position requires physical speed, much like the WR, as often it is this position they are trying to outrun. The difference in player roles creates unique environments which dictate how head impacts occur and the conditions of the event(s).

6.2 Injury Incidence

6.2.1 Concussion Rates

In general, the offensive team is most vulnerable with respect to frequency of injury. Types of plays in which concussions are more likely to occur include passing plays (35.8%), rushing plays (31.3%), kickoffs (15.9%), and punts (9.5%) [Pellman *et al.,* 2004]. Concussion is highly prevalent in ASF [Pfister *et al.,* 2016; Lincoln *et al.,* 2011], where susceptibility increases with an increasing number of sustained injuries [Guskiewicz *et al.,* 2003]. From 2009 to 2013 there were 589 reported concussions in the National Football League (NFL) [Rotoworld Premium, 2014], with 318 (54%) sustained by offensive players and 217 (46%) by defensive players. The number of concussions sustained by player positions was the highest for DB (24%), WR (16.5%) and RB (12.5%). The number of concussions was similar between the DL (11%), LB (10.5%), TE (10.5%), and OL (10%). However, OL positions have been shown to experience a higher number of symptoms that were not reported, and returning to play while symptomatic more often compared to other teammate positions [Baugh *et al.* 2015]. The player position with the least amount of reported concussions was QB (5%). With consideration of players per position on the field at one time, the TE and WR are most at risk of sustaining a concussion (62 and 48.5 per player respectively), followed by the offensive RB (36.5 per player) and DB (35.5 per player). The QB (28 per player) and LB (21 per player) present similar risks. Finally, the OL and DL showed the lowest risk with 16.5 and 11.6 per player, respectively. Nathanson et al. [2016] used a number of different metrics to determine position specific risks to injury based on concussion incidence in the 2012-2013 and 2013-2014 NFL seasons. This group estimated risk based on athletic exposure (AE), game position (GP) and a novel position play (PP) metric which accounts for the exact number of plays any given position participates. Concussion incidence based on 1000 AEs (95% CI) showed DB 11.76 (9.16-14.35), TE 11.11 (7.26-14.96), WR 9.79 (6.99-12.59) and RB 7.55 (4.80-10.30) to be the highest respectively. Following were QB 6.77 (3.09-10.45), OL 6.10 (4.23-7.97), LB 3.57 (2.14-5.00), fullback 3.13 (0.25-7.52) and DL 3.13 (1.87-4.38) respectively. A similar pattern emerged for concussion per 100 GPs (95% CI) and concussions per 1000 PPs (95% CI) although the incidence was found highest for TE (GPs = 3.33 (2.18-4.49); PPs = 0.32 (0.21-0.44)) and RB (GPs = 3.02 (1.92-4.12); PPs = 0.37 (0.23-0.50)), followed by WR (GPs = 2.45 (1.75-3.15); PPs = 0.27 (0.19-0.35)), DB (GPs = 2.06 (1.60-

2.51); PPs = 0.20 (0.16-0.25)), and QB (GPs = 1.35 (0.62-2.09); PPs = 0.20 (0.09-0.31)) positions. Concussion rates were lowest for OL (GPs = 0.85 (0.59-1.12); PPs = 0.12 (0.08-0.15)), LB (GPs = 0.83 (0.50-1.17); PPs = 0.09 (0.05-0.13)), DL (GPs = 0.63 (0.37-0.88); PPs = 0.97 (0.06-0.14)) and fullback (GPs = 0.31 (0.025-0.75); PPs = 0.13 (0.01-0.3)) [Nathanson *et al.,* 2016].

6.2.2 Diagnosed Chronic Traumatic Encephalopathy

According to a study conducted by the National Institute for Occupational Safety and Health, professional football players carry a risk of death from diseases that damage brain cells, including Alzheimer disease, Parkinson disease and ALS, almost three times higher than the general population [Lehman, 2013]. More importantly, ASF presently accounts for the highest number of diagnosed cases of CTE [Maroon *et al.,* 2015; Bieniek *et al.,* 2015; Mez *et al.,* 2017]. As research specific to CTE is in its infancy with a limited data set thus far, the true prevalence/incidence of CTE remains to be established. Recent reporting of the most extensive data set on CTE diagnosis in ASF shows different results when considering player positions [Mez *et al.,* 2017]. Of 177 confirmed cases through post-mortem examinations, OL (n=37, 21%), DL (n=33, 20%) and RB (n=31, 18%) showed the most prevalent player positions [Mez *et al.,* 2017]. Following were LB (n=26, 15%), DB (n=22, 12%), and QB (n=13, 7%), positions. TE (n=7, 4%), WR (n=4, 2%), and kicker or punter (n=2, 1%) showed the least occurrence [Mez *et al.,* 2017]. Considering players per position on the field, the RB and QB present the highest risk of incurring CTE (8.8% and 7.3% respectively). Following is DL (4.9%), LB (4.9%), and OL (4.2%) representing similar risks. The TE (4.0%), DB (3.1%), and WR (1.1%) showed the lowest risk [Mez *et al.,* 2017].

6.3 Impact Sensor Technology

Wearable technologies have become popular for measuring the dynamic response of the head to impacts by placing sensors in helmets, mouth/chin guards, on skin, or worn as headband/cap with the intension of capturing impact exposure. These sensors typically measure the frequency of impact and the acceleration magnitude experienced in ASF during a game, practice, and/or seasons ranging from youth to collegiate levels [Crisco *et al.,* 2010; 2011; 2012; Urban *et al.,* 2013; Campbell, 2014; Martini *et al.,* 2013]. The majority of these studies investigated impact

measures as averages amongst players [Schnebel *et al.,* 2007; Mihalik *et al.*, 2007; Daniel *et al.,* 2012; Broglio *et al.,* 2009; Urban *et al.,* 2013] with few distinguishing between player positions [Crisco *et al.,* 2010; 2011; 2012; Martini *et al.,* 2013 Campbell, 2014]. Guskiewicz and Mihalik [2011] estimated the average impact per football player at the collegiate level to be 950 impacts per season. In addition, again for collegiate level football, 1353 impacts per season was reported using a similar methodology using in-helmet sensors [Schnebel *et al.,* 2007]. Studies measuring hit count for high school level players, have reported 565 impacts [Broglio, *et al.,* 2009] and 520 impacts [Schnebel, *et al.,* 2007] per player during one season. These studies reported an average impact frequency for all players and do not account for the different player positions. A summary of impact frequency counts for all level of ASF are presented in Table 6-1. This research demonstrates a high number of head contact events are experienced in ASF, where higher hit counts are consistently associated with greater neurophysiological changes regardless of symptom expression [Bahrami *et al.,* 2016; Talavage *et al.,* 2014; Montenigro *et al.,* 2017]. By the time individuals reach high school levels, frequency counts are comparable to those reported at the collegiate level [Martini *et al.,* 2013; Broglio *et al.,* 2010; Mihalik *et al.,* 2007; Campbell *et al.,* 2014]. Crisco et al. [2011] conducted one of the more detailed investigations by outfitting 314 collegiate football players with helmet impact sensors to investigate the impact exposure differences between player positions. Position specific frequencies (impacts >14.9g) and magnitudes of each impact over the course of three seasons were recorded. The position experiencing the highest hit count frequency during one season was DL (718), followed by LB (592) and OL (543). The DB and RB were similar at 326 and 306 impacts per season respectively. Player positions experiencing the lowest impact frequency were WR (157) and QB (149) [Crisco *et al.,* 2011]. Examined by game, general results showed a higher frequency count amongst OL, DL and LB defensive compared to QB, RB, WR and DB. The magnitude of each impact was also measured using the helmet sensors. This group of researchers reported that the highest magnitude impacts were experienced by the RB and QB. Field positions that followed were LB and DB. Finally, the three positions experiencing the lowest magnitude impacts were DL, OL, and WR [Crisco *et al.,* 2011]. Often head impact magnitudes estimated using helmet sensors report similar average values across all player positions [Martini *et al.,* 2013; Broglio *et al.,* 2011; 2013; Mihalik *et al.,* 2007].

Table 6-1: Head impact frequency in ASF estimated using head impact sensors.

Level	Season(s)	Age	# Players	Frequency Count			Ave/Player /Game	Ave/Player /Season	Reference
				Total	Game	Practice			
Youth		7-8	7	748	307	441	5.8	107	Daniel et al., 2012
Youth		14-18	40	16502	7335	9167	15.5	412.5	Urban et al., 2013
Youth	2011-12	7-8	19	3059	1228	1831	11 ± 11	161 ± 111	Young et al., 2013
Youth		9-12	50	11978	4611	8382	10.6 ± 5.2	240 ±147	Cobb et al., 2013
Youth		11-13	22	6183	2037	3787	12	252	Munce et al., 2014
Youth	2012	7-14	22	480	109	371	3.7		Wong et al., 2014
HS	2004-06		190	99862					Greenwald et al., 2008
HS	2005		16	8326					Schnebel et al., 2007
NCAA			40	54154					
HS	2007	16.85 ± 0.75	35	19224			24.54		Broglio et al., 2009
HS	2005-08	16.7 ± 0.8	78	54247	25312	29287			Broglio et al., 2010
HS	2009	16.2 ± 0.6	42	32510	14166	16346	21.1	774	Broglio et al., 2013
HS	2009-10	15-18	24/28						Breedlove et al., 2012
HS/NCA	2005-10		1208						Beckwith et al., 2012
HS	2009		83	22091			18.3	455.8	Martini et al., 2013
	2011			13527			15.6	303.6	
HS	2013	15-18	12	224	224				Cummiskey et al., 2015
			15	231	231				
CIS	2013	20.7 ± 1.15	47	20924	10396	10528	24	394 (196)	Campbell et al., 2014
NCAA	2007		188				14.3		Crisco et al., 2010
NCAA	2007-09		314	286636			15.7	420	Crisco et al., 2011
NCAA	2005-06	19.58 ± 1.6	72	57024	12873	28610	21.12	804	Mihalik et al., 2007
NCAA	2003		38	3312	1198	2114	15		Duma et al., 2005
NCAA	2007		10	1712	570	1142			Rowson et al., 2009
NCAA	2007-2009		335	300977					Rowson et al., 2012
NCAA	2005-2010		1833	1281244					Rowson et al., 2014
NCAA	2004-2006	20.18 ± 1.8	88	104714					Guskiewicz et al., 2007
NCAA	2006-2010		98	37128	37128				Funk et al., 2012
NCAA	2007-2008		254	184358					Crisco et al., 2012
NCAA	2003-2004		52	11604	2970	8634			Brolinson et al., 2006

6.4 Summary

The variance in player roles in ASF coupled with known outcomes provides a sample to investigate the influence of brain trauma characteristics on the resulting injury. In order to prevent tissue injury, it is necessary to examine brain trauma in a manner that measures and captures this full spectrum. The use of head impact sensors have identified that positional variation in trauma exposure exists within the sport. An approach to documenting head trauma in sport needs not only identify an event, but a description of the event with quantifiable subsequent brain tissue strain is necessary.

PART III

7 Defining *Brain Trauma Profiling*

Various impact parameters contribute to the peak, duration, and shape of head accelerations, this combination subsequently affects the strain placed on neural tissues. The magnitude of the impact has long been investigated in light of the risks to various head injuries, head protection strategies and injury probability estimates. Many of these indices are based on peak head acceleration magnitudes that do not consistently associate with brain strain magnitudes [Rousseau, 2014; Post *et al.,* 2012a]. In addition, research pertaining to head impact exposure suggests that examining trauma solely based on its magnitude does not capture a full risk profile of brain injury or the long-term consequences of repetitive head impacts. Challenges in recognizing, reporting, and diagnosing concussion, limits the use of concussion data as an accurate measure for trauma in sport. It is important to appreciate that there are multiple ways to injure the brain, and the expression of injury is the consequence of various interactions/combinations of trauma characteristics that associate with risk. Research describing biomechanical forces that cause metabolic, physiologic and cellular changes in the absence of macroscopic damage and/or seemingly observable outcomes confirm the importance of magnitude and its interaction with the frequency of impact, time intervals between impacts and the duration of trauma exposure that may lead to cumulative brain damage. In order to advance our understanding of how traumatic event(s) lead to brain injury, a multidimensional approach is proposed, one that captures a more complete exposure profile.

7.1 Head Impact Conditions

Impact parameters (velocity, location, mass, compliance, vector/direction) predict the dynamic response of the head [Gennarelli *et al.,* 1982; 1987; Zhang *et al.,* 2001; Kleiven, 2003; Pellman *et al.,* 2003b; Post *et al.,* 2014a], and subsequent brain tissue damage [Willinger & Baumgarthner, 2003; Zhang, *et al.,* 2003; 2004]. The velocity and mass of an impacting object influences the amount of energy transferred from the object to the brain. However, the interaction of impact parameters determines head motion upon impact. The characteristics of the impact event establish the magnitude of head accelerations [Kendall *et al.,* 2012], affecting how the energy moves through the head and brain resulting in neural tissue damage. In sport,

especially contact/collision sports, the head can be impacted in many ways, each comprised of unique variations of the impact parameters. Many early studies reported that impacts to the side of the head (i.e., in the mediolateral direction) tended to cause the most severe injuries [Gennarelli *et al.,* 1982; Gennarelli *et al.,* 1987; Hodgson *et al.,* 1983]. Walsh et al. [2011] also reported that linear head accelerations were highest from front and side impacts, and rotational accelerations were highest from side and rear head impacts. Non-centric impacts considered oblique and outside the head's center of gravity, were consistently shown to be dangerous.

Impact events typically seen within contact/collision sports include collisions, falls, projectile impacts, and punches, each causing a distinctive combination of linear and rotational head accelerations [Hoshizaki *et al.,* 2014]. Figure 7-1 demonstrates how the type of event will influence the dynamic response of the head, creating unique loading curves. These event types were reconstructed from diagnosed concussive events and all experienced in the same sporting environment [Kendall, 2016; Clark *et al.,* 2016]. Each event shows variation in the peak magnitude of head acceleration as well as the shape and duration of the acceleration curves, which are affected by the compliance between the two systems. The level of compliance between the impacting object and the impacted body will influence how energy is transmitted to the brain. It was previously reported that impacts in which a high force is experienced during a short duration, as in a low-compliance system, would cause more serious injury, or material failure, sooner than those impacts in which the force transmission is prolonged and dampened [Hodgson, 1967; Gadd, 1966]. The force-time curve shape depends on the interactions among the striking object and the skull, brain, and surrounding soft tissues [Hodgson, 1967], and influence the peak accelerations during the resulting head response. However, there is a risk for concussion when energy absorption is prolonged through the use of head and body protection, as observed in decreased peak magnitude in head accelerations, accompanied by high brain strain values. For example, reconstructions of concussive events in ice hockey [Rousseau, 2014] have shown that events considered low risk based on acceleration magnitude still resulted in high tissue stress and strains [Willinger & Baumgarthner 2003; Zhang *et al.,* 2004; Kleiven, 2007].

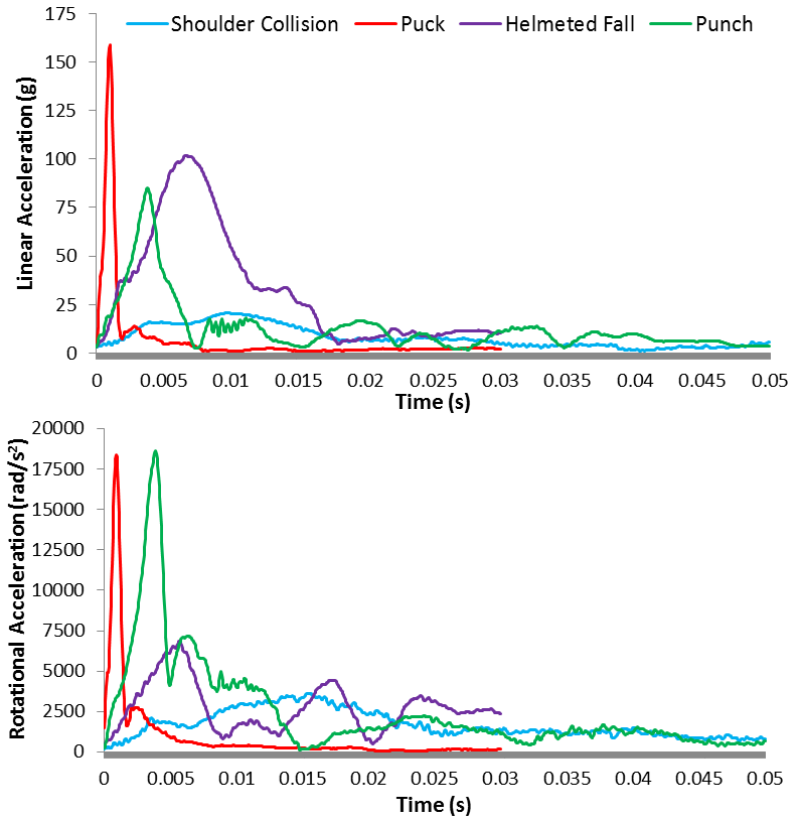

Figure 7-1: Linear and rotational head acceleration curves for four different impact events occurring in contact sport [Kendall *et al.*, 2012; 2016; Clark *et al.*, 2016].

This phenomenon can also be seen in American tackle football. Figure 7-2 compares shoulder-to-head impacts in ice hockey to helmet-to-helmet events in ASF and demonstrates how increasing the duration of the event lowers the peak dynamic response of the head [Karton *et al.*, 2017; Dawson et al, 2017]. Shoulder-to-head events have a higher level of compliance, subsequently lowering the rate of energy transfer. However, the viscoelastic nature of brain tissue results in similar levels of strain and clinically recognizable injuries for both events. These results reinforce the importance of considering the acceleration time curve (both shape and duration) when predicting neural tissue trauma [Post *et al.*, 2012b; Post *et al.*, 2014b]. Each event type creates unique dynamic responses that are further influenced by the location and direction of the applied force, and the duration/compliance of energy transmission [Post *et al.*, 2014a; Rousseau, 2014]. Furthermore, a fall in youth ice hockey will be different from one in professional-level ice hockey or in American football. These differences result from variations in impact mass and velocities, skill levels, playing surfaces, and protective equipment. Thus, the

level of play should be examined in each case to accurately describe trauma exposure and injury mechanisms specific to each sport.

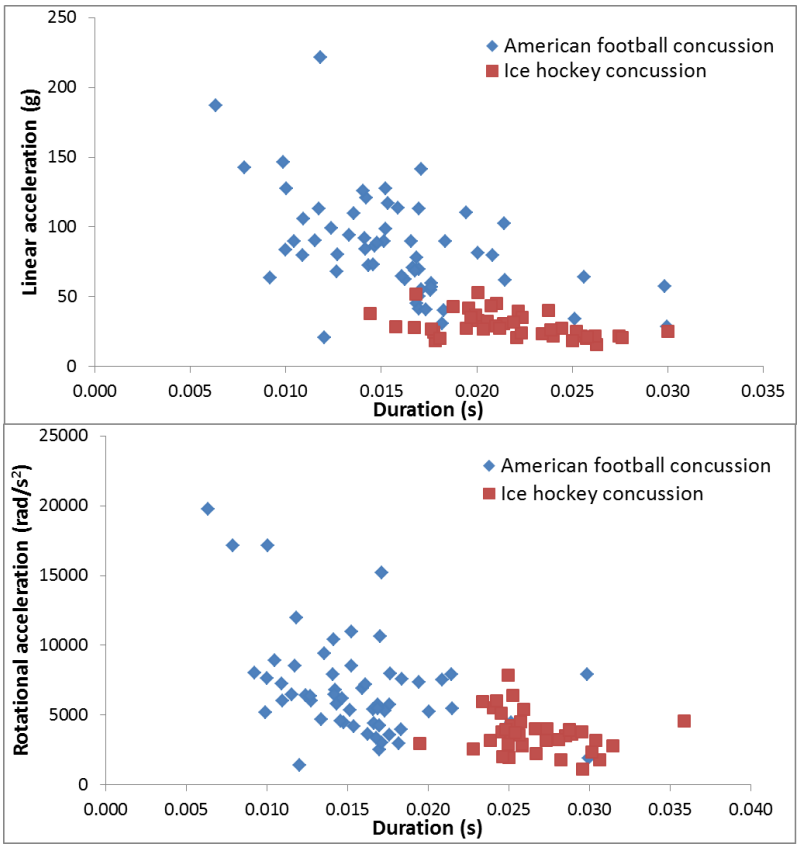

Figure 7-2: Head dynamic response resulting from concussive events from helmet-to-helmet head impacts in American football and shoulder-to-head impacts in ice hockey [Karton & Hoshizaki, 2018].

7.2 Mitigating Risk Using Head Protection

Newman [2006] described the severity of injury from an impact as a rapid onset of high forces over a short duration, and the direct result of the magnitude of the impacting force. Given the same head mass, an impact would result in a higher acceleration with an increasing impacting force [Newman, 1993]. Accordingly, as the impact force increases, the resulting accelerations would also increase proportionally [Barth *et al.*, 2001] and, consequently, influence the risk of injury. Factors in which complicate this equation include the time taken for energy transfer, and that the head is not a rigid body and, therefore, will deform and absorb energy under the influence of a force [Newman, 1993]. Impact forces can generate acceleration and deformation of the head and brain tissues, which increase the risk of an injury [Viano *et al.*, 1989; Kleiven &

von Holst, 2002]. In situations where the head is struck by, or strikes, a blunt object, helmets reduce deceleration of the skull to minimize brain movement. Their hard shells distribute the impact forces over a broad area, and dissipate the kinetic energy via soft crushable materials inside the helmet [Becker, 1998; Avalle *et al.*, 2001]. These effects also increase the duration of force transmission, decreasing the peak magnitude of the force [Nahum *et al.*, 1977; Kleiven & von Holst, 2002].

Helmet safety standards have primarily focused on focal brain injury caused by very high linear forces. Safety performance is determined based on the helmets' energy-absorbing capabilities using pass/fail criteria. Despite their different applications, many sport helmets are tested using similar protocols, in which safety performance is rated according to one mechanism of injury – a replicated fall to the ground – creating a linear dominant response. These standards primarily use centric testing protocols based on linear accelerations ranging from 250-300g or 1200 SI as indicators of injury [Snell Memorial Foundation, 2000; National Operating Committee on Standards for Athletic Equipment (NOCSAE), 2007; Canadian Standards Association, 1996]. Current safety indices such as the Gadd Severity Index (GSI) and Head Injury Criterion (HIC_{15}) do consider impact duration; rather, they are primarily based on linear acceleration and are therefore better suited for short duration events [Gadd, 1966; Snyder, 1976].

Severe, life-threatening events often result from high-energy impact situations, such as in motor racing, cycling, and ski/snowboard accidents. These events involve falling onto a hard surface with low compliance (e.g. concrete or ice), causing high-magnitude, short-duration head accelerations [Depreitere *et al.*, 2004; Post *et al.*, 2012a; Post, 2013]. These high-risk impact conditions initially led to the introduction of crash helmets [Newman, 2005]. Use of these helmets has decreased the risks of head injury and fatality for high-energy events [Haider *et al.*, 2012; Kim *et al.*, 2015]. Consequently, testing protocols equated a decrease in brain tissue response with a decrease in peak linear accelerations, even though the evidence suggests that rotational accelerations are closely related to neural tissue strains and risk of diffuse brain injury [Holbourn, 1943; Gennarelli *et al.*, 1982; Kleiven, 2007; Forero Rueda, 2010]. Therefore, helmet safety test protocols and design may not fully account for the dynamic response of the head. Concerns regarding serious injury and death in American football prompted helmet use and introduced helmet safety standards for contact sports [Newman, 2005]. Since implementation of mandatory helmets in contact/collision sports, head injuries with catastrophic outcomes are rare.

However, the increased compliance from helmet liners changed the risk from catastrophic injury (i.e. skull fracture, severe traumatic brain injury) to concussion and repetitive head impact exposure [Thunnan *et al.,* 1998; Hootman *et al.,* 2007; Wennberg, 2008; Daveshvar *et al.,* 2011; Bailes & Cantu, 2001].

It is well documented that rotational acceleration is important in causing a concussion, because of the shear strains put on brain tissue [Holbourn, 1943; Gross, 1958; Ommaya & Gennarelli, 1974]. Helmets currently used in contact/collision sports are not effective at attenuating rotational energy [King *et al.,* 2003; Rousseau *et al.,* 2009; Post *et al.,* 2011; 2013b]. Furthermore, the evidence that repetitive, lower-energy impacts with no perceivable injury can be associated with adverse long-term changes in mental health and cognition is not addressed. The protective role of helmets against low-energy impacts of low energy is arguable, and the way we continue to measure head injury risk, using peak linear head acceleration-based metrics has not proven beneficial to advancing the ability of helmets to protect against concussion and possible risks of repetitive head impact exposure. Helmet liners, the primary energy-absorbing material, are designed to function properly within a designated energy range. Consequently, they are not as effective at an inbound momentum (mass X velocity) that is either too high or too low [Avalle *et al.,* 2001]. In very low-energy impacts, the material may be too stiff to engage and therefore offer little protection against the transfer of energy to brain tissue. Helmets currently being manufactured are not designed to provide protection for lower-energy impacts from common player-to-player collisions, that may be contributing to concussion, subconcussive trauma, and repetitive head impact exposure risk [Hutchison *et al.,* 2015]. This type of contact causes head deceleration in the original vector and acceleration in a new direction, causing rotation which may be responsible for the greatest axonal injuries and impairments in neuro-behavioral outcomes [Barth *et al.,* 2001]. Fortunately, including oblique impacts (those that cause rotational violence) within helmet testing protocols, and innovations in equipment technology, are beginning to gain attention. NOCSAE has recently implemented a rotational acceleration threshold in its certification standard for new football helmets. Sporting equipment manufacturers have also begun introducing new technologies designed to attenuate rotational energy, aimed at reducing shear forces on brain tissue.

7.3 Primary Characteristics that Associate with Neurological Injury

Research involving neurological disorders with repeated brain trauma in athletes who participate in contact/collision sport describe brain injury as both an acute disorder, as well as one that may develop into chronic impairment. This knowledge reveals the need to better define exposure. To more effectively capture brain injury risks in contact and collision sports, this thesis defines the characteristics of trauma that associate with neurological injury and incorporates them into *brain trauma profiling*, involving strain magnitude, impact frequency, time interval between impacts, and duration of exposure. Brain trauma profiling captures and describes the cumulative and acute trauma associated injury risks unique to sport, level of play, and player position. The intention of this measurement method is to objectively capture and quantify head impact exposure. This method may be used to conceptually advance our understanding of the brain's many responses to impact by providing a detailed description of the trauma exposure. It is important that all contributors of injury risk be measured, to better understand what qualifies as reasonable risk versus unhealthy exposure or trauma loads leading to poor neurologic and neurobehavioral outcomes. Brain trauma profiling is a method of describing exposure using these variables.

7.3.1 Impact Magnitude

Many head contacts commonly occurring during contact/collision sports either do not present visible signs of neurologic dysfunction, or are not reported and therefore not clinically diagnosed. Figure 7-3 compares MPS levels between impacts with diagnosed concussion, versus those without diagnosed/reported concussion. Brain strain values show a large overlap between those who did and did not report concussion symptoms, regardless of sport or event type [Karton *et al.,* 2017; Dawson et al., 2017]. Abnormal changes within white matter have been detected in ASF players after one season of play with greatest changes measured in concussion patients, intermediary for 'sub-concussive' group with the least amount of neuronal change reported for controls [Bazarian *et al.,* 2012; Breedlove *et al.,* 2012]. These subtle differences address the importance of objectively measuring the effects of head impact magnitude regardless of symptom expression.

Changes in DTI measures, specifically the greater percentage of voxels with fractional anisotropy decrease, are significantly correlated to the number of head hits exceeding two magnitude values of peak rotational accelerations. Specifically, greater changes were measured

when the number of hits resulted in >4500 rad/s^2 exceeded 30-40 and number of hits >6000 rad/s^2 exceeded 10-15 over the course of a season [Bazarian *et al.*, 2014]. The influence of magnitude is demonstrated in serum and CSF protein concentrations indicative of axonal injury. Elevated levels are measured following a bout in boxing with higher concentrations found in those experiencing a knock-out compared to their opponent [Zetterberg *et al.*, 2006; Neselius *et al.*, 2012; Shahim *et al.*, 2017].

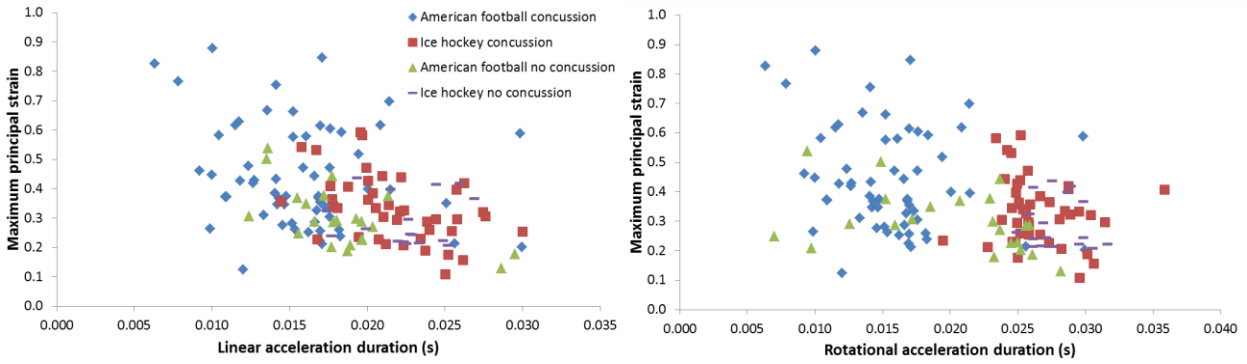

Figure 7-3: Maximum principal strain magnitudes of reconstructed helmet-to-helmet impacts in American football and shoulder-to-head impacts in ice hockey: comparison of symptomatic (reported concussion) and asymptomatic (no reported concussion) events [Karton & Hoshizaki, 2018].

7.3.2 Frequency of Head Impact

Changes in blood and CSF biomarkers indicating axonal damage is associated with the frequency of traumatic events. Risks of chronic brain disease associated with impact frequency was first observed in boxers where poor performance was correlated with the number of bouts and knock-outs [Roberts, 1969; Jordan *et al.*, 1992; Critchley *et al.*, 1957]. Increased levels of NF-L and T-tau have been reported in boxers after a bout, where the quantity of increase was greater in those with the most hits [Zetterberg *et al.*, 2006; Neselius *et al.*, 2012; Shahim *et al.*, 2017]. Elevated NF-L and S100 calcium binding protein B (S100B) levels have been detected in 'non-concussed' football players throughout, and following a season compared to baseline measurements [Oliver *et al.*, 2016; Kawata *et al.*, 2017]. Starter athletes showed higher levels compared to both non-starters and controls, with levels remaining above baseline values for up to 9 weeks postseason [Oliver *et al.*, 2016]. Further, collegiate football players sustaining higher head impact frequencies consistently showed greater elevations of plasma S100B at post-practice measurements [Kawata *et al.*, 2017]. Similar findings were also observed in hockey players

following one season compared to baseline reporting [Koerte *et al.,* 2012]. Kondo et al. [2015] have shown similar durations of elevated levels of pathogenic *cis* p-tau protein in a repeat trauma model to a single severe traumatic event. This indicates that lower magnitude brain trauma, if repetitive, shows similar pathologic outcomes to one severe event, suggesting there may be similar neurologic risks associated with the cumulative effect of trauma to neural tissues.

Imaging techniques, DTI and fMRI, are used to detect changes following brain trauma. In several studies, changes in white matter structure and neuronal activity have been reported following a single season of play among athletes involved in contact/collision sport who did not have a concussion diagnosis; in these studies, the frequency of head impacts is positively correlated with the extent of the measured changes [Breedlove *et al.,* 2012; Bazarian *et al.,* 2012; 2014; Koerte *et al.,* 2012 Talavage *et al.,* 2014; Bahrami *et al.,* 2016; Slobounov *et al.,* 2017; Kuzminski *et al.,* 2018; McAllister *et al.,* 2014]. In one study, changes in fractional anisotropy within the fornix-stria terminalis and cingulum hippocampus associated with the frequency of impact and correlated with worsening visual memory in non-concussed high school ASF players [Kuzminski *et al.,* 2018]. Again, in 'non-concussed' collegiate athletes, impact exposure correlated with white matter mean diffusivity measures throughout a number of brain regions. Specifically, the degree of postseason difference within the corpus callosum was associated with poorer performance on a measure of verbal learning and memory [McAllister *et al.,* 2014].

7.3.3 Interval between Head Impacts

The influence of time between impacts has been measured using serum biomarkers for axonal injury following both a single insult in ice hockey and repetitive impact in boxing. NF-L levels tend to return to baseline much sooner from one concussive impact in hockey (7-8 days) as opposed to repeated impact with knockout from boxing, which have been reported to take as long as 36 weeks to return to baseline [Neselius *et al.,* 2012; Shahim *et al.,* 2016]. However, if there is a cessation from participation (i.e. extended time between repetitive head impacts), studies indicate that biomarkers generally return to normal at 8-12 wks in boxers [Zetterberg *et al.,* 2006; Neselius *et al.,* 2012]. Normalization of blood and CSF biomarkers of axonal injury typically does not occur until weeks post trauma, where chronic levels of circulating waste, caused by repeat trauma with little recovery time, may lead to an overwhelmed flow and clearance system, which could last for up to 28 days following an insult [Iliff *et al.,* 2012; 2013;

2014; Jessen *et al.,* 2015; Zetterberg *et al.,* 2006; Neselius *et al.,* 2012]. Continued exposure to brain trauma without compensatory recovery may result in chronic impairment of glymphatic system flow, resulting in increased levels of interstitial tau, potentially promoting tau aggregate formation [Jessen *et al.,* 2015; Peng *et al.,* 2016].

The use of animal models has been the primary method to describe the influence of time interval between impacts. Meehan et al. [2012] reported that increasing the time interval between traumatic events attenuated the effects on cognition, and with prolonged time between impacts, cognitive recovery was attained. However, when multiple injuries were sustained daily, the effects on cognition were permanent. Cerebral vulnerability is a period of decreased glucose metabolism (CMRglc) following an insult. If a second insult is experienced before recovery, CMRglc is worsened, also reported as a consequence of repetitive insults to brain tissue [Giza & Hovda, 2001; Prins *et al.,* 2013; Effgen & Morrison, 2017]. The duration of heightened vulnerability is not well defined, however two stretch injuries within 24 hours was shown to increase tissue injury. An inter-injury interval of 120-h and 144-h was sufficient to avoid detrimental effects from repeat injury [Prins *et al.,* 2013; Effgen & Morrison, 2017]. This indicates that if the second insult is experienced after metabolic recovery, the CMRglc depression resembles that of a single injury [Prins *et al.,* 2013]. Similarly, if a secondary injury is experienced during the acute inflammatory phase, the repair process is halted and neuroinflammation is enhanced. However, if the secondary injury is experienced during the wound-healing phase, then normal processes continues [Russo *et al.,* 2018]. Following an insult, similar durations of elevated *cis* tau were observed after repetitive mild injury events within short time intervals, 7 injuries within 9 days, to that of a single severe injury event. Interestingly *cis* tau levels returned to baseline much sooner after only a single mild injury of concussive levels, when compared to both of the former scenarios (Kondo *et al.,* 2015). Weber [2007] also demonstrated that the extent of cumulative damage to cells by stretch-induced mechanical injury in vitro was dependent on the time between repeated injuries. Interestingly at stretch levels too low to cause cell damage, induced injury when it was repeated several times at short intervals of every 2 minutes.

7.3.4 Duration of Head Trauma Exposure

There are consistent findings that describe the role of length of athletic career and overall amount of exposure to head trauma as significant contributors of behavioural and cognitive abnormalities [McKee *et al.,* 2013; Banks *et al.,* 2014; Bernick *et al.,* 2014; Stamm *et al.,* 2015; Montenigro *et al.,* 2017]. Initially measured in boxers, risk factors for CTE outlined by Jordan [2000] include increased exposure to trauma, defined by duration of career and age of retirement [Roberts, 1969; Jordan *et al.,* 1992; Critchley *et al.,* 1957]. Professional mixed martial arts fighters and boxers self-reported fight exposure scores (years of fighting and fights per year) was associated with lower brain volumes and greater cognitive impairments [Bernick *et al.,* 2014]. These findings describe the cumulative effect of repetitive trauma leading to chronic injury. In a convenience sample of deceased football players who donated their brains for research, McKee et al. [2013] reported a positive correlation between years of contact sport participation and the stage of CTE progression at the time of death, where the number of diagnosed concussions alone did not predict pathologic progression [McKee *et al.,* 2013; Mez *et al.,* 2017]. The vulnerability of young developing brains to cumulative head trauma demonstrated through positive associations in predicting neuropsychological and cognitive conditions is concerning. Participating in sports with repetitive head contact is associated with depression, apathy, executive dysfunction, and cognitive deficits later in life, where lower measures in mental functioning are detected in those exposed to contact at earlier ages [Stamm *et al.,* 2015; Montenigro *et al.,* 2017; Alosco *et al.,* 2017]. Interestingly, post-traumatic metabolic changes in the immature brain appear to be shorter lasting than in adults [Thomas *et al.,* 2000], but axonal vulnerability to injury may be more prominent in the young brain [Reeves *et al.,* 2005; Prins *et al.,* 2010].

7.4 Summary

Measures of brain trauma in sport activities represented by head dynamic response and brain tissue strain limit the understanding of the neurologic origins of tissue injury. Current helmets are primarily designed to protect against high-energy impacts, reflecting specific mechanisms of injury. But brain trauma is not solely described by the magnitude of a head impact leading to severe injuries and symptomatic concussions. Rather, lower-energy magnitudes sustained at higher frequencies with shorter time intervals may result in long-term neurologic complications

even without acute symptoms of concussion at the time of initial injuries. Traditional methods using symptoms-based assessment and diagnostic tools are not sensitive enough to capture the vulnerabilities associated with brain trauma. With reported changes to neuronal structures, chemistry, and cognitive function following participation in contact/collision sport, it is imperative to effectively capture cumulative brain tissue trauma exposure. Characteristics including strain magnitude, frequency, interval, and duration of exposure all contribute to neuronal damage, and therefore define brain tissue trauma load. Brain trauma profiling methods can shed light on the effects of repetitive head impact exposure and how this predicts the risk for chronic injury, neurobehavioral impairments, or, in more extreme cases, the onset of neurologic disorders and diseases.

8 A Novel Brain Trauma Exposure Measurement Tool Differentiates Player Position in National Football League

8.1 Abstract

American-style football participation poses a high risk of head trauma resulting in acute and chronic brain injury. The complex nature of symptom expression, human predisposition, and neurologic consequences of repetitive exposure limits our understanding of what constitutes as an impact injury affecting the integrity of brain tissue. Video footage of professional football games was reviewed and documentation made of all head contact. Frequency of impact, tissue strain magnitude, and time interval between impacts was used to profile and measure exposure to trauma specific to football player field position. Differences in how unsafe amounts of trauma to the brain are experienced were found between eight different positions; where three unique exposure profiles can be observed. Exposure profiles provide interpretation of the relationship between head trauma and how tissue injury is manifested and expressed. This study illustrates how trauma is created on the field, a critical component in guiding public policy and guidelines for managing exposure.

8.2 Introduction

Various levels of head impact severity associated with brain injuries have been studied for over a century where knowledge and reporting reflected current periods' public concern and environmental context [Casper, 2018]. The scientific community, medical sectors and regulatory authorities have been working for decades to unravel the complexity of brain injury in sport, most predominantly the definition, identification, and treatment of concussions. There were obvious challenges associated with the ambiguous nature and presentation of what is regarded as a tissue 'injury' [Erlanger *et al.*, 2015; Bailes *et al.*, 2013]. Inconsistencies in injury expression and prediction, and human variability in injury predisposition limit the precision in defining the relationship between brain trauma and injury. Despite numerous reports describing the implications of both acute and chronic brain injury, only recently have repetitive exposure to brain trauma in contact sports become a real concern, and this concern has become relevant to researchers, neurologists, clinicians and athletic professionals alike. The high profile sport, ASF

has received increasing attention amongst researchers who believe that this population will help establish a better understanding of the consequences and management of repeated brain trauma.

Measuring brain injury in ASF solely on the basis of immediate signs and symptoms has proven to be insufficient in capturing the spectrum of tissue injury [Alosco *et al.,* 2017a; Montenigro *et al.,* 2017]. Moreover, as individuals recover from the clinical expression of symptoms, the assumption that neurobiological recovery has also occurred is also likely to be inaccurate [Neselius *et al.,* 2012; Zetterberg *et al.,* 2006]. A more sophisticated understanding that now prevails considers the time course of neurobiological recovery and the mental health consequences of being exposed to repeated head impacts. Oliver and colleagues [2016] report that blood concentrations of axonal injury biomarkers in college football starters remain elevated up to 9 weeks post season. The scientific debate regarding head injury in ASF has progressed from how concussion is managed, to how a person's cumulative history of neurotrauma, inclusive of asymptomatic impacts, should be managed.

Not only are a large percentage of concussions [McCrea *et al.,* 2004; Meehan *et al.,* 2013] unrecognized or underreported, but a number of modalities have been used to show changes in brain function, connectivity, activation and cognition, following what would be considered asymptomatic trauma on the football field, most notably, of repetitive nature [Talavage *et al.,* 2014; McAllister *et al.,* 2014; Bazarian *et al.,* 2012; 2014]. Many deficits associated with the long-term consequences of repeated impacts are not clinically apparent until years after the trauma is experienced [Alosco *et al.,* 2017b; Stern *et al.,* 2016]. This has raised awareness of the link between cumulative brain trauma and the development and/or initiation of neurological disorders, including CTE. CTE has been associated with exposure to repeated head impacts, and often presents with cognitive, motor and psychiatric related deficiencies [Bieniek *et al.,* 2015; Amen *et al.,* 2016; Kondo *et al.,* 2015; McKee *et al.,* 2013]. The vulnerabilities associated with duration of exposure are implicated in a number of reports showing higher plasma tau concentrations, increased cognitive impairments and reduced microstructural integrity of the corpus callosum found in retired NFL players compared to their age matched controls [Alosco *et al.,* 2017a; Stern *et al.,* 2016; Amen *et al.,* 2016; Stamm *et al.,* 2015a; 2015b]. This underlines the importance of developing a more effective and consistent way to quantify head and brain trauma in ASF and define tissue injury.

Professional ASF is associated with one of the highest rates of documented concussion and the development and pathology of neurological disorder within sport [McKee *et al.,* 2013; Nathanson *et al.,* 2016; Lehman *et al.,* 2013], and currently accounts for the greatest number of post-mortem diagnosed cases of CTE [Mez *et al.,* 2017; Maroon *et al.,* 2015]. This self-selection biased data set, however, makes it difficult to determine the true incidence and risks associated with head trauma leading to CTE development, particularly within the ASF population. However, a recent quantitative risk assessment concluded that CTE poses a public health concern, and suggests that regardless of the limited data on causation, incidence, and/or the dose-response relationship, reducing the exposure to head trauma in ASF would consequently result in a reduction in the occurrence of brain disease [Finkel & Bieniek, 2018]. It is the societal impact of repeated head injuries that will govern how public health is managed and public policy and clinical guide lines are set. One way to assist in better risk mitigation and management of head trauma in ASF is to examine brain trauma in a more holistic and universal manner, one that measures and captures its broad spectrum [Karton & Hoshizaki, 2018].

Research examining head impacts leading to metabolic, physiologic and structural alterations of neuronal cells propose an interaction between trauma characteristics that create risk for a person's brain health. Biomarker assays and various imaging techniques are sufficiently sensitive to detect changes in athletes who experience both symptomatic and asymptomatic head impacts [Oliver *et al.,* 2016; Talavage *et al.,* 2014; McAllister *et al.,* 2014; Koerte *et al.,* 2012]. The degree of alteration associates with both the intensity of impact and number of impacts received [Zetterberg *et al.,* 2006; Bazarian *et al.,* 2012; 2014; Breedlove *et al.,* 2012; Neselius *et al.,* 2015; Shahim *et al.,* 2014]. Moreover, taking time for brain tissue to recover from either frequent or intense impacts has been implicated in recurrent injury and brain health [Oliver *et al.,* 2016; Prins *et al.,* 2013; Giza & Hovda, 2001; Broglio *et al.,* 2017]. Frequency, magnitude, and interval characterize head trauma and are important and relevant to long-term psychiatric sequelae.

Head contact is integral part of ASF, resulting in hundreds of head impacts throughout a season [Martini *et al.,* 2013; Crisco *et al.,* 2010; 2011; Campbell, 2014]. The number, type and magnitude of impacts received will naturally vary based on a player's positional responsibilities [Crisco *et al.,* 2010; 2011]. Innovations designed to measure the dynamic response of the head to impacts by inserting accelerometers in the helmet, mouth guard and chin strap or through skin

adhesives, provide information in terms of impact count/frequency, however, are limited to basic dynamic measures, which poses valid concerns regarding their accuracy for predicting brain trauma [Jadischke *et al.,* 2012; Post & Hoshizaki, 2012; Rowson *et al.,* 2011]. Impact accelerometers typically report similar average head acceleration values across player position, and provide insufficient information on magnitude differences [Martini *et al.,* 2013; Campbell, 2014; Mihalik *et al.,* 2007; Broglio *et al.,* 2011; 2013]. Field positions and plays create environments that dictate a number of characteristics of the traumatic events including how a player is impacted (event type/compliance), how hard they are impacted (mass, velocity), and where they are impacted (location). These parameters create unique head kinematic motions that influence the magnitude of neural tissue loading and physical responses [Kendall, 2016; Kleiven, 2007; Gennarelli *et al.,* 1982; 1987; Pellman *et al.,* 2003; Post *et al.,* 2012a; 2012b; 2014; Willinger & Baumgartner, 2003; Zhang *et al.,* 2001; 2003; 2004]. Physical head impact event reconstruction and finite element analysis provide useful information for the investigation of the link between head motion and brain strain. Furthermore, it is clear that how often an impact occurs (frequency) and the recovery time between impacts (interval) will be unique to play position and may be implicated in the documented rates and risks of head injury and brain disease [McKee *et al.,* 2013; Nathanson *et al.,* 2016; Lehman *et al.,* 2013]. The purpose of the current study was to employ a novel method for profiling brain trauma exposure that includes frequency of impact, strain magnitude, and time interval between impacts to measure the amount and character of trauma associated with specific player field positions in professional ASF.

8.3 Materials and Methods

8.3.1 Game Video Analysis

Films of 32 professional ASF games from the 2009 to 2015 seasons were reviewed. One regular season game played by each of the 32 league teams was chosen at random for analysis. One starter player in each of eight positions was tracked and all head contacts were documented. Eight ASF field positions were included: Quarterback (QB), Running Back (RB), Wide Receiver (WR), Tight End (TE), Offensive Line (OL), Defensive Line (DL), Linebacker (LB), and Defensive Back (DB). When a tracked player was taken off the field, the substitution player was tracked for the same position. Each position was tracked throughout the entire game. Initial

analysis included clipping video when head impacts occurred and documenting the team name, position played, player name and number, type of event, time of impact, head location of impact, and estimated velocity level of impact based on recognized averages of jogging, running and sprinting speeds [Di Mascio & Bradley, 2013]. The validation process then consisted of each clip being viewed by two additional reviewers to confirm a) that a head impact occurred, b) event type, and c) location of head impact. Velocity level was later confirmed using video analysis software (see Physical Reconstruction of Head Impact Events).

Head impact frequency counts

Impacts were designated as confirmed, suspected, or multiple. Impacts were logged as confirmed if: contact with the head was clearly visible; the event type could be determined; the head location could be determined. Suspected impacts were treated as events in which the player being tracked appeared to have experienced a head impact; however, due to any of the following reasons an impact could not be confirmed: poor video quality, poor camera angle of view, point of contact was obscured by another player. Multiple impacts were documented for circumstances in which players were tackling or being tackled and entered a pile-up situation, suggesting that multiple impacts were suspected; however, the specifics of those events could neither be distinguished nor confirmed.

Time interval between head impacts

Clock time of contact was recorded and used to calculate the time intervals. Total game time and time of play was used to calculate the percentage of stop time for all games independently. Interval between every impact was multiplied by the stop time specific to each game. Intervals were calculated in minutes. A two-minute interval was added between the last impact in the first quarter and the first impact in the second quarter, similarly between the third and fourth quarter. A 12-minute interval was added between impacts occurring on either side of half time. Two games went to overtime where a 5-minute interval was added between the end of the fourth and beginning of the overtime. Time intervals between each impact within level of magnitude were calculated. Impacts were further categorized into four time intervals for the calculation of BSE/T and are as follows; very low = <15min, low = 15-30min, moderate = 31-90min, high = 91min+.

8.3.2 Physical Reconstructions of Head Impact Events

Four primary event types were reconstructed in laboratory; helmet, shoulder, hip/thigh and ground. All other events were documented as 'other'. To appropriately reconstruct an event, the following five parameters were determined and categorized: velocity, location, orientation, effective mass, and compliance. Contact velocity, and head location and orientation were obtained during video analysis; effective mass and compliance were approximated using known measurements and available literature [Plagenhoef *et al.,* 1983; Rousseau & Hoshizaki, 2015; Ignacy, 2017].

Velocity, Location, Orientation

Inbound velocity was calculated by establishing the distance separating the player's head from the contact surface (i.e. opponent shoulder) three to five frames prior to the impact (0.12-0.2 second) using Kinovea software (version 0.8.20) (Fig. 8-1A). Collision velocity (helmet, shoulder, hip/thigh) was calculated using field lines and video recording speed as described in a number of earlier studies [Rousseau, 2014; Post *et al.,* 2018]. Fall (ground) velocities were estimated by calculating the resultant velocity in a two-step process 2 frames prior to impact. Horizontal velocities were calculated using a marker system and perspective grid of known dimensions. The coordinates of the marker (representing camera movement) and the coordinates of the player's head (representing camera + player movement) were documented for three frames prior to contact and velocity was calculated based on displacement measurements (Fig. 8-1B-1). The calculated velocity of the marker (camera) was subtracted from the player (camera + player) velocity for each frame and an average velocity was calculated. Vertical distances were established by measuring the distance from the player's head to the ground two to three frames prior to contact (0.08-0.12 second) using the known helmet width or length measurement as a reference [Newman *et al.,* 1999] (Fig. 8-1B-2). Velocity calculations using Kinovea has been validated using ice hockey collision [Post, *et al.,* 2018]. See *Measurement Variation & Error in Appendix B* for a description. All impacts were categorized into five velocity levels: Collisions; very low = <2.0 m/s, low = 2.1-4.5 m/s, moderate = 4.6-7.0 m/s, high = 7.1-9.5 m/s, very high = 9.6+ m/s, Falls; very low = <2.0 m/s, low = 2.1-4.0 m/s, moderate = 4.1-6.0 m/s, high = 6.1-8.0 m/s, very high = 8.1+ m/s. If there were not sufficient field markings available to calculate velocity, a visual categorization was made. See *Measurement Variation & Error in Appendix B.*

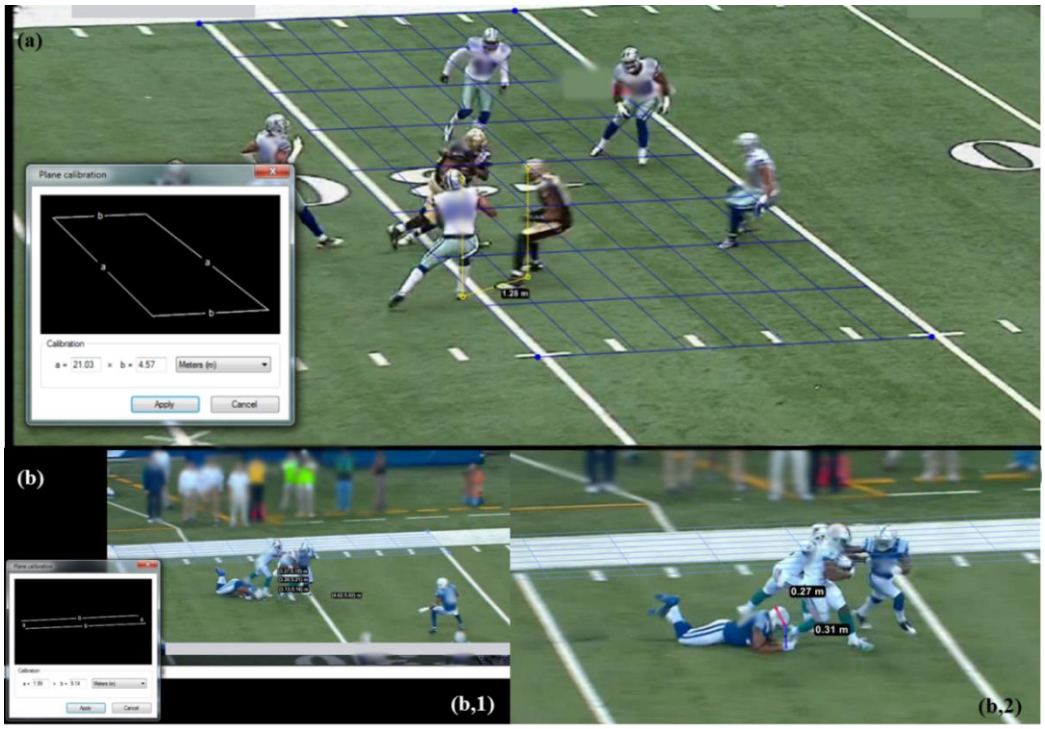

Figure 8-1: Perspective grid using known field dimensions for contact velocity calculations using game video recordings and Kinovea computer software. (A) 5 frames prior to helmet impact collision between two players. (B) Ground contact velocity calculations in a two-step process (1) horizontal using frame by frame marker system, and (2) calculating vertical distance to ground using helmet length reference measurement.

Head locations were categorized as front, front boss, side, rear boss, rear and crown and were labelled using the reference system illustrated in Fig. 8-2. In the transverse plane, the head was divided into 8 sectors of 45°, representing 5 head locations, with eyes forward being 0°. All impacts occurring at the top of the helmet were categorized as crown (Fig. 8-2A-1). Side and boss locations were treated as one location independent of occurring on either the right or left side of the head. In the sagittal plane, the distance between the base and top of the helmet was divided into five equal levels of elevation (minus crown location) (Fig. 8-2A-2). Similar methods used and outlined by Rousseau [2014] deemed the level of precision was consistent with previous investigations [Oeur *et al.*, 2014; Walsh *et al.*, 2011]. See *Measurement Variation & Error in Appendix B* for a description of the influence of impact location accuracy on head and brain response. Location and direction were verified using a high speed imaging PCI-512 Fastcam running at 2 kHz and Photron Motion Tools computer software (Photron, San Diego CA) (Fig. 8-2B).

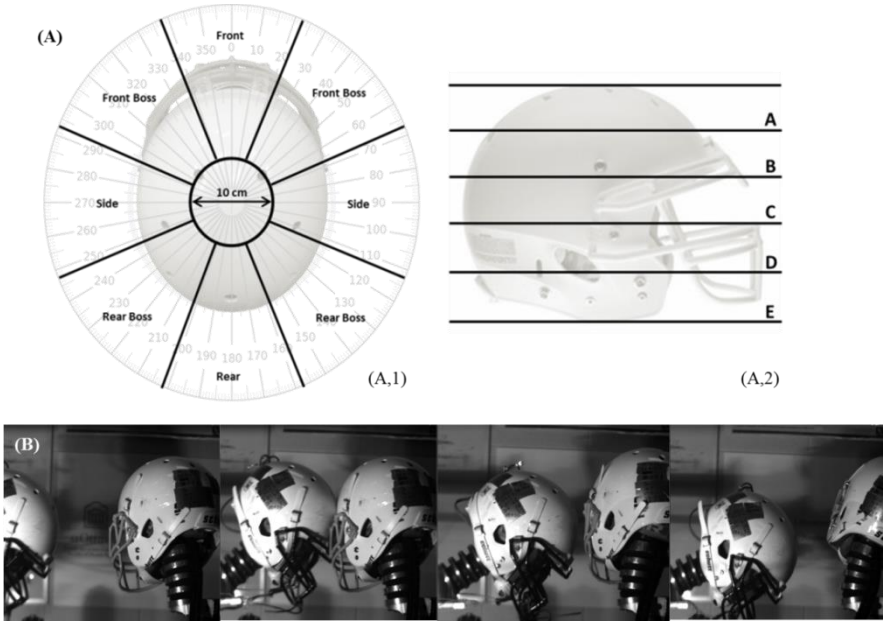

Figure 8-2: Location and direction estimation and validation for physical reconstruction of head impact events. (A) Top and side view of a football helmet demonstrating (1) the 8 sectors of 45° within the transverse plane, and (2) five levels of elevation used in the reconstruction protocol. (B) Validation of head motion post impact using high speed imaging.

Compliance, Mass

Compliance and mass were obtained using appropriate reconstruction equipment and selected based on the type of contact event. A pneumatic linear impactor (collisions) and a drop rig (falls) were used to replicate the four event types.

The linear impactor consisted of a stationary steel frame secured to a cement floor supporting a 1.28 ± 0.01 m long cylindrical, free-moving impactor arm (13.1 ± 0.1 kg) (Fig. 8-3). A Hybrid III 50th-percentile adult male head form and neutral unbiased neck form [Walsh *et al.*, 2018] (mass 6.65 kg ± 0.01 kg) was attached to a 12.78 ± 0.01 kg sliding table to allow for post impact movement. The inbound velocity matched the values obtained from the categorization of contacts. Shoulder and hip/thigh events utilized a nylon disc (diameter 13.2 mm) covered with a 142 mm thick layer of vinyl nitrile 602 foam attached to the impacting end of the arm to simulate human shoulder and hip compliance [Rousseau, 2014; Ignacy, 2017] (Fig. 8-3A,B). Additionally, a pro football shoulder pad was attached to the impacting end for shoulder collisions (Fig. 8-3A). The striking mass was 15.5 kg and 15.2 kg for shoulder and hip/thigh events respectively, representing a realistic effective mass of player-to-player collisions [Rousseau & Hoshizaki, 2015; Ignacy, 2017]. Helmet events employed an additional Hybrid III

head and neck form attached to the impacting end of the cylindrical arm via an L-frame and angled wedge to represent the striking player (Fig. 8-3C). Four different angled wedges (15°, 30°, 45° and 60°) were used to obtain the desired neck angle of the striking player. A heavier free-moving cylindrical impacting arm (16.1 ± 0.1 kg) and a stiff Hybrid III neck form were used for these collisions to represent the higher mass and minimal neck bending of a striking player [Viano *et al.*, 2005; ; Pellmen *et al.*, 2005] for a total striking mass of 24.0 kg. A monorail drop tower with turf anvil was be used to simulate the ground events (Fig. 8-3D). The helmeted Hybrid III head and neutral unbiased neck form was attached to a guided rail system via a holding carriage. The assembly was dropped unrestrained from a predetermined height onto a turf surface to duplicate the contact surface of a football field.

An exemplar event was chosen for reconstruction for every possible contact condition (event type X velocity level X head location) experienced by each of the eight positions. This resulted in 249 head impact event exemplars. All event reconstructions consisted of three impact trials for a total of 738 simulated impacts. See *Exemplar Impact Grids in Appendix D* for a completed description of the impact characteristics for each exemplar and the impact frequency each exemplar represents. Table 8-1 presents the exemplar event type classification for each field position.

Table 8-1: Event type classification and exemplar totals for eight field positions.

	Event Type				**Exemplar / Position**
	Helmet *(n)*	Shoulder *(n)*	Hip *(n)*	Ground *(n)*	
QB	5	1		10	**16**
RB	14	13	6	16	**49**
WR	9	2	3	14	**28**
TE	11	11	3	12	**37**
OL	7	8	3	5	**23**
DL	11	9	3	8	**31**
LB	10	9	3	10	**32**
DB	5	9	4	15	**33**
Total #	**72**	**62**	**25**	**90**	

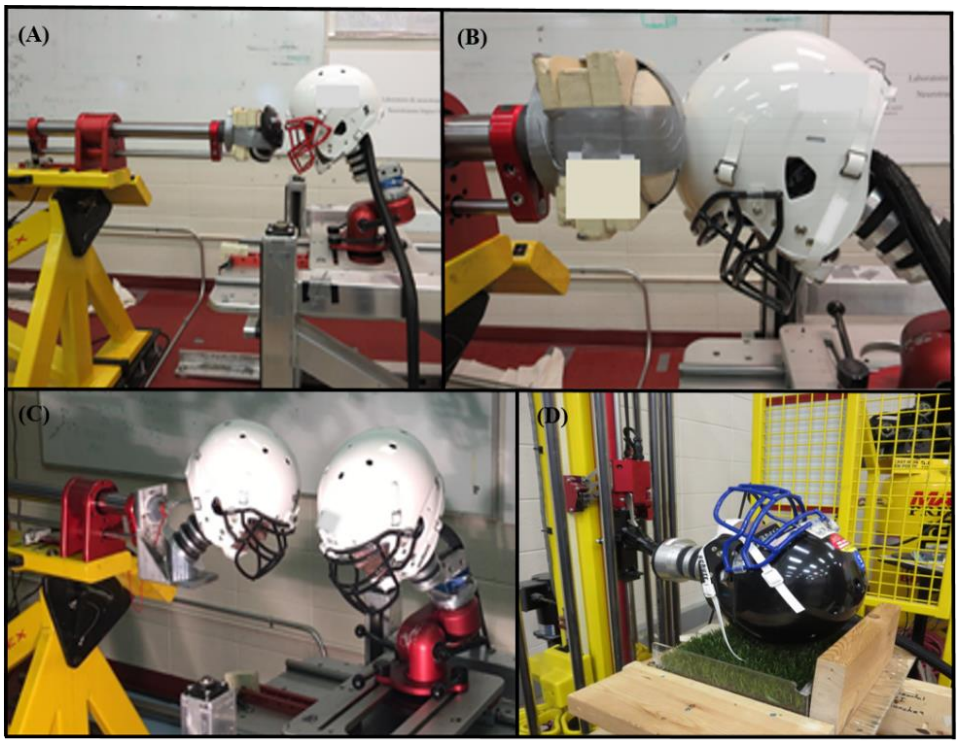

Figure 8-3: Equipment used for physical reconstructions of exemplar head contact events. (A) Shoulder events employing vinyl nitrile foam and shoulder pad cap attached to the arm of linear impactor system. (B) Foam impactor cap to replicate the compliance of hip/thigh events. (C) L-frame attachment for additional hybrid III head and neck for helmet contact events. (D) Hybrid III head attached to monorail drop system impacting field turf surface for ground events.

Impacts that met the following criteria were chosen as exemplar events in this study: the event was captured on video, multiple lines were visible in a plane of view of the camera to determine plane perspective using distortion correction algorithms, and the head location could clearly be determined. If a condition consisted of 2 or 3 contacts than an average of the calculated velocities was used for the reconstruction. The midrange value of a velocity level (i.e. low collision = 3.25 m/s) was used for reconstructions in which the exemplar represented a category with 4 or more contacts. Finally, for exemplars representing only one contact condition, the calculated velocity for that event was used for the physical reconstruction.

Collection system

Nine single-axis Endevco 7264C-2KTZ-2-300 accelerometers [Endevco, San Juan Capistrano CA] mounted in a 3-2-2-2 array in the headform were sampled at 20 kHz and filtered using the SAE J211 class 1000 protocol [Padgaonkar *et al.,* 1975; SAE, 2007]. The headform representing

the striking player used a SLICE NANO free motion data acquisition system consisting of a tri-axial accelerometer with three angular rate sensors mounted at the head center of gravity [Diversified Technical Systems]. Collection was sampled at 20 kHz and a low pass filter of 300 Hz (CFC 180) was applied to obtain clean acceleration curves derived from rotational velocity. The two different collection systems result in similar head dynamic responses under the same impact condition; see *Headform Collection System Comparison in Appendix C* for a description. Accelerometer signals were passed through a TDAS Pro Lab system [DTS, Calabasas CA] before being processed by TDAS software. An electronic time gate measured the inbound velocity just prior to head impact using National Instrument's VI Logger software.

8.3.3 Finite Element Brain Modeling

The University College Dublin Brain Trauma Model (UCDTBM) was used to estimate the magnitude of brain deformations resulting from the exemplar head contacts. The UCDBTM model geometry was developed from CT and MRI imaging of the head of a male cadaver, and the version used in this research was composed of the scalp, skull, pia, falx, tentorium, CSF, grey and white matter, cerebellum, and the brain stem [Horgan & Gilchrist, 2003; 2004]. Overall, the brain was composed of approximately 26,000 hexahedral elements. Model material characteristics were established from earlier research [Kleiven & Von Holst, 2002; Ruan, 1994; Willinger *et al.*, 1995; Zhou *et al.*, 1995] and are presented in Table 8-2. A more detailed description of the UCDBTM is presented in Section *3.4.3 University College Brain Trauma Model.* Validation of the model was conducted by comparing simulation responses to cadaveric testing that measured intracranial pressure [Nahum *et al.*, 1997] and relative brain skull motion [Hardy *et al.*, 2001]. Comparisons to real world reconstructions of traumatic brain injury incidents were also conducted as a further validation [Doorly & Gilchrist, 2006].

Magnitude of brain tissue deformation

Brain deformations from exemplar head impact events was analysed using the three-dimensional dynamic response curves obtained from the Hybrid III physical model reconstructions and applied to the centre of gravity of the model [Zhang *et al.*, 2004]. The nature of the brain deformations was characterized using the MPS, as this metric has been identified as being among the best predictors of brain injury. Five MPS magnitude categories were established to capture a

spectrum of severity that occurs in the sporting environment. These categories were based on biomechanical event reconstructive research and anatomical tissue analysis that associate with, physiological brain responses to axonal stretch, reported concussion, sub-concussion and clinical outcomes. Moderate magnitudes represent a category based on a 50% risk of concussion injury measured in the cerebrum white or grey matter [Kleiven, 2007; Zhang *et al.*, 2004; Bain & Meaney, 2000]. Strains below this range were considered very low [Singh *et al.*, 2006; Yuen *et al.*, 2009; Ahmadzadeh *et al.*, 2015; Karton *et al.*, 2016; Maxwell *et al.*, 1997] and low magnitudes [Zanetti *et al.*, 2013; Oliver *et al.*, 2016]; high magnitudes correspond to those reported as average estimates to sustaining a concussive level injury [Rousseau, 2014; Patton *et al.*, 2013]. A very high category was included to designate impacts that put athletes at substantially higher risk and represent a 50% risk of loss of consciousness and persistent symptoms [Cournoyer & Hoshizaki, 2019; Post *et al.*, 2015]. MPS magnitudes for each condition were categorized as follows: very low= < 8%, low= 8-16.9%, moderate= 17-25.9%, high= 26-34.9%, very high= 35%+. Strain magnitude values resulting from exemplar head impact reconstructions were assigned to each head impact within their represented impact condition category, thereby assigning an MPS level to each head contact within the four primary event types. See *Exemplar Impact Grids in Appendix D* for the dynamic response values resulting from each exemplar impact and the subsequent MPS value and magnitude category.

Table 8-2: Brain tissue material properties and characteristics used for the UCDBTM components.

Material	Young's modulus (MPa)	Poisson's ratio	Density (kg/m^3)
Scalp	16.7	0.42	1000
Cortical Bone	15000	0.22	2000
Trabecular Bone	1000	0.24	1300
Dura	31.5	0.45	1130
Pia	11.5	0.45	1130
Falx and Tentorium	31.5	0.45	1130
Brain	Hyperelastic	0.499981	1040
CSF	Water	0.5	1000
Facial Bone	5000	0.23	2100

	Shear Modulus (kPa)		Decay Constant (s^{-1})	Bulk Modulus (GPa)
	G_0	G_∞		
Cerebellum	10	2	80	2.19
Brain Stem	22.5	4.5	80	2.19
White Matter	12.5	2.5	80	2.19
Grey Matter	10	2	80	2.19

8.3.4 Position Specific Brain Trauma Exposure

An exposure metric, brain strain exposure per time (BSE/T), utilizing the three characteristics of trauma was created to quantify cumulative brain strain exposure for each field position throughout each game. This metric was calculated by multiplying the number of impacts within each brain tissue strain magnitude category by its severity # (very low =1; low =2; moderate= 3; high= 4; very high =5), then multiplied by the time interval in which those impacts were experienced (very low =4; low =3; moderate =2; high =1).

8.3.5 Statistical Differences between ASF Player Positions

Nonparametric rank based Kruskal-Wallis H tests were conducted to examine whether there were statistically significant effects of player field position on impact frequency, strain magnitude, time interval between impacts, and BSE/T. Impact frequency, strain magnitude, time interval and BSE/T variables were considered as dependent variables (DV's) and eight player positions as independent variables (IV's). Frequencies, magnitudes, and intervals of confirmed head impacts resulting from the four primary event types were included in the analysis. Interval was included for games where >1 impact was documented within the same game: (QB, *n*= 24), (RB, *n*= 32), (WR, *n*= 26), (TE, *n*= 32), (OL, *n*= 32), (DL, *n*= 32), (LB, *n*= 31), (DB, *n*= 28). Post hoc Dunn adjusted by the Bonferroni correction for multiple tests were performed when significance was found. Additionally, a contingency table analysis was performed to examine the distribution differences in strain magnitude levels amongst player field position. A Bonferroni correction was applied for multiple comparisons. Statistical level was set at $\alpha = .05$ for all analysis and performed using IBM SPSS Statistics 24.0.

8.4 Results

Kruskal-Wallis H tests were conducted to examine any statistically significant effects of player field position on impact frequency, strain magnitude, time interval and cumulative brain trauma measured as brain strain exposure per time (BSE/T). Additionally, a contingency table analysis was used to determine differences in frequency distributions of strain magnitude experienced by each position.

8.4.1 Characteristics of Brain Trauma Exposure

Frequency of head impacts

A total of 3439 (2941 confirmed; 498 suspected) head impacts were documented for eight player positions during 32 regular season games (Table 8-3). Frequencies are presented per position based on total frequency, average per game, and estimated frequency for a 16-regular game season in professional ASF (excludes practices). The Kruskal-Wallis H test showed statistically significant difference in impact frequency between the mean ranks of player position, χ^2 (7) = 187.21, p = .000: QB mean rank= 43.50; RB mean rank= 150.09; WR mean rank= 56.53; TE mean rank= 170.64; OL mean rank= 200.89; DL mean rank= 213.44; LB mean rank= 134.02; DB mean rank= 58.89. Dunn's pairwise showed specifically that differences were between QB, WR, DB, and the remaining five positions (Table 8-3).

Table 8-3: Head impact frequency counts for ASF positions documented from 32 regular season games played from 2009-2015.

	Confirmed Impacts					**NFL Career**			
Player Position	Total #	Per Game (ave. ± SD)	Per Season (16 games)	**Suspected Impacts**	Pile-up	ave. yrs.	est. freq #	> # games	est. freq #
QB	73	2.3 ± 2.0	36.5	23	7	3.08	112	302	694.6
RB_{a***}	468	14.6 ± 5.4	234	186	106	2.42	566.3	226	3299.6
WR	106	3.3 ± 2.9	53	33	7	2.21	117.1	303	999.9
TE_{a***}	459	14.3 ± 6.1	229.5	34	10	2.67	612.8	270	3861.0
OL_{a***b*}	637	19.9 ± 8.3	318.5	31	15	3.67	1168.9	296	5890.4
$DL_{a***b***c*}$	706	22.1 ± 8.5	353	71	53	3	1059	282	6232.2
LB_{a***}	377	11.8 ± 4.6	188.5	82	22	3	566	278	3280.4
DB	115	3.6 ± 2.5	57.5	38	10	3.17	182	295	1062.0

* significant at p < 0.05; ** significant at p < 0.005; *** significant at p < 0.001.
a= significant difference to QB, WR & DB, b= significant difference to LB, c= significant difference to RB.

Additionally, significant differences were found between LB and OL (p = .008); LB and DL (p = .000); and RB and DL (p = .017). Independent of position, the average number of contacts a player received during game play over a 16-game season was estimated at approximately 184 impacts. Hit counts are estimated for an average professional football career and for the greatest number of games played documented in NFL player history (Table 8-3; Pro-Football-

Reference.com, 2014; 2018). Suspected and multiple (pile-up) impacts are presented for the eight positions; RB with the greatest number recorded, followed by LB and DL. RB entered a pile-up twice as many times as the closest second (DL).

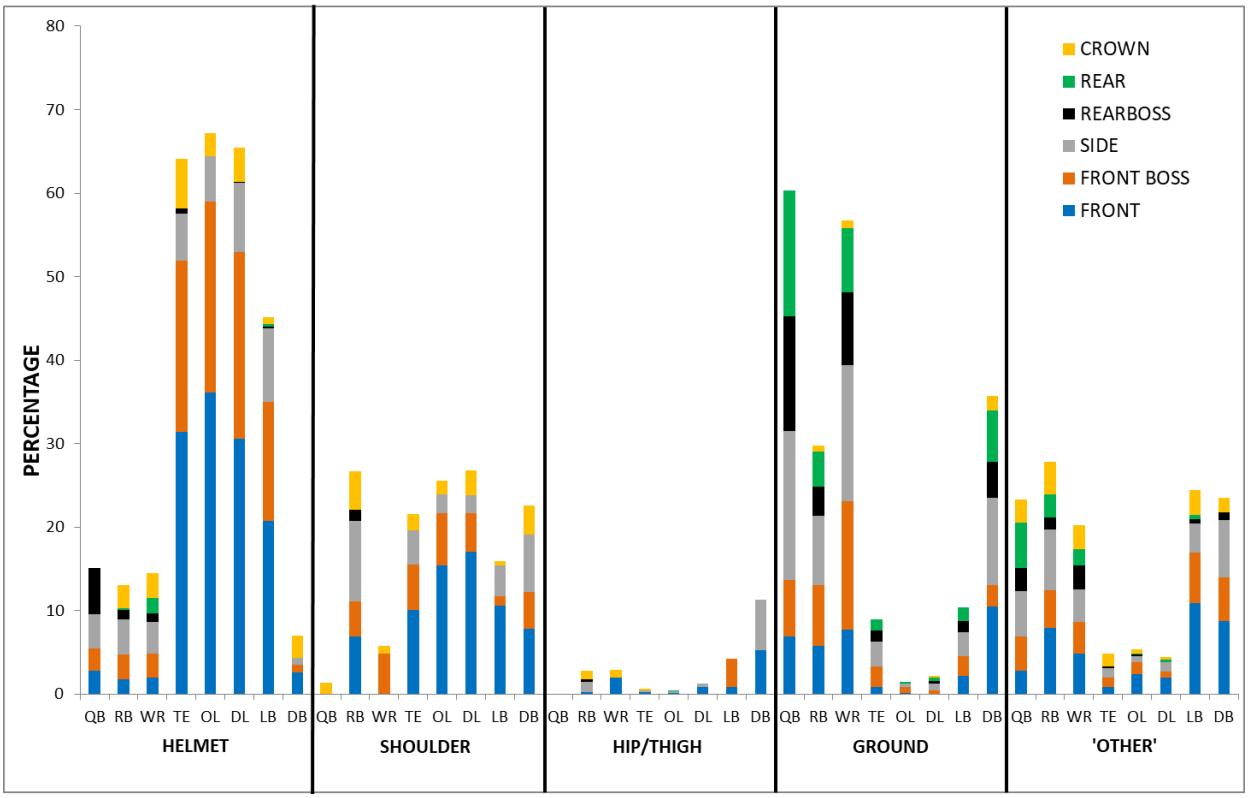

Figure 8-4: The distribution of head impact event type and head location for eight player positions in professional ASF captured from 32 regular season games. Distributions are presented as a percentage from the total number of impacts specific to each position.

With player position collapsed, helmet represent 49% of the total documented impacts. Shoulder impacts were the second most common event type with 23% from the total. The remaining two event categories accounted for the fewest documented impacts (ground = 13%, hip/thigh = 2%). 'Other' events described 13% of impacts (back = 3.4%, chest = 1.7%, stomach = 1%, arm = 2.5%, hand = 2.5%, leg =1.2%, knee = 0.6%, field goal post/wall = 0.1%). Most often LB, TE, OL and DL experience helmet impacts, and these were predominantly to the front location (Fig. 8-4). Impacts with the ground were more frequent among the QB, WR and DB positions, accompanied by a noticeable shift to include the side and rear head locations. An even distribution between shoulder and ground event types can be observed for the RB. This position also experienced recurrent head impacts to their opponents' torso represented in the 'other' category (Fig. 8-4). Side location was greatest for the RB player position.

Magnitude of brain tissue maximum principal strain

The MPS resulting from exemplar impacts for eight ASF field positions ranged from 4.6-50.6% The MPS range for each ASF position is presented in Table 8-4. MPS resulting from all exemplar impacts was further categorized into five levels of magnitude: very low= < 8%, low= 8-16.9%, moderate= 17-25.9%, high= 26-34.9%, very high= 35%+.

Table 8-4: Maximum principal strains (%) resulting from exemplar physical reconstructions of common head impacts specific to ASF field position. Results are presented as sample means. Values in square brackets indicate 95% Confidence Intervals.

Field Position	Event Type				Collapsed
	Helmet	Shoulder	Hip	Ground	
	Mean MPS with 95% CI				
QB	24.1, [15.9, 32.3]	11.9	-	27.4, [19.5, 35.3]	25.4, [19.7, 31.1]
RB	25.3, [18.7, 31.9]	16.3, [13.4, 19.2]	10.4, [4.5, 16.3]	18.0, [12.0, 24.0]	17.1, [11.8, 22.5]
WR	22.5, [0.139, 31.1]	14.1, [13.5, 14.7]	8.7, [4.9, 12.5]	25.2, [18.1, 32.3]	21.8, [16.9, 26.7]
TE	19.5, [14.4, 24.6]	17.0, [13.3, 20.7]	11.5, [3.8, 19.2]	22.7, [14.8, 30.6]	19.1, [15.8, 22.4]
OL	12.7, [8.3, 17.1]	14.1, [9.3, 18.9]	7.5, [3.7, 11.3]	20.8, [12.1, 29.5]	14.3, [11.1, 17.5]
DL	19.7, [14.0, 25.4]	17.6, [13.3, 21.9]	9.6, [0.8, 18.4]	12.5, [8.3, 16.7]	16.3, [13.4, 19.2]
LB	18.4, [14.3, 22.5]	18.3, [10.1, 26.5]	21.3, [7.6, 35.0]	17.3, [10.5, 24.1]	18.3, [14.9, 21.7]
DB	0.242, [17.8, 30.6]	18.0, [12.2, 23.8]	14.9, [0.5, 29.3]	23.5, [16.7, 30.3]	21.1, [17.1, 25.1]

Statistically significant rank mean differences in exemplar impact magnitudes with event type collapsed, were found between ASF player position (χ^2 (7) = 15.68, p = .028): QB mean rank= 172.82; RB mean rank= 123.57; WR mean rank= 139.88; TE mean rank= 128.64; OL mean rank= 92.67; DL mean rank= 109.23; LB mean rank= 122.30; DB mean rank= 138.17. Post hoc showed the significant difference was between QB and OL (p = .016).

Significant association between distribution within magnitude level and field position was shown using Pearson's chi-squared statistic in a contingency table analysis (Fig. 8-5; χ^2 (28) = 1066.27, p = .000). RB (*z*= 8.27, p=.000) and WR (*z*= 4.69, p=.000) experienced a higher percentage of 'very low' level impacts; OL showed statistically fewer 'very low' impacts (*z*= -4.30, p=.000) in comparison to the group mean. A significantly lower distribution of 'low' level impacts were found for QB (*z*= -11.46, p=.000), RB (*z*= -15.92, p=.000), WR (*z*= -8.94, p=.000), LB (*z*= -5.03, p=.000), and DB (*z*= -7.87, p=.000), and a higher percentage for OL (*z*= 12.29, p=.000) and DL (*z*= 13.56, p=.000). QB (*z*= 5.13, p=.000), RB (*z*= 13.21, p=.000), LB (*z*= 5.65, p=.000) and DB (*z*= 4.48, p=.000) were above group mean percentage for 'moderate' magnitude level impacts. 'High' level impacts accounted for a significantly larger distribution for QB (*z*= 11.87, p=.000), and the percentage of 'very high' magnitude impacts were statistically higher for QB (*z*= 6.20, p=.000), WR (*z*= 13.52, p=.000), and DB (*z*= 5.73, p=.000) when compared to the group means. The percentage of impacts for OL and DL were statistically lower for 'moderate' (*z*= -7.78, p=.000; *z*= -10.85, p=.000, respectively), 'high' (*z*= -4.96, p=.000; *z*= -4.44, p=.000, respectively), and 'very high' (*z*= -4.70, p=.000; *z*= -5.07, p=.000, respectively) magnitudes.

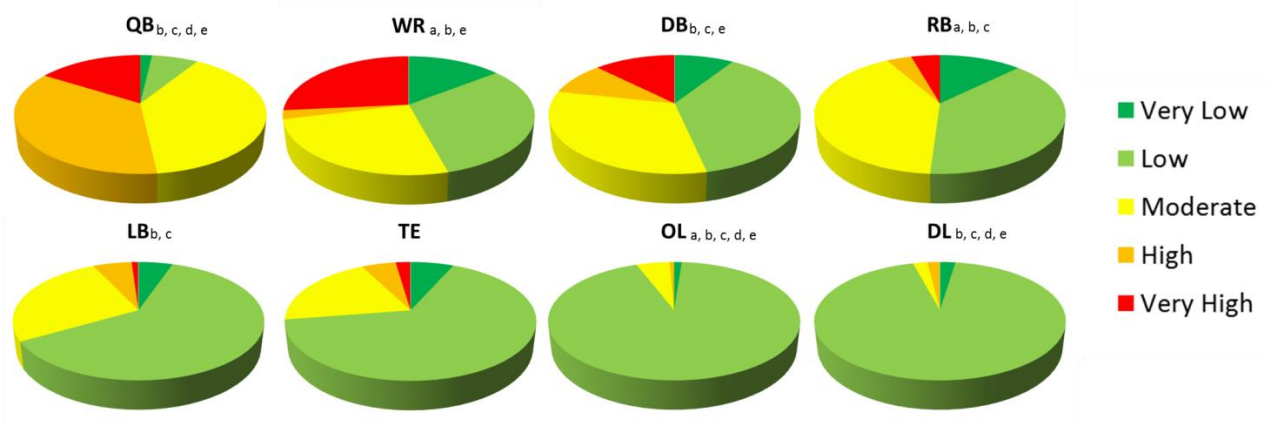

Figure 8-5: Distribution of five MPS levels of magnitude for eight player positions. Distributions are based on physical reconstruction and finite element analysis from the total frequency count documented as confirmed head impacts of 4 common event types from 32 games.
All are significant at p < 0.001.
a=significant difference in 'very low' (<8% MPS), b= significant difference in 'low' (8-16.9% MPS), c= significant difference 'moderate' (17-25.9% MPS), d= significant difference in 'high' (26-34.9% MPS), e= significant difference in 'very high' (35+ % MPS).

Time interval between head impacts

Time between impacts is presented as averages per game, both as an overall time and distributed by MPS magnitude level (Table 8-5). Evidence of statistically significant differences in time interval between the mean ranks of player field positions was provided by the Kruskal-Wallis H test (χ^2 (7) = 94.49, p = .000); QB mean rank= 178.08; RB mean rank= 120.19; WR mean rank= 155.42; TE mean rank= 93.66; OL mean rank= 62.09; DL mean rank= 46.19; LB mean rank= 118.11; DB mean rank= 153.55. Post hoc analysis showed time interval (collapsed magnitude) for OL and DL was different compared to all remaining positions excluding TE (Table 8-5). The TE position showed statistical difference to QB (p = .001), WR (p = .013), and DB (p = .019).

8.4.2 Cumulative Brain Trauma Exposure

Statistical differences in the mean ranks of BSE/T were found between the ASF field positions (χ^2 (7) = 182.34, p = .000); QB mean rank= 48.69; RB mean rank= 143.39; WR mean rank= 57.70; TE mean rank= 171.25; OL mean rank= 202.30; DL mean rank= 213.38; LB mean rank= 134.27; DB mean rank= 57.03. Specifically, QB, WR and DB experience significantly different cumulative trauma to the remaining five field positions (p = .000). Cumulative BSE/T for LB and RB was statistically different to BSE/T estimated for OL (p = .007; p = .041) and DL (p = .001; p = .004). Three unique cumulative BSE/T profiles were identified. QB, WR and DB (profile 1) experience, on average, fewer overall impacts, typically of high strain magnitude with longer time intervals (Fig. 8-6). BSE/T documented for LB and RB, (profile 2) consist of all levels of MPS magnitude of mid-range impact frequency and intervals. Finally, OL and DL (profile 3) positions experience the highest frequency of head impacts within short time intervals, predominately of low strain magnitude (Fig. 8-6). The TE position is unique in that the cumulative BSE/T was not significantly different to either field positions in profile 2 or profile 3, resulting in an overlap between the two profiles.

T**able 8-5**: Average time interval (min) between impacts and head impact frequency count (#) per game, distributed by MPS magnitude level. Interval per magnitude level was calculated only for games in which >2 head impacts of the respective magnitude was experienced during the same game. The number of games per position for interval calculations is indicated with *n* values. Averages are presented (± SD). Significance is presented for differences in interval between positions.

		Magnitude Collapsed		**Magnitude Category (MPS)**									
				<8.0%		**8.0-16.9%**		**17.0-25.9%**		**26.0-34.9%**		**35.0%+**	
			n		*n*		*n*		*n*		*n*		*n*
QB$_{a***b***c**}$	#	1.75 ± 1.72		0.03 ± 0.18		0.13 ± 0.34		0.69 ± 0.86		0.63 ± 0.91		0.28 ± 0.52	
	min	30.3 ± 14.65	*13*	--		--		53.88 ± 28.50	*6*	28.53 ± 19.03	*5*	30.33	*1*
WR$_{a***b***c*}$	#	2.59 ± 2.28		0.38 ± 0.71		0.81 ± 0.93		0.66 ± 0.94		0.06 ± 0.25		0.69 ± 0.86	
	min	25.68 ± 24.18	*19*	47.61	*1*	29.44 ± 13.47	*7*	35.39 ± 25.56	*5*	--		39.42 ± 23.34	*4*
DB$_{a***b***c*}$	#	2.75 ± 2.33		0.25 ± 0.67		1.03 ± 1.20		0.88 ± 1.10	*7*	0.25 ± 0.44		0.34 ± 0.70	
	min	24.69 ± 21.53	*19*	16.29 ± 23.02	*2*	37.78 ± 30.51	*8*	48.61 ± 38.67		--		66.68 ± 0.13	*2*
LB$_{a***b*}$	#	8.91 ± 3.49		0.47 ± 0.72		5.47 ± 2.76		2.34 ± 1.52		0.53 ± 0.76		0.09 ± 0.30	
	min	13.16 ± 7.19	*31*	64.69 ± 34.08	*4*	21.21 ± 22.42	*31*	29.82 ± 18.31	*22*	43.94 ± 48.21	*5*	--	
RB$_{a***b**}$	#	10.59 ± 4.05		1.34 ± 1.33		4.06 ± 2.54		4.13 ± 2.17		0.59 ± 0.71		0.47 ± 0.67	
	min	13.25 ± 6.90	*32*	37.47 ± 19.76	*10*	32.05 ± 27.82	*31*	25.78 ± 14.42	*27*	48.90 ± 34.04	*4*	61.67 ± 37.96	*3*
TE	#	13.66 ± 6.31		0.22 ± 0.42		10.41 ± 5.47		2.00 ± 1.68		0.72 ± 0.92		0.31 ± 0.59	
	min	10.37 ± 5.20	*32*	--		14.77 ± 12.41	*31*	36.37 ± 25.68	*17*	32.23 ± 11.43	*6*	33.74 ± 46.53	*2*
OL	#	18.84 ± 8.33		0.22 ± 0.49		17.53 ± 8.06		0.97 ± 1.75		0.13 ± 0.34		--	
	min	7.81 ± 4.61	*32*	19.31	*1*	8.30 ± 5.91	*31*	24.28 ± 14.76	*7*	--		--	
DL	#	21.19 ± 7.83		0.50 ± 0.67		19.81 ± 7.38		0.47 ± 0.76		0.41 ± 0.71		--	
	min	6.29 ± 2.13	*32*	14.25 ± 9.22	*3*	6.73 ± 2.59	*32*	54.99 ± 29.29	*3*	80.69 ± 24.80	*4*	--	

* significant at $p < 0.05$; ** significant at $p < 0.005$; *** significant at $p < 0.001$.
a= significant difference to DL, b= significant difference to OL, c= significant difference to TE.

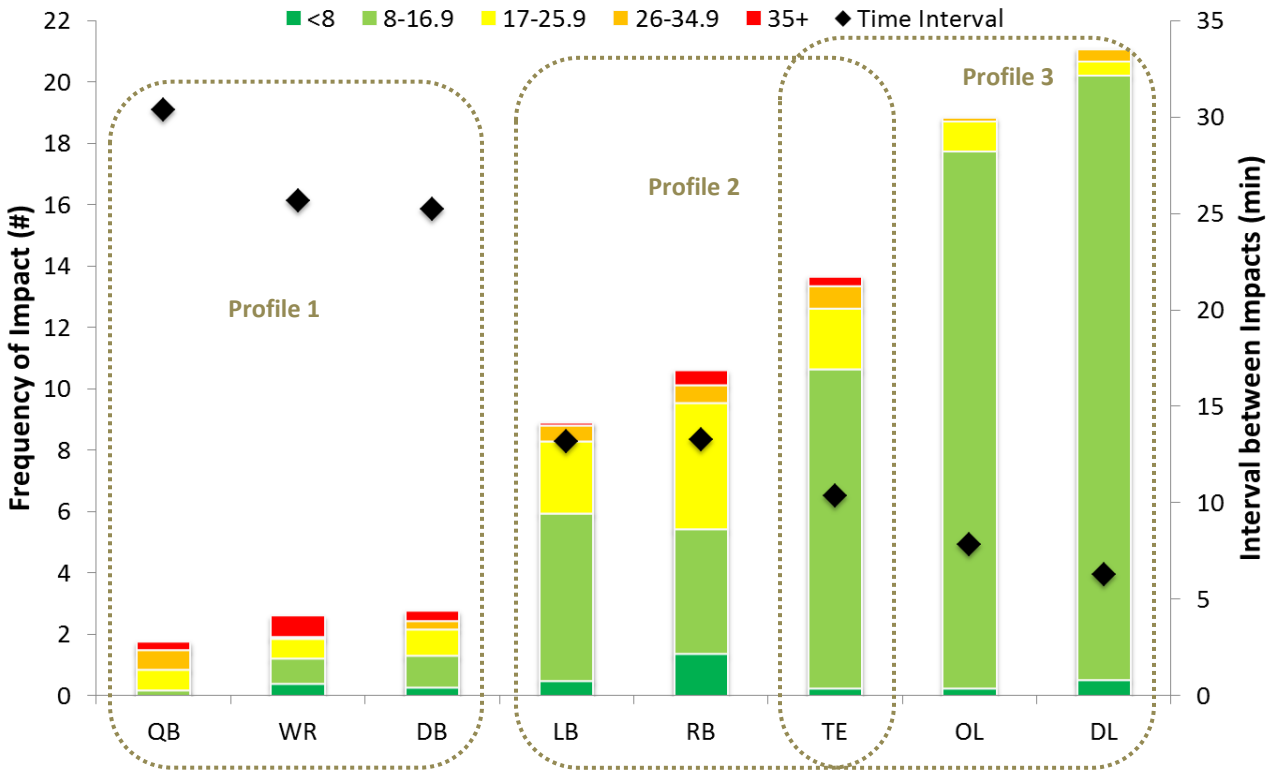

Figure 8-6: Position specific brain trauma profiles presented per game. Average head impact frequency count distributed by MPS magnitude. Interval is presented as an average time (measured in minutes) between impact frequency total (magnitude collapsed).

8.5 Discussion

The complex nature of brain injury and risk associated with history, predisposition, symptom expression, and repetitive exposure results in an uncertainty on how to manage trauma to the brain. Focusing on one head impact metric to predict injury has proven challenging and typically results in low injury prediction sensitivity, particularly when using impact sensors to measure reliable biomechanical metrics [Post & Hoshizaki, 2012; Greenwald *et al.*, 2008]. This research has employed a novel method of measuring head and brain trauma that capture the risk profile in ASF. Difference in the characteristics of brain trauma between player field positions in National Football League was described using this method. This study has provided a measure of brain trauma (frequency and strain magnitude) exposure for each position over time (interval).

Video analysis from this study yielded lower impact frequencies over a season in comparison to previous reports using impact sensors [Martini *et al.,* 2013; Crisco *et al.,* 2011], which included impacts during both games and practices. Over the course of a 12-game season collegiate level players wearing helmet sensors report an average of 128 impacts per player, comparable to the present findings [Crisco *et al.,* 2012]. In this sample, an average impact frequency per game ranges from 2.3 – 22.1 depending on position. This analysis yielded lower impact frequencies specific to position excluding RB, TE, and OL [Martini *et al.,* 2013; Crisco *et al.,* 2010; 2011]. Interestingly, the TE and RB positions experienced higher impact frequencies in this study, perhaps owing to their multiple roles on the field. This may help describe why the WR impact frequencies are lower than those reported by Crisco and associates [2010; 2011]. Their studies do not include frequency data for the TE position, and therefore this position could have been classified as either a receiver or a lineman, thereby increasing the count. Most notable are the lower count estimations for the QB and DB. This discrepancy may be explained in a number of ways: as missed impacts from being limited to those within camera view, the tendency of impact sensors to over report hit counts, or differences in play between collegiate, high school, and professional level football. The OL and DL positions sustained the highest number of impacts throughout a game; predominantly from collisions to the top/front of the head (Fig. 8-4) which has been associated with detectable changes in the dorsolateral prefrontal cortex after asymptomatic injury [Talavage *et al.,* 2014].

Based on the 32 games analysis the average NFL football athlete may experience upwards of 1000 impacts from game play throughout their career, with closer to 6000 head impacts estimated for the greatest number of games played on record (Table 8-3). These estimates account for professional level game play and not the impact history of the athlete, where length of career and age of exposure influence injury risk [Alosco *et al.,* 2017b; McKee *et al.,* 2013; Stamm *et al.,* 2015a, 2015b], and may, in addition to genetic and environmental factors, partly explain why not all former ASF athletes show signs of long-term clinical dysfunction [Bieniek *et al.,* 2015; McKee *et al.,* 2013; Casson *et al.,* 2014]. Reports identifying possible risks however are limited in describing the level of tissue deformation associated with common impacts experienced during a game [Talavage *et al.,* 2014; Bazarian *et al.,* 2012; Breedlove *et al.,* 2012; Cubon *et al.,* 2011]. Given that serum biomarker levels of axonal injury associate with higher

hours of contact [Oliver *et al.,* 2016], a better understanding of what levels of trauma associate with game play provides a useful analysis for injury risk management strategies.

Impact magnitudes obtained from the use of helmet impact sensors consistently report averages in the vicinity of 20 to 30 g and 1500 to 2000 rad/s^2 for linear and rotational head accelerations, respectively [Martini *et al.,* 2013; Crisco *et al.,* 2011; 2012; Campbell, 2014; Mihalik *et al.,* 2007; Broglio *et al.,* 2013]. These averages are found across all players presenting little separation among them. Peak head accelerations alone do not account for such loading characteristics as impact time, history and duration and therefore offer limited information with respect to brain tissue response [Rowson *et al.,* 2011]. QB, WR, and DB experienced the lowest impact frequencies but were among the positions most likely to sustain impacts of higher strain levels, largely from head to ground contact (Fig. 8-4), and are among those most vulnerable to sustaining 'extreme' hits [Campbell, 2014] and concussions [Pellman *et al.,* 2004]. Close to 95% of impacts received by OL, DL and TE were estimated at below 17% strain and under 50% probability of concussion risk (Table 8-4; Fig. 8-5) [Kleiven, 2007; Zhang *et al.,* 2004]. Although the strain levels are considered relatively low, repetitive low level impact frequencies may exhibit structural, functional, and metabolic changes that are associated with long-term mental health concerns reported by current and retired football athletes [Bazarian *et al.,* 2014; Amen et al, 2016; Lin *et al.,* 2015; Poole *et al.,* 2015; Coughlin *et al.,* 2017; Strain *et al.,* 2016].

Few impacts were recorded below 8 % MPS across all positions. Pile-up situations presumably would consist of this level of impact although the nature of this scenario is such that impacts could not be confirmed and counted (Table 8-3). As little as 5-15% strain levels have been associated with functional impairment of signal transmission in the absence of structural damage [Margulies & Thibault, 1992; Bain & Meaney, 2000; Singh *et al.,* 2006; Yuen *et al.,* 2009; Elkin & Morrison, 2007]. All impacts documented in this investigation were at or above these strain levels. In vitro strains of 5% exhibit the minimum level of injury required to observe minor undulations and induce a calcium influx [Yuen *et al.,* 2009]. Observed undulations are caused by the immediate breakage and buckling of microtubules that are a consequence of mechanical failure [Tang-Schomer *et al.,* 2010; Smith *et al.,* 1999]. Ahmadzadeh et al. [2015] have also modeled macroscopic strains of 5% causing microscopic changes in the form of protein unfolding and microtubule rupture, a consistent neuropathology of tauopathy and brain diseases [McKee *et al.,* 2013; Omalu *et al.,* 2005; 2006].

Time interval between impacts showed an inverse relationship with impact frequency (Fig. 8-6). This result was expected, since a greater number of impacts throughout a game means that each impact is of closer proximity to the next. The estimates show that impacts are experienced on average every 6-30 minutes during game play. Oliver and researchers [2016] have demonstrated that elevations in biomarkers indicative of neuronal damage consistently increase at various time points throughout a season in ASF starter athletes (20-40+ plays/game), a population most represented (starters) in the current study. Moreover, these measurements indicate that neurobiological recovery can take weeks or months, even with cessation of activity and head trauma [Neselius *et al.,* 2012; Oliver *et al.,* 2016; Bazarian *et al.,* 2014]. The relationship between interval and frequency becomes less predictable when examined individually at each magnitude level (Table 8-5). Although limited in sample size the QB and TE showed the shortest time interval between impacts of high strain magnitudes (>26% MPS). Research involving animal models has demonstrated the importance of interval between high magnitude impacts by describing an inconsistency between clinical symptom recuperation and neurobiological recovery [Neselius *et al.,* 2012; Briggs *et al.,* 2016]. Although these studies evaluate the effects of much longer durations between impacts than in the current study, the very short intervals reported here may influence the cumulative effect of asymptomatic impacts. Neurobiological damage can exist with no clinical symptoms and without a sufficient rest period there is an increased risk for cumulative injury [Neselius *et al.,* 2012; Oliver *et al.,* 2016]. The density to which asymptomatic impacts are experienced can also contribute to collective trauma, ultimately producing symptomatic injury [Broglio *et al.*, 2017].

The present study identified three profiles based on their cumulative trauma exposure (Fig. 8-6). These exposure profiles are a result of their position specific impact susceptibilities. Positions may be exposed to high magnitude impacts of lower frequency (profile 1), or low magnitude of higher frequency (profile 3), consistent with previous reports [Crisco *et al.,* 2011]. An additional profile, profile 2, consisting of player positions that are susceptible to all levels of magnitudes at relatively high frequencies has also been identified. Positions that are recognized as more vulnerable to high magnitude events, such as DB, WR and QB, report the highest incidence of concussions [Nathanson *et al.,* 2016]. Although lowest in frequency count, over 90% of the impacts documented for the QB were above moderate strain magnitudes, putting them above the 50% probability of concussion, essentially each time they are hit [Kleiven, 2007; Zhang *et al.,*

2004]. Sustaining a concussion does not inevitably lead to long-term mental disorders, nor does experiencing a greater number of concussive events consistently result in more severe cognitive decline among athletes [McKee *et al.,* 2013]. This type of trauma, very few hits of high strains, may speak to the exhibition of immediate signs of acute injury, however coupled with sufficient recovery time could be less perilous for long-term damage [Kamins *et al.,* 2017]. OL/DL positions experienced the highest frequency of lowest magnitude impacts that were experienced on average every 6-7 minutes during game play. Repetitive trauma associates with the inability to recover from injury, mental health disorders and, in most severe cases, degenerative brain disease years after head trauma [Bazarian *et al.,* 2014; Hart *et al.,* 2013; Abbas *et al.,* 2015]. Consequently, these positions are among the highest for confirmed cases of CTE [Mez *et al.,* 2017]. Profile 2, perhaps the most dangerous, seems to have a less predictable trauma exposure, as they are exposed to relatively high impact frequency counts and are vulnerable to higher impact magnitudes. The TE position showed an overlap between the profile 2 and profile 3, perhaps owing to their multiple roles on the field. The RB position too, is unique in that they represent those players responsible for both running and passing plays, and is reflected in their exposure profile. With a low number of players on the field in a TE and/or RB position at any one given time, they are considered among the most risky positions for concussion and continuing neurological damage [Nathanson *et al.,* 2016; Mez *et al.,* 2017]. In light of the current distribution of various forms of diagnosed head injury among positions, one can appreciate how an exposure profile assists in the understanding of how tissue injury is manifested and expressed.

8.6 Conclusion

Few studies have examined and reported head trauma as a cumulative exposure metric based on multiple characteristics. These studies have predominately derived data from self-reported history and/or head impact sensors, where both have correlated with objective clinical measures such as imaging and biomarker concentrations [Alosco *et al.,* 2017a; Montenigro *et al.,* 2017; Bahrami *et al.,* 2016; Urban *et al.,* 2013]. The current study enhances our understanding by providing tissue deformation values associated with a spectrum of common head impacts experienced in professional football, giving contextual meaning to trauma loads experienced on the field. The unique trauma profiles provide insight into environments that create brain injury expressed as acute symptoms or chronic mental health disease, behavior disorders and cognitive

instability. The three profiles described in this study support the notion that brain trauma and injury risk can be described using various combinations of impact characteristics.

The range in impact frequency, strain magnitude and time between impacts reported in this study demonstrates that each profile can contribute to large amounts of brain trauma. However, the combination of the characteristics of trauma exposure may present as different injuries. Based on the intrinsic nature of ASF one can appreciate that the athletes studied here may be at risk for a full spectrum of injury, regardless of playing position. The results, however, provide cognizance of the relationship between tissue injury and specific outcomes. Understanding the interaction of impact frequency, magnitude and time interval could provide a measurement tool that, when applied universally, provides an opportunity to estimate risk and make informed decisions regarding prevention strategies and public health policy within a myriad of sporting environments.

Scientists, neurologists and clinicians support integrating the biomechanics of head contact, with neuroimaging, fluid biomarkers, genotype and clinical outcomes in order to provide exposure to risk context. Establishing exposure indices to guide legislation and intervention strategies and provide league officials, athletic directors, coaches and athletes information to make decisions to better manage brain trauma in ASF.

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9 Influence of American-style Football Field Position on Regional Distribution and Volume of Strain from Common Head Impacts

9.1 Abstract

Current and former football athletes present with high rates of neurological injury. Symptom expression and cognitive impairments reflect the possible widespread brain damage. Biomechanical assessments using tissue strain have historically focused on mild to moderate impact events; however more minor events may also have deleterious effects on brain function and cognition. Regional distribution of MPS and two crticial thresholds of CSDM of 8% and 17% were measured from common head impacts experienced by eight field positions during regular season game play. Differences in CSDM were observed between field position which was a reflection of the variation in impact magnitudes and frequencies they encounter. Line positions experience impacts that cause low strains involving very little brain volume of predominantly gray matter cerebrum, however were at the highest frequencies. Skill positions experienced higher magnitude impacts, demonstrated higher brain volume involvement, and more often reaching the deeper white matter structures. Temporal and frontal lobe were the most vulnerable regions irrespective of player position, consistent with anatomical structures and pathophysiological findings of brain impairment and dysfunction. Frequency and magnitude were influential in dictating how often these regions were placed under strain, thus influencing specific field position vulnerabilities to regional strain. To better prevent neurological injury, both impact magnitude and frequency should to me managed specifically tailored to field position.

9.2 Introduction

Head injury has become commonplace in contact sports, particularly in American style football (ASF) where hitting the head is an intentional part of game play. There is increased awareness of the potential side effects of continued exposure to head trauma in ASF as concussion diagnosis, neurological impairments and brain disease found pathologies continue to be described [Mez *et al.,* 2017 Mayinger *et al.,* 2018; Nathanson *et al.,* 2016]. This has created a demand for improved prevention and management strategies. It is common to use the immediate presentation of symptoms to establish injury, and their cessation to deem an individual recovered. However,

with estimates indicating that less than half of concussions are detected, reported and diagnosed, this approach to identifying brain injury is inadequate [McCrea *et al.,* 2004; Harmon *et al.,* 2013; Meehan *et al.,* 2013]. Without symptomatic expression and/or the cessation of acute symptoms, repetitive trauma can alter the structure and function of brain cells reflecting widespread dysfunction and damage [Coughlin *et al.,* 2015; Mayinger *et al.,* 2018; Amen *et al.,* 2016; Briggs *et al.,* 2016; Neselius *et al.,* 2012]. Long-term risks are often not realized until a latency period between the trauma and the clinical presentation of brain injury has passed [Gavett *et al.,* 2011; Omalu *et al.,* 2011, Stern *et al.,* 2013]. Recent imaging and biomarker concentrations techniques with the sensitivity to distinguish current and former ASF athletes from a healthy cohort show immediate changes indicative of tissue injury. Exposure to repeated head impact trauma leads to a cumulative effect on brain tissue and reported association with a number of cognitive impairments. These impairments are usually characteristic of the areas of the brain vulnerable to injury and the extent of brain damage.

Measurable neurocognitive and neurophysiological deficiencies have been detected in former ASF athletes [Talavage *et al.,* 2014; Amen 2016; Hampshire *et al.,* 2013]. Amen and coworkers reported lower cerebral perfusion in 36 brain regions, many involving the frontal and temporal lobes [Amen *et al.,* 2016]. Participation in just one season of football associated with deficits primarily presenting in visual working memory and altered activation in the dorsolateral prefrontal cortex, where changes were connected with a significantly higher number of impacts to the top-front of the head [Talavage *et al.,* 2014]. In addition, NFL retired players showed pronounced hyperactivation and hypoconnectivity of the dorsolateral frontal and frontopolar cortices, indicative of executive dysfunction [Hampshire *et al.,* 2013], and is consistent with other reports on age of exposure and later-life impairments [Montenigro *et al.,* 2017; Stamm *et al.,* 2015]. Not all study findings are limited to the frontal cortices, Breedlove *et al.,* [2012; 2014] showed that a large number of asymptomatic athletes exhibited neurophysiological changes in-season, where the 10 most frequent locations were widespread including all brain lobes.

White matter microstructure alterations using diffusion tensor imaging has been reported by multiple researchers examining the effects of repeated head impacts in football players of various levels of play [Bahrami *et al.,* 2016; Bazarian *et al.,* 2012; 2014; Kuzminski *et al.,* 2018]. Typically differences between pre and post season measurements of mean diffusivity and fractional anisotropy are found in football players, documented in several brain regions and have

been coupled with poorer cognitive performance associated with verbal learning, memory and visual memory [McAllister *et al.,* 2014; Kuzminski *et al.,* 2018]. Many athletes suffer undiagnosed changes in brain function and continue playing seemingly unimpaired, which may exacerbate an existing deficit. In a study involving 28 NFL former athletes, white matter tract changes were found to correlate with increased depression [Strain *et al.,* 2013[. Similarly, in 30 retired professional players, a life time of concussion history correlated with severity of depressive scores, predominantly via cognitive symptoms [Didehbani *et al.,* 2013].

Playing football associates with higher concentrations of blood biomarkers indicative of axonal damage. Higher concentrations are often measured in those exposed to a higher load of repeated head impacts, specifically in starter athletes, and those identified as 'higher' impact groups [Oliver *et al.,* 2016; Kawata *et al.,* 2017]. Similar findings have been reported in former players, where a cumulative head impact score predicts later-life plasma total tau concentrations. Higher exosomal tau is associated with worse performance on memory and psychomotor speed [Alosco *et al.,* 2017a; Stern, 2016]. These outcomes reflect a cumulative effect of brain trauma which may be represented with the volume of tissue undergoing strain in frequent head impacts, where the brain is given little opportunity to recover overtime [Iliff *et al.,* 2012; 2013].

The mechanisms leading to tissue injury following various levels of brain trauma are not fully described and continue to be under investigation. Measures of local deformation, particularly strain, has been linked to structural damage of axons leading to neurodegeneration in *in vivo* and *in vitro* TBI models [Smith *et al.,* 1999; Tang-Schomer *et al.,* 2010; Morrison *et al.,* 2003; Elkin & Morrison, 2007]. Smith et al. [1999] demonstrated that axonal stretch causes undulations along the axon where despite regaining its original shape, the damage remains and eventually leads to apoptosis. If stretch is repetitive, a threshold of only 5% shows ionic perturbations caused by local swelling and impairment of axonal transport, and minor undulations are observed [Yeun *et al.,* 2009; Gennarelli *et al.,* 1998]. Biomechanical investigation using finite element modeling have also utilized tissue strain to draw relationships between the mechanical load and the outcome of injury [Kendall, 2016; Oeur, 2018; Post, 2013; Post *et al.,* 2014; Viano *et al.,* 2005], and has been associated with changes in indices of white matter integrity [McAllister *et al.,* 2012]. Inquiries specific to location of tissue response have been predominantly concentrated on concussive symptoms and severe TBI lesions. High strains have been demonstrated in the temporal lobe, and more specifically, the highest values consistently associate with the auditory

association area from concussive reconstructions of differing events, however regions showing the highest strains become more focal and convergent with TBI lesion locations [Kendall, 2016; Post, 2013; Viano *et al.,* 2005].

Cumulative strain damage measure, measures an accumulative volume of brain tissue enduring a critical level of tensile strain [Bandak & Eppinger, 1994; DiMasi *et al.,* 1995; Takhounts *et al.,* 2003]. Research has typically used this metric to predict concussion and diffuse brain injury against 'no injury' cases. Takhounts et al. estimated 0.55 of the brain needs to experience a strain of 15% for a 50% probability of concussion. Similarly using CSDM of 10%, Giordano & Kleiven [2014] reported a range of 0.09-0.23 brain volume for a 50% injury probability within various brain locations. This mechanical measure may indicate that as more tissue is traumatized, the potential for brain damage is exacerbated. CSDM may be useful to evaluate trauma from impacts common to play and based on environmental contexts observed through player field position.

Unlike many team sports, the role and skill level of each field position in ASF is very different to one another creating unique and different environments. Each player position is exposed to, and experiences specific characteristics of brain trauma. Differences amongst positions are reported in the documented rates of specific injury outcomes [McKee *et al.,* 2013; Mez *et al.,* 2017; Nathanson *et al.,* 2016] and in the vulnerability to head impact locations, frequencies and event types [Crisco *et al.,* 2010; Campbell, 2014]. Offensive line report returning to play and full contact practices after experiencing 'dings' and while symptomatic more often than most other positions [Baugh *et al.,* 2015]. Clark et al. [2018] showed that players in non-speed positions with a history of 3 or more concussions had more damage to their frontal white matter compared to those with 1 or less. Further speed positions with a history of multiple concussions did not show damage to the same degree. The authors suggest that position plays an important role in acquiring brain damage.

These studies have not examined which areas of the brain are vulnerable to strains, and to what extent strains are experienced throughout the brain based on common head impacts. An understanding of how different environments of trauma create and influence risk of brain damage is also poorly understood. The aim of the current study is to examine brain trauma experienced by specific field positions in terms of cerebral distribution of peak strain, and the volume of brain tissue undergoing strain from common head impacts. The results will inform

prevention strategies by better connecting the biomechanical characteristics of trauma to altered brain function and possible long-lasting neuropathology.

9.3 Methods

9.3.1 Video Observation

Game video from 32 regular-season professional ASF games consisting of one game played by each league team from 2009-2015 were viewed. All head contact was documented for one player in each of eight field positions including; QB, RB, WR, TE, OL, DL, LB, and DB. Each head impact was categorized based on event type, head location, and velocity level. Inbound velocity was calculated using Kinovea software (version 0.8.20) by establishing the distance separating the player's head from the contact surface (i.e. opponent shoulder) three to five frames prior to the impact. Collision (helmet, shoulder, hip/thigh), and fall (ground) velocities were calculated using field lines and video recording speed as described in a number of earlier studies [Rousseau, 2014; Post *et al.*, 2018; Cournoyer, 2019; Karton *et al.*, 2019]. All impacts were categorized into five velocity levels: Collisions; very low = <2.0 m/s, low = 2.1-4.5 m/s, moderate = 4.6-7.0 m/s, high = 7.1-9.5 m/s, very high = 9.6+ m/s, Falls; very low = <2.0 m/s, low = 2.1-4.0 m/s, moderate = 4.1-6.0 m/s, high = 6.1-8.0 m/s, very high = 8.1+ m/s. A close up view was used to determine event type and head location. Head impact locations were categorized as front, front boss, side, rear boss, rear and crown and were labelled using the reference system illustrated in Fig. 8-2 and described in *Section 8.3.2*. Exemplar impacts were identified to represent each possible permutation defined by velocity level X head location X event type experienced by each of the eight positions. This resulted in 249 head impact event exemplars. Table 9-1 presents the exemplar event type classification for each field position. Frequency of each condition was documented.

9.3.2 Physical Reconstructions and Finite Element Modeling

Physical reconstructions were performed using the exemplar impacts for four common event types; helmet, shoulder, ground and hip/thigh. A pneumatic linear impactor and a drop rig (falls) were used to replicate the collision and fall events, respectively. A helmeted 50^{th} percentile adult male Hybrid III head form outfitted with nine single-axis Endevco 7264C-2KTZ-2-300

accelerometers mounted in a 3-2-2-2 accelerometer array [Padgaonkar *et al.*, 1975], with attached unbiased neck form, was used for reconstructions. A description of the equipment, impact procedures, and collection system are found in *Section 8.3.2*.

Table 9-1: Exemplar conditions of each event type specific to eight player field positions documented from 32 regular season games.

Field Position	***Event Type***				***# Exemplar***
	Helmet	***Shoulder***	***Hip***	***Ground***	
QB	5	1		10	***16***
RB	14	13	6	16	***49***
WR	9	2	3	14	***28***
TE	11	11	3	12	***37***
OL	7	8	3	5	***23***
DL	11	9	3	8	***31***
LB	10	9	3	10	***32***
DB	5	9	4	15	***33***
Total #	***72***	***62***	***25***	***90***	***249***

Linear and rotational head form acceleration time histories from the physical reconstructions were used as input to the University College Dublin Brain Trauma Model (UCDBTM) to describe the distribution and volume of intracranial strain experienced by eight ASF positions. The UCDBTM is a human brain finite element model developed using a computed tomography scan of a male cadaver and material properties described in the literature and presented in Table 8-2 in *Section 8.3.3* [Kleiven & von Holst, 2002; Ruan, 1994; Willinger *et al.*, 1995; Zhou *et al.*, 1996]. The components of the UCDBTM are described in more detail in *Section 8.3.3.* To evaluate strain distribution the brain model was segmented into four regions; frontal, temporal, parietal and occipital lobes as each region has distinct functionality (Fig. 9-1). Many frontal lobe processes involve important cognitive skills and higher mental processing such as abstract thinking, decision making, emotional expression, impulse control and problem solving. It is also involved in language output, memory and some motor function.

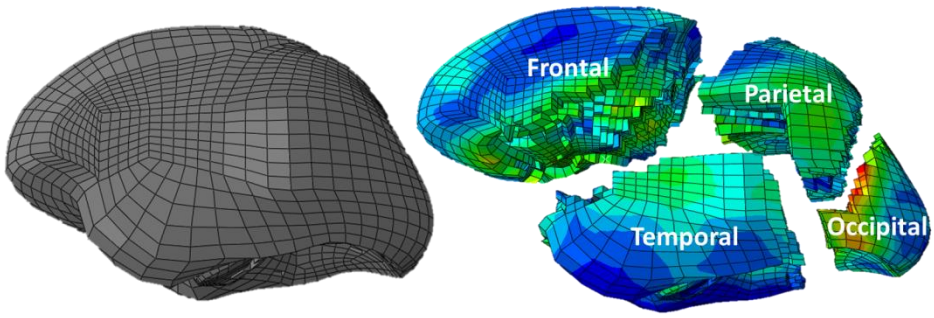

Figure 9-1: UCDBTM segmented into four brain lobes.

The parietal lobe predominantly integrates sensory information, such as spatial sense, navigation, and perception and touch primarily with the visual system. This area is also highly involved in language processing. Auditory perception and processing are predominantly done by neurons within the temporal lobe. Visual processing and interpretation are performed in the occipital lobe which includes, but is not limited to, identifying colour, contrast and object recognition [Miller & Cummings, 2006; Druback, 2000]. Peak MPS was calculated in each brain lobe. Each impact was assigned a level of MPS magnitude in each lobe based on the peak strain experienced in each respective region: 1 (Low) = <17%, 2 (Moderate) = 17-25.9%, 3 (High) = 26%+. CSDM was calculated to evaluate global tissue volumetric percentages exceeding critical levels of MPS. CSDM of 8% and 17% within the cerebrum were included the represent a range of tissues response of both asymptomatic and symptomatic impact severities [Kleiven, 2007; Zhang *et al.*, 2004; Patton *et al.*, 2013; Rousseau, 2014; Zanetti *et al.*, 2013; Karton *et al.*, 2016]. Additionally, cumulative strain was then examined in the context of impact frequencies documented that incurred >0.5 and >0.10 of the brain's volume within the cerebrum, gray matter cerebrum and white matter cerebrum for both CSDM 8% and CSDM 17%. Impact frequencies incurring <0.5 of the brains volume within the cerebrum, gray matter cerebrum and white matter cerebrum was calculated for CSDM 8%.

9.3.3 Statistical Analysis

All head impact conditions categorized as one of four primary event types were included in the analysis. Regional distribution of strain throughout four brain lobes was evaluated with a contingency table analysis using a chi-squared statistic. A significance level of $\alpha = .05$ was set,

with Bonferroni correction applied for multiple comparisons. Shapiro-Wilk (<2000 elements) and Kolmogorov-Smirnov tests (2000+ elements) deemed non-normality of the distribution of CSDM for the exemplar data set, and the frequency of impact data set, respectively. Non-parametric rank based Kruskal-Wallis H tests were performed to examine significant effects of ASF field position on the CSDM exceeding 8% and 17% MPS, in the cerebrum, gray matter, and white matter. A significance level of $\alpha = .05$ was set, and post hoc Dunn adjusted by the Bonferroni correction for multiple tests were performed. IBM SPSS Statistics 24.0 software was used for analysis.

9.4 Results

9.4.1 Impact Conditions

Documentation of 2941 head impacts was compiled from video observation. 2547 head impacts were categorized as one of the four common event types, and therefore included in the analysis. Half of the total impacts recorded were helmet to helmet (49%), followed by head impacts to the shoulder (23%), ground (13%) and hip/thigh (2%) impacts. All remaining impacts were documented as 'other'. Individual proportions of event type varied based on field position. Impact frequencies per field position are presented in Table 9-2. Impacts to the front of the head were most common to TE (43.4%), OL (54.2%), DL (50.4%), LB (45.1%) and DB (34.8%), followed by front boss and side locations. Impacts the side of the head are most often experienced by RB (30.8%) and QB (27.4%) positions. This was closely followed by front (22.4%), front boss (19.0%) and crown (13.0%) for RB and rear boss (21.9%) and rear (20.5%) for QB. The WR most often sustained impacts to the front boss (26.9%) and side (24.0%) of the head, followed by a nearly even distribution among the remaining locations. Impact locations are closely related to the type of event, where front and crown locations are common to collisions, with a shift to the side and rear locations were observed during falls (Fig. 8-4; *Section 8.4.1*).

Table 9-2: Impact frequency (#) and percent distribution (%) for each event type documented for eight field positions throughout 32 regular season games.

		Common Event Types				Categorized as 'Other'					
		Helmet	Shoulder	Hip/Thigh	Ground	Torso	Knee/ Leg	Arm/ Hand	FG Post	**Total 'Other':**	**Total:**
QB	#	11	1	--	44	5	2	10	--	17	73
	%	*14.9*	*1.4*	--	*60.8*	*6.8*	*2.7*	*13.5*	--	*23.0*	100.0
RB	#	61	125	13	139	61	18	51	--	131	468
	%	*13.0*	*26.7*	*2.8*	*29.6*	*13.0*	*4.1*	*10.9*	--	*27.9*	100.0
WR	#	15	6	3	59	7	4	10	2	23	106
	%	*14.2*	*5.7*	*2.8*	*55.7*	*6.6*	*4.7*	*8.5*	*1.9*	*21.7*	100.0
TE	#	294	99	3	41	9	10	3	--	22	459
	%	*64.1*	*21.6*	*0.7*	*8.9*	*2.0*	*0.7*	*2.2*	--	*4.8*	100.0
OL	#	428	163	3	9	13	1	20	--	34	637
	%	*67.2*	*25.5*	*0.5*	*1.4*	*2.0*	*0.2*	*3.1*	--	*5.3*	100.0
DL	#	462	189	9	15	21	1	9	--	31	706
	%	*65.6*	*26.6*	*1.3*	*2.1*	*3.0*	*0.1*	*1.3*	--	*4.4*	100.0
LB	#	170	60	16	39	51	15	26	--	92	377
	%	*45.4*	*15.6*	*4.2*	*10.3*	*13.5*	*4.0*	*6.9*	--	*24.4*	100.0
DB	#	8	26	13	41	10	6	11	--	30	115
	%	*6.8*	*22.0*	*11.0*	*34.7*	*10.2*	*5.1*	*10.2*	--	*25.4*	100.0

9.4.2 Distribution of Tissue Strain; MPS

Peak MPS within four brain lobes was calculated for all exemplar impacts for each field position, which was further assigned a level of MPS magnitude; low, moderate, high. A trend was observed, consistent to all field positions, showing an even distribution of peak strain throughout the four brain lobes at low MPS magnitudes. As peak strain magnitude increased, a pattern of distribution appeared demonstrating an ordered high to low strain wave starting with the temporal lobe, followed by the frontal lobe, the occipital lobe, and finally the lowest strain was typically observed within the parietal lobe regardless of the impact condition or field position (Fig. 9-2A). Chi-squared analysis revealed the distribution of strain throughout the brain lobes was not significant between positions based on exemplar impact conditions ($\chi^2(77) = 74.86$, $p=.560$). Accounting for the frequency of each impact condition, significance was found ($\chi^2(28) = 1066.27$, $p<.001$). Similarly, a pattern of distribution was observed when the total impact frequencies were considered for each position. The temporal lobe showed the highest percentage of high strains, followed by the frontal lobe. There was a switch for the remaining two lobes, with higher strains reported in the parietal lobe, and the lowest found in the occipital lobe (Fig.

9-2B), with the exception of LB and TE that showed a rather even distribution of MPS level between parietal and occipital lobes.

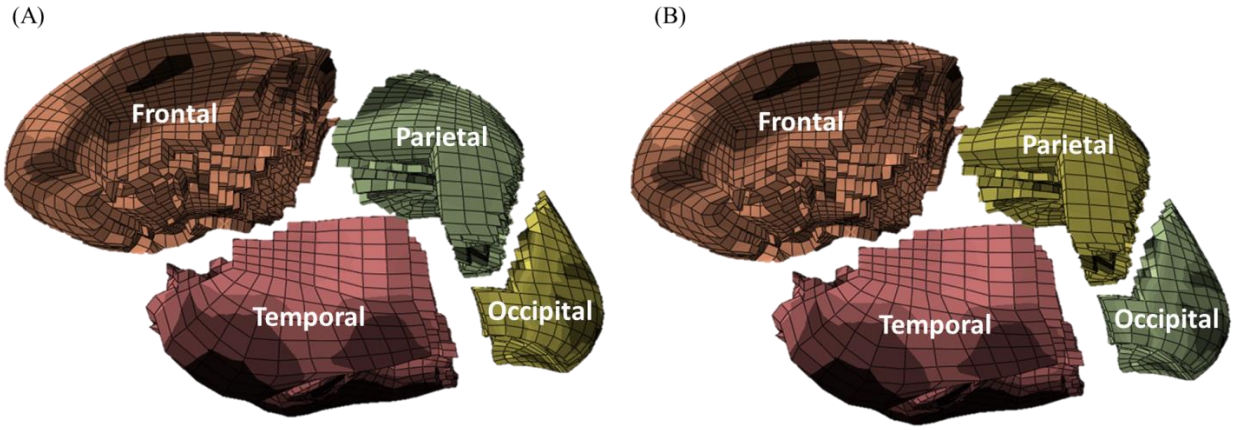

Figure 9-2: Demonstrating a pattern of lowest to highest MPS calculated in four brain regions. High to low strain is indicated in the following order; red, orange, yellow, green for (A) exemplar impacts, and (B) total documented impacts.

Contingency table analysis examining differences within each brain lobe are reported in Figure 9-3. The QB, WR, and DB experienced a higher percentage of high magnitude impacts in three, four, and two lobes, respectively. OL and DL reported a significantly higher proportion of low magnitude impacts within the temporal lobe, and typically a lower percentage of moderate and/or high magnitude impacts within all brain lobes. RB and LB often reported a higher proportion of moderate magnitude impacts compared to the other field positions. Specifically, RB showed higher moderate magnitude impacts within all brain lobes, and LB experienced a higher proportion of moderate magnitude impacts within the parietal and occipital lobes. The TE reported a lower percentage of moderate magnitude impacts within the parietal lobe, and a lower percentage of low magnitude and a higher percentage of moderate level impacts in the temporal lobe.

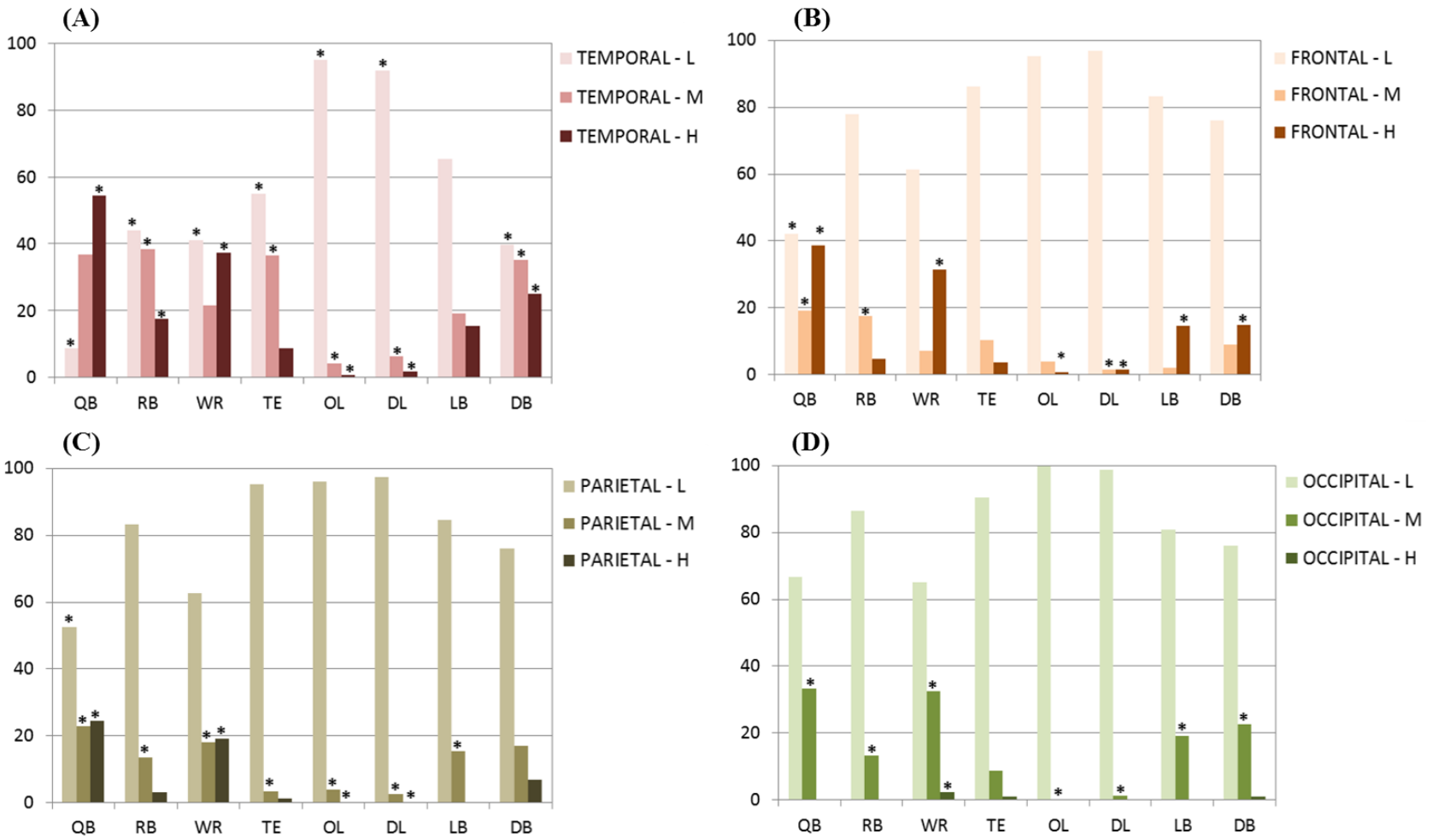

Figure 9-3: Distribution (%) of strain magnitude within A) temporal lobe, B) frontal lobe, C) parietal lobe, and D) occipital lobe documented for eight player field positions. Distributions are presented as a percentage from the total number of impacts specific to each position and individual to brain region; QB: *n* = 73, RB: *n* = 468, WR: *n* = 106, TE: *n* = 459, OL: *n* = 637, DL: *n* = 706, LB: *n* = 377, DB: *n* = 115.
*significant at $p < 0.05$.

9.4.3 Volume of Tissue Strain; CSDM

Results showed a statistically significant effect of player field position on CSDM 8% and CSDM 17% within the cerebrum, gray matter cerebrum and white matter cerebrum. Table 9-3 reports the rank means and Kruskal-Wallis H test results for eight positions. Dunn's pairwise showed significant differences ($p < .001$) in CSDM 8% strain within the cerebrum and gray matter cerebrum between each position excluding the analysis between RB, WR, TE and DB, and between DL and LB. Tissue exceeding 8% strain within the white matter cerebrum showed significant differences ($p < .01$) between individual positions excluding those between RB, WR, TE and DB, and between OL and DL. CSDM 17% within the cerebrum for the QB was significantly different to the remaining 7 positions ($p < .01$). WR also showed significant results ($p < .001$) compared to all positions excluding DB. The RB, LB and DB were statistically different ($p < .001$) to TE, OL and DL. CSDM 17% within gray matter cerebrum showed QB and WR were statistically different ($p < .05$) to all positions excluding each other. The RB and DB were statistically different to TE, OL and DL ($p < .001$) and LB was different compared to RB, OL and DL ($p < .001$). Finally, differences in CSDM 17% within white matter cerebrum showed QB was statistically different compared to all positions excluding WR, and WR was different to the remaining positions excluding DB. The RB LB, and DB were significantly different to TE, OL, DL and TE was different when compared to OL and DL.

Table 9-3: Chi square and rank means results from Kruskal-Wallis H tests performed for CSDM 8% and CSDM 17% within the cerebrum, grey matter and white matter.

	Rank Mean								***Kruskal-Wallis H****
	QB	***RB***	***WR***	***TE***	***OL***	***DL***	***LB***	***DB***	
CSDM08_CER	2235.8	1524.1	1700.9	1674.2	898.8	1130.5	1133.8	1700.1	512.5
CSDM08_GM	2241.6	1508.2	1700.1	1664.0	883.1	1132.1	1195.9	1700.8	510.2
CSDM08_WM	2244.2	1659.2	1817.5	1699.9	953.5	941.73	1235.4	1680.7	777.8
CSDM17_CER	1917.1	1400.6	1659.5	1244.5	1191.4	1179.6	1344.2	1477.6	349.4
CSDM17_GM	1902.4	1576.8	1765.1	1215.5	1157.7	1145.2	1313.7	1450.3	492.94
CSDM17_WM	1803.3	1366.7	1664.0	1268.6	1174.7	1194.1	1363.1	1500.4	372.24

*significant at $p < 0.001$.

Impact frequencies reaching critical levels of CSDM 8% and 17% within the cerebrum, gray matter cerebrum and white matter cerebrum for each field position are reported in Figures 9-4 and 9-5. Impact frequencies that incurred >0.5 and >0.10 of the brain's volume reaching critical levels of CSDM 8% and 17%, and <0.5 of the brains volume reaching CSDM 8% within the cerebrum, gray matter cerebrum and white matter cerebrum for each field position are reported in Figures 9-4 and 9-5. RB, TE and LB sustained the highest documented impact frequencies that involved >0.5 and >0.10 of the brain's volume reaching CSDM 8% in cerebrum and both gray and white matter cerebrum. Little difference was observed among the remaining positions for >0.5 and >0.10 brain volume at CSDM 8%. Impact frequencies for line positions were substantially higher than all other positions involving <0.5 of the brains volume reaching CSDM 8% within cerebrum and gray and white matter. Skill positions reported the highest impact frequencies involving >0.5 and >0.10 of the brain's volume reaching CSDM 17% within cerebrum, gray and white matter cerebrum. Most notable were frequencies for QB, RB and WR reaching CSDM 17% within the deeper white matter structures.

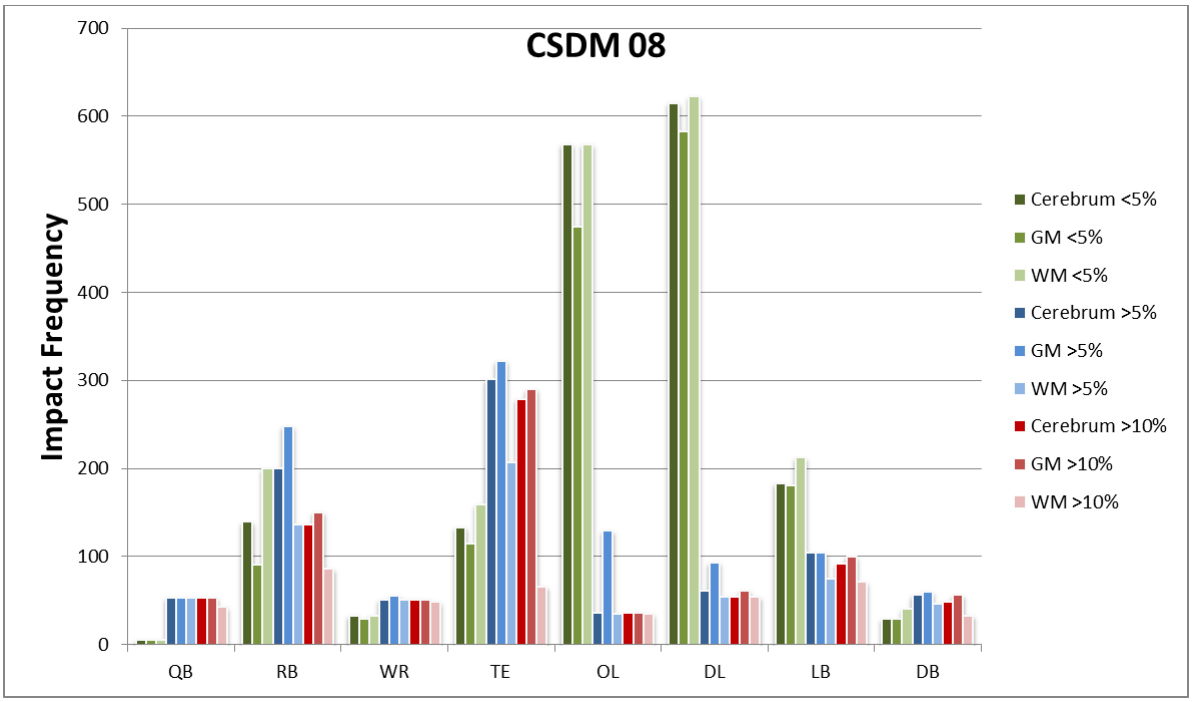

Figure 9-4: A comparison of head impact frequencies for eight player field positions throughout 32 regular season games. Frequency of head impacts incurring <5%, >5% and >10% of brain volume reaching an 8% tissue strain threshold within the cerebrum, gray matter cerebrum and white matter cerebrum are presented.

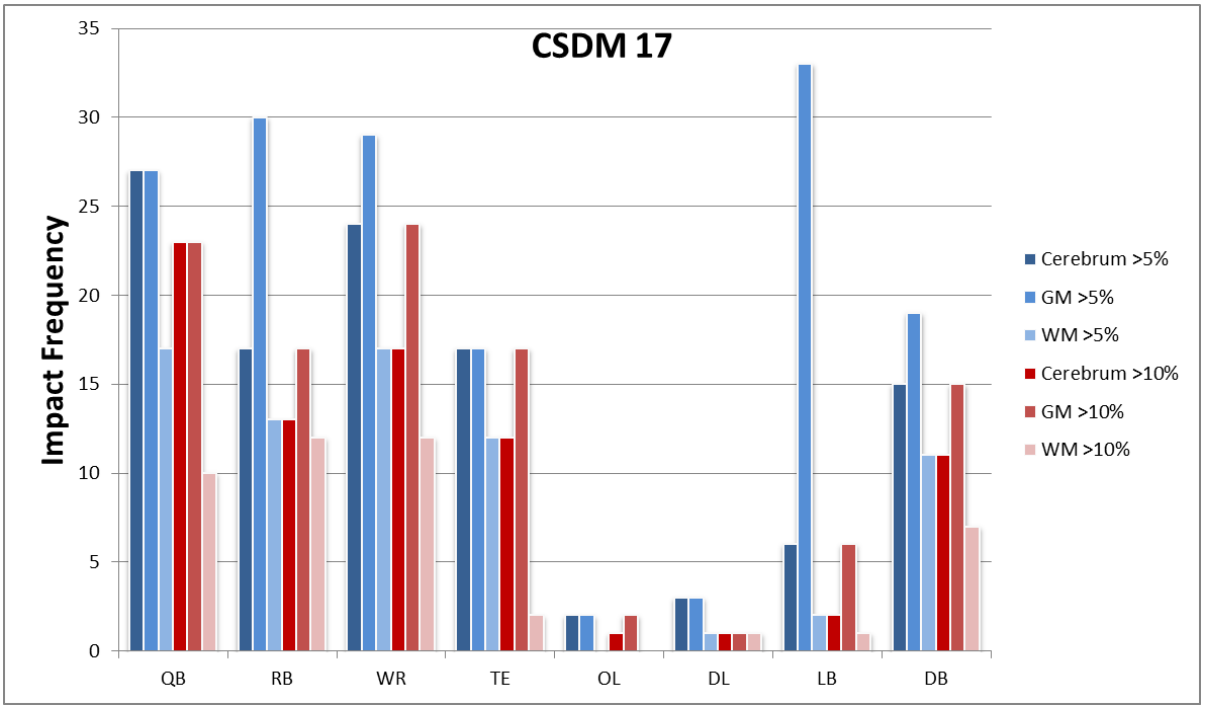

Figure 9-5: A comparison of head impact frequencies for eight player field positions throughout 32 regular season games. Frequency of head impacts incurring >5% and >10% of brain volume reaching an 17% tissue strain threshold within the cerebrum, gray matter cerebrum and white matter cerebrum are presented.

9.5 Discussion

Strains in the frontal, temporal, parietal, and occipital lobe were included in this analysis. These areas of the brain are chosen due to their distinct functions and the conceivable changes within the brain and expression of cognitive symptoms associated with cumulative brain trauma. The ASF population has been shown to suffer from mood and behavior changes, cognitive deficit and emotional impairments years after they experience head trauma [Montenigro *et al.,* 2017; Alosco *et al.,* 2017b; McKee *et al.,* 2013; Mez *et al.,* 2017].

Strain fields showed similar distributions throughout the brain between eight field positions based on exemplar impact conditions. This phenomenon was observed regardless of the variation in event conditions (i.e. velocities, event types, locations) amongst the positions. Only as the frequency at which each condition occurred was considered, based on individual positions, were differences found (Fig 9-3). This describes vulnerabilities for various parts of the brain are highly influenced by the frequency at which a particular impact is experienced. Line positions tended to experience a higher proportion of low strains within the frontal and temporal lobes, whereas skill positions, QB, DB and WR experience a higher proportion of high strains within temporal, parietal and occipital lobes. A trend on how the strain distributes throughout the brain can be observed amongst all field positions. Low level strains are often distributed evenly throughout the brain, and as the magnitude increased, a greater distinction between lobes was observed. The temporal lobe being the most vulnerable followed by the frontal lobe. This was found with all impact conditions collapsed, and across all field positions. This finding is consistent with Baylay et al. [2005] who demonstrated strains are initially found in the frontal areas of the brain due to the anatomical structures and basal tethering of the brain in this region, involving areas around the frontal and temporal junction. This is also an area implicated in the pathology of CTE, where hyperphosphorylated tau deposition initiates in prefrontal cortices and in parts on the temporal lobe in perivascular spaces [Omalu *et al.,* 2004; 2005; McKee *et al.,* 2013], and has been associated with a number of functional abnormalities [Barrio *et al.,* 2015; Small *et al.,* 2013]. Further, DTI of uncinate fascicules that connect the orbitofrontal cortex with the anterior temporal lobe and connected gray matter differentiated former football athletes from healthy controls [Goswami *et al.,* 2016]. This area is associated with increased aggression and impulsivity, and often associated with initial symptom expression in those with trauma induced tauopathy brain disease [McKee *et al.,* 2013; Stern *et al.,* 2013]. Injury reconstructions by Viano

et al. [2005] have reported observing early strain 'hot spots' in the temporal lobe initiating adjacent to the site of impact and traveling to the far temporal lobe. Depression is commonly reported to affect football players exposed to repeated impacts, which is associated with the amygdala located in the temporal lobe, and can also be associated with a hyper-regulatory effect of the medial prefrontal cortex [Davey *et al.,* 2017; Didehbani *et al.,* 2013]. Neuropsychological and a number of motor indices showed alterations in healthy retired football athletes over 30 years post trauma [Beaumont *et al.,* 2009]. This study demonstrated the chronicity and subtle changes on cognition and motor system changes that occur in athletes who did present with severe brain disease.

The parietal lobe and finally the occipital lobe seemed to be placed under the least amount of strain. Using DTI measurements, Kuzminski et al. [2018] found that a decrease in fractional anisotropy was related to impact frequency and correlated with worsening visual memory from a single season of high school football. The posterior parietal cortex, involved in mental image manipulation, has been shown to be involved in how much of a visual scene can be retained [Todd & Marois, 2004]. The occipital lobe showed the least amount of strain resulting from each head impact. This finding consistent with research showing this brain region as the least vulnerable to compression against the skull due to anatomical constraints in the more anterior regions and observations of more severe countercoup injury from occipital impacts [Bayly *et al.,* 2005; Pudenz & Shelden; 1946; Gurdjian & Lissner, 1961].

Strain distribution results reveal the magnitude of an impact is more influential to brain region vulnerabilities then how the impact occurred, for example, a helmet collision to the side of the head, compared to falling and hitting the back of the head on turf. Further, that tissue injury is influenced by the frequency of impact. Regional vulnerabilities are essentially determined by the frequency of an impact that dictates how often a particular level of strain is distributed throughout the brain. At low magnitude impacts however, strains below 17%, this study showed fairly even strain levels experienced by four brain lobes. Considering that many common head impacts occur at this level, this may indicate a regional dependent strain response, where the pathophysiological response could be more sensitive in areas associated with functional impairments and brain disease [Prange & Margulies 2013; Elkin & Morrison, 2007; McKee *et al.,* 2013; Mez *et al.,* 2017; Montenigro *et al.,* 2017]. The cumulative effects of low magnitude impacts experienced in succession, and the tissues' duration of heighted vulnerability, may also

be influenced by this pattern of strain distribution and therefore the susceptibility to microstructure alterations and regional brain tissue damage [Effgen & Morrison, 2017; Yuen *et al.*, 2009; Prins *et al.*, 2013; Iliff *et al.*, 2012; 2013; Oliver *et al.*, 2016].

Previous studies using CSDM as an indicator of injury severity have often used a 10% and 15% strain to establish predictive thresholds of concussion and DAI [Takhounts *et al.*, 2003; Giordano & Kleiven, 2014]. This is the first study to employ a CSDM metric to appreciate tissue volume strains involved in common head impacts during ASF game play. The current study examined two CSDM thresholds of 8% and 17% to include a range of severity. These thresholds were measured in the cerebrum, gray matter cerebrum and white matter cerebrum. Many common asymptomatic impacts occurring in football result in a peak strain of 8-17% [Karton *et al.*, 2018; Zanetti *et al.*, 2014] and may be associated with cumulative changes within the brain [Monteneigro *et al.*, 2014; Bazarian *et al.*, 2012; 2014; Stamm *et al.*, 2015]. Above a 17% peak strain, the risk of sustaining a concussion increases [Zhang *et al.*, 2004; Kleiven, 2007]. Not surprisingly, all recorded impacts consistently involved more of the brain's gray matter cerebrum compared to the deeper white matter cerebrum for both a CSDM 8% and 17% [von Holst & Li, 2013] (Fig 9-4 & 9-5). This is in accordance with research showing the highest deformations are consistently found in locations near the superior cortical surface from very low magnitude impacts involving living human subjects [Bayly *et al.*, 2005; Feng *et al.*, 2010].

The greatest number of impacts were documented for the line positions, where 80-90% involved <0.05 of the cerebrum reaching an 8% strain threshold, with few involving >0.05 and >0.10 brain volume reaching both the 8% and 17% threshold. These findings suggest that strains involving very little of the brain's volume may be sufficient to cause changes in brain functionality [Montenigro *et al.*, 2014; Baugh *et al.*, 2015; Mez *et al.*, 2017]. RB and TE experienced the highest number of impacts involving >0.05 and >0.10 brain volume reaching an 8% strain threshold and were amongst the positions experiencing the greatest number of hits reaching the 17% threshold. Particularly, approximately 50% and 70% of the total impacts involved >0.05 gray matter cerebrum for CSDM 8% for RB and TE, respectively. TE experienced the highest number of impacts involving >0.10 cerebrum at CSDM 8% which accounted for over 60% of their total impact frequency. The greatest number of impacts involving >0.10 white matter cerebrum reaching 8% strain was experienced by RB, due to a higher proportion of high magnitude impacts experienced by this position, causing strains deeper

within the brain [LaPlaca *et al.*, 2007; Ommaya & Gennarelli, 1974]. QB and WR received the highest number of impacts involving >0.10 cerebrum reaching the CSDM 17% threshold, followed by RB, TE and DB. The lowest total frequency was documented for QB and WR, meaning that when an impact is sustained, more often a greater brain volume is placed under high strain. These positions have high concussion rates, and the CSDM values estimated here, are comparable to 50% concussion probability reports of 0.09-0.23 brain volume reaching a CSDM of 10% [Giordano & Kleiven, 2014]. The LB position also experienced a relatively high number of impacts involving >0.05 for CSDM 17% threshold within the gray matter cerebrum. This position is exposed to moderate impact frequencies, characteristically of moderate strain magnitudes in relation to the other field positions. The results indicate that there is a relationship between magnitude, volume and frequency. Higher magnitude events involving more tissue volume may lead to an overwhelming metabolic response expressing with acute injury symptoms [Giza & Hovda, 2016]. Lower magnitude events involve less brain volume, where the physiological response would be less obvious and therefore may go undetected. As the frequency of these impacts increase however, these responses have an accumulated effect, as documented in microstructural axonal damage, potentially manifesting itself as a chronic brain injury [Mayinger *et al.*, 2018; Tang-Schomer *et al.*, 2010; Oliver *et al.*, 2016; Mez *et al.*, 2017]. Tagge *et al.*, [2018] demonstrated the relationship between magnitude and volume leading to neurological dysfunction. This group showed that focal point loading of high stress magnitudes resulted in acute neurobehavioural deficits, however lower stress magnitudes of a distributed force loading did not. In their study, the both of these scenarios lead to early pathology and functional sequelae.

9.6 Conclusion

This work characterizes the distribution and volume of tissue strain resulting from common head impacts in ASF. The results demonstrated that strain distribution is independent of field position, meaning that it is not highly influenced by the condition of a particular impact. Brain areas vulnerable to strain are dependent on the impact frequencies and magnitudes that constitute a position profile. These characteristics of trauma are what dictate how often, and by what level (magnitude), strain is experienced in each brain lobe. These characteristics therefore, should be considered when evaluating protection, risk mitigation, and position specific safety strategies.

The extent of strain measured as the amount of brain volume involved in an impact was found to be position dependent. Line positions experience impacts that caused strains involving very little brain volume of predominantly gray matter cerebrum, however were at the highest frequencies. Skill positions experiencing higher magnitude impacts, demonstrated higher brain volume involvement and more often reaching the deeper white matter structures. This has implications as to the nature of a traumatic experience and how that results in microstructure damage and functional impairment or acute concussive symptoms.

9.7 References

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PART IV

Global Discussion

Despite the on-going research involving head injury identification, treatment and management, high rates of injury among contact sports participants support the notion that characteristics of trauma that associate with lowered brain function and health that are not addressed in the current symptoms-based assessments [Bailes *et al.,* 2013; Montenigro *et al.,* 2017; Oliver *et al.,* 2016]. The structural, metabolic and cellular responses that occur within the brain from mechanical loading result in an acute response and one that manifests overtime from cumulative injury, indicating a more complete way of measuring brain trauma is required. ASF has the highest risk for head and brain injury and has been under particular interest within the scientific community. The leading objective of this thesis was to use biomechanical methods to estimate overall exposure to brain trauma among ASF players. In order to effectively and objectively capture trauma exposure, *brain trauma profiling* involving strain magnitude, frequency of impact, and time interval between impacts, over a duration of exposure was defined and presented. Trauma profiling provides a method for capturing and measuring a detailed analysis of brain trauma exposure within contact/collision sports. A combination of these characteristics creates environments that put athletes at risk for both acute issues and/or poor mental health from cumulative injury, defined as brain tissue trauma load. This method objectively measures exposure without relying on traditional symptoms-based assessment and diagnostic tools that have proven insensitive and ineffective [McCrea *et al.,* 2004; Meehan *et al.,* 2013].

Brain trauma profiling methods was used to measure and compare brain trauma associated with player field position in professional ASF. The variance in player roles among ASF positions provided a sample to compare and contrast trauma profiles. Difference in the characteristics of brain trauma between player field positions in National Football League was described. Three different profile patterns were identified. QB, WR and DB experienced a low frequency of high magnitude impacts with long time intervals between them (profile 1). RB and LB were exposed to a wide range of strain magnitude levels at moderate frequencies and time intervals (profile 2). Both DL and OL positions experienced the highest frequency of predominantly low magnitude impacts within short time intervals (profile 3). The TE position was similar to both profile 2 and 3, due to their dual roles on the field as either a line position or receiver. When examined in light

of, and in conjunction with known injury and disease incidence reports, a trend was observed and may shed light on how tissue injury is expressed. Positions within profile 1 tend to be among those who report more 'extreme' hits and concussive injuries [Campbell, 2014; Nathanson *et al.,* 2016]. These field positions experienced few head impacts but were of strain magnitudes associated with higher severities and acute injury outcomes [Kleiven, 2007; Zhang *et al.,* 2004]. Field positions associated with very high frequency of strain magnitudes below 50% risk of concussion, experienced within more condensed time frames (profile 3) are among those that currently demonstrate higher confirmed cases of long-term neurological disease [Mez *et al.,* 2017]. Trauma exposure of field positions within profile 2 were less predictable as they experience moderate levels of impact frequency and intervals within a range of strain magnitudes, including the highest levels, which may put this group at risk for both acute and chronic brain injuries [Mez *et al.,* 2017; Nathanson *et al.,* 2016].

Both acute responses and delayed symptom expression are detected in the ASF population where impairments are reflective of the areas of the brain vulnerable to injury and the extent of brain damage [Talavage *et al.,* 2014; Hampshire *et al.,* 2013; Bazarian et al 2012; 2014]. This thesis was the first to examine the distribution of strain and the volume of tissue involved in common head impacts experienced by specific field positions during game play. The results demonstrated that the regional distribution of strain was independent of field position. In the current analysis, impacts causing low magnitude strains were often distributed evenly throughout the four brain lobes. As the magnitude increased, a greater distinction between lobes was observed, with the temporal lobe being the most vulnerable, followed by the frontal lobe. Findings are consistent with research showing these areas are particularly susceptible to strain based on anatomical structures, neurobiological systems and pathophysiological outcomes [Baylay et al. 2005; Omalu *et al.,* 2004; 2005; Iliff *et al.,* 2012; 2013]. Differences in player roles dictates variation in the environments that lead to head impacts, thus indicating that strain distribution is not highly influenced by the condition of a particular event. Rather, brain region vulnerabilities are influenced by the magnitude of the strain and the frequency at which that particular level of strain is experienced, as oppose to how the impact occurred. These characteristics distinguish player position and dictate brain regions experiencing low and high levels of strain.

Contrary to regional distribution, the extent of strain measured as the amount of brain volume involved in an impact was found to be position dependent. Two threshold levels of strain were

examined. Low magnitude impacts involved little brain volume of mainly outermost cortical regions, whereas high magnitude events involved larger brain volumes reaching deeper into the brain. Distinctions between field positions were observed based on the magnitude of events they were exposed to, coupled with the impact frequency. The majority of impacts experienced by line positions involved <0.05 of the cerebrum reaching 8% strain, however experienced the highest frequency counts. QB and WR experienced few impacts, most often involving higher brain volumes (>0.10) reaching a tissue response over 17%. RB, TE, and DB were vulnerable to impacts involving >0.05 and >0.10 volume reaching both 8% and 17% strains. LB was most susceptible to impacts reaching 17% strain involving >0.05 gray matter volume.

Implications of Findings

Brain trauma profiling methods were used to identify differences among player field positions in ASF. Due to the nature of the sport, ASF athletes are, in general terms, susceptible to a spectrum of brain injury, regardless of position. Therefore the intention of this thesis was not to identify and divide specific injury outcomes/susceptibilities for specific positions. It was to demonstrate that trauma to the brain is not universally defined, but unique combinations of trauma characteristics lead to similar, or differing, injury outcomes. A position specific analysis provides insight into how an exposure profile of combined impact frequency, strain magnitude and time interval, over a specified duration, can be used to increase our understanding of how tissue injury is manifested. These methods better capture objective indices of brain trauma exposure. This provides league officials, athletic directors, coaches and athletes with a guide for intervention and management of brain trauma in ASF.

Regional vulnerabilities and volume of tissue strain were influenced by the magnitude and frequency of head impact, which are distinguishing features amongst ASF field positions. Therefore in order to effectively protect against brain injury, both characteristics need to be managed. In order to mitigate impact magnitude, an appreciation of how strain is created is required. Event conditions are position specific and therefore exposure management, either through game rule modification, enforcement or head protection will need to reflect these differences. Positions likely to experience low magnitude impacts involving little brain volume, were also coupled with high frequency counts, whereas positions that most often endure high magnitude impacts with larger volume involvement experienced fewer impacts. The variation

that is observed in trauma profiles may reflect different injury mechanisms. Events involving higher tissue volumes, and deeper within the brain, could lead to more widespread disruption of white matter connectively with consequent acute symptom expression [Ommaya & Gennarelli, 1974; Giordano & Kleiven, 2014]. Long-term brain damage pathology may require little tissue volume involvement if frequently effected [Montenigro *et al.,* 2014; Baugh *et al.,* 2015; Clark *et al.,* 2018; Mez *et al.,* 2017].

Research Limitations

The results of this thesis are presented in the context of particular limitations as outlined below.

- The head impact data in this thesis was collected using a non-biofidelic physical headform that was created and validated against anteroposterior head impact during automotive accidents. Therefore the headform may not result in the kinematic subtleties of a human response; it simply mimics a similar biomechanical reaction. The use of these models within a controlled laboratory provides a setting for comparison.
- Strain values calculated from the FE model are dependent on the tissue mechanical properties, the boundary conditions and mesh densities assigned to various anatomical regions and this will influence the resulting deformation values. Specifically, the sensitivity of variations in material tissue properties used within the UCDBTM model has been examined by Horgan & Gilchrist [2003] and Doorly [2007]. The FE model provides an approximate tissue response under loading and is a useful tool for comparison and relativity rather than absolute values. The MPS presented in this research are not meant as literal values but rather represent relative severity comparisons between groups.
- The FE model is a gross representation of the brain. Although high strain and brain disease pathologies are found within the sulcus of brain tissue, UCDBTM is not refined to distinguish strains between the sulcus and gyrus. Therefore the global distribution of strains within the entire cerebrum, and segmented into four lobes was estimated.
- Physical reconstructions involved the measurement of inbound velocity calculated using a two-dimensional video to represent a three-dimensional impact condition. This may lead to calculation error based on the perception of the video and therefore may not reflect a precise event velocity.

- One helmet model was used for all head impacts regardless of the model that was worn by the tracked player field position. As variation in helmet model protection exists this was done to provide relative differences in position by ruling out any differences being a reflection of the performance components of a particular helmet.
- Position specific brain trauma profiles from this study are based on the assumption that the same individual player is on the field throughout the entirety of the game and remains in the same position. Therefore the analysis provides an exposure load that is specific to position, and not an individual player.
- Only video of professional ASF game play was publicly available and therefore included in the analysis. Exposure during practices was not considered which consequently underestimates seasonal trauma load.
- Documentation of all direct head contact using video analysis limits the ability to count all impacts to those visible in terms of both video quality and field of view and does not account for indirect contact which may influence head motion. Frequency counts in this thesis are most likely conservative estimate as a reflection of this limitation.
- Due to the large number of impacts documented in this thesis, exemplar impacts were chosen to represent each event condition. This occasionally resulted in one impact reconstruction representing >100 impacts. Further, if sufficient field markers were not present to perform velocity calculations, a visual categorization of closing velocity was made. Categories of both impact velocity and strain magnitude were used to represent 'ranges' rather than absolute magnitudes due to these limitations.
- Research relating head trauma to neurological disorders is immature resulting in a limited human data set and understanding of disease incidence, prevalence, and risk factors. Due to the high profile of American football, this population has been studied most extensively and this has resulted in a potentially biased distribution of CTE incidence. Further, interpretation of trauma loads associated with injury in this research neglect to account for a number of biological and subject-specific factors (i.e. genetic predisposition, injury history), which may influence risk to neurological injury.

Recommendations for Future Research

Head injury research aims to draws relationships between mechanical loading and biological response with the goal of establishing how input parameters influence injury outcomes [Ommaya *et al.,* 1994]. The challenge with cumulative injury is that outcomes are latent and persistent. Due to the high profile and nature of the sport, measurement data has predominantly focused on ASF, however concerns of cumulative injury is beginning to gain traction in many contact sports including ice hockey, rugby and soccer [Lee *et al.,* 2019]. This thesis presented an objective measurement tool designed to capture cumulative brain trauma that can be applied to different sports, competition levels and age groups. Effective, accurate and objective measures of brain trauma provide a guide for prevention and innovation strategies aimed at decreasing participant exposure. Understanding how trauma occurs within various contexts allows for intervention, risk management and policy making to be tailored to specific environments, and may be of particular value for limiting trauma in high-risk populations and developing brains [Alosco *et al.,* 2017; Montenigro *et al.,* 2017].

Understanding mechanisms of brain injury is one the most challenging questions in head injury research. Trauma profiling methods are instrumental in connecting impact events to brain injury. The brain's many responses under impact loading reflect the complexity of how injury occurs. Without the understanding of the event(s) itself, there is little reference for change. Connecting the characteristics of brain trauma to specific neuronal damage and neurobiological responses is ultimately what will drive risk mitigation strategies and policy making for mental health protection and brain injury prevention.

PART V

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Appendix A:

Statement of Contributions

Scientific Journals

Accepted

1. Karton C, Hoshizaki TB, Gilchrist MD. A novel repetitive head impact exposure measurement tool differentiates player position in National Football League. *Scientific Reports.* In Press.

Book Chapters

Published

2. Karton C & Hoshizaki TB. "Concussive and Subconcussive brain trauma: the complexity of impact biomechanics and injury risk in contact sport". In B Hainline & R Stern (Eds.), *Handbook in Clinical Neurology: Sports Neurology*. Vol 158 pp. 39-49. Elsevier B.V. 2018.

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8. A Post, C Karton, M Robidoux, MD Gilchrist, TB Hoshizaki. (2019). An examination of the brain trauma in Novice and Midget ice hockey: Implications for helmet innovation. The 42nd Canadian Medical and Biological Engineering Conference, Ottawa, Canada, May 22-24.

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10. C Karton, MD Gilchrist, TB Hoshizaki. (2018). Position specific head trauma profiles in professional American football using impact magnitude, frequency and interval. AAN Sports Concussion Conference, Indianapolis Indiana, July 21-22.

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Appendix B:

Measurement Variation & Error

Accuracy of Velocity Calculation using Kinovea Software

Methods for measuring velocity using Kinovea software was validated using real-world ice hockey collisions. The average error reported for this method was approximately 10% [Post *et al.,* 2018]. The factors that influence this error were documented as; the area of the calibration field, the proximity of the calibration field to the impact event, and the orientation of the impact relative to the camera view. Based on the reported sources of error, it is likely that the error in this thesis would be equivalent or less. The field in American football contains more field markers that an ice hockey rink. This increased the likelihood that the calibration field can be set directly at the site of impact, or within close proximity. This thesis examined professional level football where the camera placements are many and typically perpendicular to the field, thus increasing the field of view and accuracy of the measurement.

Visual Categorization of Velocity Level

Due to the high number of impacts that are documented for an exposure profile and the nature of video analysis, not all impacts have sufficient field markers to perform velocity calculations. Visual estimates are made for these scenarios, with a calculated reliability of Cronbach's α of 0.92 [Cournoyer, *unpublished data*]. Events are categorized into level of velocity and not absolute values to account for this limitation.

Influence of Location and Direction Accuracy on Head Dynamic and Brain Tissue Response

The orientation of impact was estimated within a tolerance of 15° as smaller increments have little effect on headform dynamic response [Walsh *et al.,* 2011; Oeur *et al.,* 2014]. Oeur *et al.,* [2014] reported minor fluctuations in impact angles of <10° did not demonstrate meaningful differences in terms of strain magnitudes (<5%), however more meaningful differences were observed at angles greater than 15°. Changes in lateral and vertical displacement of impact location on resulting strain magnitude have also been examined [Taylor, *unpublished data*]. Physical impacts using a Hybrid III headform equipped with football helmet showed that there was minimal effect on strain if the difference in location in the lateral direction was <1.5 inches on side head impacts (<7%), or <1 inch on a front head impact (<5%) (Figure A-1).

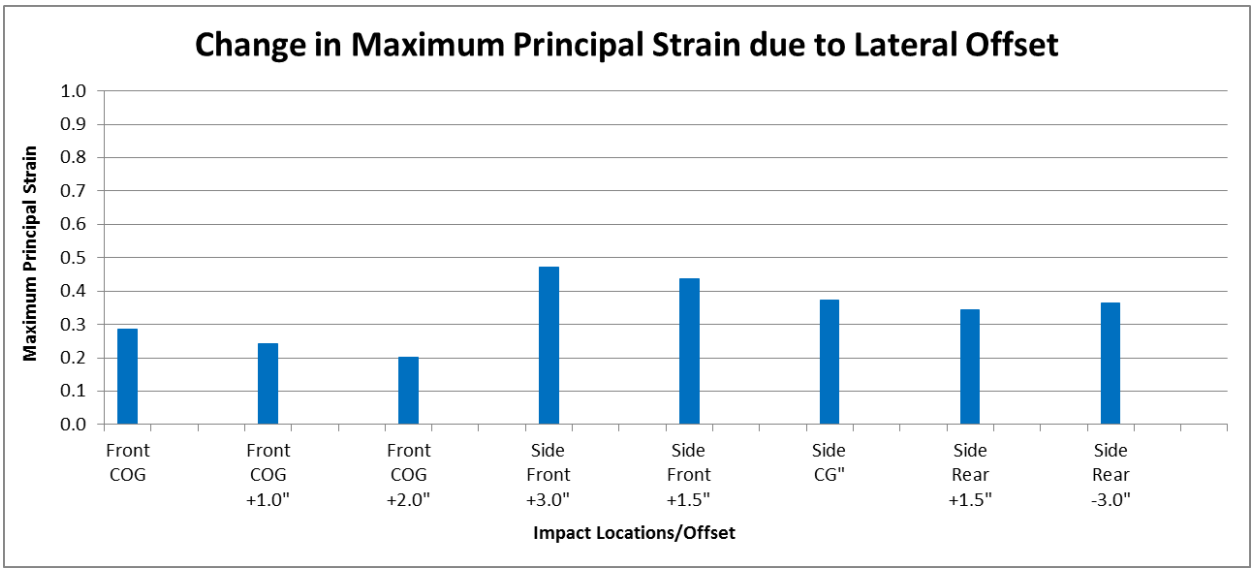

Figure A-1: Change in MPS magnitude from lateral displacements for front and side impact locations [Taylor, *unpublished data*].

The influence of vertical displacement was examined by impacting the head through center of gravity, and 1" below, and 1" above the center of gravity at 5 head rotations. A 1" displacement resulted in a change in MPS ranging from 1 - 8% (Figure A-2). Impacts were performed using a non-compliant surface at 5.5 m/s. This condition would represent the worst case scenario for this thesis as the majority of impacts were of lower velocity using higher compliant systems.

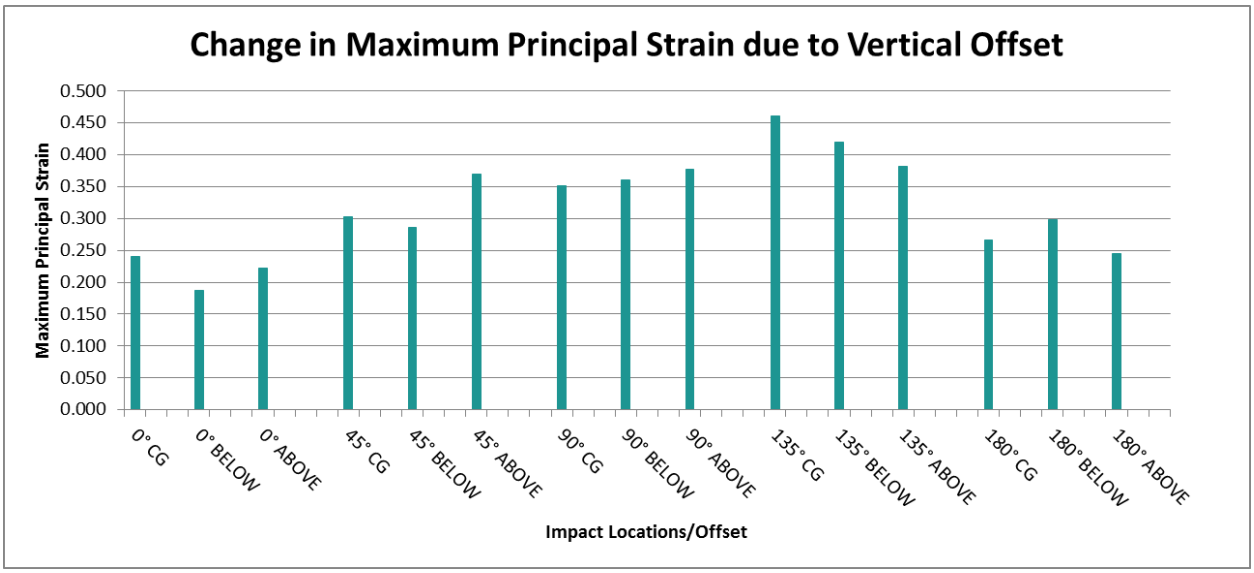

Figure A-2: Change in MPS magnitude from vertical displacements for 5 head rotations [Taylor, *unpublished data*]. 0° = front; 45° = front boss; 90° = side; 135° = rear boss; 180° = rear.

Appendix C:

Headform Collection System Comparison

Head Dynamic Response Comparison using 3-2-2-2 Accelerometer Array and SLICE NANO

The dynamic response of a helmeted Hybrid III head was measured using two different collection systems under the same impact conditions. Four head locations were impacted at 5.75 m/s using a pneumatic linear impact system and linear acceleration and rotational velocity were measured. The results are presented in Figure A-3. Linear acceleration differences ranged from 1.7 - 4.8 g. Differences in rotational velocity ranged from 3.1 – 9.3 rad/s depending on location.

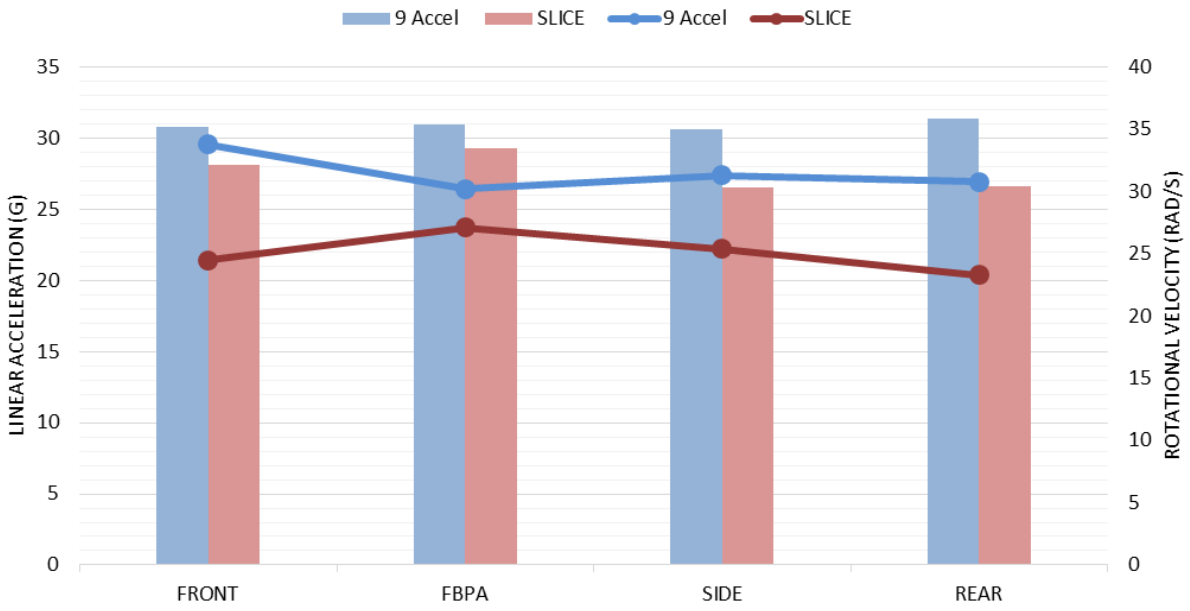

Figure A-3: Linear acceleration and rotational velocity comparison resulting from head impacts to a Hybrid III headform using 1) a 9 accelerometer array and 2) a SLICE DAS system.

Appendix C:

Exemplar Impact Grids

Quarterback

	Frequency	Characteristics of Impact					Anthropometrics		Dynamic Response		Brain Response	
Event Type	#	Location	Velocity Level	Impact Velocity	Orientation/ Elevation	Mass (kg)	Height (cm)	Weight (kg)	Res LA (g)	Res RA (rad/s2)	MPS (%)	Magnitude Level
Helemt	2	F	M	4.99 (0.23)	Front-D	24.0	196	104	30.5 (2.9)	2568.8 (349.1)	22.6 (3.0)	M
	1	FB	M	4.84 (0.10)	Right-C	24.0	188	102	45.0 (2.6)	3532.6 (305.3)	31.9 (4.3)	H
	1	FB	H	7.60 (0.07)	Right-E	24.0	193	102	32.2 (0.5)	2453.1 (131.9)	21.3 (1.7)	M
	3	S	L	3.20 (0.04)	Left-C	24.0	190	106	19.5 (3.3)	2113.0 (372.0)	10.7 (1.5)	L
	4	RB	M	5.70 (0.08)	Right-C	24.0	196	104	57.6 (12.2)	4798.2 (303.6)	34.0 (2.0)	H
Shoulder	1	C	M	6.21 (0.09)	Crown	15.5	188	101	18.3 (3.6)	1194.2 (83.9)	11.9 (0.5)	L
Ground	5	F	L	2.88 (0.10)	Front-B	6.6	188	102	31.5 (2.0)	1763.2 (299.7)	20.7 (3.6)	M
	1	FB	VL	1.30 (0.01	Left-B	6.6	188	104	5.7 (0.7)	277.7 (44.1)	5.2 (0.7)	VL
	4	FB	M	4.92 (0.02)	Right-B	6.6	193	102	76.2 (2.4)	3987.8 (156.1)	29.0 (1.3)	H
	5	S	L	2.94 (0.05)	Left-B	6.6	196	110	38.0 (1.7)	2190.4 (116.9)	21.6 (2.0)	M
	7	S	M	4.94 (0.03)	Right-C	6.6	188	102	93.7 (7.9)	6508.9 (538.2)	44.3 (3.6)	VH
	2	S	H	7.06 (0.38)	Right-A	6.6	188	102	105.7 (11.7)	6405.7 (946.9)	47.2 (3.9)	VH
	3	RB	L	3.11 (0.27)	Left-C	6.6	196	107	35.3 (1.8)	2393.3 (204.4)	19.4 (2.4)	M
	7	RB	M	4.93 (0.03)	Right-B	6.6	198	105	71.3 (2.4)	5885.5 (528.9)	32.9 (1.8)	H
	5	R	L	3.05 (0.09)	Rear-C	6.6	196	106	44.0 (0.4)	2395.8 (61.0)	19.6 (0.4)	M
	6	R	M	4.93 (0.04)	Rear-C	6.6	196	104	86.9 (1.0)	4930.7 (327.7)	34.4 (1.1)	H

Running Back

	Frequency	Characteristics of Impact					Anthropometrics		Dynamic Response		Brain Response	
Event Type	#	Location	Velocity Level	Impact Velocity	Orientation/ Elevation	Mass (kg)	Height (cm)	Weight (kg)	Res LA (g)	Res RA (rad/s2)	MPS (%)	Magnitude Level
Helmet	7	F	M	5.96 (0.08)	Front-B	24.0	183	99	59.4 (1.2)	3545.5 (244.4)	25.8 (2.2)	M
	1	F	H	8.06 (0.15)	Front-D	24.0	188	98	69.0 (5.2)	5592.5 (212.1)	47.5 (3.5)	VH
	11	FB	M	5.74 (0.00)	Right-B	24.0	188	100	57.4 (8.2)	3567.2 (255.3)	25.8 (5.0)	M
	2	FB	H	8.15 (0.00)	Left-B	24.0	185	102	78.3 (2.9)	4798.1 (105.3)	32.1 (2.2)	H
	1	FB	VH	9.84 (0.23)	Left-B	24.0	185	108	86.4 (2.9)	5926.4 (83.1)	45.1 (2.1)	VH
	6	S	L	3.21 (0.02)	Right-B	24.0	178	107	24.8 (4.2)	2146.5 (402.7)	17.4 (0.4)	M
	10	S	M	5.70 (0.08)	Right-B	24.0	178	106	66.1 (4.8)	3294.6 (185.1)	21.8 (0.3)	M
	4	S	H	7.89 (0.00)	Right-B	24.0	190	86	55.6 (10.9)	3350.8 (381.8)	34.3 (5.1)	H
	1	RB	VL	1.42 (0.07)	Right-B	24.0	183	99	6.0 (0.3)	534.5 (5.5)	5.3 (0.3)	VL
	3	RB	M	5.70 (0.19)	Right-B	24.0	185	100	43.3 (1.9)	4643.3 (954.8)	35.5 (2.9)	VH
	1	RB	H	8.42 (0.00)	Right-C	24.0	175	88	44.0 (3.8)	4914.1 (377.7)	24.9 (1.1)	M
	1	R	L	2.55 (0.00)	Rear-C	24.0	175	102	14.2 (1.5)	1015.3 (96.2)	9.5 (0.6)	L
	3	C	L	4.14 (0.09)	Crown	24.0	188	95	20.9 (5.9)	1635.6 (387.3)	11.9 (1.9)	L
	10	C	M	5.97 (0.17)	Crown	24.0	178	94	46.1 (2.5)	2573.8 (142.5)	17.6 (4.5)	M
Shoulder	14	F	L	3.31 (0.05)	Front-B	15.5	180	100	1.0 (0.1)	1203.8 (114.8)	15.1 (3.0)	L
	18	F	M	5.80 (0.00)	Front-B	15.5	180	106	23.1 (0.6)	2585.3 (569.7)	17.0 (7.4)	M
	2	FB	L	3.58 (0.03)	Left-A	15.5	180	106	9.3 (0.1)	735.1 (26.7)	9.6 (0.6)	L
	18	FB	M	5.72 (0.10)	Right-B	15.5	180	106	18.2 (2.9)	1628.2 (646.4)	16.8 (7.2)	L
	13	S	L	3.31 (0.05)	Right-B	15.5	185	97	10.8 (0.1)	1102.7 (108.3)	11.4 (0.9)	L
	24	S	M	5.80 (0.00)	Left-A	15.5	183	97	25.4 (1.9)	1845.2 (150.7)	19.6 (0.7)	M
	8	S	H	8.33 (0.16)	Left-B	15.5	190	86	37.7 (2.2)	2410.5 (254.6)	23.6 (1.9)	M
	2	RB	L	4.14 (0.00)	Right-B	15.5	183	101	11.6 (0.2)	1144.3 (38.4)	14.6 (0.7)	L
	3	RB	M	6.36 (0.09)	Left-C	15.5	180	90	24.4 (0.8)	2027.1 (49.2)	23.4 (2.5)	M
	1	RB	H	8.24 (0.16)	Left-B	15.5	183	105	22.3 (0.6)	2102.4 (60.3)	23.7 (1.3)	M
	8	C	L	3.27 (0.02)	Crown	15.5	190	86	7.5 (0.1)	601.8 (0.4)	8.1 (0.3)	L
	11	C	M	5.79 (0.07)	Crown	15.5	175	95	15.3 (1.3)	911.7 (41.9)	11.0 (0.6)	L
	3	C	H	8.33 (0.16)	Crown	15.5	180	105	42.0 (1.3)	1601.0 (109.1)	18.6 (1.6)	M
Hip/	1	F	L	2.59 (0.08)	Front-C	15.2	180	91	10.4 (0.6)	740.4 (128.2)	9.1 (1.1)	L
Thigh	1	S	VL	1.17 (0.03)	Left-B	15.2	183	99	5.2 (0.4)	303.3 (48.3)	5.1 (0.4)	VL
	5	S	M	5.78 (0.08)	Left-A	15.2	183	97	25.0 (4.3)	915.4 (44.5)	12.0 (1.5)	L
	1	RB	M	5.74 (0.00)	Left-B	15.2	180	97	28.3 (0.9)	2169.5 (26.6)	24.4 (1.1)	M
	2	C	L	3.17 (0.08)	Crown	15.2	183	101	9.7 (0.3)	387.8 (272.0)	5.3 (0.3)	VL
	3	C	M	5.38 (0.23)	Crown	15.2	173	86	21.9 (2.6)	734.4 (22.6)	6.5 (0.8)	VL
Ground	6	F	VL	1.06 (0.01)	Front-A	6.6	178	98	9.9 (2.7)	349.7 (46.1)	6.1 (1.1)	VL
	13	F	L	2.89 (0.17)	Front-B	6.6	168	82	42.9 (1.9)	1618.5 (80.7)	15.2 (1.7)	L
	8	F	M	4.98 (0.11)	Front-B	6.6	188	98	77.0 (3.3)	3236.2 (402.6)	25.9 (1.3)	M
	11	FB	VL	1.30 (0.01)	Left-B	6.6	188	104	5.7 (0.7)	277.7 (44.1)	5.2 (0.7)	VL
	17	FB	L	3.04 (0.03)	Left-B	6.6	175	88	35.3 (0.6)	2040.4 (358.0)	14.6 (0.7)	L
	6	FB	M	4.85 (0.10)	Left-B	6.6	180	90	75.2 (5.7)	4541.0 (585.1)	33.0 (3.8)	H
	9	S	VL	1.03 (0.13)	Left-B	6.6	178	102	10.0 (1.3)	493.9 (100.0)	6.1 (0.5)	VL
	21	S	L	3.07 (0.05)	Right-B	6.6	180	100	31.5 (0.5)	1852.6 (42.3)	17.0 (0.5)	M
	10	S	M	4.93 (0.01)	Right-B	6.6	175	110	93.0 (3.0)	7539.0 (39.7)	46.3 (1.7)	VH
	11	RB	L	2.93 (0.11)	Right-A	6.6	175	99	38.9 (2.5)	1557.6 (153.6)	15.0 (2.1)	L
	5	RB	M	4.98 (0.14)	Right-B	6.6	185	98	68.2 (3.9)	3494.2 (596.3)	28.3 (1.8)	H
	9	R	VL	1.09 (0.08)	Rear-C	6.6	185	97	12.8 (0.8)	569.5 (32.0)	7.4 (0.5)	VL
	9	R	L	2.97 (0.12)	Rear-B	6.6	168	82	40.3 (2.1)	2055.1 (211.3)	15.9 (0.7)	L
	1	R	M	4.85 (0.08)	Rear -C	6.6	180	97	79.8 (4.8)	4336.5 (106.9)	34.3 (1.0)	H
	1	C	VL	1.31 (0.03)	Crown	6.6	188	98	9.7 (0.3)	553.7 (29.5)	6.5 (0.3)	VL
	2	C	L	2.09 (0.02)	Crown	6.6	185	102	17.3 (1.0)	984.4 (38.1)	11.6 (1.1)	L

Wide Receiver

	Frequency	Characteristics of Impact					Anthropometrics		Dynamic Response		Brain Response	
Event Type	#	Location	Velocity Level	Impact Velocity	Orientation/ Elevation	Mass (kg)	Height (cm)	Weight (kg)	Res LA (g)	Res RA (rad/s2)	MPS (%)	Magnitude Level
Helmet	2	F	M	5.61 (0.00)	Front-B	24.0	175	86	65.6 (1.9)	2551.3 (412.0)	21.5 (1.1)	M
	3	FB	M	5.12 (0.06)	Right-B	24.0	185	91	37.3 (3.7)	2419.7 (300.5)	24.0 (6.2)	M
	3	S	M	5.78 (0.15)	Left-C	24.0	185	83	40.8 (1.7)	4738.9 (526.7)	40.1 (1.8)	VH
	1	S	VH	9.71 (0.00)	Left-D	24.0	185	98	57.9 (1.2)	5767.5 (587.2)	45.3 (1.0)	VH
	1	RB	M	6.64 (0.00)	Left-C	24.0	193	102	26.0 (2.6)	2751.6 (268.0)	16.2 (1.8)	L
	1	R	VL	1.42 (0.07)	Rear-B	24.0	183	99	6.0 (0.3)	534.5 (5.5)	5.3 (0.3)	VL
	1	R	M	5.85 (0.14)	Rear-B	24.0	196	91	69.3 (7.2)	3448.4 (672.2)	25.6 (1.9)	M
	1	C	L	2.78 (0.08)	Crown	24.0	190	93	17.9 (3.2)	1066.4 (57.0)	11.6 (0.7)	L
	2	C	M	4.95 (0.00)	Crown	24.0	183	85	33.8 (5.2)	2614.2 (188.1)	13.9 (1.1)	L
Shoulder	5	FB	M	5.92 (0.08)	Right-A	15.5	185	86	25.1 (1.6)	1205.9 (46.7)	13.8 (2.4)	L
	1	C	H	7.58 (0.13)	Crown	15.5	183	95	27.1 (0.5)	1174.8 (182.7)	14.4 (2.3)	L
Hip/	1	F	VL	1.41 (0.33)	Front-B	15.2	178	90	5.3 (1.3)	359.9 (58.7)	5.2 (0.5)	VL
Thigh	1	F	L	3.24 (0.07)	Front-A	15.2	183	95	12.1 (1.1)	795.5 (40.8)	9.1 (1.1)	L
	1	C	M	5.77 (0.04)	Crown	15.2	185	87	22.2 (1.0)	1326.5 (91.7)	11.9 (0.7)	L
Ground	7	F	L	2.89 (0.12)	Front-B	6.6	196	91	37.6 (4.9)	1391.3 (97.1)	15.8 (0.1)	L
	1	F	M	5.58 (0.43)	Front-B	6.6	183	95	95.8 (11.2)	4077.8 (596.7)	35.4 (2.9)	VH
	8	FB	VL	1.04 (0.04)	Left-B	6.6	193	102	10.2 (0.5)	604.9 (19.6)	7.2 (0.2)	VL
	6	FB	L	2.94 (0.05)	Right-B	6.6	183	95	36.5 (2.5)	2476.3 (129.3)	20.8 (0.2)	M
	2	FB	M	4.92 (0.04)	Right-B	6.6	185	91	70.5 (4.8)	5689.9 (592.0)	40.4 (5.0)	VH
	9	S	L	2.79 (0.22)	Right-B	6.6	185	95	39.4 (4.3)	2651.5 (366.3)	24.1 (3.1)	M
	7	S	M	4.85 (0.03)	Left-B	6.6	190	97	93.9 (4.0)	5214.1 (675.7)	42.8 (3.0)	VH
	1	S	H	7.12 (0.32)	Left-B	6.6	193	103	140.7 (18.4)	7838.5 (834.9)	48.6 (7.1)	VH
	2	RB	L	2.96 (0.09)	Right-B	6.6	193	102	37.0 (1.2)	2181.1 (364.6)	15.7 (0.9)	L
	7	RB	M	4.90 (0.03)	Right-B	6.6	175	80	57.4 (0.9)	6008.8 (188.2)	37.0 (1.3)	VH
	2	R	VL	0.97 (0.33)	Rear-B	6.6	183	95	11.3 (3.5)	622.7 (269.2)	7.0 (2.0)	VL
	4	R	L	2.88 (0.11)	Rear-B	6.6	190	102	41.1 (2.0)	1869.3 (186.9)	15.5 (0.6)	L
	2	R	M	4.36 (0.06)	Rear-B	6.6	175	93	53.0 (2.2)	3957.1 (139.8)	27.6 (0.4)	H
	1	C	L	2.56 (0.04)	Crown	6.6	196	94	26.6 (2.9)	1404.1 (151.3)	14.7 (0.5)	L

Tight End

	Frequency	Characteristics of Impact					Anthropometrics		Dynamic Response		Brain Response	
Event Type	#	Location	Velocity Level	Impact Velocity	Orientation/ Elevation	Mass (kg)	Height (cm)	Weight (kg)	Res LA (g)	Res RA (rad/s2)	MPS (%)	Magnitude Level
Helmet	125	F	L	3.20 (0.04)	Front-B	24.0	190	111	23.5 (3.9)	1857.5 (150.6)	11.2 (0.9)	L
	19	F	M	5.83 (0.16)	Front-B	24.0	198	116	75.5 (2.3)	3430.1 (565.6)	17.8 (1.1)	M
	70	FB	L	3.32 (0.09)	Left-B	24.0	193	108	21.0 (1.4)	1855.6 (740.1)	16.8 (5.1)	L
	23	FB	M	5.74 (0.13)	Right-B	24.0	196	116	65.0 (10.1)	2011.8 (383.8)	15.3 (1.7)	M
	1	FB	H	8.06 (0.15)	Right-B	24.0	196	107	97.1 (14.8)	6120.8 (759.8)	34.4 (4.3)	H
	11	S	L	3.24 (0.06)	Right-B	24.0	190	115	25.1 (3.8)	1660.1 (239.4)	19.0 (1.9)	M
	15	S	M	5.74 (0.13)	Left-C	24.0	201	117	57.1 (2.2)	3524.3 (405.6)	30.1 (0.9)	H
	1	RB	VL	1.42 (0.07)	Right-B	24.0	183	99	6.0 (0.3)	534.5 (5.5)	5.3 (0.3)	VL
	2	RB	M	5.02 (0.06)	Left-B	24.0	201	117	30.1 (0.6)	2385.4 (107.1)	28.8 (1.2)	H
	22	C	L	3.27 (0.02)	Crown	24.0	193	113	15.4 (0.8)	1195.7 (144.2)	13.0 (2.1)	L
	5	C	M	5.87 (0.00)	Crown	24.0	190	111	58.1 (5.0)	3097.4 (216.3)	20.3 (3.2)	M
Shoulder	43	F	L	3.23 (0.02)	Front-B	15.5	190	115	9.9 (0.4)	1038.6 (98.2)	14.3 (1.3)	L
	3	F	M	5.61 (0.13)	Front-B	15.5	193	113	20.7 (1.2)	2546.1 (14.9)	27.9 (0.9)	H
	21	FB	L	3.29 (0.02)	Right-C	15.5	190	109	12.9 (0.9)	1219.3 (181.2)	9.3 (0.5)	L
	3	FB	M	5.75 (0.26)	Right-B	15.5	198	115	19.0 (0.8)	1694.7 (118.9)	14.2 (2.3)	L
	1	FB	H	8.33 (0.16)	Right-D	15.5	198	115	17.3 (0.1)	1702.6 (156.5)	15.5 (1.2)	L
	8	S	L	3.30 (0.10)	Left-C	15.5	193	117	10.8 (0.3)	860.9 (210.9)	10.1 (1.6)	L
	10	S	M	5.62 (0.24)	Right-C	15.5	198	115	27.5 (0.9)	2091.8 (243.9)	19.3 (0.9)	M
	1	S	H	7.14 (0.12)	Right-A	15.5	198	115	27.5 (0.9)	2063.9 (140.0)	23.4 (1.2)	M
	6	C	L	3.25 (0.02)	Crown	15.5	198	115	9.6 (0.4)	669.2 (77.7)	10.0 (2.1)	L
	2	C	M	5.74 (0.13)	Crown	15.5	196	107	20.3 (0.6)	1023.1 (397.7)	19.1 (2.3)	M
	1	C	H	7.43 (0.22)	Crown	15.5	196	116	29.8 (0.5)	1345.5 (132.6)	23.7 (2.3)	M
Hip/	1	F	L	2.75 (0.08)	Front-B	15.2	198	113	10.9 (0.5)	831.4 (31.1)	10.7 (0.5)	L
Thigh	1	S	VL	1.17 (0.03)	Left-B	15.2	193	115	5.2 (0.4)	303.3 (48.3)	18.6 (0.6)	VL
	1	C	M	4.76 (0.00)	Crown	15.2	196	119	21.9 (0.4)	2010.6 (149.4)	5.1 (0.4)	M
Ground	2	F	L	2.37 (0.32)	Front-B	6.6	196	122	22.0 (2.9)	1112.1 (277.4)	11.4 (0.3)	L
	2	F	M	5.14 (0.05)	Front-A	6.6	193	115	80.4 (6.5)	3914.1 (401.4)	29.8 (3.0)	H
	4	FB	VL	1.19 (0.01)	Right-B	6.6	190	115	5.7 (0.4)	410.0 (23.4)	5.6 (0.4)	VL
	5	FB	L	2.84 (0.12)	Left-A	6.6	185	109	47.4 (2.8)	2407.3 (192.3)	20.6 (1.2)	M
	1	FB	M	4.10 (0.15)	Left-B	6.6	190	117	30.7 (0.6)	1864.3 (15.9)	16.1 (0.3)	L
	1	FB	H	6.57 (0.02)	Right-A	6.6	193	115	112.3 (3.5)	6646.7 (413.9)	47.6 (2.2)	VH
	9	S	L	2.90 (0.06)	Right-B	6.6	201	117	38.8 (0.7)	2580.4 (108.3)	21.9 (1.2)	M
	5	S	M	4.83 (0.07)	Right-B	6.6	193	115	88.6 (5.4)	6219.9 (594.0)	41.9 (3.3)	VH
	6	RB	L	2.85 (0.08)	Right-B	6.6	193	115	36.7 (1.2)	2148.5 (262.7)	15.2 (0.6)	L
	1	R	VL	1.07 (0.05)	Rear-B	6.6	193	111	11.9 (1.4)	534.8 (46.9)	7.1 (0.6)	VL
	1	R	L	3.22 (0.21)	Rear-B	6.6	193	115	45.2 (2.4)	2390.1 (190.0)	15.8 (0.4)	L
	4	R	M	4.94 (0.13)	Rear-B	6.6	196	107	73.0 (0.3)	5011.2 (632.0)	39.2 (2.4)	VH

Offensive Line

	Frequency	Characteristics of Impact					Anthropometrics		Dynamic Response		Brain Response	
Event Type	#	Location	Velocity Level	Impact Velocity	Orientation/ Elevation	Mass (kg)	Height (cm)	Weight (kg)	Res LA (g)	Res RA (rad/s2)	MPS (%)	Magnitude Level
Helmet	225	F	L	3.09 (0.17)	Front-B	24.0	193	135	20.5 (2.8)	1256.6 (125.7)	10.0 (0.8)	L
	5	F	M	5.12 (0.16)	Front-B	24.0	201	141	58.9 (3.0)	2652.3 (445.5)	18.3 (2.5)	M
	2	FB	VL	1.20 (0.04)	Left-B	24.0	193	131	4.9 (0.2)	376.5 (33.9)	5.1 (0.5)	VL
	124	FB	L	3.20 (0.02)	Right-B	24.0	198	138	15.6 (1.0)	1198.6 (79.8)	12.8 (0.6)	L
	20	FB	M	5.78 (0.08)	Right-B	24.0	188	138	42.8 (3.9)	3102.1 (440.1)	22.4 (1.5)	M
	34	S	L	3.21 (0.02)	Right-A	24.0	193	137	8.4 (0.5)	662.6 (49.9)	8.2 (0.9)	L
	18	C	L	3.23 (0.05)	Crown	24.0	201	141	22.8 (4.3)	1266.4 (41.0)	11.9 (0.6)	L
Shoulder	1	F	VL	1.28 (0.13)	Front-C	15.5	203	143	3.9 (0.8)	226.8 (27.0)	0.05 (0.0)	VL
	93	F	L	3.17 (0.06)	Front-B	15.5	196	136	10.0 (0.8)	1313.6 (152.8)	15.9 (2.2)	L
	3	F	M	5.15 (0.11)	Front-B	15.5	190	127	22.3 (3.8)	2850.3 (366.3)	28.5 (1.2)	H
	41	FB	L	3.21 (0.02)	Left-B	15.5	188	138	8.9 (0.3)	984.3 (57.1)	13.2 (1.2)	L
	13	S	L	3.21 (0.02)	Left-C	15.5	196	138	12.4 (0.8)	924.2 (140.1)	8.8 (1.0)	L
	1	S	M	4.89 (0.05)	Left-B	15.5	198	138	15.3 (1.3)	1446.3 (183.1)	15.5 (0.7)	L
	9	C	L	3.20 (0.04)	Crown	15.5	196	140	10.6 (1.1)	1015.6 (71.3)	12.7 (0.9)	L
	2	C	M	4.77 (0.09)	Crown	15.5	193	131	16.6 (1.5)	1163.5 (186.2)	13.6 (3.4)	L
Hip/	1	F	VL	1.41 (0.33)	Front-B	15.2	196	151	5.3 (1.3)	359.9 (58.7)	5.2 (0.5)	VL
Thigh	1	S	M	4.74 (0.14)	Right-A	15.2	196	138	15.0 (1.2)	1187.8 (71.0)	11.3 (3.0)	L
	1	R	L	2.76 (0.08)	Rear	15.2	196	150	5.4 (0.5)	502.9 (17.3)	5.9 (0.5)	VL
Ground	1	F	M	5.71 (0.04)	Front-B	6.6	196	138	114.2 (16.6)	4563.3 (803.6)	33.9 (1.1)	H
	4	FB	L	2.99 (0.26)	Right-B	6.6	196	151	36.4 (1.0)	2479.7 (215.4)	19.1 (1.6)	M
	2	S	VL	1.53 (0.03)	Right-A	6.6	201	140	13.2 (0.4)	547.9 (1.5)	6.8 (0.1)	VL
	1	S	L	3.25 (0.05)	Right-B	6.6	188	131	46.2 (0.4)	3180.9 (114.7)	25.5 (0.5)	M
	1	R	L	2.90 (0.03)	Rear-B	6.6	193	142	50.7 (0.5)	2574.7 (475.3)	18.8 (0.9)	M

Defensive Line

	Frequency	Characteristics of Impact					Anthropometrics		Dynamic Response		Brain Response	
Event Type	#	Location	Velocity Level	Impact Velocity	Orientation/ Elevation	Mass (kg)	Height (cm)	Weight (kg)	Res LA (g)	Res RA (rad/s2)	MPS (%)	Magnitude Level
Helmet	1	F	VL	1.20 (0.04)	Front	24.0	193	131	4.9 (0.2)	376.5 (33.9)	5.1 (0.0)	VL
	209	F	L	3.20 (0.00)	Front-B	24.0	190	140	25.5 (2.2)	1209.5 (326.2)	9.7 (1.0)	L
	5	F	M	5.70 (0.29)	Front-B	24.0	193	129	50.9 (7.6)	2004.3 (248.0)	16.6 (2.4)	L
	1	F	H	7.98 (0.15)	Front-B	24.0	185	136	62.5 (6.5)	3832.8 (791.4)	33.0 (2.9)	H
	153	FB	L	3.27 (0.09)	Left-B	24.0	185	140	21.1 (1.0)	1965.3 (181.6)	11.3 (0.4)	L
	6	FB	M	5.74 (0.00)	Right-A	24.0	196	127	59.0 (2.6)	3923.1 (381.8)	23.7 (3.0)	M
	56	S	L	3.27 (0.05)	Left-C	24.0	188	124	22.2 (1.1)	1569.1 (196.8)	15.5 (2.8)	L
	2	S	M	5.11 (0.22)	Right-B	24.0	190	140	46.7 (4.3)	4038.5 (195.1)	31.8 (1.0)	H
	1	RB	M	5.49 (0.00)	Right-C	24.0	185	138	50.5 (5.2)	3375.2 (819.3)	25.7 (4.0)	M
	28	C	L	3.24 (0.00)	Crown	24.0	198	146	24.0 (4.4)	1655.9 (489.9)	12.0 (4.3)	L
	1	C	M	6.53 (0.10)	Crown	24.0	196	127	48.4 (3.3)	3937.4 (418.9)	30.7 (3.2)	H
Shoulder	110	F	L	3.20 (0.08)	Front-B	15.5	203	127	10.7 (1.2)	1108.3 (108.6)	13.0 (0.8)	L
	8	F	M	5.83 (0.08)	Front-B	15.5	203	127	20.8 (1.1)	2953.2 (218.8)	28.3 (1.6)	H
	1	F	H	7.98 (0.15)	Front-B	15.5	193	129	32.6 (1.7)	2670.6 (35.4)	23.3 (0.9)	M
	31	FB	L	3.31 (0.05)	Right-C	15.5	203	127	11.3 (0.7)	1318.2 (71.7)	16.6 (1.2)	L
	2	FB	M	5.53 (0.07)	Left-B	15.5	196	122	19.5 (1.6)	2476.1 (157.9)	25.7 (6.2)	M
	14	S	L	3.16 (0.04)	Right-B	15.5	185	136	9.3 (0.4)	1184.4 (32.0)	14.1 (0.4)	L
	1	S	M	5.16 (0.29)	Right-A	15.5	203	127	15.8 (1.0)	1193.5 (158.4)	12.4 (1.3)	L
	20	C	L	3.19 (0.08)	Crown	15.5	190	142	9.1 (0.5)	946.6 (138.5)	9.1 (1.0)	L
	1	C	M	5.61 (0.00)	Crown	15.5	203	127	20.5 (0.6)	1580.2 (103.9)	15.8 (1.2)	L
Hip/	4	F	VL	1.41 (0.33)	Front-B	15.2	190	122	5.3 (1.3)	359.9 (58.7)	5.2 (0.5)	VL
Thigh	2	F	M	6.37 (0.18)	Front-B	15.2	193	122	34.0 (0.9)	1650.6 (145.2)	18.6 (0.6)	M
	3	S	VL	1.17 (0.03)	Left-B	15.2	198	120	5.2 (0.4)	303.3 (48.3)	5.1 (0.4)	VL
Ground	1	FB	VL	0.97 (0.03)	Left-B	6.6	190	140	14.8 (2.5)	722.1 (170.9)	6.0 (0.1)	VL
	2	FB	L	2.93 (0.04)	Right-B	6.6	185	138	36.1 (2.0)	2049.8 (128.6)	21.0 (2.1)	M
	4	S	VL	1.53 (0.03)	Right-B	6.6	193	135	10.8 (1.0)	568.5 (54.9)	7.1 (0.5)	VL
	2	S	L	2.50 (0.11)	Right-B	6.6	198	120	32.8 (1.6)	1806.0 (116.8)	13.9 (9.8)	L
	1	RB	VL	1.98 (0.02)	Left-A	6.6	190	124	19.9 (0.4)	1448.2 (40.1)	10.6 (0.9)	L
	1	RB	L	2.32 (0.17)	Right-B	6.6	190	156	33.1 (1.0)	2793.9 (241.6)	20.2 (1.4)	M
	3	R	VL	0.91 (0.08)	Rear-B	6.6	203	127	11.5 (0.6)	525.6 (42.6)	6.4 (0.5)	VL
	1	C	L	2.90 (0.04)	Crown	6.6	185	129	30.5 (2.4)	1953.1 (283.1)	15.1 (0.7)	L

Linebacker

	Frequency	Characteristics of Impact					Anthropometrics		Dynamic Response		Brain Response	
Event Type	#	Location	Velocity Level	Impact Velocity	Orientation/ Elevation	Mass (kg)	Height (cm)	Weight (kg)	Res LA (g)	Res RA (rad/s2)	MPS (%)	Magnitude Level
Helmet	55	F	L	3.24 (0.00)	Front-B	24.0	185	106	28.2 (0.8)	1117.7 (37.0)	10.7 (0.3)	L
	24	F	M	5.70 (0.08)	Front-B	24.0	190	112	73.2 (5.8)	3445.5 (162.2)	25.4 (1.0)	M
	37	FB	L	3.19 (0.05)	Left-B	24.0	188	123	25.5 (0.9)	1374.3 (89.9)	13.1 (0.5)	L
	17	FB	M	5.66 (0.26)	Left-B	24.0	185	121	53.3 (4.7)	2294.2 (133.6)	20.0 (2.1)	M
	22	S	L	3.27 (0.05)	Right-B	24.0	190	110	21.8 (1.2)	1373.3 (146.8)	15.2 (0.8)	L
	11	S	M	5.65 (0.08)	Right-A	24.0	190	110	69.8 (5.1)	4243.1 (635.1)	31.3 (4.2)	H
	1	RB	L	3.69 (0.03)	Right-C	24.0	188	111	19.6 (0.3)	1962.3 (20.3)	18.8 (1.2)	M
	1	R	M	5.49 (0.00)	Rear-C	24.0	185	111	50.1 (4.7)	2901.7 (464.5)	22.8 (1.7)	M
	1	C	L	3.27 (0.05)	Crown	24.0	190	98	14.7 (0.3)	1150.8 (164.5)	13.2 (0.2)	L
	2	C	M	6.31 (0.00)	Crown	24.0	188	108	64.1 (5.4)	2343.7 (70.2)	13.7 (1.8)	L
Shoulder	1	F	VL	1.28 (0.13)	Front-C	15.5	185	106	3.9 (0.8)	226.8 (27.0)	4.6 (0.8)	VL
	21	F	L	3.37 (0.00)	Front-B	15.5	185	99	11.4 (0.6)	1027.4 (76.0)	12.6 (0.7)	L
	16	F	M	5.96 (0.08)	Front-C	15.5	188	108	26.5 (2.9)	1944.2 (205.0)	18.3 (1.7)	M
	1	F	H	8.71 (0.00)	Front-C	15.5	185	109	37.6 (4.4)	4214.5 (522.6)	46.1 (3.8)	VH
	3	FB	M	5.87 (0.00)	Left-B	15.5	185	99	22.4 (0.8)	1265.3 (166.9)	11.9 (1.6)	L
	1	FB	H	7.43 (0.00)	Right-D	15.5	190	98	24.8 (0.1)	2698.7 (313.9)	30.2 (4.3)	H
	2	S	L	4.18 (0.03)	Left-C	15.5	188	107	16.3 (0.5)	1394.8 (201.6)	15.1 (2.9)	L
	12	S	M	5.74 (0.00)	Left-B	15.5	188	108	14.8 (1.0)	1415.6 (345.1)	13.0 (1.7)	L
	3	C	L	3.20 (0.04)	Crown	15.5	188	111	10.6 (1.1)	1015.6 (71.3)	12.7 (0.0)	L
Hip/	3	F	M	6.58 (0.10)	Front-B	15.2	188	115	31.7 (2.3)	4157.3 (203.9)	34.1 (3.6)	H
Thigh	11	FB	L	3.50 (0.00)	Right-B	15.2	190	107	12.9 (0.3)	800.4 (29.1)	10.0 (1.0)	L
	3	FB	M	6.47 (0.00)	Right-A	15.2	185	109	28.7 (0.6)	1994.8 (59.8)	19.9 (1.2)	M
Ground	5	F	L	2.92 (0.12)	Front-B	6.6	185	121	48.8 (2.9)	2086.2 (187.7)	17.9 (0.4)	M
	3	F	M	4.70 (0.04)	Front-B	6.6	185	109	47.5 (0.4)	2478.6 (183.0)	19.2 (0.9)	M
	5	FB	VL	1.54 (0.02)	Right-B	6.6	188	115	5.4 (0.5)	498.8 (60.4)	5.3 (0.4)	VL
	4	FB	L	2.76 (0.10)	Left-B	6.6	185	109	38.7 (2.7)	1868.2 (147.7)	12.5 (2.5)	L
	4	S	VL	1.12 (0.11)	Right-B	6.6	190	110	11.4 (1.7)	481.3 (56.8)	6.2 (0.9)	VL
	5	S	L	2.99 (0.09)	Right-B	6.6	185	101	39.7 (0.5)	2319.8 (64.2)	20.7 (0.7)	M
	2	S	M	4.85 (0.04)	Right-B	6.6	188	120	98.9 (5.6)	6131.8 (388.7)	38.8 (0.8)	VH
	5	RB	VL	1.02 (0.14)	Left-B	6.6	190	98	9.2 (1.6)	500.5 (96.0)	6.2 (0.5)	VL
	4	R	L	2.87 (0.07)	Rear-B	6.6	185	99	46.4 (1.6)	2301.6 (236.7)	15.6 (0.5)	L
	2	R	M	5.11 (0.07)	Rear-B	6.6	185	99	73.1 (1.3)	4272.0 (156.1)	30.5 (0.7)	H

Defensive Back

	Frequency	Characteristics of Impact					Anthropometrics		Dynamic Response		Brain Response	
Event Type	#	Location	Velocity Level	Impact Velocity	Orientation/ Elevation	Mass (kg)	Height (cm)	Weight (kg)	Res LA (g)	Res RA (rad/s2)	MPS (%)	Magnitude Level
Helmet	1	F	L	2.65 (0.03)	Front-C	24.0	180	86	26.0 (6.2)	1479.9 (150.2)	13.6 (2.0)	L
	2	F	H	8.43 (0.28)	Front-A	24.0	180	86	80.5 (5.3)	3619.9 (166.6)	24.0 (2.2)	M
	1	FB	H	8.42 (0.00)	Right-A	24.0	183	88	106.2 (7.4)	5533.9 (943.8)	27.8 (1.6)	H
	1	S	M	5.90 (0.00)	Right-B	24.0	178	91	68.2 (0.9)	3760.1 (370.6)	33.3 (3.8)	H
	3	C	H	8.24 (0.16)	Crown	24.0	185	97	114.4 (11.1)	5019.3 (1635.8)	22.4 (4.1)	M
Shoulder	7	F	L	3.32 (0.05)	Front-A	15.5	183	91	12.3 (0.2)	1145.2 (21.8)	14.0 (0.6)	L
	3	F	M	6.11 (0.09)	Front-B	15.5	178	89	23.7 (0.4)	2492.3 (526.9)	27.7 (6.8)	H
	4	FB	M	5.62 (0.31)	Right-C	15.5	178	83	17.4 (0.6)	1152.4 (131.7)	11.6 (1.4)	L
	1	FB	VH	10.98 (0.00)	Right-C	15.5	183	87	46.7 (1.7)	3404.1 (296.4)	34.9 (2.9)	H
	1	S	L	2.71 (0.02)	Right-C	15.5	185	91	11.1 (0.2)	829.3 (28.7)	10.5 (1.1)	L
	4	S	M	5.79 (0.03)	Right-C	15.5	185	92	14.3 (0.6)	1521.6 (55.6)	14.5 (1.0)	L
	2	S	H	8.33 (0.16)	Right-A	15.5	183	88	33.9 (0.5)	2561.2 (221.2)	24.8 (1.8)	M
	1	C	M	5.33 (0.23)	Crown	15.5	178	89	18.5 (1.2)	1056.1 (18.5)	11.1 (0.3)	L
	3	C	H	7.50 (0.13)	Crown	15.5	178	88	31.8 (4.3)	1301.5 (26.8)	12.8 (0.7)	L
Hip/	5	F	VL	1.41 (0.33)	Front-B	15.2	183	88	5.3 (1.3)	359.9 (58.7)	5.2 (0.5)	VL
Thigh	1	F	M	6.53 (0.10)	Front-C	15.2	173	86	26.2 (3.1)	2923.4 (414.5)	36.3 (4.8)	VH
	1	S	VL	1.17 (0.03)	Left-B	15.2	180	93	5.2 (0.4)	303.3 (48.3)	5.1 (0.4)	VL
	6	S	M	5.74 (0.26)	Right-B	15.2	183	92	25.1 (1.0)	2185.8 (375.5)	13.0 (0.3)	L
Ground	1	F	VL	0.06 (0.01)	Front-A	6.6	178	98	9.9 (2.7)	389.8 (25.8)	6.1 (1.1)	VL
	4	F	L	2.92 (0.02)	Front-B	6.6	185	92	30.2 (1.5)	1537.4 (111.1)	13.1 (1.6)	L
	6	F	M	5.14 (0.05)	Front-C	6.6	180	86	59.2 (9.6)	2641.8 (484.8)	19.2 (1.4)	M
	1	F	H	6.92 (0.22)	Front-B	6.6	183	88	124.0 (12.6)	5616.3 (823.2)	39.4 (6.7)	VH
	3	FB	L	2.80 (0.03)	Left-B	6.6	185	87	38.3 (1.8)	2263.9 (82.3)	19.9 (0.5)	M
	1	S	VL	1.12 (0.11)	Right-B	6.6	190	110	11.4 (1.7)	481.3 (56.8)	6.2 (0.9)	VL
	5	S	L	2.99 (0.20)	Right-B	6.6	178	88	39.6 (1.3)	2372.6 (168.3)	21.0 (0.8)	M
	4	S	M	5.10 (0.19)	Left-B	6.6	185	90	96.5 (0.3)	4793.2 (201.5)	40.3 (1.0)	VH
	2	S	H	7.07 (0.04)	Right-B	6.6	180	87	138.4 (7.0)	9366.1 (625.4)	50.6 (1.4)	VH
	2	RB	L	2.68 (0.02)	Left-B	6.6	180	86	35.5 (1.5)	2891.0 (253.9)	23.6 (1.0)	M
	3	RB	M	4.94 (0.08)	Right-B	6.6	180	86	64.8 (0.8)	5851.8 (148.6)	35.9 (0.6)	VH
	5	R	L	2.81 (0.10)	Rear-B	6.6	185	90	46.1 (2.5)	2527.9 (83.5)	19.7 (0.9)	M
	2	R	M	4.76 (0.14)	Rear-B	6.6	183	92	59.7 (3.1)	4238.6 (830.7)	32.4 (0.5)	H
	1	C	VL	1.74 (0.09)	Crown	6.6	185	87	12.5 (1.0)	768.5 (93.7)	8.2 (0.9)	L
	1	C	M	3.95 (0.03)	Crown	6.6	185	97	48.9 (4.4)	2073.6 (197.4)	16.8 (0.2)	L