

A Survey on Research Gaps in Chronic Traumatic Encephalopathy and
American Football Players

by
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ABSTRACT

BRENT FERGUSON: A Survey on Research Gaps in Chronic Traumatic Encephalopathy and American Football Players (Under the direction of Matthew Morrison)

Chronic Traumatic Encephalopathy (CTE) has recently received extensive media coverage, significantly increasing interest in concussions and their relation to the brain disease. As research continues on the disease and the protein Tau that is associated with it, it is imperative to find a correlation between any possible causation other than concussions. All American football players suffer subconcussive impacts, yet only some are diagnosed with the disease, leading most to believe there is something missing.

Interviews were conducted with multiple university officials who work in sports and health, former football players, and team doctors. After interviews, 18 former football players who died of CTE were researched to determine possible correlations that could become a link between CTE and athletes. After this survey, further research was done on specific topics that were mentioned frequently as possible correlations, such as age of first exposure, longevity of play, position on the field, HGH, painkillers, and alcohol. Longevity of play was frequent with the players researched, while the mechanism of alcohol favored the mechanism of the Tau protein. From this research, possible correlations can be further researched to begin the process of discovering the missing link between CTE and athletes.

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CHAPTER 1

Introduction

The game of football is arguably the most loved sport in the United States. During the months of August through February, one sport takes over the weekends, and all focus is on grown men leaving everything they have on the field for either a university or a professional team. It's a game of passion, built through leadership, teamwork, and dedication. However, while this game brings joy and passion from its fans and players, concerns have begun to come forward about the health of the players of this game. The nature of football leads to violent head-to-head collisions on each play. Players risk their physical bodies every day, fighting to be the best player they can be. However, recently the outside, visible body is now overshadowed by a concern for the body's most important organ: the brain.

The brain is susceptible to major injury from the game of football, as it involves major collisions and impacts that can cause the brain to hit the wall of the skull, causing a concussion. Concussions used to be considered irrelevant, however, now they are known to be extremely dangerous. Recently, concussions have been linked to a disease called chronic traumatic encephalopathy (CTE), which is closely associated to a problem with a protein in the brain called Tau. The Tau protein is also associated with Alzheimer's disease, making it an extremely important protein in the brain that needs to be regulated. However, neither Alzheimer's nor CTE have definitive causes, making them extremely dangerous. The major question that many people have towards these diseases is why do

some people have the disease and some do not? With CTE, thousands of athletes put themselves in dangerous positions during sports, but only some have been found with the disease. So what is missing? Is there a link between CTE and athletics that makes players more susceptible to the disease? In this study, interviews were conducted, and research was performed to discuss multiple different possibilities of a missing link between CTE and athletics. From this research, I hope to open up discussions and future research into possible links between this dangerous disease and athletics that we love.

Chapter 2 introduces the tau protein and its mechanism inside of the brain and its malfunction in neurodegenerative disorders, especially Alzheimer's disease and CTE. Next, Chapter 3 introduces Alzheimer's and its association with tau, which is then followed by Chapter 4, which introduces CTE. Chapter 5 begins the discussion of CTE and its association with athletics, focusing on football. Then, Chapter 6 presents the research from the 18 players and develops the possible correlations between CTE and tau protein and different links. Finally, Chapter 7 concludes the survey by discussing future implications and the importance of the research that needs to be done.

CHAPTER 2

Tau Protein

The tau protein is a microtubule-associated protein that is involved in the stability of neurons and neural connections in the central nervous system. It can be found in glial cells; however, it can also be found in the heart, kidneys, lungs, muscles, and fibroblasts. In the DNA of humans, the information for the protein is found over 100kb on the arm of chromosome 17 at the band position 17q21. The band lacks a TATA box, meaning that it has multiple initiation sites along the DNA when being transcribed. After transcription has occurred, alternative splicing can lead to one of six different isoforms of the protein, each with a different number of amino acids, ranging from 352 to 441, and weight, ranging from 45kDa to 65kDa [1]. The differences in size can be seen in Figure 1.

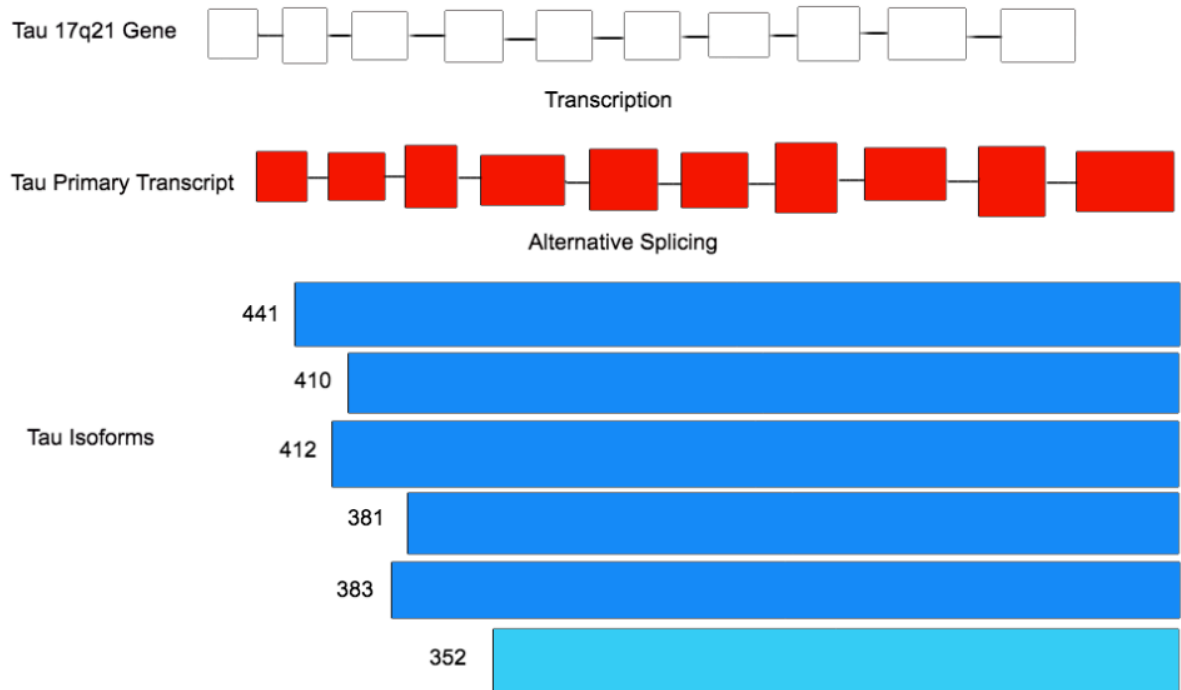


Figure 1. Figure 1 differentiates between the six different isoforms of the tau protein, and the general processes in which they are made. Isoform 6 is of a different shade, as it represents the fetal form of the tau protein.

Tau works to stabilize the neurons by residing on the axons of different cells. Especially crucial in stability of the axons between neurons is the N-terminal of tau. This terminal of the protein also permits interactions between axons and the neural plasma membrane [1]. These connections are of extreme importance in the human brain, as it ensures that messages are able to fire between cells correctly and efficiently. Without the stabilization of tau, the synapse between neurons, which is the space in which neurons are able to communicate, will be altered, causing a disconnection between neurons.

Tau has a total of 79 serine (Ser) and threonine (Thr) phosphorylation sites on its longest isoform. Of these 79, 30 have been described, most of which are either Ser-Pro or

Thr-Pro motives. Tau can be in multiple different states of phosphorylation, which are usually due to the activity of kinases or phosphatases. Kinases phosphorylate tau proteins of the brain; however, many kinases, proline-directed and non-proline directed, must work together in order to complete the phosphorylation of the protein [1].

Tau protein is involved in the organization of the neuron, affecting its polarity and its growth. Phosphorylation of the tau protein involved with a microtubule can affect its identity and physical characteristics, such as its rigidity, length, stability, and interactive capacity with other organelles. Non-phosphorylated tau proteins are more effective than phosphorylated tau proteins on microtubule assembly [1].

Phosphorylation is the process of adding a phosphate group (PO_4^{3-}) to a biochemical molecule. In this case, the kinase enzyme speeds up this addition by causing a conformational change in the protein and adding the phosphate group to the protein's R group. Phosphatases counteract kinases by dephosphorylating tau. If there is a major increase of kinase activity or major decrease of phosphatase activity, the tau protein will become hyperphosphorylated [1]. Hyperphosphorylation of a protein occurs when a protein is saturated of phosphate groups. Usually, the protein that is phosphorylated has multiple sites for phosphorylation to occur. When this hyperphosphorylation occurs, aggregation of the protein will follow, which is associated with neurodegenerative diseases, such as Alzheimer's disease and Chronic Traumatic Encephalopathy [1].

The abnormal hyperphosphorylation of tau is what causes the neurodegenerative disorders and dementia that are seen as a result of tau protein aggregation.

Hyperphosphorylated tau aggregates in the soma, or cell body, of the neuron that is affected. Caused by a mutation, the mutated tau is actually a more favorable substrate for

abnormal hyperphosphorylation in the brain, suggesting that mutations in the tau could be causing the abnormal aggregates seen in neurodegenerative diseases. However, the affects of hyperphosphorylation also occur in non-mutated tau, which could in turn block the intracellular movements in the neuron and neuron-neuron communication. The abnormal proteins are no longer able to attach to the microtubules that they stabilize due to its aggregations, which is what leads to the blockades seen in neurons. For the six human isoforms of tau, all of them have been seen to promote aggregations in the brain when hyperphosphorylated, meaning that humans are extremely susceptible to this biochemical mutation. However, if the protein can be depolarized back to its normal state, then the protein is able to restore its biochemical structure [15].

CHAPTER 3

Alzheimer's Disease

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that is linked to mild cognitive impairment, gradual loss of memory, and mood disturbances. The disease itself affects many people around the world; however, it is primarily seen in adults over the age of 65. On average, about 10% of the population of 65 years or older have the neurodegenerative disorder. There are two types of brain lesions seen in AD, which can differentiate the disease from other diseases that similarly cause dementia: senile plaques (SP) and neurofibrillary tangles (NFT). These plaques are caused by the accumulation of a specific peptide known as $A\beta$, or $A\beta$ amyloid. This peptide is made from a precursor protein, the β -amyloid precursor protein (APP) [1].

APP is a protein of the cell membrane that protrudes from the cell outward. It has a specific process in which it is cut into different peptides, which can either have a positive or negative effect on the brain and its functioning. A specific enzyme called separase is used to cut APP in a specific sequence so that the protein is able to function properly. However, there are three different cuts that separase makes, in which the order is extremely important: alpha, beta, and gamma. APP is cut twice to form either the $A\beta$ amyloid, which aggregates into plaques that cause AD, or $A\alpha$ amyloid, which is the normal occurring protein. The first cut by separase is the

deciding factor. If the cut made is an alpha cut, then the protein made will be the healthy amyloid protein. However, if the first cut is the beta cut, then the resulting protein will be the A β amyloid, which will plaque. Following either an alpha or a beta cut is the gamma cut, which is made to shorten the protein so that it can be used properly in the neurons. In a healthy adult, there is only about a 5-10% occurrence rate for the A β senile plaques. However, in a brain affected by Alzheimer's disease, there is a 40-50% occurrence rate [2].

AD is characterized by a number of factors, which can also be seen in other neurodegenerative disorders. The main symptom of AD is progressive dementia, which cannot be stopped. It begins as mild cognitive impairment, eventually leading to mood disturbances, perceptual disturbances, and gradual loss of cognitive function altogether [2].

Pathologically, AD is found mainly in one area of the brain called the hypothalamus, specifically the entorhinal cortex. This area is associated with memory encoding and recall, which gives rise to the dementia associated with AD. Historically, the Nucleus Basalis of Meynert is the first part of the brain affected in cases of AD. Future research can be focused on this area of the brain to discover the occurrence of the disease [2,3].

The appearance of tau protein in AD is not as distinct as that of other neurodegenerative diseases, such as CTE. AD is characterized by A β amyloid plaques, as well as some occurrence of tau NFTs. AD is characterized by six stages, as found by researchers Braak and Braak. In Stage I, the appearance of neurofibrillary lesions occurs in the transentorhinal region of the hypothalamus. In Stage II, the severity of the damage

to this region increases, and the affected region also spreads to the entorhinal layer of the hypothalamus. These two stages are considered the “silent stages” of AD, as there are no cognitive impairments associated with this damage. Once AD has grown to Stage III, severe NFTs and neurofibrillary lesions begin to form in the same areas of the hypothalamus mentioned in earlier stages. Also, the first extracellular NFTs are seen in this damage, which increases the severity of the disease and begins the onset of cell death. During stage IV, the lesions begin to grow deeper into the layers of the hypothalamus. Stages V and VI are characterized by the spread of the severe lesions to association areas of the brain [3]. Tau protein filaments appear as paired helical filaments (PHF) about 95% of the time, which appear with a diameter of 8-20nm. In AD, all of the six isoforms of the tau protein occur, each of which is hyperphosphorylated when found [3].

By performing procedures post mortem of AD patients, it was discovered that these tau tangles were never separate from the neurofibrillary lesions found in the entorhinal cortex. Also, it was associated alongside the A β plaques found in AD; however, these plaques are absent in other neurodegenerative diseases, setting AD apart. Also, tau pathology is strictly limited to nerve cells in AD, not expanding to glial cells, as in other disorders [3].

CHAPTER 4

Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy (CTE) is a progressive neurodegenerative disease that has risen to fame recently due to the amount of cases in athletics. The increase of the disease is believed to be caused by multiple traumatic brain injuries (TBI) to the head, including both concussive and subconcussive injuries [4]. Similar to AD, CTE causes dementia in patients, along with confusion, aggression, paranoia, depression, and impulse control problems. These symptoms may last for months or decades after the TBIs have occurred, meaning that the disease can only be defined post mortem [5]. As many of the cases arise from athletics, many scientists believe that CTE is the only “fully preventable cause of dementia,” which has led to the multiple changes to the protection of the head in contact sports recently [4].

While concussive and subconcussive injuries due lead to an increase of CTE, not all individuals with major TBIs and repetitive brain trauma (RBT) develop CTE. Recently, this is believed to be in part to the genetics of patients, especially those with the APOE ϵ 4 allele. This allele is associated with AD and β -amyloid, and it may have direct neurotoxic effects that affect the mitochondria and the cytoskeleton. However, more research needs to be done on the APOE gene before any tie between it and CTE can be confirmed [7]. For future research, if a genetic cause can be confirmed, then a possibility of determining the reason for the disease will increase dramatically.

Characteristically, CTE patients have extensive injuries inside of the cortex of the brain, usually caused by aggregations of proteins into neurofibrillary tangles (NFT) or plaques. This damage is widespread throughout the brain and is not centralized to one area. However, it is noted that in the entorhinal cortex, the focus of AD, there is typically no damage in CTE, separating the pathologies of the two diseases [1,6]. From research of multiple cases, CTE spread to numerous regions of the brain, including the cerebral cortex, the medial temporal lobe, the subcortical white matter, the thalamus, the hypothalamus, and the brainstem [4]. Also unique to CTE is the appearance of NFTs around the blood vessels of the brain, followed by their appearance in the sulci. This has become a defining factor of CTE when diagnosing a patient post mortem [5].

The tau proteins in CTE are misfolded due to the repeated injuries to the head. These proteins change shape and are released into the neurons of the brain where they aggregate and form the NFTs associated with the disease. These NFTs then cause cell death and can spread to nearby cells, causing the spread of CTE to numerous regions of the brain [5].

CHAPTER 5

CTE and Football

The initial cases of CTE were discovered in 1928 in boxers. Originally, it was not considered a serious issue, but instead, it was known as a symptom of a concussion injury called “punch drunk syndrome” [5]. Before 2005, the disease was unknown and believed to just be post concussion problems. In 2005, the first case of CTE was diagnosed in American football with the case of Mike Webster. Webster was an offensive lineman for the Pittsburgh Steelers organization, meaning that he received multiple hard hits to the head each time he was on the field. After retirement, psychologically, Webster had developed a change in his normal personality, exhibiting signs of a dysthymic disorder, which is a neurotic depression. Dr. Bennett Omalu performed the autopsy of Webster and found multiple plaques and NFTs in each of the lobes of the brain, as well as the cingulate cortex and the insula. However, none were found in the entorhinal region, which strayed him from Alzheimer’s [6].

As of 2005, there had been 300,000 cases of minor traumatic brain injury (MTBI) or concussion in the United States, and the number has risen increasingly annually. Also as of 2005, there were a reported 0.41 concussions in each National Football League game, in which 92% of those players returned to practice in a week or less. According to research done by Dr. Omalu, nearly 68% of concussions are caused by head to head collisions [6]. According to further research done, there are 1.6 to 3.8 million sports-related concussions annually. Many athletes have multiple concussions, possibly leading

to a mild TBI. Of those athletes, 17% of them will develop CTE, although the exact incidence of the disease occurring cannot be found. Of the 51 cases of CTE diagnosed as of 2009, 46 occurred in past athletes, not limiting to professionals [8]. There are cases of professional, collegiate, and even high school athletes suffering from CTE.

Looking at statistics from past few years, every player that plays American football will receive a head to head contact hit that can lead to subconcussive injury. In the National Football League, players risk having up to about 1400 hard hits to the head each season, including practice. Per game, there are about 100 head to head contact hits in the NFL, some players having up to 14 individually [9,10]. For professionals, these numbers can be alarming; however, the numbers for youth are the same. On average, there are 240 head to head contact hits a in a youth football game, leading to an average of over 100 subconcussive hits in a single season for one individual. Because most brain development occurs during childhood and adolescence, these head to head hits can internally damage a child's development [11].

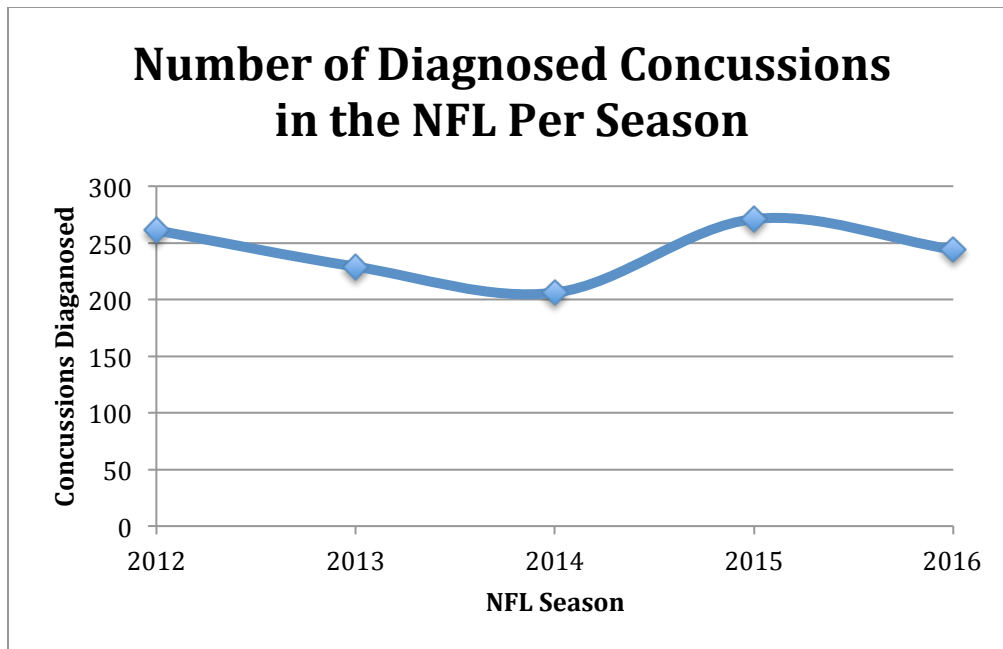


Figure 2. Figure 2 shows the distribution of concussions officially reported per season in the NFL. This data includes concussions that were reported in preseason games, regular season practices, and regular season games [12,13].

In the 2016 NFL season, the amount of concussions was decreased by about 11%. As the rise of data and research into the correlational link between concussions and CTE, players have begun to admit when they feel like they have been concussed. Dr. Robert Heyer, the team physician for the Carolina Panthers and the President of the NFL Physicians Society, reiterated this by stating, “Players are more likely to speak up if they believe they have a concussion” [12]. Also, the NFL has increased the precautions for concussions during on the field incidents. In July of 2016, the NFL released a new enforcement protocol for concussions [13]. However, even with this new protocol and newfound knowledge of CTE, there was a decrease in concussions reported, when an increase would have been expected.

There has also been a rise in the incidence of CTE among players that have passed away. In 2013, both Junior Seau and Jovan Belcher, both former NFL players, were discovered to have CTE after both died of self-inflicted gunshots. Just recently, in 2016, Ken Stabler, former Oakland Raiders quarterback, was found to have CTE when he died. As this rise in CTE cases continues, former players have begun to speak out. A group of players, at one time led by Dan Marino before he removed his name, sued the NFL for concussions, stating that the NFL knew of the correlation between concussions and long-term neurological problems, but failed to inform the players [12]. During the 2016-2017 NFL season, NFL Hall of Fame player Bo Jackson revealed that he wished he had never played football now that he knew the possible health issues. Jackson stated, “We’re so much more educated on this CTE stuff, there’s no way I would ever allow my kids to play football today” [14]. With all of this new information and data, football has been placed under the radar, leaving room for new discoveries to be made on how the game can be safer without reducing the game that so many love.

CHAPTER 6

What Could Be the Missing Link?

It seems that nearly each time that a new brain is given to research for CTE, it is found with Tau NFTs and plaques. However, usually these brains that are given to research have a backstory. Mike Webster's brain was researched due to his psychological changes. Junior Seau's brain was given due to the fact that he was a star player in the NFL, who then went on to commit suicide. A player like Tyler Sash, former Giants safety who won a Super Bowl, was only 27 when he died of an overdose, and he already had behavior that was not normal, according to his mother [16]. So, what makes some players get CTE? And why do some walk away from the sport seemingly unharmed? Thousands of athletes play football in high school and college and do not make it to the NFL. However, there are incidents of CTE in athletes who did not even make it to the professional level, such as Mike Borich who played at Western Illinois and an anonymous high school player [17]. There must be a missing link between abnormal tau hyperphosphorylation and subconcussive injuries that has not been found.

To look into possible missing links, 18 specific football players who died with CTE were researched. The players are seen in the Table 1. Also, multiple interviews were conducted with former players, both in the NFL and college, current athletic trainers of college teams, current team doctors for both NFL and college teams, and an Associate Athletic Director of a college program.

<u>Name</u>	<u>Age of Death</u>	<u>Cause of Death</u>
Anonymous 18 year old	18	Unknown
Chris Henry	26	Car Accident
Tyler Sash	27	Drug Overdose
Just Strzelczyk	36	Suicide – Car Crash
Mike Borich	42	Drug Overdose
Junior Seau	43	Suicide
Andre Waters	44	Suicide
John Grimsley	45	Gunshot Wound
Terry Long	45	Suicide – Drank Antifreeze
Tom McHale	45	Drug Overdose
Mike Webster	50	Heart Attack
Dave Duerson	50	Suicide
Ray Easterling	62	Suicide
Ralph Wenzel	69	Dementia
Ken Stabler	69	Colon Cancer
Earl Morrall	79	Parkinson’s
Lou Creekmur	82	Dementia
Frank Gifford	84	Naturally

Table 1: List of former players who died of CTE, including their age when they died and their cause of death [17,18, 19, 20].

Years in the NFL

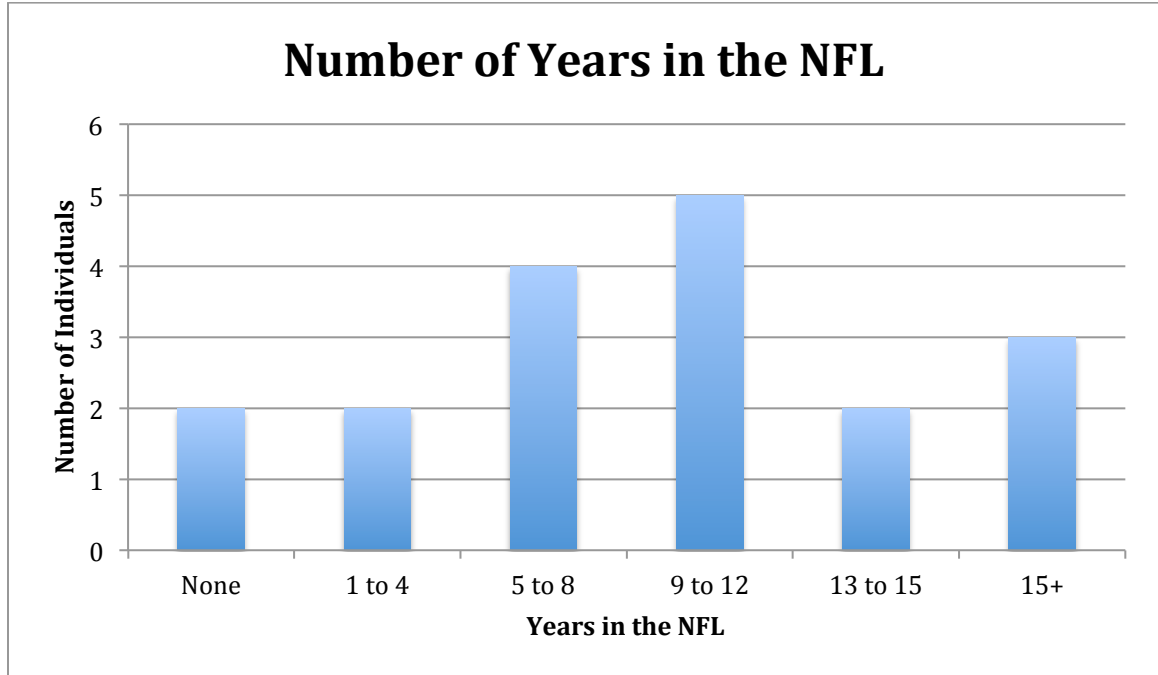


Figure 3: Fig. 3 shows the number of years in the NFL played by the 18 former players researched, ranging from 0 to 21 [17, 20].

One of the most intriguing cases of CTE in recent years is the case of Junior Seau. Seau was a 20-year veteran of the NFL, who was a leader and a fan favorite for multiple teams, especially the San Diego Chargers and New England Patriots. However, after his retirement in 2010, Seau’s psychological state changed drastically, including reckless behavior with financials, withdrawal from his family, and heavy alcohol consumption. On October 18, 2010, he was arrested for domestic violence against his girlfriend. About two years later on May 2, 2012, he was found dead from suicide by gunshot [20].

After Seau’s death, the teams in both San Diego and New England reached out to the media to ensure that the former star’s death had nothing to do with alcohol or drugs, stating that he never had drug problems and only consumed alcohol “socially” [18]. Also,

Gary Plummer, a former teammate and linebacker partner of Seau's for the San Diego Chargers, released that Seau had to have had over 1,500 concussions over his career. While that number may seem incredibly exaggerated, he supported these claims by defining a Grade 1 concussion. A Grade 1 concussion, according to a seminar that Plummer had heard, is defined as when a player "sees stars" after a hit. Plummer admitted that he had over 1,000 during his career, meaning Seau, who played longer, had to have over 1,500 [21].

Imagine 1,500 hits to the head. If the tau protein's abnormal hyperphosphorylation that is concurrent with CTE is caused by a concussive hit, then imagine the brain damage that Seau endured during his career. Seau's hippocampus, nucleus accumbens, hypothalamus, and forebrain all had excessive presence of tau NFTs, affecting his memory, cognition, and the links between the nervous system and endocrine system [18]. Seau's injury introduces a possible missing link of length of time in the sport of football. Seau played 20 years in the NFL, as well as in college and high school [20]. Therefore, as a veteran, Seau induced many more severe hits to the head than a player who did not. However, this missing link can be contrasted by the cases of Chris Henry, Tyler Sash, Mike Borich and an anonymous 18-year old.

Chris Henry was 26 years old and had played only 4 seasons in the NFL when he died from a car accident, in which he was thrown from the back of a moving truck. Tyler Sash was 27 years old when he died from an accidental painkiller overdose. Sash was determined to have progressed to Stage 2 of CTE, which is the same stage that Junior Seau was at when he committed suicide. Sash had only played 4 seasons in the NFL, and yet he had the same stage of CTE as a man who played 20 years [16]. However, Sash had

played football for 16 years, beginning when he was 9 years old [36]. Still, how could a man who was only 27 years old have the same stage of CTE as a 43 year old veteran? Could the intensity of the NFL be the factor that led to CTE?

The intensity of the NFL is like no other level. The speed increases, which in turn increases the amount of force that a player can take in a game. While this could easily be seen as a possible link between subconcussive injuries and CTE, Mike Borich's case argues against that claim. Mike Borich played college football for Western Illinois before retiring from the sport and becoming a coach for the Chicago Bears. After retiring, Borich experienced depressive symptoms and substance abuse issues that led to his death from a drug overdose. His brain was sent to Boston University's CTE Center, where Dr. Ann McKee said that his brain had trauma that she had never seen before for someone who had never played in the NFL. The fact that Borich had never played in the NFL opened a new realm of interest in CTE, as it began a discussion on younger individuals playing football [22, 17].

Boston's CTE Center also was able to research an anonymous former high school athlete who had died. This athlete was a multi-sport athlete in high school, including football. From their research, they saw the beginning stages of CTE, and it is the earliest signs of the disease found to date [17]. While playing in the NFL for multiple years increases a player's susceptibility to subconcussive injuries, head injuries in younger adults who have never played in the NFL also can induce the hyperphosphorylation of tau exemplified in CTE. From the 18 players researched, the ages ranged from 18 up to 84 years old. Also, players ranged from no NFL experience to over 20 years of experience. While age and time in the NFL could be a link between CTE and athletes, there must be

another aspect to these men's lives that are causing them to develop this neurodegenerative disease.

Position

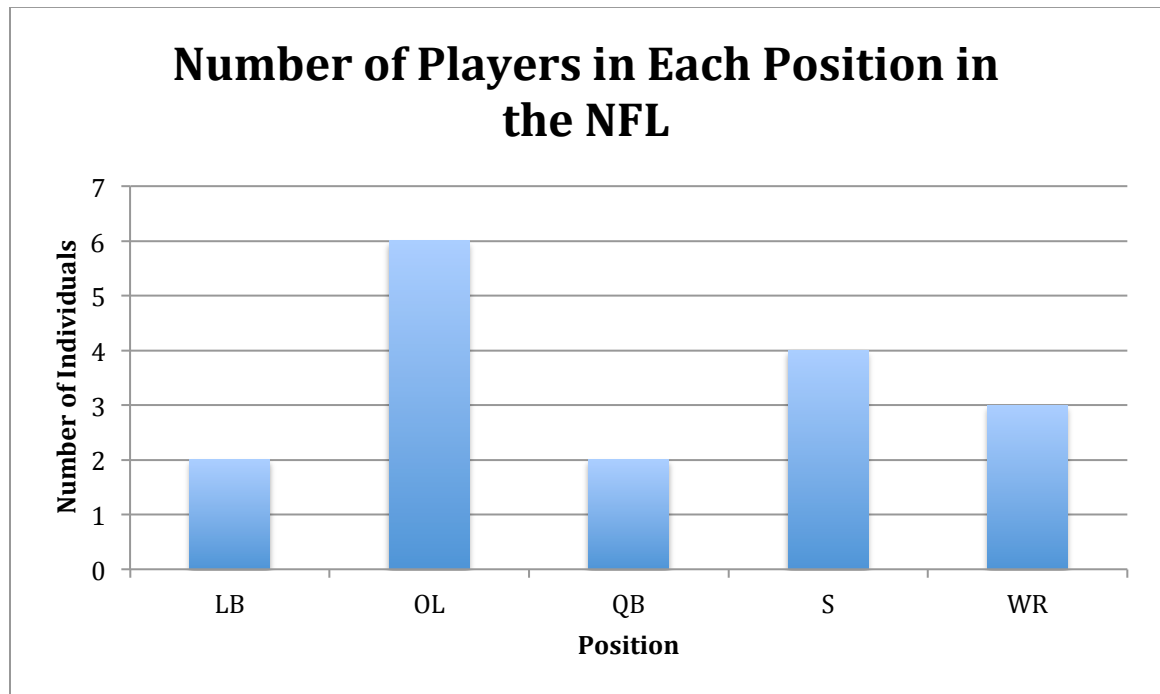


Figure 4. Fig. 4 shows the distribution of positions played by the 18 players researched. Most players were either offensive lineman or defensive players [17, 20].

Football is a dangerous sport no matter what, however, there are some positions on the field that are more susceptible to big hits than others. Quarterbacks, protected by an offensive line, are much less susceptible to taking concussive or subconcussive hits than the offensive line that is protecting him. From the players researched, there were 2

linebackers (LB), 6 offensive linemen (OL), 2 quarterbacks (QB), 4 safeties (S), and 3 wide receivers (WR).

In the 2014 NFL season, there were 206 reported concussions during the NFL preseason and season. In 2015, there were 271 reported concussions during the NFL preseason and season [12,13]. Of those concussions that were reported during the season, the number of concussions reported per position is listed in Table 2. The report from the 2015 season is in Table 3.

2014 Concussion Report During the Season	
Cornerback (CB)	22
Safety (S)	20
Wide Receiver (WR)	19
Tight End (TE)	16
Linebacker (LB)	15
Running Back (RB)	15
Defensive End (DE)	11
Offensive Guard (OG)	9
Offensive Tackler (OT)	8
Quarterback (QB)	6
Center (C)	4
Defensive Tackle (DT)	4

Table 2. Table 2 shows the number of concussions per position in the NFL during the regular season. This data only accounts for the first 15 weeks of the 17 week NFL season [23].

2015 NFL Concussion Report During the Season	
CB	41
LB	24
WR	24
S	17
TE	17
OT	15
QB	12
RB	11
OG	10
DE	10
C	9
DT	7

Table 3. Table 3 shows the number of concussions reported per position in the NFL during the 2015 NFL regular season [24].

Of the players researched, there were 6 OLs that had confirmed cases of CTE, 33% of the total group. From the 2014 and 2015 season, OLs combined had the second most concussions in the NFL, only behind CBs [23, 24]. Of each of the positions, linemen take the most hits during a football game, going full speed head to head against an opponent each down. The amount of subconcussive hits taken by an OL each year has to be extremely large. The first few cases of CTE were linemen, such as Mike Webster and Terry Long, who both played OL for the Pittsburgh Steelers. However, OLs are

outnumbered by CBs when it comes to concussion numbers, and there were no significant CBs named in the research done on former players with CTE. The most predominant defensive position was S, which was second in 2014 and fourth in 2015 in concussions reported [23, 24]. CBs are first in both 2014 and 2015 in concussions and were not listed in the research of former players with CTE, meaning that the specific position that a player plays does have some impact on the possibility of concussions and subconcussive hits. However, position on the field must not be the only factor when it comes to CTE in football players.

Human Growth Hormone

According to Eddie George, former RB for the University of Tennessee and the Houston Oilers, performance enhancing drug (PED) use in the NFL is “very rampant” [25]. Substance abuse could be an issue in the NFL that links players with CTE to those who do not suffer from the disease. NFL players take on many potential injuries during the season, leading to the use of many painkillers that could be a potential harm to player’s bodies. Also, players are always ensuring that they are the best players that they can be, leading to the use of steroids, especially human growth hormone, or HGH. Could either of these substances be the missing link between those players that do and do not get CTE after football?

In the NFL, HGH has become the go-to steroid drug for players. After Peyton Manning was accused of using HGH, Bleacher Report reported that between 10-40% of NFL players used HGH. According to a veteran player, players know that it is extremely difficult to catch someone on HGH. While Bleacher Report said that nearly 40% of

players were using HGH, former quarterback Brady Quinn said that he believes it could be upwards of 50% [26].

HGH is a polypeptide hormone that is naturally made in the anterior pituitary gland located in the brain. As a peptide hormone, it is unable to cross the membranes inside of cells, meaning it cannot cross into the cytoplasm of a cell. Using a growth hormone receptor (GHR) on the outside of the cell membrane, HGH stimulates the growth and development in the body. The activated GHR activates JAK2 tyrosine kinase, which is an enzyme that works to phosphorylate the protein JAK2. This protein then activates the signaling process that sends information to multiple sites in the body, including the muscles and liver [27]. In the liver, HGH stimulates insulin-like growth factor 1 (ILG-1) which is involved in insulin regulation and skeletal muscle development [28].

Tau protein's hyperphosphorylation is usually induced by a mutation that can be onset from head trauma. HGH, which works in skeletal muscles and the liver mainly, does not seem to correlate with tau protein's mechanism. However, the use of HGH could make a player more susceptible to larger force impacts due to the strength and speed gained from HGH. Whether it is a link or not, HGH increases the speed and strength of players, resulting in larger head to head impacts of those that use the drug.

Painkillers

Painkillers are also rampant around the NFL, especially the drug Toradol. Toradol, the brand name for a drug called Ketrolac, is a non-steroidal anti-inflammatory that can be given either as a pill or as an injection and works extremely fast and potently.

Essentially, the drug works as a super Advil, working stronger and faster, so that players can remove the pain from their injuries throughout the season [29]. Toradol inhibits cyclooxygenase, an enzyme that works to stimulate inflammation and pain. By inhibiting the enzyme, Toradol removes the pain and inflammation that is caused during injury [30].

Cyclooxygenase works with prostaglandins, which are lipids derived from arachidonic acid that work in the promotion and possibly the resolution of inflammation. The drugs competitively inhibit the active sites of the enzymes, meaning that they physically block the prostaglandins from being able to bind to the enzyme by binding to its active site. Without these drugs, prostaglandins are able to produce the cardinal signs of acute inflammation, which are redness, heat, swelling, and pain [30]. By taking these drugs at the rate that many NFL players do, there could be a lasting effect on the body, mainly in the cardiovascular system, as it is paired with cardiovascular disease. Three of the four major prostaglandins affect the brain, and one in particular, Prostaglandin F₂ (PF₂) has been found to play a significant role in brain injury, especially in ischemic stroke patients [31]. Due to the intake of Toradol, and other painkillers such as Vicodin and OxyContin, NFL players could be more susceptible to brain injury, such as ischemic stroke. Also, if PF₂ can harm the brain, there could be further research needed to see if tau protein is affected in anyway. The painkiller problem in the NFL could be causing further damage to the brain than we know, leaving another open area for a possible missing link between CTE and football players. Unfortunately, there are many players who are not worried about these health risks.

The mindset around taking Toradol in the NFL is extremely nonchalant. Injured or not, a player is going to play, so Toradol is seen as a way to make it more comfortable.

Bleacher Report ran a survey of 50 players asking about if they were concerned about the long term damage they could have while taking Toradol, and 40 replied with either mildly concerned, or not concerned at all. Only 4 responded that they were gravely concerned about their future health. In some cases, the painkiller has been taken for years, so that they do not lose their positions, or more importantly their jobs. A major example introduced by players is Tony Romo. Romo, a long-time starting quarterback for the Dallas Cowboys, injured his back and now sits on the bench watching a rookie take his job. Anti-inflammatories increase the risk of stomach ulcers and gastrointestinal bleeding, and Toradol is not different. Actually, Toradol can increase the susceptibility to these issues even more due to its high potency. However, players still would rather play and keep their job, then be injured and have the possibility of losing their position [29]. Although health risks are rampant, players want to ensure that they can play, for they are afraid that they will lose their jobs if they do not.

Two of the researched players died of misuse of painkillers: Tom McHale and Tyler Sash. Tom McHale was 9-year veteran of the NFL when he quit the game. Unfortunately, throughout his life after the NFL, he struggled with an addiction to the prescription painkiller OxyContin, and it got worse when his wife told him to leave their house for taking cocaine in their home. After McHale's death, his wife Lisa began to believe that the head trauma that he encountered from football led to his problem with drugs, which could have been the case [35]. CTE affects the brain in many ways, causing paranoia and depression, which McHale could have been fighting by using these drugs [5]. From a study ran by Washington University after McHale's death, it was found that 98% of misusers of pain medications suffered an undiagnosed concussion, as compared

to 81% of players who did not misuse painkillers. In McHale's case, however, the drug use began after the NFL, when his brain was already damaged from the head trauma and had presumably already deteriorated to a degree [35]. Tyler Sash, who also died of painkiller overdose, was taking these drugs as he played, giving a different perspective. Sash died of an overdose of hydrocodone, another prescription painkiller that was given to him while playing and after playing for a shoulder injury he had endured [36].

Painkillers revolve around football because it is a dangerous sport filled with injuries. Players need these drugs to continue to play, but unfortunately they are misused and abused. Cases like McHale and Sash show that there could be a link between painkiller use and the onset of CTE. However, both players played football for an extended period of time, meaning that still there is no definitive answer of if it could be a missing link.

Alcohol

In 2012, a horrific tragedy struck the NFL when Josh Brent, then a player for the Dallas Cowboys, crashed his car, killing his teammate Jerry Brown, Jr. Brent was intoxicated while he was driving and charged with intoxication manslaughter. Alcohol is an issue with many people, and it does not leave out football players. In college, players are seen as royalty, and sometimes that can go to players' heads. In the NFL, Friday nights are the most anticipated of the week, other than Sundays, because that meant that practice was light and players got to enjoy themselves. Former NFL player Akbar Gbajabiamila called Fridays "the most dangerous night in the NFL." It is the only day of the week when players do not have to think about the consequences the next day, as there

were no practices before the games on Sunday [32]. Alcohol is dangerous for NFL players, just like it is for everyone; however, could it be potentially putting players at risk for CTE?

Alcohol affects multiple neurotransmitters in the brain, and it can be inhibitory or excitatory. The three major neurotransmitters affected are GABA, glutamate, and dopamine. Alcohol binds to GABA and glutamate receptor sites causing an inhibitory response, slowing down movement and speech, as these two neurotransmitters are important for those actions. Alcohol binds to dopamine receptors and causes an excitatory response, increasing the amount of dopamine in the pleasure center of the brain, causing the pleasure euphoria from alcohol. If alcohol consumption is chronic, cognitive problems will begin to arise from damage done to the brain, and thiamine levels begin to diminish [33]. If these thiamine levels persist, it could cause a disease called Wernicke-Korsakoff Syndrome (WKS). WKS can cause two individual syndromes: Wernicke's encephalopathy and Korsakoff's psychosis. Wernicke's encephalopathy leads to difficulty walking, mental confusion, and the inability to move the eyes. If it continues to progress, the encephalopathy, or death of the nerve tissue in the brain, can lead to the inability to walk completely or total mental confusion, to the point where a patient cannot even find the way out of a room [34].

While not nearly as severe, WKS causes damage to brain tissue similar to CTE. In both diseases, brain tissue is deteriorating, reducing the normal functions of day-to-day activity. While the areas of the brain may differ, the symptoms and mechanisms of the two diseases have similarities. If football players consume a dangerous amount of alcohol, while also taking on the stresses of head to head collisions from the sport, it

could have an additive effect on the brain. Looking into the backgrounds of the players researched, it was difficult to find any players with significant alcohol problems that were publicized. However, cases such as Josh Gordon show that alcohol is still prevalent in some players in the NFL, and it could possibly be a link between CTE and athletes.

CHAPTER 7

Why is This Important?

The game of football is a dangerous sport. There's no way of getting around that fact. Also, the game of football is an incredibly popular sport, especially in America, making it extremely difficult for people to oppose certain aspects of the game, such as big hits and major collisions. However, people are starting to realize the importance of health after football, making the game adapt to new ideas and new rules, such as changing the landscape of preseason practices or adapting to the targeting rule. Whether you agree with it or not, the game of football is under a microscope due to the emergence of CTE, and it is important that the changing of the game is dealt with correctly, so that players can remain as safe as possible, and we do not lose the game that we love so dearly.

A major reason that the game has been under fire is because of youth involved in the game. "The game of football is under attack because of the concern of concussions and our youth," a former collegiate and professional player stated during his interview. A prime example of youth football affecting someone's future is Tyler Sash, who died at the age of 27 after playing football since he was 9 years old. Youth football programs, such as Pop Warner, could be hurting more than helping the youth of today, as they enter into the sports world.

The major concerns mentioned during the interviews were that the Pop Warner coaches were not good enough and that the youth were too young to be involved in full contact sports. One university official who specializes in sports and health backed up his

argument stating that age development between ages 9 to 13 is extremely important, which is the age where youth begin to play full contact football in the Pop Warner leagues. Some Pop Warner leagues allow youth at the age of 5 years old to play full contact tackle football, which puts youth at danger from a very young age. Also, the coaches are taught under a program called Heads Up Football, which has been backed by multiple NFL coaches, such as John Harbaugh and Bruce Arians [37]. However, there are still concerns that Pop Warner is not learning the skills that they need to continue in football. One team physician of an NFL team spoke against the Pop Warner league, saying that it was not worth putting youth at risk because they were not even learning the correct techniques of the game.

Most interviewees, including former players and current team officials, agreed that Junior High School was the first time that youth should be allowed to play full contact sports. One recent player interviewed, however, stated that he understood the Pop Warner league, as most of the parents and coaches played football themselves at that age. He said, “I would [allow my son to play football] just because I did as a younger kid.” Also, others who are for Pop Warner and other youth football leagues, such as those in the Football Moms Initiative of Pop Warner, argue that youth football teaches boys to become young men, through teamwork, leadership and discipline [37]. No matter which side of the argument you fall, youth football has become a major concern for many. Therefore, if longevity of the game and age are links between CTE and athletes with the disease, which Dr. Ann McKee of Boston University has suggested [36], then extra measures need to be taken for these youth leagues to ensure that the love of the sport is not inducing the effects of CTE on the future athletes.

Another major concern of the football that was increasingly mentioned in the interviews performed was preseason practices. Multiple sources stated that they have changed the way that they practice in the preseason and during the season to reduce the amount of concussive and subconcussive hits taken by players. One university's team has reduced their practices to full practices in the morning only, leaving the afternoon practices for only walk-throughs. He said that it gives the coaches an opportunity to see the players' form in the morning and fine tune in during the afternoon to ensure that they are using correct technique. Another university official stated in his interview that concussive hits actually drop two-thirds during the season. In preseason practices, it is basically asking players to play a full game six days a week, including full pads and full contact hits. A recent player of the game at a university reiterated that preseason practices were much more intense, stating that, "Spring and Fall camps are a lot more intense being out of season, and we scrimmage mostly every day with more hitting drills."

So, what is being done to pull back the intensity of these preseason camps? If most concussive hits occur in camps, which were mentioned by a university official close to their football team, then what rules can be put in place to reduce these hits? NCAA recommendations for football preseason camps have been updated recently, and they recommend that the two-a-day practices only occur if the afternoon practice is a walk through only, just as one university official stated that they were doing earlier. However, camps are longer due to the removal of two-a-days, meaning that there are more days of the week that players are taking repeated blows to the head. Finally, NCAA states that if a scrimmage occurs, the following practice must be a "non-contact/minimal contact" practice or walk-through [38]. By implementing these rules, there will be rest time

between major blows to the head; however, players are still taking repeated blows every day in game-like situations. Therefore, preseason camps are still a major threat to a players' health, especially if they are "playing a game for six days every week" like one interviewee stated.

Preseason camps may need to be regulated even more than they already are, as players' health can severely be damaged. Recommending that scrimmages and full contact drills can only happen a few times a week, rather than every day, would reduce the amount of hits taken by players in the preseason. However, this could take away from the quality of the game, as players are taught how to tackle and the proper technique of their position during camps. Finding the proper balance between health and the sport we love is a continuing battle, but the importance of player health is beginning to take the forefront of people's minds, making it plausible to see more regulations on preseason camps in the near future.

Regulations have already been put in place due to the emergence of CTE, such as the targeting rule. When it first arrived, the targeting rule changed the game, reducing the amount of blatant, big hits that were seen in the secondary of the field, where the wide receivers and cornerbacks/safeties battle each other. New rules has players thinking about if the big hits are necessary, said one university official who works close with the football team. Most people agree that the new targeting rule helps the health of the players, but it has changed the dynamic of the game. What used to be a normal, big hit, is now seen as a direct target of someone's personal health. A recent player at the collegiate level he is "in between" on the rule, as he understands the health side, saying that he knows that safeties will see a defenseless wide receiver and leave their feet and shoot for the player, rather

than making a football play on the ball. However, he feels that many of the calls can be questionable, and they need to be definitive when making the calls. Overall, all people around the sport that were spoken to like the health benefits from the rule, meaning we are taking one step forward towards a safer game.

Due to the emergence of CTE and its link to concussions, the game has already begun to change tremendously when it comes to concussions and the diagnosis of them. A team doctor for a professional football team stated that attitudes towards concussions are different. In the past, players would know that they had a concussion, but they would ensure to keep that information from the coaches and medical staff, so that they could continue to play. Today, players are willing to speak up about their injuries, as they understand the dangers of head injuries more than in the past. Also, he said that before 2009, if players were asymptomatic within 15 minutes after a concussion, they could be cleared to return the game. Now, players are immediately out of the rest of the game once a concussion is diagnosed, putting a great deal of pressure on medical staff to get the decisions correct. There is pressure coming at them from players, who he called “passionate warriors” who always want to return to the field. However, there is also pressure to get the decision right, as if he does not, it could turn into national news, such as the repercussions giving to the Miami Dolphins after their quarterback Matt Moore returned to a game after a major collision in a postseason game against the Pittsburgh Steelers [39].

A former player who played in the NFL and college game in the 80s and 90s reiterated the team doctor’s comments about the game changing tremendously. When he was a player, for a concussion, there were times where he would just be asked, “how

many fingers am I holding up?” and players knew that the answer was going to be either 2 or 3. This was because when he played, big hits, or “dings,” were essentially celebrated. He knows that he was sent back into the game too early now, however, at the time, it was expected to be sent back into the game if all you had was a “ding.” Today, players have to be removed from the field whenever they are thought to have a concussion, and many times, they do not return to the field. The emergence of CTE has changed the way medical staffs respond to head injuries, making the game safer and more cautious when it comes to concussions.

Finally, it is important to find the link of CTE and athletes to preserve the game that we love so much. When Bo Jackson was quoted saying that he would have never played the game had he have known about this new data, it was felt with mixed emotions in the football community [14]. “I think it’s easier for him saying that now that he is retired,” said one former player. He believes that as a college student especially, the will to compete and the want to play in front of thousands and become a professional trumps anything else. Most were concurrent with his view also, with one university official asking, “What other reaction could be expected?” Another university official said that had Bo Jackson of known of CTE when he was player, he probably would have played anyway just like the players of today. He said that the players play off of their own accord, and they leave the statistics for after the game, which has some people asking, is CTE used as an excuse after the game? Did some players not prepare for life after the game, and do they use CTE as a way to get out their mishandling of their lives? Whether true or not, CTE has caused people to question the game they have always loved, which is a perspective that needs to be changed, so that we do not lose the sport completely.

Simply put by one former player, “if you play football, you are going to get a concussion.” Our job now is to control and contain these injuries. “The answer is not to stop playing football,” this former athlete continued. Instead, we need to manage athletics with the right techniques, management, doctors, and technology. The players just want to ensure that their quality of life is not affected by CTE caused by their love of the game. By finding the missing link between those who get the disease and those who do not, we can be able to give these players the quality care they deserve and preserve the quality of their lives after the game. The game is changing throughout due to the emergence of CTE, and finding the cause of this disease can change everything moving forward with athletics, not just football. The disease has affected former players in hockey, soccer, and boxing, as well. Whether the link is one of the aforementioned possibilities, HGH, alcohol, youth exposure, etc., there is a reason that some players are affected by this disease and some are not, and it is time that we research this disease and discover the true link between CTE and athletics.

References

- [1] Buée, Luc, Thierry Bussièrre, Valérie Buée-Scherrer, André Delacourte, and Patrick R. Hof. "Tau Protein Isoforms, Phosphorylation and Role in Neurodegenerative Disorders" These Authors Contributed Equally to This Work." *Brain Research Reviews* 33.1 (2000): 95-130. Web.
- [2] White, Stephen W. "Alzheimer's Disease." Brain & Behavior Class Lecture. MS, Oxford. 18 Oct. 2016. Lecture.
- [3] Spillantini, Maria Grazia, and Michel Goedert. "Tau Protein Pathology in Neurodegenerative Diseases." *Trends in Neurosciences* 21.10 (1998): 428-33. Web.
- [4] Stern, Robert A., "Recurrent Sports-Related Traumatic Brain Injury and Tauopathy" Washington, DC. 2011. Lecture.
- [5] "What Is CTE?" *Concussion Legacy Foundation*. N.p., 27 July 2016. Web. 05 Oct. 2016. <http://concussionfoundation.org/learning-center/what-is-cte>
- [6] Omalu, Bennet I., Steven T. Dekosky, Ryan L. Minster, M. Ilyas Kamboh, Ronald L. Hamilton, and Cyril H. Wecht. "Chronic Traumatic Encephalopathy in a National Football League Player." *Neurosurgery* (2006): n. pag. Web.
- [7] Andrikopoulos, J., P. H. Montenegro, and R. A. Stern. "Clinical presentation of chronic traumatic encephalopathy." *Neurology* 83.21 (2014): 1991-993. Web.
- [8] McKee, Ann C., Robert C. Cantu, Christopher J. Nowinski, E. Tessa Hedley-Whyte, Brandon E. Gavett, Andrew E. Budson, Veronica E. Santini, Hyo-Soon Lee, Caroline A. Kubilus, and Robert A. Stern. "Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury." *J Neuropathol Exp Neurol Journal of Neuropathology & Experimental Neurology* 68.7 (2009): 709-35. Web.
- [9] Sauser, Brittany. "Analyzing Hard Hits on the Football Field." *MIT Technology Review*. MIT Technology Review, 22 Oct. 2012. Web. 22 Jan. 2017.
- [10] Higgins, Matt. "Football Physics: The Anatomy of a Hit." *Popular Mechanics*. N.p., 17 Dec. 2009. Web. 22 Jan. 2017.

- [11] Stamm, J. M., A. P. Bourlas, C. M. Baugh, N. G. Fritts, D. H. Daneshvar, B. M. Martin, M. D. Mcclean, Y. Tripodis, and R. A. Stern. "Age of first exposure to football and later-life cognitive impairment in former NFL players." *Neurology* 84.11 (2015): 1114-120. Web. 22 Jan. 2017.
- [12] NFL Concussion Fast Facts. (2016, August 1). Retrieved February 13, 2017, from <http://www.cnn.com/2013/08/30/us/nfl-concussions-fast-facts/>
- [13] Maese, R. (2017, January 26). Concussions were slightly down during NFL's 2016 season. Retrieved February 13, 2017, from https://www.washingtonpost.com/news/sports/wp/2017/01/26/concussions-were-slightly-down-during-nfls-2016-season/?utm_term=.327d0d07120b
- [14] Nightengale, B. (2017, January 12). Bo Jackson's startling hindsight: 'I would have never played football' *USA Today*. Retrieved February 13, 2017.
- [15] Wang, J., Xia, Y., Grundke-Igbal, I., & Igbal, K. (n.d.). Abnormal hyperphosphorylation of tau: sites, regulation, and molecular mechanism of neurofibrillary degeneration. Retrieved February 13, 2017, from <https://www.ncbi.nlm.nih.gov/pubmed/22710920>
- [16] Graziano, D. (2016, January 27). Tyler Sash CTE level 'had advanced to stage rarely seen' at age 27. Retrieved March 20, 2017, from http://www.espn.com/nfl/story/_/id/14655379/tyler-sash-former-new-york-giants-safety-had-high-level-cte
- [17] Case Studies » CTE Center | Boston University. (2013). Retrieved March 02, 2017, from <http://www.bu.edu/cte/our-research/case-studies/>
- [18] Azad, T. D., Li, A., Pendharkar, A. V., Veeravagu, A., & Grant, G. A. (2016). Junior Seau: An Illustrative Case of Chronic Traumatic Encephalopathy and Update on Chronic Sports-Related Head Injury. *World Neurosurgery*, 86. doi:10.1016/j.wneu.2015.10.032
- [19] Habib, H. (2016, February 09). Earl Morrall's son: Father's final years suffering with CTE 'horrific'. *Palm Beach Post*. Retrieved March 20, 2017.
- [20] NFL players with CTE. (2016, February 09). Retrieved March 20, 2017, from <http://www.cbsnews.com/pictures/nfl-football-players-with-cte/>
- [21] Klemko, R. (2012, May 04). Ex-teammate: Junior Seau had 1,500 concussions. Retrieved March 20, 2017, from <http://content.usatoday.com/communities/thehuddle/post/2012/05/ex-teammate-junior-seau-had-1500-concussions/1>

- [22] Schwarz, A. (2009, October 21). Concussion Trauma Risk Seen in Amateur Athlete. Retrieved March 20, 2017, from <http://www.nytimes.com/2009/10/22/sports/ncaafootball/22concussions.html>
- [23] Which Position Suffers The Most Concussions? « CBS Denver. (2014, January 12). Retrieved March 20, 2017, from <http://denver.cbslocal.com/2014/01/12/which-position-suffers-the-most-concussions/>
- [24] Concussion Watch. (2015, January 25). Retrieved March 20, 2017, from http://apps.frontline.org/concussion-watch/#positions_2015
- [25] Wire, S. (2015, January 08). Eddie George tells SI steroids are 'very rampant' in NFL. Retrieved March 20, 2017, from <http://www.si.com/nfl/2015/01/08/former-nfl-running-back-eddie-george-steroids-very-rampant-nfl-today>
- [26] Popper, D. (2015, December 30). Peyton Manning report blows lid off NFL's HGH problem. Retrieved March 20, 2017, from <http://www.nydailynews.com/sports/football/peyton-manning-report-blows-lid-nfl-hgh-problem-article-1.2481234>
- [27] Carter-Su, C. (1996). Molecular Mechanism of Growth Hormone Action. *Annual Review of Physiology*, 58(1), 187-207. doi:10.1146/annurev.physiol.58.1.187
- [28] White, S. (2017, February 14). *Drugs & Behavior*. Lecture presented in Mississippi, Oxford.
- [29] Dunne, T. (2017, January 11). 50 Secrets of the NFL's Go-To Pain Drug, Revealed. Retrieved March 20, 2017, from <http://thelab.bleacherreport.com/nfl-toradol-use-players-survey/>
- [30] Ricciotti, E., & Fitzgerald, G. A. (2011). Prostaglandins and Inflammation. *National Institutes of Health*. Retrieved March 22, 2017.
- [31] Saleem S, Ahmad AS, Maruyama T, Narumiya S, Doré S. PGF(2alpha) FP receptor contributes to brain damage following transient focal brain ischemia. *Neurotox Res*. 2009;15(1):62–70.
- [32] Gbajabiamila, A. (2012, December 13). For players, Friday is the most dangerous night in the NFL. Retrieved March 22, 2017, from <http://www.nfl.com/news/story/0ap1000000110872/article/for-players-friday-is-the-most-dangerous-night-in-the-nfl>
- [33] Short & Long-Term Effects of Alcohol On Brain Function & Cognitive Ability. (2017). Retrieved March 22, 2017, from <http://americanaddictioncenters.org/alcoholism-treatment/mental-effects/>

- [34] Alcohol's Damaging Effects on the Brain. (2004, October). Retrieved March 22, 2017, from <https://pubs.niaaa.nih.gov/publications/aa63/aa63.htm>
- [35] Barr, J. (n.d.). OTL: Concussions may impact drug use. Retrieved March 23, 2017, from <http://www.espn.com/espn/eticket/story?page=110128%2FPainkillersCTE>
- [36] Pennington, B. (2016, January 26). C.T.E. Is Found in an Ex-Giant Tyler Sash, Who Died at 27. Retrieved March 23, 2017, from https://www.nytimes.com/2016/01/27/sports/football/former-giants-safety-tyler-sash-found-to-have-cte.html?_r=0
- [37] Football. (n.d.). Retrieved March 24, 2017, from <http://www.popwarner.com/football.htm>
- [38] Year-Round Football Practice Contact Recommendations. (2017, January 17). Retrieved March 24, 2017, from <http://www.ncaa.org/health-and-safety/year-round-football-practice-contact-recommendations>
- [39] Kerr-Dineen, L. (2017, January 08). This disgusting cheap shot is everything that's wrong with the NFL. Retrieved March 26, 2017, from <http://ftw.usatoday.com/2017/01/bud-dupree-matt-moore-hit-pittsburgh-steelers-miami-dolphins-video-suspend>