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# Traumatic brain injury in contact sports

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BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

**TRAUMATIC BRAIN INJURY IN CONTACT SPORTS**

by

**JAVIER S. RIOS**

B.S., The University of Texas at El Paso, 2010

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

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# **TRAUMATIC BRAIN INJURY IN CONTACT SPORTS**

**JAVIER S. RIOS**

## **ABSTRACT**

Traumatic brain injury is a topic that in recent years has received increased scrutiny by the media and is viewed as a cause for public health concern in athletes that are participating in contact sports. There has been an apparent rise in the reported number of traumatic brain injuries over the last decade possibly due to a number of factors such as an increase in enrollment of sports and suspected better understanding of brain injury in the sports world. Direct or indirect impact forces applied involving acceleration/deceleration and linear/angular forces primarily cause trauma to the brain. This insult results in evident diffuse axonal and focal injuries to varying degrees in brain tissue. The spectrum of pathophysiology in traumatic brain injury involves structural, neurochemical, metabolic, vascular, inflammatory, immunologic, and ultimately cell death, which plays a hand directly in the nonspecific presentation of symptoms reported by athletes as well as the progression of recovery. Traumatic brain injury is typically associated with short- and long-term sequelae, however, inducing repetitive episodes of trauma over a career, as may happen in sports, may lead to a progressive neurodegenerative disease known as chronic

traumatic encephalopathy. Chronic traumatic encephalopathy has been known to affect boxers previously, but in recent years the attention has shifted and found this disease in athletes from other sports. The spectrum of disease in chronic traumatic encephalopathy involves a progressive tauopathy that spreads across different regions of the brain in a classified four staged grading system. Several risk factors have been identified in placing athletes at risk for traumatic brain episodes, however no risk factors have been directly linked to chronic traumatic encephalopathy. Much information is lacking in a complete understanding of traumatic brain injury and chronic traumatic encephalopathy, therefore emphasizing the importance of further research and consistently improving modifications in the protocols for assessment, recognition, management, and return to play criteria for injured athletes. Furthermore, despite the gaps in knowledge, preventative measures should serve a particular role in reducing the incidence of detected traumatic brain injuries, which should include policy changes, sport rule changes, and especially changes to the accepted sports culture through mandatory education.

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## LIST OF ABBREVIATIONS

3 R tau	3 Repeat tau
4 R tau	4 Repeat tau
A/D	Acceleration/Deceleration
A $\beta$	Amyloid Beta
AD	Alzheimer's Disease
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ALS	Amyotrophic Lateral Sclerosis
Aph-1	Anterior Pharynx-Defective 1
ApoE	Apolipoprotein E
ATF-3	Activating Transcription Factor 3
ATP	Adenosine 5'-Triphosphate
$\beta$ -APP	Beta Amyloid Precursor Protein
BACE1	Beta-Site Amyloid Precursor Protein Cleaving Enzyme 1
BESS	Balance Error Scoring System
CDC	Centers for Disease Control and Prevention
CN V	Cranial Nerve Five
CNS	Central Nervous System
CP-13	Citrullinated Protein 13

CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTE	Chronic Traumatic Encephalopathy
DAI	Diffuse Axonal Injury
DTI	Diffusion Tensor Imaging
fMRI	Functional Magnetic Resonance Imaging
FTLD	Frontotemporal Lobar Degeneration
GCS	Glasgow Coma Scale
JNK	c-Jun N-terminal Kinase
LOC	Loss of Consciousness
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NFL	National Football League
NHL	National Hockey League
NMDA	N-Methyl-D-Aspartate
NP	Neuropsychological
NSAID	Non-Steroidal Anti-Inflammatory Drug
p-tau	Phosphorylated tau
PCS	Postconcussion Syndrome
PD	Parkinson's Disease
Pen-2	Presenilin Enhancer 2
PET	Positron Emission Tomography

PNS	Peripheral Nervous System
PTA	Post-Traumatic Amnesia
pTDP-43	Phosphorylated Transactivation Responsive Region Deoxyribonucleic Acid-Binding Protein 43
RNA	Ribonucleic Acid
RTP	Return to Play
SAC	Standardized Assessment of Concussion
SCAT-2	Sport Concussion Assessment Tool 2
SIS	Second Impact Syndrome
SPECT	Single-Photon Emission Computed Tomography
TBI	Traumatic Brain Injury
TDP-43	Transactivation Responsive Region Deoxyribonucleic Acid- Binding Protein 43
UCLA	University of California, Los Angeles

## INTRODUCTION

Traumatic brain injury (TBI) is a common Central Nervous System (CNS) insult that has received increased scrutiny in recent years, both in medical literature and in the social media, due to widespread public awareness of its consequences in athletes. As the number of participants in youth sports continues to rise, the risk of injury is increasing considerably (Gilchrist et al., 2011). TBI is actually a collection of pathologic processes, which involve direct and indirect damage to the cortex and deep white matter. There is a greater awareness of potential short- and long-term sequelae of athletes suffering TBIs, which include an increased propensity for reinjury and chronic traumatic encephalopathy (Sahler & Greenwald, 2012). Federal and State governments, as well as many sport's governing bodies are implementing rules and policies designed to protect athletes and to establish a standard of care for athletes suffering TBIs. The purpose of this thesis is to explore the overall impact and current knowledge on TBI including the potential effects from repeated trauma such as chronic traumatic encephalopathy (CTE) on athletes participating in contact sports. This will include definitions, epidemiology, and pathophysiology of TBI and CTE. Finally, this thesis will evaluate the influences that may cause and affect athletes participating in sports in an unbiased manner. It will include an overview of the known risk factors predisposing athletes to brain injury and a phenomenon associated with brain reinjury before the resolution of the previous

trauma resulting in permanent damage or even death. An evaluation of the diagnostic tools used in the assessment/management of athletes after sustaining TBI will be made, and is to include the known criteria for return to play. Finally, this thesis will attempt to provide a proposal for further research in areas that have currently not been explored or fully determined, which may prove to be beneficial in the diagnosis, management, and ultimately improving the prognosis of the injured athlete.

## **Traumatic Brain Injury Basics**

Prior to discussion, several terms and concepts will be defined.

### ***Definition***

According to the American Association of Neurological Surgeons, TBI is defined as a biomechanically induced force on the head resulting in disruption of normal brain function, which can be temporary or permanent (American Association of Neurological Surgeons, 2011). TBI may fall under two classifications: Acquired Brain Injury, which may include any direct damage caused by events after birth that is not to include genetic, congenital, perinatal illness, or hypoxia, and Non-Traumatic Brain Injury, which does not involve external mechanical forces such as strokes, infections, brain tumors, hypoxia, ischemia, and poisoning (Chapman et al., 1999; Collins & Dean, 2002). In

research literature, generally the term 'traumatic brain injury' is typically used to refer to acquired brain injury that occurs after birth and very commonly to non-penetrating TBIs (although that may not always be the case), which will be the focus of study in this thesis. All TBIs are considered head injuries, although head injuries may refer to injuring other parts of the head not including the brain such as the skull or scalp making it a much broader category of classification (Jennett, 1998). Also an important notification is that there is the possibility of sustaining a head injury without actually having brain injury and the possibility of having a brain injury without any other form of head injury. TBIs fall under the classification of CNS and neurotraumatic injuries that are usually based on severity, anatomical findings of the injury, and the mechanism of injury such as the causative forces (Arciniegas & Beresford, 2001; Weber & Maas, 2007; Saatman et al., 2008).

Symptoms of TBI can range from mild, moderate, to severe depending on the extent of damage to the brain. Acute brain injury comprises mild TBI or is interchangeably used with concussion, which is defined as a short-term loss of brain function in response to injury that may or may not include loss of consciousness (Blennow et al., 2012). This may also be followed by physical, cognitive, emotional, and/or sleep related symptoms. On gross inspection, there is no significant evidence of pathology such as hemorrhage, or abnormalities in structural brain imaging (Harmon et al., 2013). Alternatively, catastrophic brain injury comprises severe brain injury, which would include intracranial bleeding or

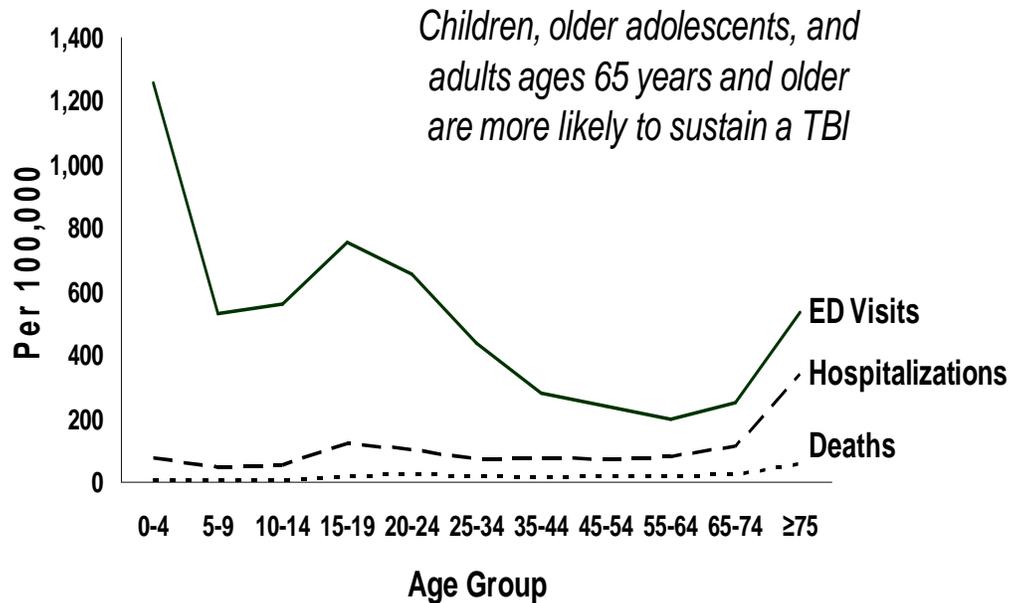
cerebral contusions making it potentially fatal (Blennow et al., 2012). Cerebral contusions are small collection of blood from microhemorrhages forming in the cerebral cortex. The most common cause of death in catastrophic brain injury is subdural hematomas, which is a blood collection between the arachnoid matter and the Dura matter (Mangat, 2012). Considered more of an acute complication of TBI would be epidural hematomas, which is a blood collection between the Dura matter and the skull (Chen et al., 2012). Both subdural and epidural hematomas can place a considerable amount of pressure on the brain leading to damage at different extents due to the location of the bleeding episode. Symptoms associated with catastrophic injuries to the brain may include severe headaches, repeated vomiting and nausea, convulsions or seizures, an inability to awaken from sleep, dilation of one or both pupils of the eye, slurred speech, weakness or numbness in the extremities, loss of coordination, and increased confusion (Biros & Heegaard, 2009).

## **Epidemiology**

The Centers for Disease Control and Prevention indicate that approximately 1.7 million TBIs occur each year in the United States with estimates closer to 3.8 million (Faul et al., 2010; Guskiewicz et al., 2000). Of these numbers, there were about 52,000 deaths (contributing to a third of all injury-related death in the United States), 275,000 hospitalizations per year, and

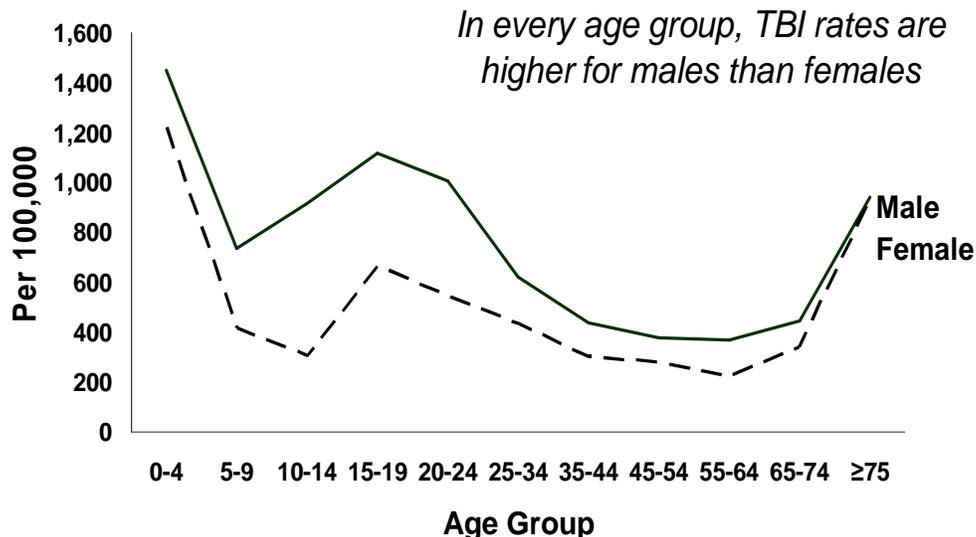
1,365 million treated and released from the emergency department (Faul et al., 2010). In the United States there is roughly 3.2 to 5.3 million living in disability from TBI (Selassie et al., 2008). Direct medical costs such as medical expenses and indirect costs such as lost wages of TBI totaled an estimated \$76.5 billion in 2000 (Corso et al., 2006). It is important to note that the actual incidence of head injuries may potentially be higher because reporting agencies such as CDC does not include non-emergency department visits such as primary care and special office visits as well as less severe head injuries that may very well be self-treated.

The leading causes of TBI in the United States are falls (35.2%), motor vehicle-traffic accidents (17.3%), struck by or against events (16.5%), and assault (10%), which about 75% of those numbers are considered mild TBIs. Motor vehicle crashes and traffic-related incidents reported the largest percentage of TBI-related deaths with the risk highest in 16 to 19 year old age groups. Falls cause about half of TBIs among children the ages of 0 to 14 years and 61% of all TBIs among adults aged 65 years and older (Faul et al., 2010). The rates of fall-related TBI hospitalizations tend to increase with age, with highest rates in individuals 85 years and older being more than two times that of individuals aged 75 to 84 years old, and six times greater than individuals aged 65 to 74 years old (Coronado et al., 2005). The highest incidence of TBIs by age tend to peak at children aged 0 to 4 years, older adolescents aged 15 to 19 years, and older adults aged 65 years and older (Figure 1).



**Figure 1: Annual Average of Traumatic Brain Injuries in the United States by Age Group:** The following graph is depicting the estimated annual average rates of TBI-related emergency department visits, hospitalizations, and deaths by age groups in the United States. The x-axis represents age in years and the y-axis represents the rate per 100,000 population. Very young children ages 0 to 4 years had the highest rate of TBI-related emergency department visits at 1,256 per 100,000 population, followed by older adolescents ages 15 to 19 years at 757 per 100,000. Then an evident decline from ages 20 to 64 years before they rise at ages 65 to 74 years. The highest rates of TBI-related hospitalization and death occurred among adults 75 years or older at 339 per 100,000 and 57 per 100,000 respectively. Figure was taken from Faul, Xu, Wald, & Coronado, 2010.

In every age group, rates for TBIs are higher in males than females and are about 1.4 times more likely to sustain a TBI. Males aged 0 to 4 years of age have the highest rates of TBI-related emergency department visits as depicted on Figure 2.



**Figure 2: Annual Average of Traumatic Brain Injuries in the United States by Sex:** The following graph displays the estimated annual average rates of TBI-related emergency department visits, hospitalizations, and deaths combined by gender in the United States. The x-axis represents age in years and the y-axis represents the rate per 100,000 population. Males from 0 to 4 years of age had the highest rates at 1,451 per 100,000. In every age group, males had a higher rate of TBIs than females. Figure was taken from Faul, Xu, Wald, & Coronado, 2010.

In relation to TBIs in sports, there are about 300,000 reported injuries in the United States from which most are retrieved using existing national data sets such as the National Sports-Related Injury Surveillance System Reporting Information Online through certified athletic trainers affiliated with the National Athletic Trainer’s Association (Langlois et al., 2006; Marar et al., 2012). Other reporting systems may include the United States Consumer Product Safety Commission tracking product-related injuries through its National Electronic Injury Surveillance System (American Association of Neurological Surgeons, 2011). The United States emergency departments treat approximately 173,285

sports and recreational activities related brain injuries ages ranging from birth to 19 years old (Gilchrist et al., 2011). It is important to note that most of these reported numbers included athletes that reported a loss of consciousness. Some studies suggest that only about 8% to 19.2% of sports-related TBIs occur with a loss of consciousness (Langlois et al., 2006). Taking this into consideration, a more accurate approximation may be 1.6 to 3.8 million sports-related TBIs occurring each year including those for which no medical care is sought. It is very likely that this estimate may still be low because many of these injuries often go unrecognized and thus not counted as many athletes often fail to report concussive symptoms.

Recent research shows that young athletes are more susceptible to TBIs than older athletes (Buzzini & Guskiewicz, 2006). This may have very important implications because of the ongoing neurocognitive development that occurs throughout adolescence, which can be altered by the severe acute and long-term complications of concussion in young athletes (Patel & Greydanus, 2002). Reduction of TBI in sports is a major public health concern especially noting how the number of participating high school athletes has increased, with more than half of all high school students in the 2009-2010 school year (over 3.1 million girls and 4.2 million boys) participating in sports (Meehan & Bachur, 2009).

Previous investigations involving a range of high school and college sports show concussion rates higher in competition than in practice as well as a disparity between genders showing that females sustain higher concussion rates

than males comparing the same sports with same rules (Gessel et al., 2007). Some evidence further suggests a discrepancy between male and female athlete reported symptoms, TBI recovery times, and post concussion outcomes on neuropsychological testing indicating the need for a complete understanding of TBIs in younger athletes as research signals younger athletes are more prone to second impact syndrome often having catastrophic consequences (Covassin et al., 2003; Broshek et al., 2005; Buzzini & Guskiewicz, 2006; Dick, 2009).

Over a 10-year study period, emergency departments treating sport related TBIs increased by 60% annually. During this period, mild TBIs in organized sports doubled in ages 8 to 13 years and more than tripled in 14 to 19 year age groups. Approximately 71% of those individuals were male and 70.5% were aged 10-19 years old (Gilchrist et al., 2011). Overall the activities that demonstrated a significant amount of TBI-related emergency department visits were bicycling, football, playground activities, basketball, and soccer (Gilchrist et al., 2011). In another study, it was indicated that 40% of athletes in 18 of 20 sports studied, concussion symptoms resolved in 3 days or less, ¼ of all athletes recovered within a day, and 2% returned to play the same day of the concussion (Marar et al., 2012).

Overall, these statistics are alarming and clearly imply the need for a complete understanding of TBIs, particularly in athletes participating in sports. In order to achieve a reduction in long-term disability and potential reinjuries, proper recognition of TBIs is required, careful documentation of signs and symptoms,

monitoring of brain function through neuropsychological profiles, as well as accurate and consistent medical care would be crucial.

## MECHANISMS OF INJURY

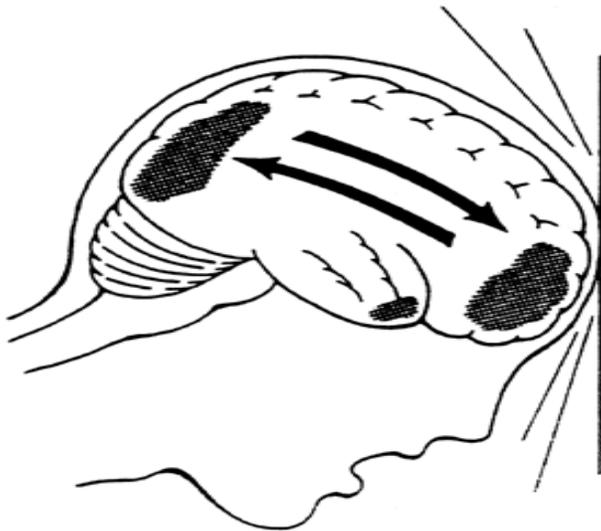
TBI or intracranial injury occurs when an external force can induce trauma to the brain. Typically trauma to the head that leads to TBIs can either be in the form of a closed injury (meaning non-penetrating or blunt), which occurs when the brain is not exposed, or an open injury (meaning penetrating head injury) where an object pierces the skull and breaches the Dura mater. In closed head injury, brain tissue damage is caused by deformation from mechanical loading, which may be categorized from both contact forces (impact loading) and inertial forces (impulse loading or inertial loading), which is acceleration/deceleration movement causing brain tissue displacement with or without contact. In penetrating brain injuries, tissue damage occurs by way of direct tissue disruption from a missile/projectile and its dissipated energy. Higher velocity missiles cause much greater damage (Hannay et al., 2004; Blisitt, 2006; Maas et al., 2008).

Injuries to the brain can be caused by direct or indirect impacts. Direct impact typically denotes a blow that makes direct contact with the head. An indirect impact (A/D type movements) refers to an impact that sets the head in motion without directly striking it. Even in the absence of direct impact, significant acceleration/deceleration of the head can cause TBI. Linear (translational) or angular (rotational) A/D movements are traditionally described to happen in indirect impacts. Arciniegas and Beresford described linear forces “occurring when the force vector passes in a straight line through the center of

mass of the brain” and angular forces “occurring due to application of force to the brain outside its center of gravity, resulting in rotation of the brain around its center of mass” (Arciniegas & Beresford, 2001). During real-world activities, combinations of both direct and indirect impacts along with a mixture of both types of A/D movements characteristically occur in a realistic setting as most forces applied during injury occur at least somewhat off-center (Hardman & Manoukian, 2002; Guskiewicz & Mihalik, 2011).

In many cases, coup and contrecoup injuries may be caused as a result of direct and indirect impacts. These injuries are considered cerebral contusions or bruises caused by a force or blow that can damage or destroy blood vessels leading to multiple microhemorrhages (Lury & Castillo, 2004). Typically, coup and contrecoup injuries result in contusions after a strong blow/acceleration/deceleration to the head that will cause the brain to slam against the inside of the skull in a ricochet fashion. Injuries occurring underneath the point of impact are referred to as coup. Injuries occurring on the opposite side (although not limited to other sites) of the point of impact due to a possible rebound effect of the brain inside the skull are referred to as contrecoup as illustrated in Figure 3. Although the exact mechanism of these injuries is subject to much debate, it is likely these injuries can occur individually (meaning only coup or only contrecoup) as well as simultaneously together. It has been demonstrated in many cases that when a moving object impacts the stationary head, coup injuries result, and when the moving head strikes a stationary object,

they result in contrecoup injuries (Morrison et al., 1998; Poirier, 2003). Characteristically, these injuries are for the most part, although not limited to, considered focal brain injuries (as they occur only at the site of impact) as opposed to diffuse injuries that may occur over a widespread area throughout the brain (Hardman & Manoukian, 2002). Coup-contrecoup injuries may also be the cause of additional complications such as hematomas, brain swelling, disruptions in cerebrospinal fluid (CSF) flow, and possibly problems with skull fragments compressing or entering brain tissue (Shaw, 2002).



**Figure 3: Coup and Contrecoup Injury:** Displayed is an image of the coup-contrecoup phenomenon as a result of ricochet of the brain within the skull. Damage underneath the point of contact is considered a coup injury. Damage resulting opposite or away from the point of impact is referred to as a contrecoup injury. Figure was taken from University of Iowa Hospitals and Clinics Health Care Section, 2013.

There remains to be no known threshold of impact to cause TBI despite recent investigations using in-helmet accelerometer research suggesting various values in gravitational force units (Guskiewicz & Mihalik, 2011). Many factors make the study of biomechanics of TBI very difficult to pursue, such as the current ethic standards that have made the use of primate and other mammalian animal models very difficult to pursue (limiting to only small mammals and rodents) as well as the limitations of using postmortem cadavers not providing a way to study impact mechanics in the context of everyday activities (including sport activities and work). Also postmortem cadavers lack certain variables such as muscle tonus and have decreased CSF that further make it difficult to study TBIs *in vivo*. The biomechanics of TBIs continues to be an elusive area of study to determine why some individuals can withstand very high magnitude impacts to the head without much deficit, while others struggle with significantly lower-end impacts. This also brings about questions about why every direct or indirect impact received in everyday life does not result in an injurious episode. Various factors are speculated to play a role in the body's ability to dissipate head impact forces such as an individual's differences in CSF levels and function, as well as vulnerability to brain tissue injury, relative musculoskeletal strengths and weaknesses, and anticipation of an incoming direct or indirect impact (Guskiewicz & Mihalik, 2011). Due to the various magnitudes and locations of impacts resulting in TBIs (as well as other factors such as prior TBIs and frequency of smaller magnitude impacts that don't result in symptomatic TBIs)

make it very difficult to establish a threshold for a clinically diagnosed TBI. This indicates that any proposed theoretical injury threshold should still be interpreted with caution and further substantiates the notion that TBIs be managed carefully.

### **Impact Loading**

A direct impact is also referred to as Impact Loading, or contact phenomena, which are forces applied to the brain tissues directly underneath the point of contact. Those forces being directly imparted to the brain with or without laceration or skull fracture. The forces applied can cause localized contusions and damage to the brain just underneath the point of contact as described in coup-contrecoup injuries. These forces send shock waves through the skull and brain resulting in tissue damage. Shock waves caused by penetrating injuries can also directly destroy nervous tissue along the path of a projectile/missile (Valadka, 2004). Impact loading is the case of most focal injuries in TBIs (Saatman et al., 2008).

In sports, this can range from helmet-to-helmet collisions, striking an opponent's head with a stick/bony landmark (such as elbow, knee, foot, or fist), being struck in the head by a projectile used in the sport (such as a soccer ball, basketball, or hockey puck), and falls that involve head striking floor/object (Guskiewicz & Mihalik, 2011).

## **Inertial Loading**

An indirect impact is also referred to as Inertial Loading, or impulse loading/noncontact phenomena, which is more commonly described as A/D type injuries where there is movement of the brain inside the skull. With inertial loading, it is really the rotational acceleration that is the important cause of tissue damage in the brain (rotation around a point). With this kind of rotational movement, the rotational forces tend to center deeper in the brain (particularly around the midbrain and thalamus). During inertial loading, the brain tends to get displaced within the skull particularly with these rotational forces and result in physical distortions of the brain tissue within the skull leading to shear injuries (shear strain). Shear injuries cause axonal damage due to force applied to the long axis of the axon pulling (tensile strain) and rupturing the cells is created when brain tissues slide against each other (is very poorly tolerated). The brain is a relatively fluid organ that tends to be stretched and pulled apart causing these shear strains, and it is really the shear strain on the tissues that cause most of the damage (and not so much the tensile or compressive strains). This type of injury typically leads to diffuse injuries in the brain (Saatman et al., 2008).

In sports, this is associated with tackling or body checking, which are the result of abruptly stopping an opponent's body from traveling in the direction where it was headed. This would be the equivalent of the effects experienced by passengers in an automobile (or any form of high speed transportation) that

quickly accelerates or stops (hence a significant and leading cause of TBI and will always be an important cause of injury) (Guskiewicz & Mihalik, 2011).

## **NEUROPATHOPHYSIOLOGY OF TRAUMATIC BRAIN INJURY**

Multiple concomitant, successive, and interacting pathophysiologic processes may occur across a wide range of severities. Brain injury, which comprises mild TBI (including its short-term sequelae) as well as catastrophic brain injury that may lead to death, fall under the classification of acute brain injury. Two main types of pathophysiologic brain damage due to trauma have been categorized: diffuse and focal pathology (Blennow et al., 2012). The main type of diffuse injury is termed Diffuse Axonal Injury (DAI) and the main type of focal injury is commonly referred to as focal cortical contusions. Diffuse injury is primarily caused by stretching and tearing of the brain tissue often seen in inertial loading leading to shear strain and associated microvascular injury such as petechial hemorrhages and small subarachnoid and intraventricular hemorrhages. During diffuse injury, there is no need for skull fracture, direct impact, or a crush injury to the brain to cause damage. The associated pathophysiology of diffuse axonal injuries can be described as a process occurring and not as a single event (associated with primary and secondary pathological events) (Gennarelli & Graham, 1998). Focal injuries is primarily caused by severe direct impacts on the brain that includes cortical or subcortical contusions and lacerations leading to intracranial bleedings such as subarachnoid hemorrhages and subdural hematomas. Due to the severe nature of injury caused in focal injuries, it is most often categorized in severe cases of

TBI only (ranging from moderate to severe TBI) (Blennow et al., 2012). Furthermore, the pathophysiology associated with focal cortical contusions may also be divided into primary and secondary events.

It is seldom the case that these two pathological processes occur individually in nature and usually result in combination where neural and vascular injurious events result in synchrony (Gennarelli & Graham, 1998). Often when the human brain is subject to A/D forces that are moderate to severe in nature, a combined pattern of diffuse and focal injuries result. The degree to which diffuse and focal injuries each develop depends largely on the circumstances of the injurious event (Povlishock, 1993). An example of this would be an individual that is subject to severe deceleration forces associated with a high speed motor vehicle accident occurring with no head impact resulting in predominantly diffuse axonal injury with associated petechial hemorrhages from minor focal trauma. On the opposite end of this continuum can be a gunshot wound to the brain that will cause an obvious primary focal deficit leading to secondary ischemia and neurometabolic injurious events accompanied by minimal diffuse axonal trauma as a consequence of tissue deformation. Usually noted in sports, mild injuries typically produce diffuse axonal damage with minor vascular change as opposed to moderate to severe injuries that most often result in vasculature damage (Gaetz, 2004). The apparent interaction between the pathophysiological processes of diffuse axonal injuries and focal cortical contusions together

indicate a worsened clinical outcome and may usually present with combined features symptomatically (Gaetz, 2004).

Several *in vivo* and *in vitro* methods have been used to determine the time course and pathophysiology of these two pathological processes. Some of the most common examples of study used are the fluid-percussion model, where models produce brain injury by injection of saline or blood rapidly introduced into the closed cranial vault (McIntosh et al., 1984; McIntosh et al., 1989; Povlishock et al., 1994). Also used are acceleration injury devices (impact acceleration model) and weight drop models in which both involve creating indentations into the brain (Gennarelli et al., 1982; Lighthall, 1988; Shohami et al., 1994; Marmarou et al., 1994). Other commonly used models would be the optic nerve stretch injury models and *in vitro* axonal stretch models (Gennarelli et al., 1989; Smith et al., 1999a). Many of these procedures are used in conjunction with the use of many tracers such as horseradish peroxidase (HRP) and immunolabeling methods in order to identify damaged axons and changes to the cytoarchitecture as well as the time frame involved in the process (Gaetz, 2004). These current methods of study however come with limitations due to the current lack of *in vivo* models that accurately mimic the human brain.

## **Diffuse Axonal Injury**

Although a detailed understanding of the pathophysiology of TBIs is lacking, it has been demonstrated through the various *in vivo* and *in vitro* studies that closed head injuries involving acceleration/deceleration (A/D) forces to the brain cause a multifaceted cascade of neurochemical changes affecting brain function. This process is initiated by the mechanical forces applied to the head leading to stretching and disruption of axonal cell membranes in the brain as well as shearing of endothelial cells in small blood vessels. These small vascular lesions may play a role in impairing regulation of the blood-brain barrier as well as cerebral blood flow leading to secondary events such as cerebral ischemia and brain edema. During axonal membrane disruption, typically neuronal cell bodies and myelin sheaths are less affected, thus most of the damage appears to occur at the nodes of Ranvier within the axon (Spain et al., 2010). This rent that occurs in the axolemmal membrane causes a deregulated flux of ions where there is a sudden efflux of potassium ions and influx of calcium. This abnormal ion flux leads to several consequences affecting normal axonal physiology. A notable consequence of the influx of calcium ions through the disrupted voltage-gated calcium channels within the cell leads to an enhanced release of excitatory neurotransmitters (particularly glutamate). Glutamate then binds to *N*-methyl-*D*-aspartate (NMDA) receptors leading to further depolarization of other cells (Giza & Hovda, 2001; Barkhoudarian et al., 2011). This widespread depolarization of

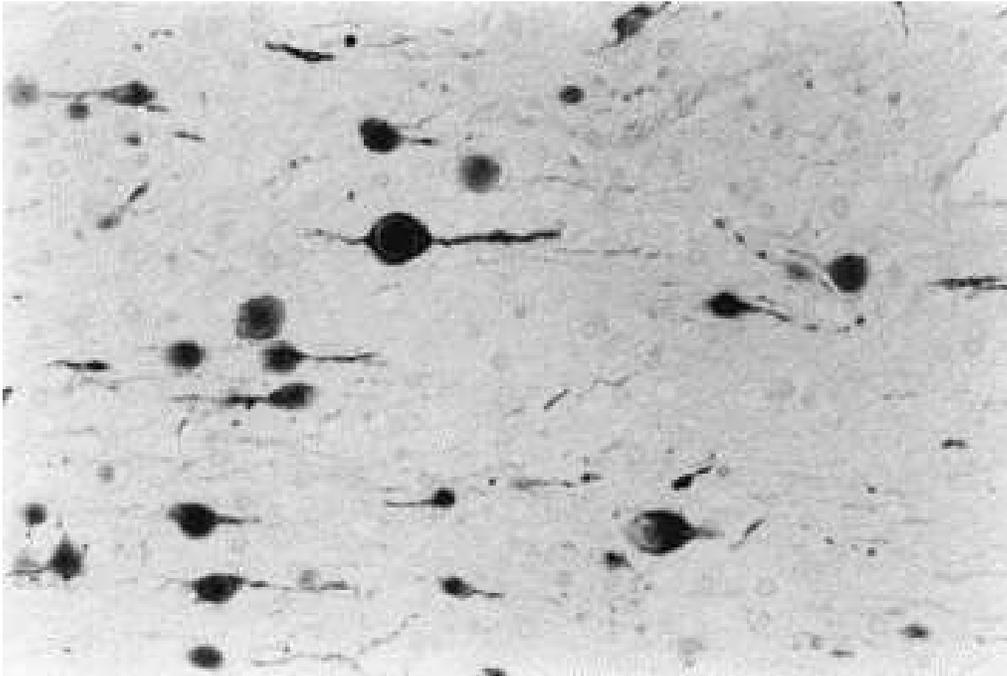
other cells leads to further influx of calcium ions in a positive feedback manner which then result in suppression of neurons due to glucose hypometabolism. The cells then respond to the glucose depletion by increased activity in membrane pumps to restore ionic balance by raising glucose consumption by glycolysis. This then depletes energy stores (ATP), causing a calcium influx into mitochondria impairing oxidative metabolism (Blennow et al., 2012). Mitochondrial injury has also been reported in this cascade rendering a decrease in local production of ATP within the cell, which alternatively hinders ion homeostasis within the axon due to ion pump failure (Radi et al., 1994; Giza & Hovda, 2001; Barkhoudarian et al., 2011). Eventually secondary events result from anaerobic glycolysis with lactate production which might lead to acidosis, free radical release, and strong oxidant production from increased neuronal depolarization. It is also likely that heightened cytosolic calcium ion levels can combine with diacylglycerol and activate protein kinase C leading to alterations of calcium channels within the cell further enhancing calcium influx (Choi, 1988).

Another consequence involved in intracellular calcium ion overload is caspase and calpain-mediated spectrin proteolysis activation. Calcium ion homeostasis is the main regulator of calpain/caspase activation. These proteases are involved in cytoarchitecture destruction. More specifically, neurofilament compaction and microtubule disassembly directly result from proteolysis of neuronal structural proteins such as neurofilament polypeptide sidearms, microtubule-associated proteins, tubulin, and spectrin (Radi et al.,

1994). Caspase-linked spectrin proteolysis along with cytochrome c release from the mitochondrion might also lead to secondary events such as neuronal apoptosis (programmed cell death) (Radi et al., 1994; McCracken et al., 1999; McGinn et al., 2009; Saatman et al., 2010). It is important to note that cytoskeletal disassembly may also be caused by direct effect of dynamic axon stretching by the mechanical forces applied (Tang-Schomer et al., 2010). A sudden acceleration or deceleration of the head can increase the forces to a threshold necessary to cause deformation to the cytoplasm and cell membrane that subsequently will cause immediate breakage and buckling of the intraaxonal and intracellular cytoskeleton (Povlishock, 1993; McLean & Anderson, 1997). That threshold can be defined as the “point where the elasticity (defined as the inherent capacity for recoverable strain) of the substance is exceeded and the material object will not return to its original geometric and physical shape once the force is removed” (Meythaler et al., 2001). It is also speculated that the length of time applied to that exceeded threshold has important implications determining the amount of DAI over spread areas of the brain as energy can dissipate to adjacent axons rendering shear stress between them as well (Meythaler et al., 2001). The longer those forces are applied, means more work is performed, which can result in more intracellular cytoplasmic deformation and injury. Three crucial factors have been associated with the extent of injury, being the type of A/D forces applied (angular rather than translational), the duration of

A/D forces applied (long rather than short), and the direction of the head movement in during injury (coronal rather than sagittal) (Meythaler et al., 2001).

As a result of cytoarchitecture destruction, there is an eventual blockage of axonal transport resulting in an accumulation of organelles that are transported in the axon forming axonal swellings called axonal retraction balls or axonal bulbs. Within 24-48 hours post-injury there is an eventual deafferentation (loss of these axon's targets downstream) and axotomy (sometimes referred to as axonotmesis) displayed at the distal portion of the axon from the swelling, meaning disconnection does not occur immediately. Under light microscopy using histological techniques, it is evident that this phenomenon occurs over time (particularly within the first or second day post-injury which may have important clinical implications on late symptomatic presentation), and displays remaining proximal axonal swellings representing the proximal ends of broken axons. These remaining proximal axonal swellings are the acute and subacute microscopic signatures of diffuse axonal injuries which are displayed on Figure 4. It is these axonal disruptions that cause diffuse/multifocal downstream denervation at the sites of the axon terminals, and in effect causing widespread disconnections throughout the CNS. In lay terms it can be described as pulling off the microscopic wires of the brain.



**Figure 4: Histological Stain of Reactive Axonal Swellings:** This image displays a positive immunostain with antibodies expressing Beta Amyloid Precursor Protein ( $\beta$ -APP) immunoreactivity at the parietal white matter of a patient at X100 view.  $\beta$ -APP is an integral axonal membrane protein normally found in axons implicated in a possible regenerative phenomena after trauma. Aparent is the typical representation of bead-like formation of disrupted axons which are reactive axonal swellings as a result of sustained DAI after trauma to the brain using immunohistochemistry. Figure was taken from Meng, Arai, Deguchi, & Takashima, 1997.

This neuronal damage is multifocal, but tends to predominate in certain areas occurring in a surface to deep and anterior to posterior gradient. The predisposed areas include the cortical sulci at the interface between gray and white matter, parasagittal white matter of the cerebral cortex in the frontal areas, corpus callosum (off midline), and the dorsolateral midbrain (the pontine-mesencephalic junction adjacent to the superior cerebellar peduncles) (Adams et

al., 1977; Adams et al., 1989). For this reason it may be valid to acknowledge that the term “Traumatic Axonal Injury” may be the more appropriate term in describing this pathology since damage to axons occurs to individual axons among many non-injured cells or appears in grouped damaged axons in predominantly discrete regions of the brain, therefore not completely considered truly “diffuse” (Gaetz, 2004). Despite DAI being a potential misnomer for not being truly diffuse to the whole brain, it has been widely accepted in literature describing this particular pathological process.

The final process described in this pathological destruction of axons is Wallerian Degeneration (Johnson et al., 2012). This process involves degenerating the separated axon distal to the injury and neuronal cell body (also known as anterograde or orthograde degeneration) (Kerschensteiner et al., 2005). This process has been described in both the central and peripheral nervous systems. Weeks after the axon has undergone complete fragmentation, it is followed by degradation of the myelin sheath and infiltration by microglial cells that usually may continue for months and years in the CNS (Maxwell et al., 1997). This infiltration of immune cells can also be due to the high levels of intracellular calcium which are believed to activate several phospholipases, which result in the production of arachidonic acid leading to inflammatory eicosanoids from broken down cell membranes (notably also contributing to the production of oxygen free radicals and enzyme generated superoxide radicals) (Choi, 1988; Bazan et al., 1995). Microglial/Macrophages and Schwann Cells

serve to clear the debris from these degraded axons. This process is said to occur slower in the CNS than in the peripheral nervous system (PNS). It may be in part due to the slower recruitment of microglial cells as opposed to macrophage recruitment in the PNS (taking an approximated three additional days in the CNS). Also clearance rates of microglia may be slower in the CNS due to a decreased permeability of the blood-brain barrier after trauma, hindering macrophage infiltration (George & Griffin, 1994; Vargas & Barres, 2007). The rate of degradation and clearance may also be affected by the diameter of the axon, where larger axons require a longer time for cytoskeletal destruction and thus longer time to degenerate.

This process of degeneration brings out about the importance of microglial activation. Microglial cells play a vital role in CNS Wallerian degeneration and particularly in the immune system of the brain as they are key mediators of the inflammatory response after TBI. Experiments using animal models show that microglia migrate towards lesioned tissues forming extended cytoplasmic processes in direct contact with damaged axons (Davalos et al., 2005; Shitaka et al., 2011). This response is associated with pro- and anti-inflammatory genes, chemokines, and other inflammatory mediators (Ziebell & Morganti-Kossmann, 2010). However, it is still unknown whether treating this inflammatory response may have beneficial outcomes. It may be possible to reduce inflammation by pharmacological intervention and improve neuronal survival, but this may hinder

axonal regeneration after injury as it is believed that microglia may have a hand in a regenerative phenomena (Loane & Byrnes, 2010).

Interestingly, after DAI, very rarely there seems to be an elicited plasticity regenerative response that includes dendritic and synaptic sprouting with an increased dendritic arborization and synaptogenesis (Keyvani & Schallert, 2002). Alterations in certain transcription factors such as c-Jun (which can also trigger apoptosis) and ATF-3 have been reported in DAI and have implications in axonal regeneration (Greer et al., 2011). Furthermore, there are structural proteins such as adhesion molecules and growth proteins (e.g. growth-associated protein GAP-43) that have also been noted in neurite sprouting (Christman et al., 1997). Also important in a possible neuronal regenerative phenomenon is the significance of apolipoprotein E (ApoE) in the CNS. ApoE is a main component of lipoproteins in plasma and carries important functions in cholesterol and lipid transport. Even though peripheral ApoE is synthesized in the liver, astrocytes seem to also synthesize ApoE primarily (although neurons and microglia also may contribute to its production) in the CNS (Huang et al., 2004). It has been demonstrated in both animals and humans that after TBI, astrocytes increase the ApoE expression and release in response to large amounts of membrane lipids, cholesterol, and other lipids released from damaged axons in order to scavenge and reuse those lipids during axonal and synaptic regeneration (Poirier et al., 1991; Poirier et al., 1993; Horsburgh et al., 2000b). Although it has been found that the neuronal cell body is not destroyed even though it may atrophy some, in

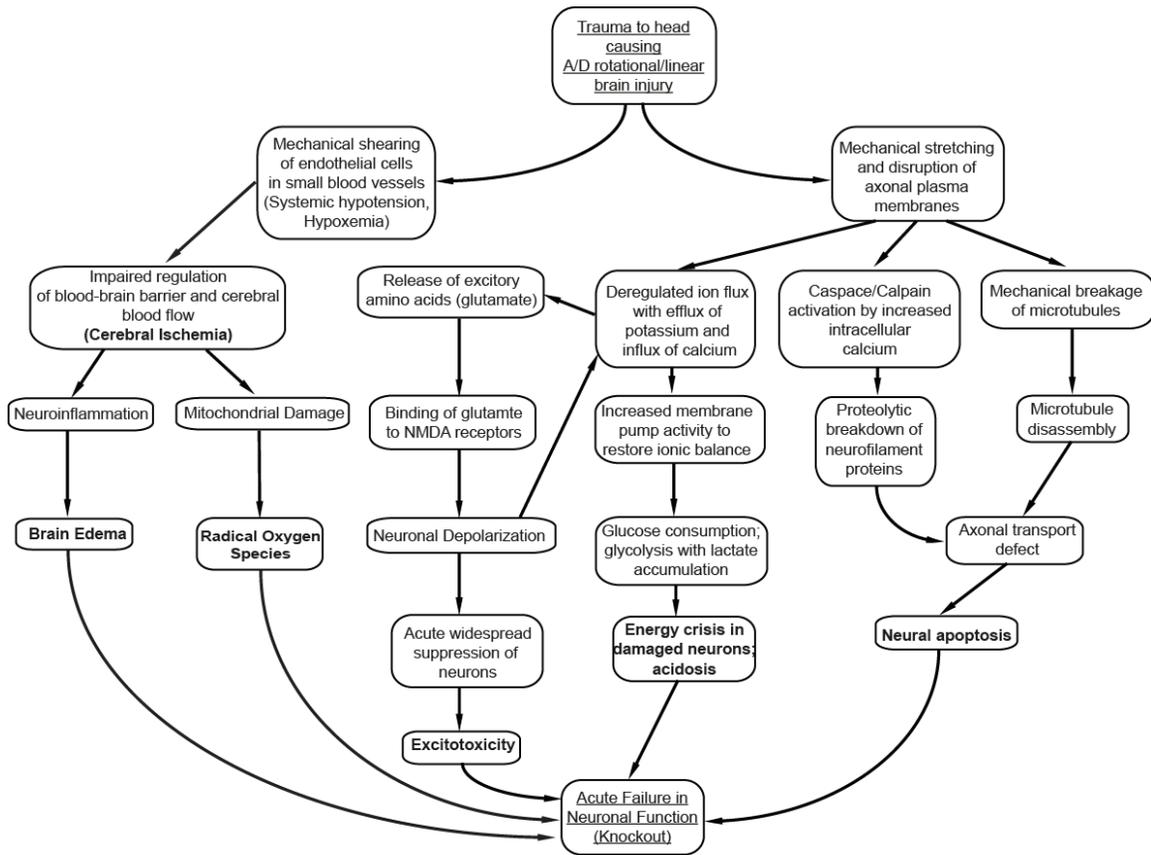
general there happens to be little regenerative response that occurs at many of these damaged axons usually proving ineffective where axons do not grow back to its targets.

This entire pathological process is not only confined to the axons of neuronal cells bodies, but may also be seen to damage the glial cells such as astrocytes and oligodendrocytes (Radi et al., 1994; Bazan et al., 1995; Campfl et al., 1997). Damage that may occur to other cells in nervous tissue such as motoneurons, sensory neurons, interneurons, astrocytes, and oligodendrocytes may possibly involve distinct pathological cellular pathways that are specific for that type of cell and differ from the ones described above. There is also speculation that some of these cells may be more susceptible to injury than others (Maxwell et al., 1997).

The sequence involved in mild TBI typically begins at the surface of the brain, and if the forces applied become more severe, they affect deeper structures. A system of classification for DAI was developed to identify the grades of cerebral injury associated with disruptions of consciousness. This classification system ranges from mild, moderate, to severe type injuries. Mild injuries (Grades I and II) can be said to be involved in cortical-subcortical disconnection, which can be involved in memory disturbance without loss of motor control and partial impaired awareness (suggesting that significant mechanical strains did not reach the reticular system). Moderate injuries to the brain (Grades II and III) can be best described as involving cortical-subcortical

and diencephalic disconnections. Finally, severe injuries (Grade IV and V) are categorized by cortical-subcortical, diencephalic, and mesencephalic disconnection of axons. These severe cases are demonstrated by greater degrees of diffuse damage along with irreversible damage to axons. When these type of severe DAI occurred, it usually results in a grade V coma (Ommaya & Gennarelli, 1974).

Figure 5 displays a schematic flow chart summary of the potential pathophysiological consequences of sustaining a DAI after TBI described above.



**Figure 5: Pathophysiology of Diffuse Axonal Injury:** This is a schematic flow chart of the molecular changes that occur following trauma to the brain by A/D and rotational/linear forces leading to a DAI. This chart represents a summary of the above text. Adapted from Beauchamp, Mutlak, Smith, Shohami, & Stahel, 2008 and Blennow, Hardy, & Zetterberg, 2012.

### **Clinical Presentation**

The particular pathophysiology of DAI may very well directly correlate with the way patients present symptomatically. It is important to consider that the number and type of symptoms present may vary from patient to patient, as some may show externally while others do not, and that these symptoms may overlap or come as a result of the concurrent focal pathologies (Comper et al., 2005). The onset of symptoms may be immediately following injury or may have a

delayed onset of minutes/hours to days/weeks later and may all play a part in short- and long-term complications (Kelly & Rosenberg, 1997; Mayo Clinic, 2012). Another very important consideration to make about the clinical presentation of patients after sustaining DAI is that most symptoms are nonspecific and may only be part of more broader differential diagnosis for many other disorders that may have already been present such as depression, attention deficit disorder, or can be part of other common sport-related conditions such as poorly fitting helmets, dehydration, migraine headache, and heat exhaustion/stroke to name a few examples (Sahler & Greenwald, 2012; Harmon et al., 2013). Therefore it is imperative that careful assessment of patients and proper history taking be made by physicians to determine whether these symptoms overlap with other disorders or are directly associated with a sustained DAI.

The most common physical symptoms present after injury are headaches, followed by nausea, vomiting, dizziness, lack of motor coordination, and difficulty balancing or other problems with movement (Kushner, 1998; Mayo Clinic, 2012; Harmon, et al., 2013). It is easy to understand why coordination and balance may be disrupted if the number of functioning fibers in the cerebellum as well as other motor control centers of the brain are affected. This may cause a significant slowing of the neural conduction speed directly associated with the rapid sensory input and output needed for balance and movement (Meythaler et al., 2001). Other physical problems that may present in some patients include

sensation problems such as numbness or tingling in the extremities. Visual problems may include sensitivity to light, seeing bright lights, having blurred vision, or double vision (Rees, 2003; Mayo Clinic, 2012; Harmon et al., 2013). Other problems such as sensitivity to noise may be reported by some, which can come as a result of tinnitus or ringing of the ears (Rees, 2003; Mayo Clinic, 2012; Harmon et al., 2013). Finally, physical problems such as fatigue, feeling dazed or stunned are also commonly reported following trauma (Mayo Clinic, 2012; Harmon et al., 2013).

Cognitive problems are also commonly reported following trauma. Included are symptoms of confusion or feeling mentally “foggy”, disorientation, feeling “slowed down”, difficulty concentrating, reasoning, or focusing attention, difficulty remembering, and forgetful of recent information and conversations which may all translate to difficulty performing everyday activities (Kushner, 1998; Lee, 2007; Mayo Clinic, 2012; Harmon et al., 2013). These patients may provide clues of a cognitive problem by sometimes responding to questions or directions slowly, repeating questions often, displaying a vacant stare, or having slurred/incoherent speech (Quality Standards Subcommittee of the American Academy of Neurology, 1997; Anderson et al., 2004).

An important note is that loss of consciousness may occur, but is not necessarily directly correlated with the severity of the TBI if it presents over a brief period (Cantu, 2006). Typically only about 10% of mild traumatic brain injuries are associated with an episode of loss of consciousness (Harmon et al.,

2013). More severe cases of DAI usually involve impairment of consciousness, which typically result at the moment of injury. This is the most common cause of persistent vegetative state and severe long-term disability (Meythaler et al., 2001).

Emotional or affective problems may also arise following injury to the brain. This may include a state of irritability or crankiness, mood changes or mood swings, depression or sadness, a potential state of anhedonia in favorite activities or items, more emotional (e.g. tearfulness), nervousness, anxiousness, or displays of emotion that are inappropriate to the situation (Anderson et al., 2004; Mayo Clinic, 2012; Harmon et al., 2013). Finally, problems with sleep patterns may also be evident. These can include drowsiness, sleeping more or less than usual, and difficulty falling asleep (Rees, 2003; Mayo Clinic, 2012; Harmon et al., 2013).

Other potential dysfunctions that may occur following a more severe DAI may include endocrine function disturbance by sustaining insult to the hypothalamus and pituitary gland. Damage to the hypothalamus and pituitary gland have been previously noted following severe TBIs, in which there has been evident decreases of pituitary hormone release and alterations in pituitary functions (Jambart et al., 1980; Valenta & De Feo, 1980). Other potential results from a mild TBI involving DAI are concussive convulsions. These are not very common but if these seizures do occur, they are not considered the same as post-traumatic seizures and are not predictive of post-traumatic epilepsy, which

requires some form of structural brain damage from focal injuries. These convulsions may result from temporary inhibition of motor function and are not associated with epilepsy or damaging focal injuries. These potential seizures have the same favorable outcomes as most concussions without convulsions (McCrorry & Berkovic, 1998; Perron et al., 2001).

Many minor head trauma patients may have persistent complaints and symptoms that will last for weeks, months, and even years post-injury. This phenomenon has been described as Postconcussion Syndrome (PCS). About 40%-80% of these patients exposed to mild trauma experience some PCS symptoms (Hall et al., 2005; Sterr et al., 2006). Symptoms of PCS are often vague and non-specific making the diagnosis very difficult. Typically the symptoms involved in PCS may be divided into three domains that may include any combination of the individual problems. The first domain is somatic problems such as commonly reported headaches, fatigue, low energy, sleep disturbances, nausea, vision changes, tinnitus, dizziness, balance problems, exercise intolerance, and sensitivity to light and noise. The second domain is emotional/behavioral changes that may include lowered frustration tolerance, irritability, increased emotionality, depression, anxiety, clinginess, and personality changes. Finally the third domain is cognitive problems such as slowed thinking, slowed response time, mental foginess, memory loss, poor concentration, distractibility, trouble with learning and memory, problem-solving difficulties, and disorganization (Kirkwood et al., 2006; Blennow et al., 2012; Harmon et al.,

2013). The potential risk factors involved in PCS include an increasing age, female gender (which may be better detected than males due to the fact that most females are more likely to seek medical care when symptoms are present), or non-sports-related TBIs such as falls, vehicle accidents and assault. There is no proven correlation between the severity of the injury and the likelihood of developing persistent PCS symptoms, as well as developing structural damage in the brain or any disruption of neurotransmitter release, and the presence of any psychological factors (Harmon et al., 2013). Evidently, any of these symptoms may persist or present in the long haul (despite the resolution of every other symptom or problems including PCS) as a long-term consequence of TBI, such as a chronic neurocognitive impairment indicating permanent damage and long-term disability.

Notably in sports during 2012, 59% of college athletes reported mild TBI symptoms with no history of head injuries and 50%-84% of high school athletes reported similar symptoms at baseline testing. This was reported with no consistent differences between male and female symptoms (Harmon et al., 2013). Clinical presentation of patients having sustained a sport-related TBI are similar in younger and older athletes altogether (Kirkwood et al., 2006).

### ***Natural History of Progression***

The natural history of progression in diffuse pathology follows a general pattern that occurs across the spectrum of severity. This natural history of

progression can be described in the context of three principal phases of recovery: unconsciousness or loss of consciousness phase (which occurs immediately following injury without lucid interval), post-traumatic confusion and amnesia phase also known as post-traumatic amnesia (a period of time where no new memories are being formed), and the postconfusional restoration of cognitive function. The duration of each of these phases along with the severity of impairments involved in each phase directly correlate with the severity of diffuse injury to the brain. It is this proportionality that can be the basis for predicting a potential time course of recovery and outcome (Levin, 1995).

Patients that sustain a mild traumatic brain injury (mild concussion) may not even experience loss of consciousness or may evolve through unconsciousness in a matter of seconds to minutes and through the post-traumatic amnesia (PTA) or confusional phase usually in minutes to hours, followed by a postconfusional recovery period and subsiding symptoms typically lasting days to weeks. In mild injuries, this transition through the early stages may be brief and even unwitnessed making recognition difficult. Patients experiencing moderate to severe traumatic brain injuries typically can experience a trajectory of recovery of hours to days for the unconsciousness phase, days to weeks for the PTA phase, and potentially months to years in the postconfusional and restoration of cognitive functioning stage. In very severely injured individuals, recovery through the stages may include days to weeks for the unconsciousness stage, weeks to months for the confusional stage, and months

to years for the postconfusional residual recovery period. The time course of recovery for severe TBI patients is among the longest observed. In some cases, those with the most severe diffuse injuries may stall at certain phases of the recovery process (e.g. stalled unconsciousness phase renders a permanent vegetative state) (Katz, 1992; Katz & Alexander, 1994).

Other schemas commonly used to further describe the pattern of recovery elaborated above include the Rancho Los Amigos Scale of Cognitive Functioning and the Braintree Neurologic Stages of Recovery as described on Table 1.

<b>Rancho Los Amigos Levels of Cognitive Functioning</b>	<b>Braintree Neurologic Stages of Recovery</b>	<b>Defining Characteristics</b>
1. No response	Coma	Unconscious, no-arousal, eyes closed
2. Generalized response	Vegetative State (VS)	Unconscious, sleep-wake cycles
3. Localized response 4. Confused, Agitated	Minimally Conscious State (MCS)	Inconsistent, simple purposeful behavior
5. Confused, Inappropriate, Nonagitated 6. Confused, Appropriate	Confusional State (CS/PTA)	Resume interactive communication or appropriate object use, inattentive, amnesic
7. Automatic, Appropriate	Post-confusional/Emerging Independence (PC/EI)	Resolved PTA, developing household independence
8. Purposeful, Appropriate	Social Competence/Community Reentry (SC/CR)	Basic household independence achieved, emerging independence in community

**Table 1: Scales of Cognitive Functioning and Neurological Recovery:** Displayed are the Rancho Los Amigos Levels of Cognitive Functioning and the Braintree Neurologic Stages of Recovery with their respective defining characteristics. Adapted from Katz, Polyak, Coughlan, Nichols, & Roche, 2009 and Rancho Los Amigos National Rehabilitation Center, 2012.

The clinical consequences associated with diffuse injuries are currently the most widely used clinical measures of injury severity. The traditional indices used for measuring injury severity are the Glasgow Coma Scale (GCS) score, duration of loss of consciousness (LOC), and the duration of PTA. The GCS typically measures the severity of particular clinical problems at index times postinjury using a point scale assessing the level of consciousness and neurologic functioning of patients (Table 2). These clinical severity measures have important implications and have been used in many studies as a form of

clinical predictors of outcome measures in DAI. LOC phase is usually measured by the time it takes a patient to follow commands and is another common measure of injury severity (Table 3). PTA phase may be measured by the time a patient becomes fully oriented, but other measures such as the resumption of day to day episodic memory and the capacity to learn new information may be a better characterization of the resolution of PTA. A commonly used tool to track PTA is the Galveston Orientation and Amnesia Test. In general, the duration of PTA is a better predictor of functional outcome than GCS and LOC in patients with DAI (Dikmen et al., 1995; Corrigan et al., 1998; Dikmen et al., 2003; Pangilinan Jr. et al., 2013).

Feature	Scale (Responses)	Score (Notation)
Eye Opening	None	1
	Opens to Pain	2
	Opens to Command	3
	Opens Spontaneously	4
Motor Response	None	1
	Extension	2
	Flexion (Abnormal)	3
	Flexion (Normal)/Withdrawal to Pain	4
	Localizes Pain	5
	Obeys Commands	6
Verbal Response	None	1
	Incomprehensible Sounds	2
	Inappropriate Words	3
	Confused Conversation	4
	Alert and Oriented	5

**Table 2: Glasgow Coma Scale and Score:** A common scale using a scoring system to classify TBI severity at the time of injury. It consists of three sections, each of which is scored. The total score of the combined sections can range from 3 to 15 points and is used as the indicator of severity. A GCS score of 13-15 commonly denotes that a mild TBI has occurred. A GCS score of 9-12 denotes a moderate TBI. A GCS score of 6-8 is considered a severe TBI, and if a GCS score of 3-5 is achieved, then it is considered a very severe TBI. Adapted from Teasdale & Jennett, 1974.

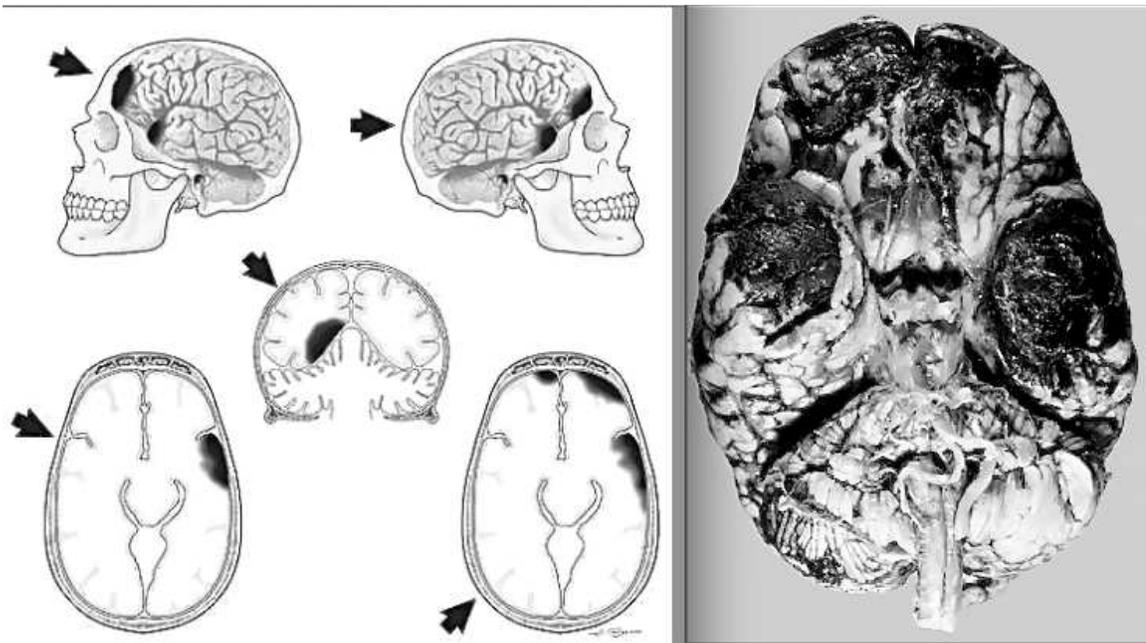
Severity of TBI	Finding
Mild	Mental Status Change or LOC < 30 minutes
Moderate	Mental Status Change or LOC 30 minutes to 6 hours
Severe	Mental Status Change or LOC > 6 hours

**Table 3: Classification of Traumatic Brain Injury Severity Based on the Duration of Loss of Consciousness:** Another common measure of TBI severity using time based on how long a patient is subject to loss of consciousness. Table taken from Pangilinan Jr., Kelly, & Hornyak IV, 2013.

## **Focal Injury**

The pathophysiology of focal brain injuries is considered to be somewhat less complex than the progression of sequelae in DAIs. Focal refers to localized areas of brain tissue damage as opposed to what a diffuse injury would encompass. Focal brain injuries typically occur in the form of contusions or frank disruptions of brain tissue which can come as a result of either open or closed head injuries commonly referred to as focal cortical contusions (Gennarelli, 1993). It is important to keep notion that another form of focal injuries can be strokes that are classified as either occlusive (blockage of blood supply that can be caused by atherosclerosis or thrombosis) or hemorrhagic (ischemic event that occurs in neural tissue deprived of blood supply due to bleeding from the supply vessel) that will not be discussed further in this thesis as they go beyond the scope of focal injuries in TBIs (Brust, 1991). Hemorrhagic strokes can, however, occur as a secondary injury following contusions or TBI associated hemorrhage. Even though focal contusions may occur at the point of impact, the most predisposed locations of injury in this type of pathology are primarily observed at the anterior and inferior portions of the frontal and temporal lobes of the brain as well as the lateral surface of the temporal lobes and cortex above the Sylvian fissure on occasion as shown on Figure 6. These are the main areas of predilection despite the direction of impact in movement due to the physics of the brain within the skull and how the brain is relatively encased in those areas

(directly related to the inner skull architecture confining these areas), causing maximal tissue strain at impact (Gennarelli & Graham, 1998).



**Figure 6: Predisposed Usual Locations of Focal Cortical Contusions Following Traumatic Brain Injury:** The anterior and inferior portions of the frontal and temporal lobes of the brain are the most susceptible and usual locations for focal cortical contusions despite the direction of impact due to the skull architecture confining those areas of the brain. This may come as a direct result of the coup and contrecoup mechanism type injury associated with focal cortical contusions. The left image arrows represent the direction of the impact on the skull and the dark shaded areas on the brain represents the resultant common contusional damaged areas. The latter image is a display of an inferior view of a gross pathological brain with focal damaged frontal and temporal lobes following a severe TBI. Figure was taken from Agamanolis, 2013 and Joseph, 2013.

High velocity angular acceleration of short duration (as may occur in a fall) may cause focal injuries resulting with disturbance or rupturing (affect more superficial structures) of blood vessels either at the extradural (epidural) space,

subdural space, subarachnoid space, intracerebral areas, or intraventricular spaces leading to traumatic hemorrhages and hematomas in these spaces (Gennarelli, 1993; Granacher, 2007). These injuries most often occur at the apex of gyri in the brain and appear as multiple punctuate hemorrhages or streaks of hemorrhages which eventually progresses to bleeding into adjacent areas of white matter (Gennarelli & Graham, 1998). It is this bleeding into adjacent cortex that causes neurons to undergo secondary necrosis due to ischemia (Gennarelli & Graham, 1998). Focal cortical contusions may also be subject to missile or puncture wounds of the brain leading to primary events involved in direct neural and vascular tissue injury followed by secondary events such as ischemic injury (Cooper, 1993). Ischemia is actually considered to be the most significant factor related to damage that occurs following focal injuries.

Focal cortical contusions are believed to cause progressive concentric zones of damage extending outward from the primary site of injury because the set of secondary phenomena associated with diffuse injuries can be the same as in focal injuries. The primary site of injury may not only be subject to destruction of blood vessels, but may include destruction of neural tissue that may progress pathologically similar to the way diffuse axonal injuries occur. There is also a second zone of injury involving primary traumatic damage (breaking blood vessels) without the destruction of neural tissue in the brain. Finally, a tertiary zone may involve a potential delayed insult associated with ischemia and edema (Gennarelli, 1993). Often seen as a product of ischemia are inflammatory and

cytotoxic mechanisms of injury which may or may not develop in a more delayed fashion (Lindenberg et al., 1955; Gennarelli, 1993). These zones of profound reduced cerebral blood flow lead to neuronal necrosis. Edema is an important factor associated with secondary injury to the brain. In severe cases edema may be involved in herniation of structures within the cranial vault typically occurring at the frontal lobes across the cerebral falx (transfalcine herniation) and in the middle to posterior fossa (transtentorial/uncal herniation) due to pressure buildup and swelling leading to death (Gaetz, 2004). Some of these focal lesions associated with edema may be subject to surgical evacuation to prevent herniation and further brain swelling that may be treated with craniectomy in addition to medical treatment for brain swelling.

Edema is usually considered the end point of several pathological processes that occur following this type of injury. Two types of cerebral edema have been described: vasogenic and cytotoxic (Fishman, 1975). As a result of moderate to severe focal injuries, vasogenic edema can be triggered by the physical disruption and breakdown of the endothelial tight-junctions that make up the blood-brain barrier either through trauma, arterial hypertensive responses from trauma, late stages of cerebral ischemia, or release of vasoactive and endothelial destructive compounds such as arachidonic acid from trauma that causes permeability for small and large tracers that induce edema (Wahl & Schilling, 1993; Hayes & Dixon, 1994). Cytotoxic edema on the other hand does not involve the blood-brain barrier which remains intact. During ischemia

following focal cortical contusions, the lack of oxygen and glucose in cells leads to the breakdown of adenosine triphosphate (ATP) dependent calcium and sodium-potassium pumps rendering abnormal levels of calcium and sodium intracellularly. This in turn leads to rapid uptake of water into the cells leading to massive swelling due to osmotic pressure difference (Fishman, 1975; Bullock et al., 1991). The abnormally high levels of intracellular calcium due to the hypoxia and hypoglycemia in cells plays a critical role in neuronal depolarization increasing the levels of extracellular glutamate. This in turn will activate a wide variety of receptors and lead to depolarization of cell membranes allowing for activation of voltage dependent calcium channels. This leads to an influx of calcium into the cells which will then propagate glutamate neurotoxicity in a positive feedback fashion further stimulating the release of this neurotransmitter (Choi, 1988; Gennarelli, 1993). There is speculation that other amino acid neurotransmitters such as glycine are also involved in this process, which may have important implications in seizure activity and neurotoxicity in the same fashion as glutamate is involved (Nilsson et al., 1994). This increased amount of extracellular excitatory amino acids can cause acute swelling in dendrites and cell bodies due to opening of membrane channels causing sodium influx and secondary influx of chlorine and water resulting in excitotoxic swelling. Studies have showed that immediately following moderate to severe focal trauma, there have been increased levels (as large as 10-15 times normal levels) of extracellular neurotransmitters such as glutamate and aspartate released from

regions adjacent to focal contusions as well as hippocampal regions lasting up to four days (Faden et al., 1989; Hayes & Dixon, 1994; Gaetz, 2004). In zones where ischemia may not reach critical levels, glutamate neurotoxicity may play a critical role in tissue damage and death (Choi, 1988; Bullock et al., 1991). Finally, a last cause of cytotoxic swelling associated with focal trauma results directly from mechanical deformation of the neuronal membrane leading to a massive potassium efflux into the extracellular fluid with consequent astrocytes swelling from attempting to maintain cellular homeostasis (Bullock et al., 1991; Schroder et al., 1995). Astrocytic damage primarily demonstrates as cytoplasmic disruption along with disrupted cell membranes and cytotoxic edema occurring at the feet (Bullock et al., 1991). In most cases, both vasogenic and cytotoxic edema occur together and rarely appear individually following trauma. Studies have reported that following fatal injuries in humans extreme edema not only develops in astrocytes, but in grey and white matter as well. A final point regarding the important implications in this pathophysiological process is that secondary mitochondrial failure and free radical production along with its associated damage from cellular destruction is usually linked with both vasogenic and cytotoxic edema further enhancing the damage in focal injuries (Ellis et al., 1991; Kontos et al., 1992; Nelson et al., 1992; Povlishock & Kontos, 1992; Sutton et al., 1993).

A short summary of the pathophysiological hallmarks in focal injuries by comparison to diffuse injuries is illustrated on Table 4.

	<b>Diffuse</b>	<b>Focal</b>
<b>Primary Events</b>	-Diffuse Axonal Injury -Small White Matter Hemorrhages	-Focal Cortical Contusion -Extracerebral Hemorrhage -Deep Cerebral Hemorrhage
<b>Secondary Events</b>	-Hypoxic-ischemic injury -Microvascular injury -Swelling -Excitotoxicity -Delayed neuronal injury	-Hypoxic-ischemic injury (stroke) -Herniation damage -Swelling -Excitotoxicity and neuronal injury -Late hemorrhages

**Table 4: Neuropathological Consequences of Traumatic Brain Injury:** This table represents a summary of the above text regarding the neuropathological consequences of both diffuse and focal injuries following traumatic brain injury.

### ***Clinical Presentation***

Focal injuries may present symptomatically very similar to diffuse injuries in some cases, but can very well be as a direct result of the concurrent pathologies occurring at the same time. Depending on the severity of the individual's injury, patient's may experience any collection of nonspecific symptoms that include headaches, confusion, sleepiness, dizziness, loss of consciousness, nausea, vomiting, seizures, difficulties with coordination, movement, memory, vision, speech, hearing, managing emotions, and thinking (Kushner, 1998). However, depending on the cerebral contusion's location as a result of the focal injury may be a direct predictor of potential cognitive and behavioral syndromes according to the brain's functional location such as the usual limbic and heteromodal association areas of the anterior frontal and temporal lobes. For example, this regional cortical vulnerability to focal lesions in

the dorsolateral prefrontal cortex may have associated dysfunctions in executive function including problems with sustained and complex attention, memory retrieval, abstraction, judgement, insight, and problem solving. Also lesions in the orbitofrontal cortex may lead to emotional and social responding problems that may present as social disinhibition. Focal lesions in the anterior temporal cortex may present with problems with memory, language, emotional responding, and face recognition (toward the temporal to occipital regions of the brain). A direct lesion to the amygdala of the brain will result in emotional learning and conditioning, which include fear and anxiety. The hippocampus is involved in declarative memory, and may be directly affected by a focal injury at this site. Finally, the ventral brainstem may also be affected by direct insult from a focal injury and will involve problems with arousal as well as directly affect the ascending activation of the diencephalic, subcortical, and cortical structures that may lead to further symptoms (Arciniegas & Beresford, 2001).

As discussed above, a secondary event associated with a direct focal cortical contusion is cerebral edema. Morphological changes to the brain's structure have been noted as a result of edema such as smoothing and softening of brain structures as the cranial vault overfills, gyri (ridges) of the brain become flattened, sulci (grooves) become narrowed, and there is compression of ventricular cavities (Raslan & Bhardwaj, 2007). This may result symptomatically as nausea, vomiting, blurred vision, faintness, and in severe cases lead to seizures and coma (Raslan & Bhardwaj, 2007). If brain herniation should occur

as a complication, potential symptoms would include headache, lethargy, loss of consciousness, coma, cardiac arrest (no pulse), respiratory arrest (no breathing), dilated (wide) pupils, no movement in one or both eyes, or loss of brainstem reflexes such as blinking, gagging, or pupils reacting to light. Patients with potential brain herniation can typically present with high blood pressure, slow pulse, irregular pulse, or irregular breathing (Stippler, 2012; Peterman & Smirniotopoulos, 2013). Four common types of herniation have been recognized, which may all fall under a supratentorial herniation type. The most common type of herniation is the subfalcine herniation, which is when the cingulate gyrus of the frontal lobe is pressed beneath the falx cerebri. Another type is the central transtentorial herniation which is apparent when the basal nuclei and cerebral hemispheres are pushed downward while the diencephalon and adjacent midbrain are pressed through the tentorial notch. A third type of herniation known to happen is the uncal herniation where the medial edge of the uncus and the hippocampal gyrus are displaced medially and over the ipsilateral edge of the tentorium cerebelli foramen resulting in midbrain compression. In uncal herniation, it is also possible that the third cranial nerve be stretched or compressed as a result. Finally, cerebellar herniation involves infratentorial herniation, which is characterized when the cerebellar tonsil is pressed through the foramen magnum causing compression of the medulla resulting in respiratory arrest and bradycardia (Dawodu, 2013).

Another common event associated with focal lesions are epidural hematomas. Typical locations of epidural hematomas are the temporo-parietal locus commonly associated with the middle meningeal artery (often resulting from skull fracture in 90% of cases), the frontal locus affecting the anterior ethmoidal artery, the occipital locus affecting the transverse or sigmoid sinuses, and the vertex locus affecting the superior sagittal sinus. Epidural bleeding is usually rapid, as it typically and most often involves the arteries, which are high pressured vessels (Arciniegas & Beresford, 2001; Verive et al., 2013). As the epidural hematoma expands in the cranial vault, it begins stripping the dura matter from the inside of the skull causing an intense headache clinically. These hematomas can become quite large and raise intracranial pressure leading to brain shifting and compression, as well as blocking blood supply. The larger the hematoma is, the larger the damage associated with it. Typically in patients there is lucid interval following trauma which is then followed by a delay of symptoms such as unconsciousness (Verive et al., 2013).

Potential complications of epidural hematomas may be compression of the brainstem causing unconsciousness, abnormal posturing (meaning increased involuntary flexion or extension of arms and legs), and abnormal pupil responses to light. Feared events include compression of the medulla (from transtentorial or uncal herniation after epidural hematoma) leading to respiratory arrest. Also if the pons is suppressed, it may lead to trigeminal nerve (CNV) obstruction but may not be a significant clinical presentation on the patient, as by this point, the

patient may already be dead. Herniation in the posterior cranial fossa (cerebellar herniation) is tonsillar and causes the Cushing's triad (hypertension, bradycardia, and irregular respiration). Other potential manifestations that may appear may include weakness of the extremities on the opposite side of the lesion due to the impingement of the crossed pyramidal tracts. If the posterior cerebral artery is affected, it may become evident by the loss of the visual field on the opposite side of the lesion (Price & Wilson, 2012). Despite the fatality associated if not treated by prompt evacuation, there is typically no neurological and neuropsychiatric complications in the absence of an underlying cortical contusion (Arciniegas & Beresford, 2001).

Unlike epidural hematomas, subdural hematomas usually include bridging veins manifesting as a gradual rise of headaches and confusion and may form as a consequence of a high magnitude A/D forces (implying they are frequently associated with underlying brain tissue injury such as DAI). There is a slower onset of symptoms because it involves veins, which are lower pressured vessels than arteries (therefore bleeds will be slower). Signs and symptoms may present in minutes (if not immediately) to a potentially delayed two weeks later (Arciniegas & Beresford, 2001; Sanders & McKenna, 2001; Biros & Heegaard, 2009). If the bleeding becomes too large, it may also present complications such as herniation of brain structures and increased intracranial pressure (Wagner, 2013). Most signs and symptoms for subdural hematomas include any combination of loss of consciousness, fluctuating levels of consciousness,

irritability, seizures, pain, numbness, headaches (either constant or fluctuating), dizziness, disorientation, amnesia, weakness, nausea, vomiting, loss of appetite, personality changes, inability to speak, slurred speech, ataxia (difficulty walking), altered breathing patterns, hearing loss, tinnitus, blurred vision (visual disturbances), or a deviated gaze (abnormal movement of the eyes) (Biros & Heegaard, 2009).

If an intracerebral hemorrhage were to occur as a result of a focal injury (usually by way of depressed skull fractures, missile wounds, or deep shearing injuries), it would involve intraparenchymal bleeding that would lead to symptoms associated directly with the damaged functional area of brain often associated with significant neurological and neuropsychiatric impairment (Arciniegas & Beresford, 2001). Also involved would be an increased risk of increased intracranial pressure. Severe headaches and vomiting are hallmarks of intracerebral hemorrhages and in some cases, patients may even go into a coma before the hemorrhage is even noticed (Vinas & Pilitsis, 2013).

Also involved in focal injuries can be intraventricular hemorrhages. These types of hemorrhages have only been found in about 35% of the cases involving moderate to severe TBIs (Barkley et al., 2006). This type of hemorrhage requires a great deal of force to cause it and thus occurs with extensive associated damage rendering poor outcome. Prognosis for this type of injury is very poor and may become even worse if hydrocephalus follows the bleed (Yadav et al., 2007). This usually is involved with an increased intracranial

pressure and potentially fatal brain herniation involved. It is important to note that many of these injuries may come with cerebral laceration and that patient's level of consciousness decreases as the laceration bleeds and blood collects within the skull (Dawodu, 2013; Vinas & Pilitsis, 2013).

Along with the secondary events associated with focal pathologies, there is potential for later complications such as the ones mentioned already. However other complications commonly associated with moderate to severe TBIs can include late hydrocephalus related to hemorrhage, other disruption of arachnoid granulation absorption of CSF, or obstruction of CSF flow elsewhere (by way of mechanical blockage) may occur in some patients usually within the first 3 months after injury (Katz, 1992). Other notable complications after sustaining significant brain damage can include coma, vegetative state of consciousness, minimally conscious state, locked-in syndrome (rarely the case), susceptibility to infection after an open head injury, blood vessel damage, cranial nerve damage, and persistent cognitive, communicative, behavioral, emotional, or sensory dysfunctions (Mayo Clinic, 2012). Other potential complications following brain damage may include deep vein thrombosis following TBIs, particularly in patients which may be immobile, have a lower extremity fracture, are paralyzed, and have a disruption in coagulation and fibrinolysis. This raises potential for further problems as a pulmonary embolism. Although not entirely understood, heterotopic ossification has also been documented as a complication after heavy brain injury, which is characterized by ectopic bone formation in the soft tissues

surrounding the joints causing pain and decreasing the range of motion. Apparent also, is increased spasticity, which is defined as velocity-dependent increase in muscle tone apparent after lesions in the upper motor neurons. Finally complications regarding gastrointestinal problems (stress ulcers, dysphagia, and bowel incontinence), urinary tract problems (urethral strictures, urinary tract infections, and urinary incontinence), and gait abnormalities have all been reported (Pangilinan Jr. et al., 2013).

Many of these contributing factors associated in TBIs (given that the injury was not fatal) have a potential in leading to an increased risk of developing diseases associated with a gradual degeneration of brain cells and gradual loss of brain function through the development of Alzheimer's disease, Parkinson's disease, or Chronic Traumatic Encephalopathy (Mayo Clinic, 2012).

### ***Natural History of Progression***

The natural history of progression associated with focal pathology following a TBI largely depends on the lesion's characteristics such as the location, size, depth, bilaterality (especially involving homologous areas), and associated secondary damage (Povlishock & Katz, 2005). Typically focal injury is not directly associated with unconsciousness unless there is significant secondary mass effect, direct bilateral affected areas on the mesencephalon or diencephalon, or associated diffuse axonal injury. Post-traumatic amnesia is common with focal injuries due to the secondary metabolic and excitotoxic

effects that are directly associated with the focal lesion or the concomitant diffuse injury. The specific clinical effects of focal pathology often overlap in the evolving clinical recovery of diffuse injuries in patients. Because focal and diffuse injuries hardly occur in isolation, it may be difficult to distinguish the separate effects. Most resultant syndromes may be identical in both cases (Katz, 1992; Katz & Alexander, 1994; Levin, 1995).

In occasions when there is more severe associated diffuse injury, the overall outcome is driven largely by the effects caused by diffuse injury rather than by those of focal injury. However, in situations when there is a mild to moderate associated diffuse injury, it is the large focal lesions that may dictate the overall outcome of recovery. In focal injuries, small differences in the depth of the lesion where it may involve greater proportions of white matter pathways as they converge at deeper levels from the surface make large differences regarding the clinical effects and recovery. Furthermore, bilateral lesion involvement may suggest a worse prognosis compared to patients that only suffer unilateral focal lesions as they can have considerable recovery (Corrigan et al., 1998; Dikmen et al., 2003).

## **LONG TERM EFFECTS OF RECURRENT TRAUMATIC BRAIN INJURY**

It had long been speculated that recurrent TBIs increased the risk of developing gradual degeneration of brain cells and loss of brain functions from Alzheimer's Disease (AD; progressive loss of memory) and Parkinson's Disease (PD; disease associated with movement problems). However it has recently been accepted that recurrent trauma triggers the development of progressive widespread deposition of hyperphosphorylated tau (p-tau) as neurofibrillary tangles causing brain damage similar to AD and PD (McKee et al., 2009). Particularly in contact sports where there is a high propensity for recurrent or repetitive episodes of TBI throughout an athlete's career, for example, boxing has been long associated with chronic neurological problems. The progressive neurodegeneration was originally described by a New Jersey pathologist, Harrison Stanford Martland, in 1928 as he described the progressive chronic brain damage that occurred in boxers after sustaining repetitive brain trauma leading to the name "Punch Drunk Syndrome" (Martland, 1928). Several years later in 1937, Millspaugh renamed this syndrome "Dementia Pugilistica" (Millspaugh, 1937). Later came the recognition this neurodegeneration was not limited to boxing but was associated with other activities involving recurrent brain trauma leading to the preferred description "Progressive Traumatic Encephalopathy" later followed by the establishment of the presently associated

name known as “Chronic Traumatic Encephalopathy” which established a broader usage (Critchley, 1957; Stern et al., 2011).

### **Definition of Chronic Traumatic Encephalopathy**

Chronic Traumatic Encephalopathy (CTE) can be generally defined as a progressive neurodegenerative disorder associated with repetitive brain trauma (particularly very mild to mild TBI) characterized pathologically by the accumulation of tau protein and neurofibrillary tangles in various areas of the brain (McKee et al., 2012). CTE is considered a chronic brain syndrome where there are currently no generally accepted guidelines for a clinical diagnosis or a way to distinguish from other neurological degenerative changes that occur in aging or AD. Diagnosis of CTE can only be made in post-mortem brains by confirmatory histopathological assessment. The incidence and prevalence of this condition is currently unknown (McKee et al., 2012). CTE appears to occur in midlife, usually many years after athlete’s sports careers have ended (McKee et al., 2009).

A clinical diagnosis of CTE based on known previous studies and a broad review of the literature is marked by the presence of hyperphosphorylated tau in immunoreactive astrocytic tangles and neurofibrillary tangles. These tangles are found in perivascular foci (adjacent to blood vessels in the foci) as well as the superficial layers of the cerebral cortex. They have an irregular cortical-

distribution of hyperphosphorylated tau in immunoreactive neurofibrillary tangles and astrocytic tangles (with preference for the depths of the cerebral sulci), and clusters of periventricular astrocytic tangles in the diencephalon, basal ganglia, and brainstem (McKee et al., 2012).

There are some important considerations to make about the development of CTE. First, CTE is not considered a continuum of PCS but rather develops decades after exposure to many TBI episodes. Second, there are athletes that were diagnosed with CTE post-mortem that had previously not reported any form of concussion or TBI. This raises speculations that potentially repetitive “sub-concussive blows” or very minor trauma to the brain associated with no known recognized clinical symptoms or diagnosis of a TBI may contribute to the development of CTE. Finally, given that there is a large number of athletes participating in contact sports presently with a potentially high degree of propensity to repetitive blows to the head/brain and there are so few actual known diagnosed cases of CTE, a consideration can be made that other factors such as genetic predisposition may play a major role in its development (Harmon et al., 2013).

### **Neuropathophysiology of Chronic Traumatic Encephalopathy**

Early studies in boxers during the 1970s who were subject to multiple TBIs throughout their careers reported neurofibrillary tangles in neocortical areas of

the brain as CTE (Corsellis et al., 1973). Since then more studies have confirmed more findings of extensive tangle pathological formation in other subjects exposed to multiple TBIs. Along with the neurofibrillary tangle formation were also noticed neuropil threads and glial tangles as hallmarks of CTE in post-mortem individuals (McKee et al., 2009). Several animal experimental models exposed to rotational acceleration brain trauma have also displayed a buildup of phosphorylated tau and neurofilament proteins in damaged axons by showing tau immunoreactivity immediately following trauma. These abnormalities also indicated a correlation with the type of injury severity exposed (Smith et al., 1999; Tran et al., 2011). It is these pathological hallmarks in individuals exposed to various episodes of trauma to the brain that further substantiate the notion that it occurs in response to brain damage.

Tau is a normal intraaxonal protein found in the CNS that binds to microtubules via its microtubule-binding domains therefore stabilizing axons by promoting microtubule assembly and stability. It is not considered toxic nor associated with neurofibrillary pathology. In the normal mature human there is existence of six different tau protein isoforms that each contain either three or four repeat microtubule-binding domains (3 R and 4 R tau respectively) with many serine or threonine residues that have the potential to be phosphorylated (Blennow et al., 2012). Following a TBI event associated with axonal damage, microtubule deficits may result and although the neurochemical disturbances that may trigger tau pathology in CTE are not known extensively, evidence

shows that the mechanisms responsible most likely include abnormal intracellular calcium influx from a TBI, glutamate receptor-mediated excitotoxicity from a TBI, and abnormal activation and accumulation of kinases such as JNK that mediate the hyperphosphorylation of intracellular tau's serine and threonine residues (McKee et al., 2012). Recent studies have shown that JNK was markedly elevated in damaged axons, and that inhibition of this kinase displayed a reduction of total phosphorylated tau protein (Tran et al., 2012). The resultant tau phosphorylation associated with trauma reduces microtubule assembly and stability causing microtubule disassembly leading to impaired axonal transport. This process then leads to a compromised neuronal and synaptic function followed by an increased propensity of this hyperphosphorylated tau protein to aggregate and misfold. It may also be subject to being proteolytically cleaved by calpains and caspases from the effects of TBI forming subsequent insoluble fibrils and tangles. It is the resultant imbalance of kinases and phosphatases that leads to hyperphosphorylated tau protein leading to an abnormal tau aggregation into neurofibrillary tangles and neuropil threads found intracellularly in the cytoplasm of neurons following damage to axons. In summary, it is these cellular and molecular changes that further compromise normal neuronal function and associated with neurotoxicity (Blennow et al., 2012).

There is also recent evidence of interneuronal tau transfer suggesting the possible route and spread of tau pathology to different regions of the brain. Two theoretical mechanisms of the spread of tau may be due to a prion-like templated

misfolding of tau or by the calcium ion imbalance on the receiving neuron. The spread of tau is thought to occur either through the association of neuronal synapses, glial to glial spread, and through periventricular and diffuse extracellular tau migration patterns (McKee et al., 2012). CSF fluid may have important implications in the potential for pathological tau spread as well. CSF fluid enters the brain parenchyma through the Virchow-Robin spaces, which surround the penetrating arteries of the brain and is cleared by the paravenous drainage pathways. It has been demonstrated that amyloid- $\beta$  ( $A\beta$ ), a hallmark in AD and other neurodegenerative diseases, is cleared by this pathway and might be similarly shown in tau pathology. It is this clearance through the CSF and paravenous flow pathways of potentially phosphorylated tau and other protein aggregates such as Transactivation Responsive Region Deoxyribonucleic Acid-Binding Protein 43 that may be an explanation for the frequent pathological findings of phosphorylated tau tangles and characteristic of CTE in perivascular, subpial, and periventricular locations of the brain (as the CSF and venous system normally function in removing any harboring extracellular proteins to make up for the lack of lymphatic circulation in the CNS) (McKee et al., 2012).

Although p-tau immunoreactive neurofibrillary tangles is the main pathological hallmark of CTE, other potential associated pathological abnormalities may have important considerations in CTE. Even though  $A\beta$  peptide deposits or plaques such as the ones seen in AD are not considered a hallmark in CTE (reported in less than 50% of the cases), there have been cases

of reported A $\beta$  deposits in brains from athletes who also had substantial neurofibrillary tangle formation from repeated trauma (Roberts et al., 1990; Roberts et al., 1994; Ikonovic et al., 2004). A $\beta$  is generated from  $\beta$ -APP by cleaving enzymes. Under normal conditions, neurons have expression of  $\beta$ -APP which may be implicated in important neurotrophic functions such as the promotion of axonal sprouting, synaptogenesis, and neurite outgrowth that contribute to neuronal survival after axonal damage occurs. Many studies have demonstrated that  $\beta$ -APP is upregulated in neurons and axons in response to brain trauma and axonal damage occurring within a few hours after brain trauma ranging from mild to severe in nature. The two enzymes responsible for cleaving  $\beta$ -APP to produce A $\beta$  are  $\beta$ -secretase and  $\gamma$ -secretase.  $\beta$ -secretase is identified by the  $\beta$ -site APP-cleaving enzyme 1 (BACE1) and  $\gamma$ -secretase consists of a complex made up of four components including presenilin, nicastrin, Pen-2, and Aph-1. The component presenilin is the main one identified at the active site of the  $\gamma$ -secretase complex. It is the translocation of the  $\beta$ -secretase (BACE1) and  $\gamma$ -secretase (presenilin) by axonal transport to the synapses of the neuron where  $\beta$ -APP can be cleaved to produce A $\beta$  (Blennow et al., 2006; Blennow et al., 2012).

The proposed mechanism from subsequent studies of A $\beta$  deposits in CTE have to do with an increased  $\beta$ -APP expression as a response to trauma following a TBI with axonal damage. Axonal damage is associated with

microtubule deficits causing axonal transport defects as discussed above. This is then followed by an accumulation of  $\beta$ -APP and key enzymes  $\beta$ -secretase (BACE1) and  $\gamma$ -secretase (presenilin) due to transport defects. Already due to the large reservoir of  $\beta$ -APP and secretases in response to trauma at the axonal bulbs there is an increased  $A\beta$  generation at the axonal bulbs.  $A\beta$  then continues to accumulate until subsequent release from the damaged axons into the parenchymal tissue results in  $A\beta$  diffuse plaque formation outside the cells (Blennow et al., 2012). This proposed mechanism suggests that the upregulated  $\beta$ -APP expression from trauma may have an affect on regenerative axonal sprouting and neurite outgrowth. Also, it is important to notice that treatment with a  $\gamma$ -secretase inhibitor may show a decrease in this amyloid pathology, but does not affect the TBI-induced tauopathy tangle formation. This suggests that the tau pathology is not a downstream effect of  $A\beta$  accumulation and potential diffuse plaque formation (Tran et al., 2011).

Several experiments using animals induced with rotational acceleration brain trauma display a buildup of  $\beta$ -APP and subsequent  $A\beta$  within damaged axons throughout the white matter, as well as a subset of these subjects showing  $A\beta$  diffuse plaques accumulating (Smith et al., 1999). Other animal studies suggest that increased repetitive mild TBI increases  $A\beta$  deposition (Chen et al., 2004; Tran et al., 2011). Despite these speculated mechanisms of action, what is known for certain is that intraaxonal  $\beta$ -APP accumulation is an established

marker for DAI and is usually considered the gold standard in identifying DAI in routine forensic medicine (Blennow et al., 2012). As previously discussed above, DAI is a process of axonal degeneration through an extended period which may include an abnormal  $\beta$ -APP metabolism leading to subsequent  $A\beta$  generation of diffuse plaques, particularly in repetitive traumatic episodes.

Another potential pathological association seen in CTE that may have important implications in the disease pathophysiology is the presence of the protein Transactivation Responsive Region Deoxyribonucleic Acid-Binding Protein 43 (also known as TAR DNA-Binding Protein 43 or TDP-43) (McKee et al., 2010; Johnson et al., 2011). TDP-43 is normally a RNA binding protein responsible for regulating gene expression that is to include regulation of transcription as well as aspects of RNA processing and functioning such as splicing, stability, transport, translocation, and microRNA maturation. This protein is mainly concentrated in the nucleus of the cell, however it has been reported shuttling back and forth between the nucleus and cytoplasm (Xu, 2012; Janssens & Van Broeckhoven, 2013). Even though the exact mechanism of this pathological process and the functioning of TDP-43 in TBI is still not well understood, animal experiments in which they are exposed to axonal damage by trauma have shown results of an upregulation of TDP-43 expression in cells along with its redistribution from the nuclear compartment of the cell to the cytoplasm (Moisse et al., 2009). Other studies have also shown that TDP-43 may also appear in a phosphorylated state of pathology (pTDP-43) (Neumann et

al., 2009). Recent studies of CTE investigations have displayed widespread accumulation of TDP-43 post-mortem in athletes that participated in boxing and American football after repeated brain trauma throughout their careers (McKee et al., 2010). These accumulations appeared in several areas of the brain such as gray matter structures including the brainstem, basal ganglia, cortical areas, and subcortical white matter.

There is also speculations that other proteinopathies such as accumulation of alpha-synuclein may present in CTE pathological cases as well and should also be considered. Alpha-synuclein is a protein normally abundant in the presynaptic terminals of neurons. Although its function is not fully understood, studies point towards its importance in maintaining a supply of synaptic vesicles in the terminals as well as potentially regulating the release of dopamine (Bartels et al., 2011; United States National Library of Medicine, 2013). Alpha-synuclein is pathologically significant when it is mutated and aggregates form fibrils that become part of Lewy bodies (abnormal neuronal cytoplasmic protein aggregates). These are primary pathological characteristics of PD, dementia with Lewy bodies, and multiple system atrophy (Arima et al., 1998; Arima et al., 1999; Arima et al., 2000). Even though data on CTE indicate a relative absence of alpha-synuclein proteinopathy, there have been several cases of CTE found with comorbid neurodegenerative disease such as AD, PD, and Frontotemporal Lobar Degeneration (FTLD) indicating the possibility that CTE's tauopathy may be promoting the aggregation of other pathological

proteins through a potential cross-seeding effect. This cross-seeding effect may explain the role of TDP-43 in the majority of the known CTE cases especially in the brains with severe CTE. Although still subject for more research, the frequent association of CTE with other neurodegenerative disorders presenting  $A\beta$ , TDP-43/pTDP-43, and alpha-synuclein accumulation suggest that this repetitive trauma causing hyperphosphorylated tau deposition may be stimulating deposits of these other abnormally aggregated proteins (McKee et al., 2012).

It is currently unknown why some individuals do not develop CTE while others do after being exposed to the potentially same amount of TBI experiences throughout a sports career brings into question if there is a genetic susceptibility for CTE. The literature on CTE indicates that ApoE may have a hand in such indications. ApoE, as previously noted in TBIs, may serve a special purpose in a neuron regenerative phenomena. There are three known alleles for ApoE (ApoE  $\epsilon$ 2, ApoE  $\epsilon$ 3, and ApoE  $\epsilon$ 4) (Blennow et al., 2012). The most commonly found in the general population is ApoE  $\epsilon$ 3 and there is strong evidence that the ApoE  $\epsilon$ 4 allele is a susceptibility gene for AD (Roses, 1996). A series of studies on ApoE  $\epsilon$ 4 showed indications that this particular allele may not help restore neurite sprouting and actually reduce neurite sprouting as a whole unlike the actions ApoE  $\epsilon$ 3 allele (Teter et al., 2002; Ji et al., 2003; Dumanis et al., 2009). Other scientific studies have reported that high-exposure boxers that were severely impaired from CTE carried at least one ApoE  $\epsilon$ 4 allele (Jordan et al., 1997). Also in agreement to these studies was a meta-analysis of 14 cohort studies reporting

that athletes severely injured from TBI carrying the ApoE  $\epsilon$ 4 allele were associated with poor long-term outcome, although this study may be subject to some controversy as other studies found no significant correlation (Zhou et al., 2008). Finally, ApoE  $\epsilon$ 4 allele has also been linked to the generation of A $\beta$  deposits and plaque formation in severe TBI individuals. Further studies showed that trauma patients who displayed A $\beta$  deposition had a clear overrepresentation of ApoE  $\epsilon$ 4 allele (Nicoll et al., 1996). Animal experimentation on AD transgenic mice exposed to TBI showed that mice coexpressing the ApoE  $\epsilon$ 4 allele displayed a greater A $\beta$  plaque deposition than mice expressing ApoE  $\epsilon$ 3 allele (Hartman et al., 2002). Although the exact mechanisms are unknown, this data suggests that ApoE  $\epsilon$ 4 allele may play an important role in triggering A $\beta$  deposition and plaque formation as a response to brain injury. Although these studies on ApoE genetic susceptibility to CTE and poor outcome association in TBI have raised questions on potential genetic counseling for athletes participating in contact sports, they should be interpreted with some caution. Other large prospective studies have found no overall association between ApoE genotype and six month outcome after TBI (Blennow et al., 2012). Furthermore, a meta-analysis of the study on the effect of the ApoE  $\epsilon$ 4 allele on long-term outcome after severe TBI shows it is statistically not significant and is relatively minor (Zhou et al., 2008). McKee et al. 2012 also reported that the proportion of the sample of CTE individuals carrying at least one ApoE  $\epsilon$ 4 allele was not significantly different than that observed in the general population. Although

ApoE may or may not appear to be a risk factor for the development of CTE or associated with the severity of CTE pathology and apart from the ethical issues linked to genetic counseling, large prospective population-based studies are needed to address this issue before such approach can be considered valuable from a preventative or clinical standpoint.

Due to the ordered and predictable progression in the spectrum of disease, four stages of pathology have been categorized in CTE. Research suggests that CTE pathology usually begins at very focal points located perivascularly at the depths of the sulci in the cerebral cortex slowly spreading locally to other areas such as the neocortex, medial temporal lobe, diencephalon, basal ganglia, brainstem, and spinal cord over the course of the years. This occurs in conjunction with notable widespread axonal disruption and loss throughout the stages. Stage I CTE is considered very mild disease that has been noted in a range as early as 17 years old to 56 year old subjects (mean of 28.3 years of age  $\pm$  13.5). Stage II CTE is considered a mild disease state and has been observed in the age range of 21 years to 87 year old individuals (mean of 44.3 years of age  $\pm$  16.7). Stage III CTE is considered moderate diseased state and seen in individuals ranging from 38 to 83 years of age (mean of 56 years of age  $\pm$  14.2). Finally Stage IV CTE is considered a severe state of disease that has been discovered in individuals ranging 51 to 98 years of age (mean 77.4 years of age  $\pm$  11.7). The stages of CTE do show a correlation with duration of exposure in a sports career, survival after career ended (particularly

American football), and age at death as progression occurs (McKee et al., 2012). Figure 7 provides a histopathological sample of the progressive stages of pathology seen in CTE.

### ***Stage I***

According to the findings in the progression of CTE, Stage I or very mild pathology of disease was primarily described as having perivascular hyperphosphorylated tau neurofibrillary tangles in focal points at the depths of the sulci located in the superior, superior lateral, or the inferior frontal cortex. The predisposed location at the depths of the sulci is probably due to the physics of the injury when the brain undergoes the stretch phenomenon during trauma. It is really at those locations where is high degree of compression and little area to expand resulting in greatest axonal shearing. Apparent also may be very sparse TDP-43 and axonal injury ranging from multifocal next to vasculature to axonal varicosities in the cortex and subcortical white matter. Clinically, this pathology was directly associated symptomatically with headaches, loss of attention, and concentration usually beginning about eight to ten years after having experienced repeated mild traumatic brain injuries such as the ones seen in sports careers. Due to the small amount of tau focal pathology, it may be likely that the axonal loss and dysfunction from what could have been multiple TBIs accounts for the clinical symptoms with the early stages of disease (McKee et al., 2012).

## ***Stage II***

Mild disease pathology described in CTE was primarily associated with having neurofibrillary tangles located in the superficial cortical layers adjacent to the focal injuries at the depths of the sulci, as well as neurofibrillary tangles found in the nucleus basalis of Meynert and locus coeruleus. Sparse TDP-43 inclusions may start to become noticeable at this stage of pathology. Individuals who were diagnosed with Stage II CTE primarily presented clinically with experienced depression and mood swings, explosivity, loss of attention and concentration, headaches, and short-term memory loss (McKee et al., 2012).

## ***Stage III***

Changes to the brain grossly on macroscopic inspection tend to become noticeable in late stages of the disease (early stage CTE brains look essentially normal on gross inspection). On gross inspection of the brain evidence showed mild cerebral atrophy, septal abnormalities, ventricular dilation (expansion of the ventricles), a sharply concave deviation of the third ventricle (indicating the thalamus is affected and atrophied in these patients), and depigmentation of the locus coeruleus and substantia nigra. Microscopic evidence of pathology displays a tremendous loss and damage to axons (disturbed/distorted array of axons) along with neuroinflammation. This was characterized by evidence of dense hyperphosphorylated tau buildup located at the medial temporal lobe structures (hippocampus, entorhinal cortex, and amygdala), and in widespread

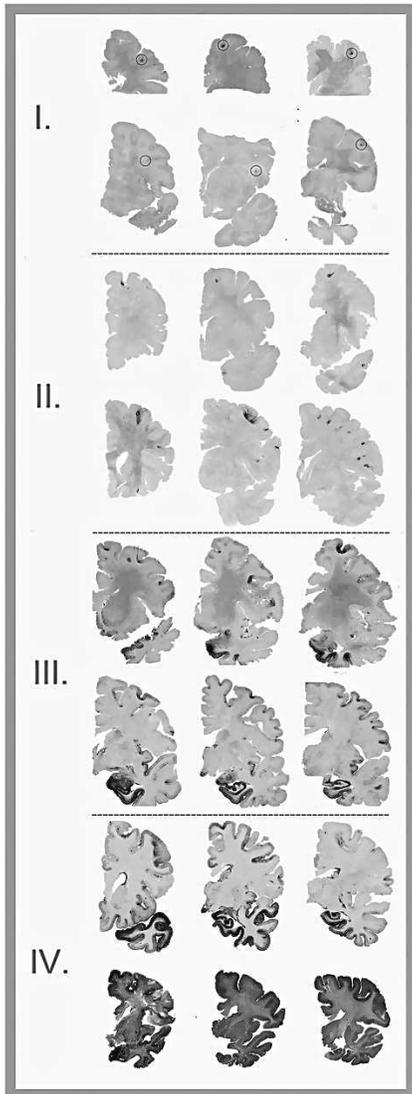
regions of the frontal, septal, temporal, parietal and insular cortices. Other regions also affected by tau pathology noted were the diencephalon, brainstem, and spinal cord. TDP-43 deposition may also be more apparent at this stage of disease. Also noticeable at later stages of pathology is the severe diffuse axonal loss in the cortex and white matter. At this moderate stage of disease most patients displayed cognitive impairment with memory loss, executive dysfunction (such as poor planning, organization, multitasking, and judgement), loss of attention and concentration, depression, explosivity, and visuospatial abnormalities (McKee et al., 2012).

#### ***Stage IV***

Finally, at an advanced stage of disease, further abnormal changes of normal brain physiology were described. Macroscopic changes involved further cerebral, medial temporal lobe, hypothalamic, thalamic, and mammillary body atrophy. Other changes included septal abnormalities, ventricular dilation and pallor of the substantia nigra and locus coeruleus (may give rise to parkinson like symptoms). Evidently these characteristics in advanced pathological stage directly correlate with a significant decrease in brain weight (loss of gray and white matter). In addition to the microscopic changes evident among the other stages, in Stage IV CTE hyperphosphorylated tau pathological involvement was characterized by its involvement of widespread regions of the CNS that is to include the white matter and substantial evidence of prominent neuronal loss and

gliosis of the cerebral cortex. Also a hallmark in Stage IV CTE on microscopic inspection is hippocampal sclerosis. Finally, TDP-43 accumulation may be identified as a widespread deposition throughout the CNS. These characteristics all correlate directly with the clinical symptoms expressed by patients of advanced disease. Subjects with CTE were uniformly demented with profound short-term memory loss, explosivity and aggression. Most of these individuals also displayed depression, paranoia, impulsivity, and visuospatial abnormalities. Other potential signs of CTE in advanced stages may become evident through gait problems, parkinsonism, and speech abnormalities (McKee et al., 2012).

The typical symptoms and behaviors preceding death of the individuals with CTE indicated a link between the neuroanatomical areas of the brain affected by the pathology and the neurobehavioral patterns displayed (Harmon et al., 2013). McKee et al. 2012 study on the spectrum of CTE reported that the majority of the causes of death associated with the disease were from respiratory failure, cardiac disease, drug or alcohol overdose, suicide (most have heightened suicidality issues), or the failure to thrive associated with end-stage dementia and malignancy.



**Figure 7: The Pathological Stages of Chronic Traumatic Encephalopathy:**

A representation of the progressive tauopathy in the four stages of Chronic Traumatic Encephalopathy. All images are CTE brain 50- $\mu\text{m}$  tissue sections immunostained with CP-13. Stage I CTE shows p-tau pathology in very discrete focal points on the cerebral cortex usually around small blood vessels and deep in the sulci. Stage II CTE displays p-tau at multiple locations at the depths of the cerebral sulci and spread of neurofibrillary tangles to the adjacent cortical superficial layers. Stage III CTE displays a widespread p-tau pathology that is to include neurofibrillary degeneration in the frontal, insular, temporal, and parietal cortices, as well as spread to the amygdala, hippocampus, and entorhinal cortex. Stage IV CTE shows severe p-tau pathology spread affecting the majority of the cerebral cortex and medial temporal lobes. Figure was taken from McKee et al., 2012.

## **Criteria for CTE Versus Other Neurodegenerative Pathologies**

CTE is a progressive neurodegenerative disease very similar in characteristics as diseases such as AD and PD and may be difficult to diagnose when comparing to other neurodegenerative diseases. Also, a high number of reported cases diagnosed with CTE have been seen with co-morbid neurodegenerative diseases such as motor neuron disease, PD or Lewy body disease, AD, and Frontotemporal lobar degeneration (McKee et al., 2012). Although it is possible that the accumulation of misfolded phosphorylated tau aggregates described in CTE may promote the abnormal aggregation of other pathological proteins such as A $\beta$ , TDP-43, and alpha-synuclein, it is important to consider the criteria for CTE when comparing to other neurodegenerative diseases.

### ***CTE with Motor Neuron Disease***

A subset of cases with known CTE were also diagnosed with motor neuron disease (63%). In addition to the accepted pathological diagnosis for CTE, as defined above, a clinical diagnosis of definite amyotrophic lateral sclerosis had to be made to classify CTE with motor neuron disease. Also, on pathological inspection, there had to be a presence of notable degeneration of lateral and ventral corticospinal tracts of the spinal cord, a marked loss of anterior horn cells from cervical, thoracic and lumbar spinal cord with gliosis, and

presence of TDP-43 or pTDP-43 positive neuronal, glial, neuritic, or intranuclear inclusions in anterior horn cells and white matter tracts of the spinal cord. The majority of the subjects diagnosed with CTE and motor neuron disease presented with symptoms of motor weakness, atrophy, and fasciculations years before the onset of the developing cognitive and behavioral symptoms seen in CTE. Only a minor portion of the known cases of CTE with motor neuron disease did the symptoms of CTE appear years before the development of the motor neuron disease symptoms (McKee et al., 2012).

### ***CTE versus Alzheimer's Disease***

Tau pathology and tangle formation is not only a key component in CTE but is a hallmark of AD. The tau isoform profile is frequently found in a hyperphosphorylated form in AD, very similar to CTE (Schmidt et al., 2001; Mandelkow & Mandelkow, 2012). In fact, similarities between hyperphosphorylated tau pathology between AD and CTE include a presence of all six tau isoforms present with 3 and 4 repeat tau, as well as neuronal tangles and pre-tangles present. Marked distinctions between AD and CTE are to include that CTE has prominent astrocytic tangles (with predominantly immunoreactive for 4 repeat tau) and its topographical distribution compared to the reported medial temporal lobe in aging and AD. The typical distribution of tau pathology found in CTE and not present in AD is prominent neurofibrillary tangles and astrocytic tangle formation perivascularly (near vasculature), at focal points

at the depths of the cerebral sulci, in an irregular and patchy cortical distribution, and prominent subpial/periventricular astocytic tangles (may be directly due to the direction of shearing forces induced during trauma). Also a distinctive feature is that CTE tangles are predominantly found in cortical laminae II-III and AD is characterized by the prominent presence of neurofibrillary tangles in cortical laminae III and V (McKee et al., 2009; McKee et al., 2012).

Other important distinctions between CTE and AD tau pathology involves the distribution of neurofibrillary tangles in the various stages of pathology. In mild AD pathology, neurofibrillary tangles are predominantly limited to the entorhinal cortex, amygdala, and hippocampus. However in mild CTE, neurofibrillary tangles are primarily seen at focal centers in the cerebral cortex (usually the frontal lobe). In advanced AD, tau pathology manifests itself in a particularly uniform distribution in widespread cortical areas and medial temporal lobe, but has low densities of tangle formation in the basal ganglia, brainstem, and no appearance in the mammillary bodies or white matter tracts. Unlike AD, advanced CTE displays a patchy irregular distribution throughout widespread cortical areas and medial temporal lobes and high densities of tangle formation in the thalamus, hypothalamus, mammillary bodies, brainstem, and white matter tracts. Also apparent in CTE is a moderate amount of neurofibrillary tangles in the basal ganglia (especially the nucleus accumbens) (McKee et al., 2012).

Despite the identification of  $A\beta$  deposits comparable in intensity on severely damaged boxers with CTE and AD patients (Roberts et al., 1990), the

most distinctive reason CTE is not AD is because A $\beta$  is not present in most cases of CTE (more than 50% of the cases of CTE did not have A $\beta$  deposits). AD is defined by the presence of A $\beta$  aggregation and plaque formation (McKee et al., 2012).

### ***CTE versus Parkinson's Disease and Lewy Body Disease***

Parkinsonism has often been associated particularly in boxers with CTE, for which the term “pugilistic parkinsonism” has been utilized in the past decades. Parkinson's disease and Lewy Body Disease is defined diagnostically by the presence and distribution of alpha-synuclein positive Lewy bodies (McKee et al., 2012). Even though the advanced stages of CTE may demonstrate a loss of neurons in the substantia nigra (a key element of PD) and display a presence of alpha-synuclein in some cases, many cases of CTE are observed in the absence of Lewy bodies and the accumulation of alpha-synuclein (Corsellis et al., 1973; McKee et al., 2009).

### ***CTE versus Frontotemporal Lobar Degeneration***

Intraneuronal TDP-43 accumulation was originally considered a key distinguishing feature of FTLD and ALS only (Neumann et al., 2006). However, more recent studies discovered TDP-43 pathology in other common neurodegenerative diseases such as CTE, AD, and dementia with Lewy bodies (King et al., 2010). Due to the similarity in TDP-43 deposition in late stages CTE

and FTLN, the clinical appearance of CTE can be mistaken for frontotemporal dementia (McKee et al., 2012). Therefore, specific established criteria for FTLN have to be used at diagnosis post-mortem to distinguish it from other neurodegenerative disorders.

## **THE NUMBERS IN CONTACT SPORTS**

The number of reported TBIs in sports each year is extremely alarming and may be subject to rise due to the increase of participants and awareness in sports each year. The American Association of Neurological Surgeons reported approximately 46,948 TBIs in American football, 34,692 TBIs in basketball, 24,184 TBIs in soccer, 8,145 TBIs in hockey, 5,794 TBIs in rugby/lacross, and 28,716 TBIs in water sports (such as water polo, diving, scuba diving, swimming, or water skiing) treated in United States hospital emergency rooms during 2009 using the National Electronic Injury Surveillance System. These numbers may still be very conservative and also exclude athletes across the globe (American Association of Neurological Surgeons, 2011).

Long term disabilities associated with sports, particularly in boxers, were first described about forty years ago as dementia pugilistica (now yet known as CTE) (Corsellis et al., 1973). However, after many years of documenting the pathological changes in boxer's brains it became evident that the similar chronic brain condition CTE also occurred in other athletes who participated in contact sports and had histories of repeated episodes of head trauma such as American football, hockey, wrestling, and rugby (McKee et al., 2009). The first reported autopsy from an American football player was published in 2005 (Omalu et al., 2005). Table 5 documents the neuropathologically confirmed cases of CTE as of year 2012.

	<b>Boston University Center for the Study of Traumatic Encephalopathy (2012)</b>	<b>Boston University Center for the Study of Traumatic Encephalopathy (2009)</b>	<b>Other Reported Studies (2009)</b>
Boxing	8	2	37
American Football	50	1	4
Hockey	5	0	0
Wrestling	1	0	1
Rugby	1	0	0
Other (Physical abuse, history of head banging, blast exposures in military veterans, and poorly controlled epilepsy)	3	0	6
<b>TOTAL</b>	<b>68</b>	<b>3</b>	<b>48</b>

**Table 5: Neuropathological Confirmed Cases of Chronic Traumatic Encephalopathy:** The table displays a summary of the identified confirmed cases of CTE post-mortem. Adapted from McKee et al., 2009 and McKee et al., 2012.

## **EVALUATING TRAUMATIC BRAIN INJURY IN CONTACT SPORTS**

TBI is a present day increasingly popular topic in sports as the numbers of reported injuries has increased over the years. This may be actively due to the rise of participation in contact sports and particularly in young athletes training more aggressively at an earlier stage. The prior thinking that TBI only occurred in certain sports is not a valid statement as many epidemiological studies have demonstrated reports of TBIs in a wide range of sports in both males and females across all age groups participating in sports and not limited to the elite or professional athletes. Despite the growing awareness of the effects of TBI and efforts to educate athletes, coaches, physicians, athletic trainers, and parents about recognition and management, much information such as diagnosis, management, prevention, and development of short-/long-term consequences remains highly controversial and elusive making it difficult to interpret. Furthermore, the chances of enduring a head injury is very incidental in most sports, but in certain contact sports the chances of injury are a fundamental part of the game. This raises the likelihood of increased susceptibility to multiple TBIs. To date, there has been a link found between the development of the neurodegenerative disease CTE and a history of repetitive episodes of TBI. Much attention has been raised over the last decade as many cases of CTE have been diagnosed post-mortem in athletes other than boxing.

This raises controversy and a significant impact in the way sports are played to date being more protective of head and neck contact directly affecting youth, collegiate, and professional contact sports across the globe. Worries about the potential long-term effects of repetitive trauma to the brain such as CTE has prompted youth, college, and professional programs in the United States to limit the exposure of contact athletes experience in practice and games. Notably in efforts to support the cause, the National Football League (NFL) has banned the dangerous helmet-to-helmet hits (Reuters Health Information, 2013). This research will also raise TBI related legislation concerning education of athletes, removal from participation of sports in suspected injury, evaluation, management, and return to play criteria.

### **Risk Factors for Sports-Related Traumatic Brain Injury**

There are various recognized risk factors that may place athletes in a position of sustaining a TBI and potentially prolonging the time course of recovery after injury. Notably a history of previous TBIs may increase the risk of sustaining another TBI about 2 to 2.5 times higher (Harmon et al., 2013). It is possible that athletes with a history of previous TBI may report a higher number of symptoms at baseline after a TBI than those athletes with no history of TBI. There is also conflicting research regarding the time course of recovery in athletes with histories of previous TBIs and those without a history of TBI making

it difficult to establish a timeline in management of these patients. However, the higher number, increased severity, and longer duration of symptoms following a TBI episode correlate directly with a prolonged state of recovery in athletes (Harmon et al., 2013).

Recent research has also indicated the importance gender and age play in the risk of sustaining TBI in athletes. Epidemiological studies have indicated that females participating in sports with similar rules as their counterpart males usually sustain more TBIs. It has also been noted that females also report experiencing a higher number and increased severity of symptoms as well as a prolonged time course of recovery. This difference may be due to physiological differences between genders such as a decreased head and neck segment mass of female athletes compared to male athletes that may contribute to sustaining greater angular acceleration type injuries to the brain after impact, leading to a more severe injury as a result of greater shearing of axons (Harmon et al., 2013). However, this discrepancy between genders may also be due to the lack of self reporting in males as females are more likely to seek care and report symptoms. Athletes may not always appreciate fully the negative implications a TBI may pose to their health and the culture may dictate that the game and the team are more important than their individual health (Institute of Medicine of the National Academies, 2013). Furthermore, younger athletes are more susceptible to TBI accompanied by catastrophic injuries. They are also subject to longer recovery periods than adult athletes. The physiological differences that may play an

important role in TBI between the developing brain in youth and adults are the brain/water content (meaning the smaller brain in youth may be “knocked around” within the skull after a blow to the head), degree of myelination, blood volume, blood-brain barrier, cerebral metabolic rate of glucose, blood flow, number of synapses, and geometry and elasticity of the skull’s sutures (Kirkwood et al., 2006). It remains unclear whether age has an effect on long-term disabilities or the potential development of the progressive neurodegenerative disease CTE following multiple TBIs later in life. It has been suggested that the younger brain may also better compensate and recover after brain injury due to the increased plasticity compared to adults (Stern et al., 2011). It is difficult to make a comparison of studies regarding prolonged recovery at different levels of competition (such as high school, college and professional sports) due to differences in methodology, in risk tolerance, return to play protocols, or a combination of all of these. Also apparent, there has not been an adequate amount of recovery pattern studies in athletes younger than fifteen (Harmon et al., 2013).

The sport played, position played, and the athlete’s individual playing style dictate varying degrees of risk involving TBI. TBI is also affected by the varying level of play from youth to professional sports. The mechanisms by which concussive blows or various forms of TBI occur vary from sport to sport including the level of competition. However, the most common mechanism of TBI is usually by way of player-to-player contact. It is of no surprise that certain sports

and positions involved in frequent body collision impacts report higher number of TBI episodes. Certain sports such as boxing, ultimate fighting championship (UFC), kickboxing, wrestling, and other martial arts sports directly involve trauma to the head. According to reports from boxing, there have been a substantial amount of boxing-related deaths (approximately 488 between January 1960 to August 2011) where over 60% were caused by TBIs directly. These particular sports have been directly associated with the high likelihood of developing long-term disabilities from repetitive blows to the head such as CTE (American Association of Neurological Surgeons, 2011). Other studies have demonstrated that in American professional football the quarterbacks, wide receivers, runningbacks, and defensive backs have three times higher likelihood of sustaining a TBI than the linemen. This study also revealed that kickoff plays during the game had a four times higher chance of resulting in a TBI than rushing or passing plays. A high school American football study revealed that linebackers were the most commonly injured on the defensive end of the plays and the runningbacks on the offensive side of the plays (Harmon et al., 2013). Another recent study using accelerometer-based system in the helmets of three college American football teams studied throughout an entire season demonstrated that linemen (both offensive and defensive positions) and linebackers received the most head impacts in practices and games than any other positions. This system also showed that lineman, linebackers, and defensive backs had more impacts to the front of the head than the back, and

quarterbacks had higher impact location to the back of the head compared with the front (Crisco et al., 2010).

Although all contact sports deserve special attention regarding the different mechanisms of brain injury, soccer is a sport that should be carefully considered and is an increasing concern as trauma to the head of an athlete is an established part of the game. According to some studies, TBI in soccer players most commonly occurs as a result of player to player contact both at the high school and college levels of play. The United States Consumer Product Safety Commission used by the American Association of Neurological Surgeons reported that 40% of concussions result from head to player contact, 10.3% are result of head to ground/goal post/wall contact, 12.6% are head to soccer ball contact (including accidents), and 37% are not specified. These numbers indicate that TBIs in soccer may be more frequent than reported (American Association of Neurological Surgeons, 2011). Another notable contact sport is hockey where the most common form of brain injury results from body checking (Stern et al., 2011).

The specific nature of the brain trauma necessary for the development of CTE is still not known. It is completely unknown if CTE is more likely to develop after a few severe TBI episodes or exposure to numerous repetitive subconcussive blows (very minor TBI that does not result symptomatically). Further complications may also arise when studying impact type in different sports to determine the development of CTE. For example, it is widely known

that boxing and American football both have a high degree of impact exposure to the brain, but studies revealed that boxers are exposed to higher amounts of rotational force impacts which result in greater amount of shearing and brain damage as opposed to American football players who receive more linear blows (Stern et al., 2011).

Another component that may place athletes at risk of developing a neurological injurious event or the development of CTE can be genetically linked. As previously discussed, studies may indicate a link between ApoE  $\epsilon$ 4 genetic allele and poor recovery after TBI as well as promoting CTE. There has been conflicting data on this and further research is needed to make such assumptions at this point.

Finally, other factors that may affect athletes sustaining TBI may be the pre-existing presence of mood disorders, learning disabilities, attention disorders, and migraine headaches. There is currently no evidence that a pre-existing mood disorder may predispose an athlete to TBI, however, a mood disorder that was pre-existing or as a result of injury further complicates both diagnosis and management of the injury. When evaluating these athletes it may become challenging to determine which symptoms were present before injury, which symptoms were caused by injury, and which symptoms were worsened by injury. Mood disorders may also directly affect neuropsychological testing further complicating the test interpretation of injury. Like mood disorders, pre-existing learning disabilities, attention disorders, and migraine headaches may further

complicate diagnosis and management of a TBI as they all share common symptomatology as post-injury TBI. Presence of learning disabilities, Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder (ADD/ADHD), or migraine headaches may be associated with increased cognitive dysfunction and prolonged recovery after injury (Harmon et al., 2013). Knowing the presence of preinjury mood disorders, learning disabilities, attention disorders, and pre-existing migraine headaches is fundamental in optimizing the evaluation and management of athletes with a subsequent TBI.

### **Second Impact Syndrome**

There is a tremendous amount of potential health risks involved in returning an athlete to play with persistent TBI symptoms or before a previous TBI has completely resolved. Typically there is an increased susceptibility to a repeated episode or more severe TBI event and a prolonged duration of symptoms and recovery time (Harmon et al., 2013). A TBI is known to decrease the cognitive and physical reaction abilities therefore in theory placing an athlete at increased risk of sustaining a second brain impact during play. On a pathophysiological basis, typically cells that have been injured after trauma to the brain through A/D rotational/linear forces leading to focal and diffuse axonal injuries may initially have the metabolic capability to “hold on” and survive, but are pushed over the edge to cell death by all the secondary factors in the

cascade that increases calcium influx into the cell (discussed above). After a second impact to the brain will only further worsen the cellular metabolic changes already occurring as a result of the first impact and may even occur as a result of a lower threshold impact than the initial TBI increasing long-term disability and morbidity.

Second Impact Syndrome (SIS) is considered a rare form of reinjury of brain tissue before the complete resolution of the initial TBI. SIS is considered to result directly in a diffuse loss of cerebral autoregulation of the brain's blood supply, leading to massive cerebral edema, which may then subsequently lead to a marked increase in intracranial pressure causing cerebral herniation and coma/death. It is typically associated with adolescents and children younger than 18 years of age. This may be due to the physiological differences already described compared to adults, which may result in prolonged and diffuse cerebral edema with increased sensitivity to glutamate after a second TBI further stimulating secondary injurious events in the brain. Even though SIS is considered rare, it should be considered carefully due to its associated high morbidity and mortality (Sahler & Greenwald, 2012; Harmon et al., 2013).

### **Clinical Diagnosis**

Diagnosing TBI in sports is challenging due to the numerous signs and symptoms that may evolve over a period of hours to days after the injurious

episode. Notably, in most cases LOC does not always result visibly after TBI and may very well go unrecognized making diagnosis difficult. There is also the possibility of delayed symptoms in athletes as studies have demonstrated that collegiate and high school players demonstrated neuropsychological deficits and symptoms after injury (Sahler & Greenwald, 2012). This implicates the importance of careful assessment and management of athletes post-injury. Also important in diagnosis of TBI in sports is being able to recognize other conditions that may affect an athlete's ability to respond adequately to assessment of injuries not directly related to TBI.

Care for athletes with TBI should begin with an adequate preparation prior to the participation in practices or competitions (pre-season) that should include the development of an emergency action plan and a preparticipation assessment which is composed of baseline neurocognitive/balance testing, a complete history of TBI (number, frequency, severity, and recovery), and the presence of any pre-existing mood, learning, attention, or migraine disorders. The information provided by preparticipation assessment may be particularly beneficial in determining risk and may be used as a historical reference in the case of sustained brain injury. Baseline neurocognitive/balance testing has not shown any particular short-term or long-term benefits for athletes, however it may be very important when considering high risk athletes with history of TBI, athletes with confounding conditions (mood disorders, learning disabilities, attention disorders, and migraine headaches), or athletes participating in contact sports

with a high incidence of TBI (Harmon et al., 2013). The reliability of baseline testing in all athletes prior to participation in sports is still controversial as results vary from athlete to athlete and depend on age, sport, gender, and confounding medical conditions making them difficult to interpret. Other factors that may affect baseline testing is the changing ongoing normal maturation and developmental process of the athlete throughout the year and can also be affected by current mood or fatigue from participation. More research is needed to determine which tests should be performed with a particular set of athletes (such as high risk TBI athletes). Baseline testing is common in medical practice and recommended when possible, but should never be used as a sole factor when considering the decision-making management of that player (Harmon et al., 2013).

### ***On the Field Assessment and Management***

On the field management of a collapsed player suspected of injury should proceed with initial evaluation of vital signs (assessment of airway, breathing, and circulation) followed by a physical evaluation. Given that similar mechanism of action for TBI may result in cervical spine injury, if suspected, immediate neck immobilization (without removal of gear such as helmet and shoulder pads) and transfer to an emergency department which is capable of using advanced neurological imaging and proper management of cervical spine trauma. If severe brain trauma is suspected due to signs of LOC, deteriorating mental status, or

suspected focal neurological findings (from abnormal or unequal pupil reaction, abnormalities with extraocular movements, or abnormalities on screening motor/sensory assessment) immediate stabilization and transfer to an emergency department should follow (Sahler & Greenwald, 2012; Harmon et al., 2013). However, most athletes will not sustain severe cervical spine or brain injuries and may be assessed on the sidelines for TBI symptoms and cognitive/balance problems.

Unfortunately, there may not be a licensed healthcare provider at every sporting venue including practices and games. However if an athlete is suspected of any TBI, that player should be subject to immediate removal from total participation without return to play until the player can receive proper evaluation. Previous protocol for sideline evaluation of players sustaining a TBI such as a concussion focused on grading the severity of the injury and managing the athlete according to the grading they received at the time of initial assessment (Cantu and Colorado Guidelines) (Cuccurullo, 2004). This however is no longer the recommended form of medical practice, and since then the paradigm has shifted to focusing more on detecting injury and characterizing it accordingly. This requires a standardized approach using a physical exam (to rule out more severe brain injury or other type of injury such as orthopedic and evaluating balance), a medical history, and cognitive exam (Sahler & Greenwald, 2012; Harmon et al., 2013).

Several screening tools have been devised to properly assess athletes suspected of TBI to reduce the amount of subjective results provided by the medical professionals and alternatively reporting standardized objective measures that can be used to make rapid and precise decisions in the diagnosis. These common sideline measures have proven to be useful, and if used in combination, the likelihood of increasing the sensitivity (likelihood that the athlete with TBI will be correctly identified) and specificity (likelihood that an athlete without TBI will be correctly classified) of the diagnosis is increased (Harmon et al., 2013). The most common adopted and used standardized measure used to date is the Sport Concussion Assessment Tool-2 (SCAT-2), which incorporates key components from other scales such as a review of subjective symptoms, the GCS (Table 2), the standardized assessment of concussion (SAC) cognitive assessment, Maddocks score, and an evaluation of balance and coordination (BESS). This screening tool was adopted from a consensus of guidelines established during the Third International Conference on Concussion in Sports in Zurich 2008 by sports leaders in the field of TBI (McCrory et al., 2009). There are currently no prospective studies establishing its efficacy, however, it is still considered one of the best screening tools available due to its incorporation of multiple screening tools, in theory increasing the sensitivity and specificity of the assessment tool. Although the SCAT-2 is considered most effective when compared to a baseline screen, the summated scores do not reflect a “normal

score” or a cut off score that allows an athlete to return to play (Sahler & Greenwald, 2012; Harmon et al., 2013).

Despite the need for further research on the validity and efficacy of TBI screening tools, some of the current available sideline tests have reported that usually as the sensitivity of the test increases, the specificity of the test declines. This may directly affect athletes without a TBI, as they may be held from returning to play and be incorrectly diagnosed. However, physicians are encouraged to “err on the side of safety” and “when in doubt sit them out” as they evaluate for TBI on the sidelines (Harmon et al., 2013). If the complete sideline evaluation for TBI was performed and found negative, and the player is allowed to return to play, then it is highly recommended that serial evaluations be performed throughout the practice or competition to ensure the proper decision was made. Alternatively, if a player is diagnosed with a TBI, then that athlete is required to sit out the remainder of the practice, game, or competition and should not return to play on the same day. A recommended good safety strategy is to sequester an essential piece of playing equipment from an athlete diagnosed with TBI that is allowed to stay at the sporting venue to avoid an “inadvertent” return to play. Sideline management of an athlete with TBI allowed to stay on site includes not leaving player alone and constantly monitoring for any subsequent physical or mental status deterioration.

Management of athletes on the sidelines requires a proper decision of where to place a player diagnosed with TBI (emergency department, home, or

remaining on site until the end of the contest). It is not always considered an easy or straightforward decision and usually constant re-evaluation is necessary before such decision can be made. Initial management of a player with TBI should begin with treating the symptoms such as reducing the physical and cognitive stressors found in the sporting event. In some cases the bright lights or loud noise at sporting events may be cause for removal of athletes completely from the athletic complex. Common practice includes arranging someone to accompany or monitor injured athlete if allowed to leave the competition area, and physicians are responsible for arranging or discussing the follow-up evaluation (parent/guardian presence required if dealing with a minor aged athlete). It may be imperative that written take home information be provided along with verbal notice of the potential signs and symptoms that may prompt an emergency room visit, physical or cognitive exertion that may worsen status, avoiding alcohol or aspirin/NSAIDs (due to the theoretical risk of further bleeding), and when to be seen for a follow-up visit. Along with having properly trained medical professionals, it is important to properly educate the athlete, athletic trainers, coaches, and family on the potential signs and symptoms and proper management of the injured player.

Current recommendations for management post-sideline includes complete physical and cognitive rest (allowing for plenty of sleep) until follow-up evaluation with a physician can be made (Sahler & Greenwald, 2012; Harmon et al., 2013). During the follow-up evaluation by a physician, office management of

TBI should include citing a detailed history of the mechanism by which the injury occurred, the course of symptoms displayed, and reviewing any past history of TBIs. The scores elicited by the screening tests may be very useful especially if there were baseline scores available so that progress can be assessed more objectively. It is important to note that some screening tests that are appropriate for initial assessment on the sideline, may not be at all useful during an office follow-up visit (such as the BESS, as balance may return to normal within a three day period). There are currently no specific recommendations on specific medication treatments to manage an athlete's TBI acute symptoms. The approach is based on treating the individual symptoms that may arise in a cautious manner (often addressed very conservatively, without medications) to avoid masking the progress of resolution in the athlete or exacerbate other symptoms that may affect recovery (Harmon et al., 2013).

### ***Neuropsychological Testing***

Neuropsychological (NP) testing has become a common tool, particularly over the last decade, in assessing the athlete post-injury during the subsequent follow-up medical office visits. It is not currently considered a diagnostic tool for injured athletes, however, it has become increasingly useful as a monitoring tool during the recovery period of injured athletes. Current literature in TBI suggests that cognitive impairments after injury may be prolonged and evident after resolution of symptoms has occurred (Bleiberg & Warden, 2005). NP testing has

shown to have a moderate sensitivity in the detection of cognitive impairments during an athlete's recovery process from TBI (Fazio et al., 2007). NP varies by test type, however, it evaluates several domains focused on the areas most affected in a TBI such as memory, cognitive processing speed, and reaction time.

There currently exists two different methods of taking the NP test. This includes a paper and pencil test, and a computerized test. The paper and pencil test is typically more comprehensive and are typically administered and interpreted by a neuropsychologist. The advantage of this type of testing method is that it may assess other domains and may aid in identifying other conditions such as PCS. However, the disadvantage of a paper and pencil test is that usually they are more costly financially and requires a significant amount of time to administer. Paper and pencil NP tests may not be available to every athlete. Computerized tests may have significant advantages over paper and pencil tests as they are less expensive, take less time to administer, may be administered to a group of athletes in the same setting, and require only minimal human resources. Computerized tests also provide instant results to the provider and have more precise measures of reaction time (Harmon et al., 2013).

Not enough information is available to suggest that comparing an athlete's baseline measures has significant advantages over comparing results to normal values (van Kampen et al., 2006). If baseline measures are used to compare an athlete's evaluation, then care should be taken to make sure that baseline and

post-injury variables such as fatigue (physiological factors) and distractions (environmental factors) are as similar as possible when administering testing to avoid affecting the results of the test drastically (Echemendia et al., 2001). Other factors that may affect NP testing results in general, whether a baseline test is present or not, can be age, effort given, gender, cultural background, primary language, mood disorders, headache migraines, and previous history of TBI (Grindel et al., 2001). Although there are no established recommendations for the use of NP testing (the only evidence of recommendations that exist is based on expert opinions), there are at least three reasons why NP testing should always be considered. First, in high risk athletes with a previous history of TBI or pre-existing conditions, NP testing adds information to the medical provider that may aid with decisions of return to play (RTP) upon monitoring the athlete's recovery status. Secondly, some athletes may deny symptoms altogether in the evaluation recovery process to RTP sooner. NP testing in every case may determine persisting deficits in athletes who may deny symptoms or actually have complete symptom resolution. Finally, NP testing may directly aid in establishing medical policies regarding the management of athletes sustaining TBI.

NP tool screenings is the cornerstone to TBI diagnosis/management and is only an additional resource used in the complete evaluation and judgement used in the recovery process of athletes sustaining TBI (McCrory et al., 2009). NP testing may not be necessary in the majority of the cases of TBI in sports but

proves to be valuable particularly in high risk athletes. These types of tests should always be carefully interpreted by a proper healthcare professionals who are trained and educated in administering each different NP tests including knowledge of the limitations of each test provided. At this point, NP testing should not be used in isolation in the evaluation of an athlete with TBI, but should be used as an additional resource in part of a more comprehensive management strategy.

### ***Neuroimaging***

Typically the vast majority of athletes that sustain a TBI during a sporting event such as practice or competition do not require neuroimaging (as most injuries are considered mild in nature also known as concussions). Neurologic imaging does not play a primary role in the evaluation or management of injured athletes with mild TBI. Certain criteria in more moderate to severe cases of TBI in athletes may push for the use of urgent neurological imaging to rule out significant structural damage and intracerebral hemorrhages (seen in focal injuries). Other criteria that may imply the use of imaging can include a prolonged LOC without lucid interval, persistent mental status alterations, a suspected open or depressed skull fractures, multiple episodes of vomiting, severe acute headaches, athletes 65 years or older (as their brain and vascular tissues may be more fragile at baseline), or any significantly dangerous mechanism (such as falls from significant heights) (American Academy of

Neurology, 1997; Stiell et al., 2005). Other potential reasons for the use of neuroimaging in TBI cases would be the display of worsening symptoms, pronounced amnesia, progressive balance dysfunction, or focal neurological deficits upon evaluation as these may imply signs of intracranial pathology (Sahler & Greenwald, 2012; Harmon et al., 2013).

The most common standard neuroimaging techniques used in TBI are generally Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans. CT scans are best used for the evaluation and detection of bone fractures in the skull, intracranial hemorrhages, contusions, and mass effects (brain stem herniations). MRI can provide a more accurate assessment of focal structural damage of brain tissue. Notably, CT scans exposes the brain to radiation, and therefore should be used cautiously and only if moderate to severe damage is suspected (Harmon et al., 2013).

When the predominant mechanism of injury involves focal injuries and its associated pathology, the primary role in clinical diagnosis is based on neuroimaging to look for severe structural and severe hemorrhagic events in the given case that invasive intervention is needed in the emergency setting. However, TBI athletes with a predominately DAI (the case for most concussions), on initial inspection typically display very minimal changes and often appears normal on CT and MRI scans primarily associated with the microscopic nature of the injury. Characteristic findings that may appear on neuroimaging in roughly 10% of DAI patients display as petechial white matter hemorrhages, small

subarachnoid and intraventricular hemorrhages (Meythaler et al., 2001). There is a poor correlation between the number of hemorrhages detected and the severity of DAI. Due to the poor detection of DAI in neuroimaging due to its mechanism of injury, there is a very low predictability of the functional outcome of patients with TBI after using CT or MRI scans. However, there is a correlation of severity depending on the location of hemorrhagic lesions detected by imaging (Grade I is associated with just subcortical hemorrhages; Grade II is associated with any subcortical and corpus callosal hemorrhages; Grade III is associated with subcortical, corpus callosal, and brainstem hemorrhages) (Ommaya & Gennarelli, 1974). The greater the depth and location of the hemorrhagic punctate lesions is associated with more severe injuries, which may be a better predictor of outcome in DAI.

Late neurological imaging findings (months after injury) should be relatively normal except for a potential enlarged ventricles and generalized atrophy of the midbrain, brainstem, corpus callosum, and the parasagittal white matter which correlate with the initial site of injury. The amount and location of atrophy also correlates with the initial injury severity and may also be a more direct predictor of outcome in DAI (Meythaler et al., 2001).

Alternative imaging modalities exist, but are still evolving in research for the use in TBI. Current limitations of these other neuroimaging techniques include the expensive financial cost, limited equipment availability, and its lack of evidence guiding changes in the management of athletes with TBI. Although

most of these techniques are very informative into the pathophysiology of TBI, there are currently no definitive clinical correlations connecting these imaging modalities and the diagnosis/management of TBI or development of CTE to make them applicable to patient care. An example of these evolving imaging techniques in the sports related TBI field include Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) imaging which is typically associated with measuring the glucose uptake and regional cerebral flow with the use of an injected radioisotope. This process may be very time consuming and currently has an undetermined predictive value making its use clinically very difficult and limited. However, recent research at UCLA on CTE has used PET imaging in an attempt to find traces of the disease in living athletes (Small et al., 2013). These studies on CTE are still preliminary considering the small sample size provided and the lack of autopsy confirmation, but offer promise for future research. Diffusion Tensor Imaging (DTI) has also shown promise in the field of sports related TBI as it provides structural images of the white matter fiber tracts by measuring the movement of water within the brain, capable of providing a better direct reflection of DAI. Other advancing techniques in the sports related TBI are functional MRI (fMRI) which is capable of displaying neuronal dysfunction by measuring location changes of blood oxygenation patterns in response to commands an athlete has to perform and Magnetic Resonance Spectroscopy (MRS) which measures neurometabolites (primarily N-acetylaspartate, creatinine, choline, myoinositol, and lactate)

distribution changes in different areas of the brain (McCrory et al., 2009; Harmon et al., 2013). Despite these advanced modalities, interpretation should proceed with caution, particularly in CTE, as the presence of axonal injury is not enough alone to diagnose and much less determine who may develop the disease.

### **Return to Play Criteria**

There are currently no established guidelines made particularly for youth and adolescents for when to return a player to school after having suffered a TBI. It may be possible that these athletes may experience increased symptomology upon being exposed to the cognitive stresses of school. If that is the case, then student athletes may require informal academic accommodations which can include reduced workload, extended time to complete class work and tests, breaking down complex tasks into simple steps, providing a distraction free area of work, a shortened school day, or even taking days off from school. Athletes in this situation should not be allowed to return to play or participation of any sports type until they are able to return to their academic baseline after injury. It has been noted that athletes may have persistent neurocognitive deficits despite having no symptoms after TBI. These athletes with more persisting and lasting problems perhaps would directly benefit from a more formal academic accommodation intervention through policy such as individualized education programs (a tailored educational plan obtained through the special education

system) (Kirkwood et al., 2006; Sahler & Greenwald, 2012; Harmon et al., 2013). Educating the athlete, coaches, athletic trainers, teachers, and parents on symptoms to look out for and knowledge about TBI is essential to ensure a true optimal recovery through adjustment of academic expectations according to apparent ongoing problems. The key to successful recovery lies in close monitoring by all personnel involved and a gradual transition back to school treating each case individualistically and with prudent considerations.

RTP criteria in the current standard of care in athletes with TBI was recommended by the consensus guidelines established at the Third International Conference on Concussion in Sports in 2008 (McCrory et al., 2009). This RTP guidelines are established for the protection of the health of athletes which is based on knowledge the initial injured brain has a lower threshold of reinjury in the first days and weeks. It is important to note that recovery in children and adolescents may be longer than in adults due to the differences in physiology as discussed previously and if returned too soon, may be associated with potential loss of or future functional disruption and potentially catastrophic consequences such as the rare fatal SIS (Kirkwood et al., 2006). Therefore young athletes should be managed very conservatively. The current approach recommended is based on an individualistic approach to each athlete (as each case is different), and is a gradual and progressive six step graduating program for RTP used in all levels of competition (including the elite athletes). The first step in the RTP protocol involves no physical activity and neurocognitive rest with the objective of

accomplishing complete resolution of symptoms. Before advancing to the next stage, the athlete should have a normal neurological exam and a normal cognitive and balance evaluations which should be ideally compared to a pre-injury baseline measure of that individual if available. Once the athlete is asymptomatic (that is to include symptom free from academic cognitive stress if applicable) and returned to their baseline measures if available, a gradually medically supervised stepwise incremental return to physical activity is initiated. The second step in the program involves light aerobic exercise with the objective of increasing heart rate. The third step involves sport-specific exercise, followed by a fourth step of non-contact training drills to increase exercise, coordination, and cognitive load. Finally step five includes full contact practices assessing functional skills and restoring the athlete's participation confidence. The final step (six) is allowing the athlete to RTP with documented medical clearance from a licenced healthcare provider trained in the evaluation and mangament of TBI. This six stepwise RTP guidelines represent the progression of an uncomplicated TBI. However, if the athlete develops any symptoms with an increase in activity level, then the progress through the program is stopped, and the athlete is returned to the previous phase when complete resolution of symptoms can be attained.

The progression through the RTP protocol may take days to weeks to months depending on the athlete's individual responses to each phase and modifying circumstances provided along the way. PCS that may present in

athletes poses a potential delay in the RTP protocol as it presents long after injury. Management of PCS is generally time including working with a specialized support team, and can involve a long and slow process of recovery which may become very frustrating for many athletes as it removes them from their normal endeavours in school and sports. Prior to beginning the RTP protocol, it is important to consider the individual factors that may increase susceptibility and/or prolong recovery such as the mechanism of injury, duration of symptoms, the past history of TBI, and the presence of prolonged symptoms. Also important is that athletes progressing through the RTP protocol be symptom free without the use of any pharmacological agents or medications that may mask or modify the symptoms during the recovery phases. The goals of these RTP guidelines is to achieve full physical, cognitive, and metabolic recovery to the damaged brain before placing it back in an environment subject to reinjury by the same forces (Sahler & Greenwald, 2012; Harmon et al., 2013).

### ***Disqualification from Sports***

There are no current guidelines established for the special case of having to disqualify an athlete from participation the remainder of the season or retirement from the sport due to TBI. However some recommendations available from TBI expert clinicians claim that the presence of structural abnormality on neuroimaging, multiple lifetime TBIs, persistent deficits in the academic or workplace setting, persistent PCS symptoms, prolonged recovery course, and a

perceived reduced threshold of sustaining recurrent TBIs is subject to special consideration of removing the athlete entirely from participation in sports (Harmon et al., 2013). There has been no set recommendations or guidelines on how many sustained diagnosed TBIs an athlete can endure before being subject to removal from participation in sports. An individualized approach with each injured athlete (as each case may be different) and carefully considering all factors (deliberating it with all parties involved) with an understanding of the risks and unknowns is needed to make an appropriate decision regarding the special case of disqualification from sports.

### **Further Research Needed**

Much remains unknown about the extent sports related TBI can have in athletes. What is known to date about TBI and CTE in sports is very minimal and raises awareness of these significant public health issues about the efforts that are needed to improve prevention, detection, and management of these conditions. Many questions arise in sports related TBIs and CTE bring about gaps in knowledge and the need for further research. It may be incredibly difficult and impossible to establish unknowns such as an established TBI threshold and why some athletes are able to withstand very high magnitude impacts without an onset of significant deficits or any symptoms (as well as why others struggle with significantly lower magnitude impacts). Modern technology

such as the use of accelerometers placed in helmets of athletes may serve a special purpose in determining the value of an average TBI threshold and should be subject to much more research prospectively using a significantly higher sample of players (such as requiring all professional NHL, NFL, and amateur boxers to wear it), which may ultimately aid in estimating the total number of impacts received in a sports career and translating it to information on the risks of developing CTE based on sport and positions played. Other research that would serve critically in potentially preventing TBI is not only protective equipment development (such as improving helmet designs), but establishing the importance of neck strengthening programs as theoretically it may limit the transmission of A/D forces seen by the head when struck. The difference in head to neck segment mass has been marked in gender between males and females, which may account for the differences underlying TBI incidences between genders. Although potentially useful as a significant intervention effect, establishing the vulnerability of strong neck muscles in accidental impacts where the athlete has no time to react or prepare as often occurs in sport rule infractions is also important.

Other recommendations for further research is specifically addressing an established and tested clinical criteria for the diagnosis in both TBI and CTE (in live individuals) using advanced neuroimaging or CSF biomarkers which may prove essential in the future of diagnosis. This also raises the importance of establishing an improved management of both TBI and CTE, which may include

a more accepted standard of care where treatments are available for the acute presentation of these conditions.

Large-scale controlled prospective longitudinal studies are needed to address many of the limitations in CTE research such as the lack of established incidence and prevalence in all age groups and sports, risk factors, genetic risk factors involving susceptibility and resistance to disease (the significance of ApoE  $\epsilon$ 4 genetic allele in the population), the significance of confounding drug and alcohol abuse in certain diagnosed athletes and its potential role in the development of the disease, and the roles of other potential environmental exposures in triggering CTE. For this research to be possible, approved validated animal studies may be very useful and is needed to further understand the basic mechanisms of injury and the progressive nature of the disease. Furthermore, it is widely unknown how many exposures or TBIs (including the type of impact and frequency) are needed to cause the development of CTE in athletes. Therefore, future studies with control subjects who were exposed to multiple TBIs and did not develop behavioral and cognitive abnormalities will be extremely helpful in future research designed to delineate the critical aspects of CTE.

Despite the high reported number of TBIs each year in sports (which may still be very low), there have only been very few confirmed cases of CTE. No CTE has been confirmed in other contact sports such as soccer, basketball, lacross, water polo, and martial arts sports such as kickboing and ultimate

fighting. Furthermore, females athletes have not been studied or diagnosed post-mortem and there has been limited research performed (both in TBIs and CTE) on athletes participating in intramural and club sports as well as children younger than high school age. There are approximately 15,000 ex-professional football players alive today alone, and the story of their overall mental health has not been looked into (Cearnal, 2012). This implies the even higher number of current and ex-athletes that have participated in a wide range of contact sports across the globe where their stories of overall mental health have not been told. It is essential to reach out to those athletes in efforts to better understand TBI and CTE and not limiting to certain sports. This approach to close data gaps in TBI and CTE should call for a mandatory policy establishment requiring all sports across the world (including all levels of play and genders) to report on a TBI surveillance system in order to accurately determine incidence. The information that might serve essential in such system when reported should include a wide range of factors related to the participating athletes such as demographic information, TBI history, the use and kind of protective equipment, the cause/mechanism/extent of the TBI, sport played, level of competition, type of event, location of the impact on body, and the symptoms observed as a result of TBI.

## CONCLUSION

Physical activity can never be made completely safe, and it is almost inevitable that deliberate and inadvertent TBI episodes will happen when participating in contact sports. As long as there is participation in sports, there will always be a level of risk of sustaining a TBI, however it is important to consider what is the acceptable level of risk and reasonable level of reform. Although there is a reasonable amount of health benefits from participating in sports, it is imperative to be mindful of the disadvantages that may present as a result of physical contact such as musculoskeletal and brain injuries which may potentially outweigh the good. There is a great degree of unknown knowledge on TBI and CTE implying the significance of preventative measures when participating in sports. Current and future research should focus on such measures to reduce the likelihood of potential fatal or long-term disability in sports.

Improving protective equipment such as advancing helmet designs has shown to reduce injuries such as scalp lacerations, skull fractures, and other bony head trauma. However, these designs do not protect against TBI and still have an immensely high probability of associated injury. This is due to the mechanism of injury by A/D forces, as helmets may reduce linear A/D forces but not the more damaging rotational A/D forces (also may in fact increase rotational forces experienced), which lead to a more DAI without physical impact. In order

to continue to participate in sports at an acceptable level of risk, it is critical that there be continued development of protective equipment with proper safety standards and impact monitoring systems that can effectively report and provide a better understanding of the biomechanical factors that influence brain injury.

Often overlooked in sports, is the possibility that the use of this “protective equipment” against head injuries may bring about increased risk of TBI by a change in an athlete’s behavior who may assume a more dangerous playing style as well as using the helmet as a part of “acceptable” physical contact against other players. This raises the importance of education regarding TBI in sports as an essential piece to prevention. There are still immense misconceptions and a complete lack of overall understanding of the significance regarding the impact TBIs have on an athlete’s health. Education of TBI and CTE in athletes, coaches, athletic trainers, sports physicians, teachers, school administration, and family play a vital role in the health and safety including reducing the risk of long-term complications and disabilities in athletes participating in sports. This also requires a change in attitude and expectations on the part of all parties involved (including fans).

It is important to consider that athletes are a unique population with an accepted “sports culture” based on a mentality to push themselves beyond their perceived physical and mental abilities in the face of adverse conditions and a multitude of injuries. Athletes are willing to risk their own bodily harm to better themselves on the field and help their team win. Misconceptions that “getting

their bell rung” (common expression used by athletes referring to a hard hit to the head) is part of the normal competition are often made, and often result in lack of reporting symptoms for fear of being removed from participation. Other special considerations in this culture is that the competitive nature of the players, coaches, parents, and fans (particularly in high profile competitions such as playoff games) or special cases of incentives and outside motivators to perform well in the athletic arena (such as the presence of professional scouts, potential scholarships, advancement to a higher-level team, or money) may all be subject to underreporting symptoms and the presence of potential brain injury. Presently, a culture change in sports is needed through large-scale efforts to educate and implement a strong policy that will positively influence athlete’s self-reporting of TBI and their adherence to RTP guidelines ensuring the health and well-being of participants.

Although actions to ban contact sports to completely prevent the risk of TBI and potentially CTE may seem extreme and unrealistic, it is evident that TBI and CTE is beginning to have an impact on policy and rule changes in sports to make them safer. Such examples may include but are not limited to banning “spear tackling” in American football, enforcing no “checking from behind” in ice hockey, and limiting “elbow to head” in soccer (Harmon et al., 2013). Further changes that could benefit player’s health should probably consider banning the use of the head in sports like soccer, or significantly reducing the amount of bouts and hits to the head allowed in other sports like martial arts (boxing,

kickboxing, wrestling, and ultimate fighting). Already evident in the NFL is the limited number of full contact practices allowed per week in efforts to reduce injury, which should be the basis of all sports across the wide range of levels of play. The impact of current knowledge on TBI and CTE also goes to the corporate level in professional sports affecting business (such as the multibillion dollar NFL industry) and may prove essential in disclosing the health risks at play and providing players health benefits beyond their careers in the case of potential long term disabilities as seen in CTE. Rigorous consistent modelling of policy and rule changes in all sports by coaches and officials is key to reducing the likelihood of injuries through the establishment of clean and fair play and penalizing, fining, or suspending players who may intentionally impact opposing individual's head as a way to discourage TBIs.

TBI in sports has become an alarming health concern for athletes that has a major impact on many levels. Despite the present day sports rich culture across the world, it is important to consider how vital neuronal loss from one TBI can impact an athlete's health and even more through repeated episodes. Therefore, there should be a belief in the present day sports culture that TBIs are serious injuries affecting the vital brain, and conservative measures should be emphasized in the care and management for injured athletes until full recovery, which serves fundamental in improving the safety in all competitions.

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VITA

