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The Progression of Neurological Impairment in Sport-Related Brain Injuries

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A Thesis Submitted to Fulfill the Requirements of the Honors Program at Assumption College

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Abstract

Millions of Americans sustain traumatic head injuries each year when participating in various high and low-risk activities. Athletes, in general, are more prone to sustaining brain injuries than others, particularly those that participate in collision sports. This thesis discusses brain damage and long-term effects incurred by collision sport-related traumatic brain injuries such as the formation of amyloid-beta plaques in brain tissue and the increased possibility of developing neurodegenerative diseases such as Alzheimer's. In addition, brain development and plasticity over time are reviewed revealing the concept that brain plasticity and brain development are key processes that occur throughout childhood, adolescence, and to some degree into adulthood. Together, the discussions of these topics are the basis for the creation of a logical and analytical hypothesis as to whether young or adult athletes have the potential to incur more severe, long-term damage. The resulting hypothesis is that it is worse for young athletes to sustain head injuries since brain development largely impacts an individual's quality of life. However, their injuries might be less apparent than in an adult because of the brain's plastic abilities enabling them to compensate and remain functioning at a high level despite their injuries.

Introduction

Brett Favre, a well-known quarterback who played in the NFL for twenty years, voiced his concerns regarding his memory and the damage his brain underwent as a result of the head injuries he amassed while playing such an intense contact sport. This concern surfaced when he realized that even though he remembered some of the activities and sports his daughter played, he “couldn’t remember [his] daughter playing youth soccer, just one summer [even though he has]...a pretty good memory” (ESPN, 2013). Many current athletes can relate to Favre’s situation and emotions: “For the first time in 44 years, that put a little fear in me;” especially when the similarity of their complaints (for example: memory loss, headaches, dizziness) become apparent, as there have been many reports of mental difficulties arising in athletes as a result of head injuries such as concussions (ESPN, 2013).

The injuries and complications that approximately 1.7 million Americans receive per year according to data collected throughout the United States from 2002-2006, including Brett Favre, suffer from are the result of the condition known as Traumatic Brain Injury (Faul et al., 2010). Traumatic Brain Injuries (TBIs) are wounds that differ from other injuries in that even the ones labelled “mild” are actually rather severe injuries as they have hidden and unforeseen consequences. Traumatic Brain Injury is a term used to describe brain damage caused by a blow to the head or blow to the body that is strong enough to reach and affect the brain and cause damage. Annually 1.7 million Americans are documented to have been either brought to an emergency room, hospitalized, or have died from their head injury. However, there are still individuals who have unreported TBIs either because they did not receive any medical assistance

for their head injury, or received care from another type of medical facility (Faul et al., 2010). Over 50,000 of the estimated 1.7 million Americans died because of their head injury while the other 1.65 million Americans either were taken to an emergency room or were hospitalized (Faul et al., 2010). Sometimes, depending on the circumstances of the injury, damage or symptoms may not be observed immediately or at all. However, this does not mean that these individuals did not receive a TBI or that they will not develop symptoms as time passes. In reality, the damage resulting from any TBI cannot be measured directly after the blow since there is a delay, known as the latency period, between the stimulus (the blow) and the symptoms or effects from the injury (Dekosky et al., 2010). Symptoms and complications from the injury can develop soon after the blow that caused the injury and in many cases decrease over time. Others, have little to no symptoms immediately following their brain injury, or the symptoms they do experience alleviate but years, even decades later, they begin to experience an onset and progression of other symptoms that increase over time (Dekosky et al., 2010). This progression of symptoms develops into various psychological, cognitive, and motor functioning problems or diseases known as Chronic Traumatic Encephalopathy (McKee et al., 2009). Currently, Chronic Traumatic Encephalopathy (CTE) is the term used to identify the condition where TBI's later lead to the progression of various mental and physical complications due to the degeneration of the brain (McKee et al., 2009).

Even though brain injuries can occur while engaging in a large variety of tasks or activities, some as simple as walking or driving, there is an increased rate of receiving a TBI when playing certain sports. Collision sports, those that involve intentional collisions with other athletes and objects such as football and ice hockey, have a much higher prevalence for such injuries. Based upon the data collected from 2002–2006 on Traumatic Brain Injuries, it was

estimated that 10% of all recorded TBIs were a result of assault, 35.2% from falls, 16.5% were involved in events in which they were struck by or against a person or object, 17.3% from vehicular accidents, and lastly, 21% from unknown or other sources (Faul et al., 2010). Out of all verified cases of CTE, a condition that can develop from incurring TBIs, about 90% were the result of sports-related injuries (McKee et al., 2009). The high occurrence of sports-related TBI's and long-term trauma combined with the advertised problems many professional athletes are facing from head injuries has increased concern and awareness about TBI's as well as CTE. However, even after all the focus and attention on brain injuries, and all of the progress that has been made, for instance in determining what occurs in the brain during a TBI and the changes that occur afterwards, there is still a large amount of information that is not known. This, in part, is related to the fact that the brain itself is not wholly understood and is extremely complicated.

When an individual sustains a Traumatic Brain Injury, the force applied to the head is of a strong enough nature that the head swiftly moves back and forth resulting in the brain hitting the skull. The impact of the brain against the skull can cause bruising, or contusions, as well as axonal shearing, a term that refers to the tearing of the axons of neurons (Dekosky et al., 2010). At the cellular level in the brain, billions of neurons connect and communicate to one another, sending signals necessary in bodily functions. The cell's structure includes a shaft, known as an axon, where chemical signals pass through in order to reach the next neuron. These cells pass the signals up the spinal cord and send them to the appropriate part of the body. The brain is the control center of this system, delivering and processing all chemical signals. Therefore, the brain is responsible for controlling all of the processes and sensations that occur within and around the body. Among many things, it is responsible for memories, thoughts, decisions, personalities, language, and movement. Considering that each part of the brain has different functions, it is

easy to conclude that damage to varied areas of the brain can result in different short and long-term consequences. Lastly, damage resulting in the death of these cells can have serious consequences because they do not have the ability to regenerate; the paths in the body and brain that were previously used, have to be altered so that the body and brain can still function smoothly and efficiently.

Even though there are many different changes in behavior and mental state that can occur after a blow to the head, Traumatic Brain Injuries may also be considered a silent problem. The problem is silent because in many circumstances, the damage that has occurred in the brain by TBI's is not always apparent. Only some aspects of the damage shows, while the rest are hidden and can remain so for long periods of time. The damage also might not show until later in life. These lurking conditions resulting from a TBI injury may be likened to an iceberg where the majority of the ice is hidden beneath the surface of the water. Thus, while it might appear as if the patient has recovered, studies have shown that cognitive declines ensue later in life as a result of TBI's (Dekosky et al., 2010).

Not only do TBI's create immediate complications in patients' lives, but they also produce problems that arise years later. Some long-term effects of TBI's are alterations in medical and psychiatric health. Examples of these health complications are depression, ALS (Amyotrophic Lateral Sclerosis, also known as Lou Gehrig's disease), Alzheimer's disease, and Chronic Traumatic Encephalopathy (CTE). A study observing the connection between Alzheimer's disease and TBI's exhibited evidence that not only do brain injuries increase a person's risk of developing Alzheimer's, but they also increase the risk of developing the disease at an earlier age. Furthermore, they also stated that the formation of inflammation in the brain because of the brain injury may continue for as long as seventeen years (Giunta et al., 2012).

This is important because persistent inflammation can cause more harm in the brain; the label or term for inflammation in the brain is secondary damage.

The extent of damage that Traumatic Brain Injuries can cause in both the short and the long term is still under study, but the information that has already been determined is concerning. Any person can receive a head injury, but there are certain activities and sports, such as football, that expose participants and athletes to a higher risk of obtaining brain damage from a blow to the head. A concern about these contact sports is that many children begin participating in them at young ages; many begin training for these sports in elementary, middle, and high school. However, not much information is known on the effects of playing these contact sports at such young ages and whether the incidences of head injuries at younger ages is significant in terms of short and long-term effects. Consequently, this review of literature will focus on the difference between athletes that underwent training in contact sports before the age of 18 (before college), and those that began their training after the age of 18 (college and onwards). The knowledge contained in the literature review led to the creation of the hypothesis that it is worse for young athletes to sustain head injuries even though their brains are very plastic and can more easily compensate for the injury, retaining high levels of brain function in spite of the injury, when compared to adult brains.

Important Anatomical Features of the Head

The body, via anatomical structures and functions, already has its own protective structures and mechanisms that are present in order to lessen or prevent damage to an essential organ, such as the brain. The skull, a bony shell that encompasses the brain, provides the first source of protection. A hard, protective structure serves to prevent the brain from penetrations by foreign objects and bruises from ordinary actions and accidents. Between the hard skull and the soft, fleshy brain matter, are three tissue layers that work to support and protect the brain. These three layers, known as the meninges, named in order from superficial to deep are the dura mater, arachnoid, and pia mater.

Cerebrospinal fluid (CSF), a clear liquid, primarily consists of blood plasma. This fluid surrounds the brain, fills the ventricles, or spaces, of the brain, and also is found surrounding the spinal cord. The body closely monitors the pressure of the cerebrospinal fluid in order to make sure that there is enough to support and nourish the brain, but not so much that the pressure from the fluid damages the brain. The CSF provides nutrients, removes wastes, and supports the majority of the brain's weight. In addition, it also works as a cushion and helps inhibit neuron damage: it prevents the brain from hitting the sides of the skull in everyday head movements.

Brain tissue consists of both gray matter and white matter. The gray matter in the brain is typically superficial to the white matter and contains the cell bodies, dendrites, and unmyelinated axons of neurons. The white matter, which is deeper than the gray matter, mainly consists of the

axons of neurons that are myelinated. The different “matters” of the brain also have differing densities. This plays a significant part in the damage that occurs when the head incurs trauma.

Types of TBI's

When the head is the recipient of a blow, the cerebrospinal fluid is not enough to protect the brain: it can prevent the brain from hitting the skull during everyday movements, but not when there is such a strong and rapid force applied to the head. Therefore, the brain moves and hits the inside of the hard skull. A concussion, a type of mild Traumatic Brain Injury (mTBI), can be described as biomechanical forces causing a linear and/or rotational force(s) being applied to an individual's brain (Harmon et al., 2013). In addition, there is documentation that swift acceleration and deceleration of the brain and impact deceleration contributes to the head trauma (Jordan, 2013). When a brain is subjected to rotational forces, the neurons in the brain generally are stretched and sheared leading to the concussion or axonal injury the individual is diagnosed with or experiences (Jordan, 2013). In linear acceleration, the brain receives contusions (bruising) from hitting the skull in an anterior-posterior fashion (Jordan, 2013). Impact deceleration occurs when an individual's head suddenly experiences a deceleration due to contact with an inanimate or animate object; it is possible that coup and/or contrecoup injuries can develop from this type of impact (Jordan, 2013). Coup injuries are those that occur on the same side as the initial impact is experienced. Contrecoup injuries, however, is damage resulting on the opposite side of the initial impact. Depending on the circumstances of the injury, either one or both of these injuries could be sustained, but it is typically larger forces that are able to generate the injury to both opposing sides of the brain. If a person happened to fall and hit the

left side of their head on the ground, then the left side of the brain experiences the coup injury. If the force was great enough to send the brain in an opposite motion after coming into contact with the left side of the skull, then the coup-contrecoup injury takes place (injury on both opposing sides based upon the initial impact).

Traumatic Brain Injury is a broad term that encompasses a wide variety of head trauma. The different brain injuries that individuals receive can be placed into one of the two categories of TBI's: Open head wounds or closed head wounds (Schwarzbold et al., 2008). Both the open and closed categories result in a considerable amount of brain damage typically correlating with the severity of the impact. Since the brain cannot produce new neurons to replace the nerve cells that died from the wound, this damage is essentially irreversible.

A classic case of open-TBI, an injury where the skull is fractured thereby exposing brain matter, is Phineas Gage, an American railroad worker who received an open-head TBI when an explosion at work sent a large metal rod up through his skull (Damasio et al., 1994). The area damaged from the passing of the rod through his head resulted in extensive frontal lobe damage. As a result of the injury, he underwent a drastic change in his personality and behavior. Before the accident, he was a friendly, responsible, and hard-working man (Macmillan, 2000). However, after his brain damage, he was irreverent, immature, used profane language, was not responsible or respectful, and became very selfish, throwing tantrums and refusing to give in to something that went against his wishes (Harlow, 1869). He became incapable of holding a steady job, his wife and children left him, and he later died from epileptic attacks. The drastic changes observed in Gage's personality and behavior led to the discovery of the functions of different parts of the brain. By studying the areas of damage in addition to the alterations that were present in Gage,

scientists were able to deduce which areas of the brain are responsible for different aspects of behavior and mental processes.

Most athletes, however, do not experience open-head injuries. In collision sports such as football, ice hockey, and wrestling, the impact with other players and the ground do not usually result in fractures to the skull, and therefore, fall under the category of closed-wound head trauma. This damage is oftentimes more difficult to diagnose because it cannot be as easily observed with the naked eye. If athletes with undetected concussions continue to play, then this increases the probability for these athletes to receive multiple concussions while playing sports, intensifying the development of various cognitive, behavioral, and mood changes after a latent period. In fact, some studies have shown that athletes who return to sports practice and compete before their concussion or TBI has completely healed are more likely to obtain another concussion or TBI thereby adding to the harm caused by the primary injury.

There is another division amongst TBI's, but this division occurs within the different levels of damage that befalls the brain following trauma. The two levels of devastation are primary and secondary damage (Escobedo et al., 2013). The primary category includes damage resulting from the initial impact and mainly occurs to the parenchyma, the functional tissue of the brain also known as nervous tissue (Escobedo et al., 2013). Secondary damage is that which transpires following the initial impact up to years post-trauma (Mannix and Whalen, 2012). The belief is that the cause of secondary damage is a result of inflammation or swelling in the brain known as edema (Escobedo et al., 2013). However, inflammation stemming from the blow to the head can occur in the brain for as long as seventeen years (Giunta et al., 2012).

NFL Concussion Protocols and Considerations

Concussion protocols cover the definition and symptoms of a concussion, as well as what qualifies a player to return to the field. The latter topic is a source of contention as the decision could play an important role in the recovery and long-term injuries of the player. According to Doolan et. al. (2011), there are several different factors that are taken into account when deciding if an athlete can return to play. The authors listed CTE, extended recovery times for multiple concussions, and second impact syndrome as the three main factors that are considered. They explained that second impact syndrome is an event causing a second concussion occurs before the individual has completely recovered from the first concussion. Doolan et. al. (2011) also mentioned the very high mortality and morbidity rates of this syndrome, 50% and 100% respectively.

The first two factors involved in return to play decisions, CTE and multiple concussion recovery times, are related as the second can influence and lead to the first. It is known that those who begin playing sports before they have sufficiently recovered from their first concussion are more likely to injure themselves a second time, extend the amount of time it takes for them to recover completely, and can increase the severity of certain symptoms such as some memory-loss and confusion. In addition, there is a positive correlation between the number of concussions

or TBI's sustained and the development of CTE, a condition characterized by atrophy of brain tissue.

The international consensus report on sports-related concussions in 2008 provides a process that sports teams refer to in concussion assessments, in order to gauge the extent of injury and gradually ease the injured athlete back into playing full time (McCroory et. al., 2009). The return to play protocol agreed upon in the consensus began with the athlete resting and refraining from any type of activity to allow his or her body to have a recovery time. The next step, light aerobic exercise intended to begin increasing the player's heart rate, is followed by participation in sport-specific exercises, and then more complex non-contact training drills intended to enhance the strength, coordination and cognitive abilities of the athlete. The final stage is the reintegration of the athlete in full contact playing once cleared by a doctor. The consensus formed these steps as a way to prevent further injury and promote full recovery after a concussion.

TBI-Related Consequences

TBIs cause undefined microscopic cascades of events in the brain. It is known that the force applied to the brain in a TBI causes inflammation in the neural tissue, neuronal atrophy, and tearing and inflammation in axons in addition to alterations in glial cell behavior (Saulle and Greenwald, 2012). However, a theory of the cascade of damage undergoing in the neuronal tissue was described by Gavett et. al., (2011). The authors mentioned that the stretching of the axons leads to their inflammation and tearing, which in turn, triggers many different events and complications including shifts in the flux of ions such as calcium and the changing of membrane potentials, both of which wreak havoc on the ability of the neurons to properly function by communicating with other neurons. Gavett et. al. (2011) also mentioned that there is a discharge of capases and calpains, which lead to the malformation of proteins and their aggregation, preventing proper brain function as they continue to aggregate over time. This theory is supported by the evidence found in many retired athletes' brains in the form of neural tissue atrophy observed in the physical decrease in the size of certain parts of the brain and the visible brown-gray patches, the visual evidence of extensive malformed protein clusters. For instance,

the brain tissue from a deceased retired NFL player showed the presence of plaques and tangles throughout certain brain structures such as the hippocampus, mimicking the initial characteristics found in diagnosed sporadic AD patients (Omalu et. al., 2005). It was mentioned that certain characteristics observed in the NFL player's brain allowed an official diagnosis of CTE.

Others such as Ewing-Cobbs et al. (2008), mentioned that a TBI results in damage to both myelinated and unmyelinated neurons, and even the neuron cell bodies. The two fronts of injury following a TBI, primary and secondary injury, are what cause this type of damage to neurons. The authors listed some types of damage that could occur because of bruising, bleeding, release of neurotransmitters from sheared neurons, and swelling. They also mentioned a specific type of injury known as Wallerian-type axonal degeneration, which essentially involves the gradual breakdown of myelin sheath in certain areas of the brain including the corpus callosum. As myelin plays an important role in the transduction of neuronal signals from one neuron to another, pathways weaken with disuse and signals are not received, preventing proper and normal functioning of the nervous system. However, damage to the brain from sustaining a TBI can differ and affect many pathways, not just the presence of myelin and the transduction of action potentials. It can also trigger a cascade of events eventually ending in tangled abnormal proteins that cause neuronal death and influence or aggravate the onset of various neurodegenerative diseases (Figure 2).

Proteinopathy

Many neurodegenerative diseases that surface in individuals who have received TBIs are linked to a deformation in various proteins. The proteins, when folded correctly, are able to perform their specific functions. However, since their shape is integral to their function, the proteins can no longer operate when they are denatured. Rodolfo et al. (2010) mentions how the specific protein(s) that causes the disease by its abnormal formation and aggregation vary amongst neurodegenerative diseases. In addition, similar to how the majority of individuals who obtain TBIs develop neurodegenerative diseases years to decades later, the authors explained that aggregation of the misfolded proteins in the Central Nervous System (CNS) occurs earlier in life with the physical manifestation of the disease occurring in the middle to late years of life. Proteinopathy plays an important role in the formation of the four following neurodegenerative diseases that develop in many TBI patients: CTE, Alzheimer's disease, Parkinson's disease, and Motor Neuron disease. The four deformed proteins that contribute to the formation of these neurological diseases are the Amyloid-Beta peptide, the Tau protein, alpha-Synuclein and TAR DNA-binding protein 43 (TDP-43).

Amyloid-Beta

The protein Amyloid-Beta, a derivative of the amyloid precursor protein, is mostly known for its role in the neurodegenerative disease called Alzheimer's disease. Studies have shown that there are correlations between amyloid-beta plaques in the brain and the extent of memory and cognitive impairment that is characteristic of Alzheimer's disease. However, the amyloid protein is not always harmful. In fact, it is a protein that dwells in cell membranes including the membranes that surround neurons. When it is not in its pathogenic form, the proteins work to keep the neurons healthy and nourished. It has recently been found that smaller amounts of the proteins play a role in the development, growth, and synapsing of neurons in addition to influencing synaptic plasticity and the formation of memories (M. del C. Cárdenas-Aguayo et al., 2014).

The pathogenic nature of the protein is unleashed when the amyloid precursor protein clips into fragments known as amyloid-beta (Zheng and Koo, 2011). This pathogenic derivative of the amyloid precursor protein (APP) is considered a main factor and cause of neurodegeneration in the brain. The dangerous nature of this peptide is due to its aggregation into

long fibrils or depositions, caused by the peptide's adhesive qualities, and the fact that amyloid-beta peptides continuously form in the brain from its precursor protein. Over time, the amyloid-beta deposition slowly grows as more peptides add onto the group of existing ones and eventually, the deposition impedes normal neuronal functioning. O'Brien and Wong (2011) discussed the findings of various studies in order to determine the interaction and effects of amyloid-beta plaques on neurons. They explained that from these studies, they learned that the toxicity of the amyloid-beta fibrils is so severe that neurons exposed to the fibrils degenerate and die within one day's worth of exposure. O'Brien and Wong (2011) also mentioned the negative effects on neuron health and function from being near the peptide fibrils. These in vivo experiments, executed with mice, showed that when amyloid-beta deposition was present, the main changes and observations made were that there was an increase in inflammation in addition to synaptic complications, such as a decrease in working terminals, and abnormal scoring on various cognitive tests.

As mentioned by Roberts et al. (1994), depositions of amyloid-beta are observed in 30% of patients suffering from a head trauma with the severity of the plaques being positively correlated with the age of the injured individual. In addition, according to Gavett et al., (2010), a study on CTE noticed that amyloid-beta proteins were found in approximately 40-45% of the brains of CTE diagnosed individuals. It was hypothesized that head injuries cause the APP to become more reactive, thereby producing more amyloid-beta peptides after a head injury than normal (Roberts et al., 1994). The head injury also leads to an increase in enzymes that play a role in the formation of more beta-amyloid peptides (Mannix and Whalen, 2012). These enzymes include α -, β - and γ - secretases (Santos et al., 2011).

While acknowledging the fact that amyloid-beta peptides are a common feature in both TBI's, CTE and AD, Mannix and Whalen (2012), suggested that microglia and inflammation in the brain could also play a role in the development of Alzheimer's. A suggestion is that microglia play a part in the brain degeneration since they are responsible for clearing out the harmful peptide plaques in both the primary and secondary injuries resulting from the trauma. However, Mannix and Whalen (2012) explained that in the process of doing so, the microglia cause inflammation that can harm and possibly even lead to neuronal cell death. This occurs even though they also produce anti-inflammatory cytokines and nerve growth factors. In addition, they mentioned that there was another way in which the microglia could cause harm to neurons after head injuries. This would transpire when the microglial cells produce substances such as nitric oxide and superoxide free radicals, which in turn produce reactive oxygen and nitrogen species.

As explained by Rodolfo et al. (2010), the accumulation of amyloid-beta deposits directly affects the production of reactive oxygen species. They went on to describe that overproduction of the reactive oxygen, or a lapse or breakdown of the protective mechanisms of the mitochondria can result in destruction via oxidative harm to the proteins, DNA, and lipids that reside in and enable the mitochondria to function. The authors also elucidated that the damage to the mitochondria initiates a degenerative cycle by increasing amyloid-beta aggregation in addition to furthering the damage done to the mitochondria. They said that when the mitochondria are harmed, not only is production of ATP effected, but also the intake of oxygen, the membrane potential of the energy-producing organelle, and changes in redox homeostasis. When the amyloid-beta peptide deposits are present in the nervous tissue, nitric oxide forms and is believed to instigate damage as well as a loss of synapses (Rodolfo et al., 2010).

Tau Protein

The tau protein's function is to aid tubulin in maintaining the stability and flexibility of microtubules in neurons. It is also present in small quantities in some glial cells such as oligodendrocytes and astrocytes. As stated by Buée et al. (2000), there are six different forms of this protein, known as isoforms, all of which can be found in the brain and differ from each other in the carboxyl region or the amine group. The authors clarified that the carboxyl groups will either have three or four repeat-regions while the amine groups can differ in that some will either have none, one or two inserts, thereby allotting each of the isoforms with different functions.

Tau plays a vital role in the health and ability of the neurons as the microtubules, which they support, form tracks along the axons. The cell uses these organized and straight pathways to transport nutrients and action potentials throughout the cell. Without proper pathways to deliver

the nutrients, the neuronal and glial cells can perish, and the action potentials will no longer travel through the neuron and reach the synapse, or be received by the post-synaptic neuron. This is what occurs when tau degrades and becomes tangled and consequently is no longer able to function as it should. When the tau protein is abnormally processed, it begins to clump together into neurofibrillary tangles, the most common type of inclusion body (Buée et al., 2000; Rodolfo et al., 2010). These tangles, located on the inside of the neurons, disrupt the organized pathways used to carry nutrients and send electrical potentials.

The genetic influence from the 17th chromosome leads to the formation of tau protein tangles and the amounts of the abnormal protein that form (Buée et al., 2000). Mietelska-Porowska et al. (2014) explained that the presence of other proteins including amyloid-beta peptides, can cause the tau proteins to aggregate and tangle together, thereby causing difficulties with synapses in the neurons. In addition, the authors discussed how the more phosphorylated the tau proteins become, the more harm they cause in undoing their normal task of stabilizing the microtubules, inhibiting the transport of nutrients and synapses down the axons and causing complications in the post-synaptic cell. Consequently, the phosphorylation of the protein is where problems arise. The attachment of phosphates to tau depends on the protein's structure. The strength and ability of tau to bind to the microtubules and stabilize them depends upon the extent of the protein's phosphorylation (Mietelska-Porowska et al., 2014). Therefore, the structure or formation of tau proteins can directly influence cognitive abilities.

According to Mietelska-Porowska et al. (2014), the tau protein is a dipole and influences the neurofibrillary tangles. The authors explained that tau proteins are able to bind to themselves, and form tangles since each end of the protein are opposites in charge. However, this difference

in charge is also the quality that facilitates the proteins in stabilizing the microtubules by allowing the tau to bind to microtubules.

Another theory about the denaturation of tau resulting in tangles comes from Binder et al. (2005) who expounded upon the specific states and formations the tau protein takes on as it becomes malformed. They explained that the original and helpful tau conformation would first transform to the Alz50 state where the amine group (N-terminus) binds to the microtubule-binding repeats on the protein. This state of tau allows the protein to begin the unhealthy aggregation that leads to complications within the neuron and eventual cell death. The next formation tau transforms into is what the authors mentioned as the Tau-66 state. They explained that the Tau-66 state forms once the tangle has begun developing, when the N-terminus somewhat overlaps its binding site when binding with the microtubule-binding repeats, and when the amine, carboxyl group, or both groups are severed from the protein. The removal of the carboxyl group triggers more cuts to the protein; this occurs at the E³⁹¹ and D⁴²¹ sites on the carboxyl end of the protein (Binder et al., 2005). Therefore, that over time, as tau changes forms and the neurofibrillary tangles progress, the proteins composing the tangles become increasingly cut and condensed.

Studies performed on the mutations causing tau accumulation in the neurons and glial cells showed that there were two main types of mutations: exonic and intronic. The exonic mutations were responsible for an escalation in the filament developmental activity by tau, while the intronic mutations end in an excess of four microtubule-binding repeats compared to the production of the three microtubule-binding repeats (Binder et al., 2005). The authors described another experiment where the testing of tau filament was completed to determine if filament overproduction was the cause of the neurodegeneration or if the presence and formation of tau

proteins was the causative factor of atrophy. The experiment found that it was indeed the formation of the tau proteins that influenced the atrophy of cells as plasmids that contained tau cDNA, after being injected into lamprey neurons, led to neurodegeneration while the overproduction of neurofilaments did not result in any harm to lamprey neurons (Binder et al., 2005).

Since tau proteins effect the health of the neurons by influencing the stability of the microtubules and, in turn, the ability of the neuron to transport substances using the pathways in the axons, malformation of the protein can lead to cell death. This occurs because the neuron cannot move nutrients where they are needed, nor can they properly send signals to the post-synaptic neuron. Without nutrients and proper supplies, the neurons begin to weaken and eventually die. This leaves a gap in that specific neuronal pathway, typically in the CNS, thereby inhibiting the ability of the nervous system to communicate with other areas of the brain and body. When this cycle of neurodegeneration continues, a decreasing amount of neurons are able to properly sustain themselves and complete the sending and receiving of neuronal signals. The neurons cannot replace the gaps the dead neurons create since the majority of neurons do not undergo cell division. Therefore, once the gaps are created, another pathway needs to be located and used in order to obtain the same result as before, if possible. As the process or cycle of atrophy progresses in severity, it becomes increasingly difficult to find alternate pathways. In fact, over time, many of the lost connections are not recoverable since these diseases are incurable. Consequently, the malformed tau proteins initiate cognitive impairments that manifest themselves and gradually worsen over time.

Alpha-Synuclein

Alpha-synuclein is a protein most often found in or around synapses located in the central nervous system. In particular, the protein congregates at the axon terminals of presynaptic neurons. Even though the primary location of the protein is known, the role of the properly folded protein has not been fully uncovered. However, possible roles have been deduced using information about α -synuclein's location in addition to the proteins' roles in neurodegenerative diseases (Cheng et al., 2011). Two possible roles include aiding in the formation and functioning

of the synaptic vesicles that release neurotransmitters into the synapse, and the release of one particular neurotransmitter known as dopamine.

The SNCA gene produces alpha-synuclein. As explained by Cheng et al., (2011), the protein, also known as NACP, is linked to the amyloid-beta peptides found in AD. The authors also explained that the linkage to amyloid-beta is the result of the fact that both proteins derive from NAC, the precursor for the non-A β -component and the suspected cause of toxicity and aggregation of the misfolded α -synuclein and amyloid-beta proteins. They mentioned that some studies now provide evidence that NAC peptide is inducing the formation of the misfolded proteins, which in turn coaxes the NAC amyloid to form.

The formation of the abnormal α -synuclein deposits is similar to other proteinopathy mechanisms. Just as amyloid-beta forms plaques, and tau proteins form tangles, misfolded α -synuclein forms Lewy bodies, bundles of proteins inside the cells in the nervous tissue that harm and prevent normal cell functioning. This protein can also be found in the processes of the neurons, the axons and dendrites, and are known as Lewy neurites (Irwin et al., 2013). The bundling of α -synuclein leads to stress and a reduction in health of the neuronal tissue resulting in cell death since the formation of abnormal protein buildups disrupt transport within the cells, and can disturb other cellular processes in addition to aggravating or overstimulating the pathways that cause proteins to be broken down (Yu and Lyubchenko, 2009). The authors explained that it was not clear as to how the malformations of the proteins is initiated, or is it known how those processes may be inhibited to either prevent or slow down the formation of neurodegenerative diseases. However, as stated by Cheng et al. (2011), there is a link between normal behavior of the protein and the presence of its C-terminal. The authors explained that the C-terminal half of the α -synuclein protein works to inhibit aggregation and when the C-terminal

is cleaved from the protein, the remaining portion of the protein is more likely to cluster and form deposits or filaments. In addition, the C-terminal assists in the folding and unfolding processes of proteins, lipids, carbohydrates, and nucleic acids in addition to acting as a preventative measure for oxidative stress.

There are different theories about how alpha-synuclein interacts in the neuron and what its function is. The different theories come from the varied and sometimes conflicting experimental results. One theory maintains that the proteins work to regulate the vesicles in the axon terminals of central nervous system neurons. This theory involves the following process explained by Bellani et al. (2010). In the presynaptic component of the synapse, there is a section where synaptic vesicles are retained. These vesicles are not ready for exocytosis, but are being stored in what is known as the reserve pool, until the neuron becomes more active in sending signals to the postsynaptic neuron. Bellani et al. (2010) went on to discuss that when the excitability of the neuron increases, the vesicles are transported, loaded and primed for exocytosis and the release of neurotransmitters. The authors stated that these vesicles are then placed into another area, the readily releasable pool. The influx of calcium into the terminal end of the neuron activates the vesicles to perform exocytosis, sending chemicals into the synapse to communicate and affect the next neuron. The results of knock-out experiments in mice showing a decrease in the size of the reserve pools in the axon terminals led to the belief that α -synuclein proteins are the managers of this system that work in containing the number of vesicles that are transferred from the reserve pool, primed, and moved on to the next pool to perform exocytosis. This theory also includes the concept that Alpha-synuclein proteins negatively correlate with the rate of firing action potentials and inhibit the priming stage of the vesicles. Bellani et al. (2010) also explained that there are other theories, some of which involve the concept that actin

filaments essentially bind the vesicles together and prevent them from moving through the process towards exocytosis by reducing their motility. Even though there are differing opinions on the role of alpha-synuclein, many researchers agree that the protein is involved in the maintenance and effectiveness of the synaptic vesicles.

TAR DNA-Binding Protein 43

TAR DNA-binding protein 43, otherwise known as TDP-43, is a protein coding gene more recently suspected to be involved in neurodegeneration, preventing proper neuronal functioning with the presence of deposits of abnormal proteins. Since this abnormal form of the protein and its frequent presence in the neural tissue of those suffering from a variety of neurodegenerative diseases has been identified more recently, there is little knowledge about the

protein and the deposits that form when it is malformed compared to the other types of proteinopathy. Scientists know, however, that unlike amyloid-beta and tau whose denaturation and aggregation primarily causing cognitive problems, the effects of TDP-43's toxicity and aggregation can result in neurodegeneration leading to a wider variety of symptoms including cognitive as well as motor complications, paralysis, and eventual death. The aggregation of TDP-43 resides not only neural inclusion bodies, but also glial inclusion bodies and different shaped neurites (McKee et al., 2010). These inclusion bodies and neurites settle in CNS neurons and in motor neurons (Lagier-Tourenne et al., 2010). In a study performed by McKee et al. (2010), TDP-43 aggregation dwelled in the majority of the athletes examined, all of which received TBI's and displayed CTE symptoms. At the end of the study, they surmised that TDP-43 deposits contributed to a portion of the malfunctioning of the nervous systems. For the individuals who displayed weakness and other motor complications, the TDP-43 accumulations were observed in the spinal cord as well as the more common location of deposition in the brain.

The TAR DNA-binding protein primarily resides in the nucleus but also inhabits other areas of the cell, since it is able to aid in the carrying of RNA and protein in and out of the nucleus. As explained by Lagier-Tourenne et al. (2010), the protein, when in its normal state, mostly remains in the nuclei of the cells. They expounded upon that by articulating that once abnormal accumulation of TDP-43 begins, the protein frequently inhabits various inclusion bodies and neurites throughout the neurons and even in glial cells. The protein is involved in many cellular functions from the regulation of RNA splicing to having a role in both dendritic and somatodendritic RNA transportation and in the synthesis of dendritic proteins that are important for neural plasticity (Scotter et al., 2015). The authors refer to the discovery that both an increase as well as a decrease in the functioning of the protein can result in malformation and

aggregation, which in turn, lead to neurodegeneration. The basis of this theory was various experiments that focused on the identification of the qualities and features of TDP-43 that cause aggregation or are linked to its pathogenicity. The results from these studies indicated that a forced, but temporary reduction in the gene expression of the TAR DNA-binding protein led to the denaturation of the protein and consequently, neurodegeneration. Some other experiments that contributed to the theory about the increase and decrease of the protein's functioning discovered that TDP-43 located in muscle cells or glial cell also display similar characteristic neurodegenerative symptoms when TDP-43's gene expression is either exaggerated or temporarily reduced.

Neurodegenerative Diseases

Neurodegenerative diseases refer to all conditions caused or influenced by the Nervous system. These diseases increasingly worsen over time and end with severe loss in the function of the Nervous system, or even death. There are various causes of the different diseases including genetic mutations, and the presence of various proteins or chemicals in the nervous tissue.

However, all of these diseases have deposits of denatured or abnormal proteins, even though in many cases the protein in question is different (Taylor et al., 2002). Some irregular proteins that are involved in causing these diseases are amyloid-beta, tau, alpha-synuclein and TDP-43. The changes that occur in the proteins, making them abnormal, are the factors that result in the atrophy of certain types of cells or neuronal tissues, causing a wide variety of impairments that include motor skills, sensory abilities or cognition. Each disease that falls under the category of a neurodegenerative disease has its own causes and symptoms, thus making each unique. Four diseases or conditions in which the deterioration of nerve cells and tissues have been identified as the cause of the observed symptoms, and that have manifested and progressed in many individuals that have received TBIs are CTE, Alzheimer's disease (AD), Parkinson's disease (PD), and Motor Neuron disease (MND).

Chronic Traumatic Encephalopathy

It is difficult to diagnose CTE considering that the condition typically results from repetitive or numerous mild brain injuries or concussions. Neither the number of contributing head injuries or the severity of each TBI that will ultimately result in the medical condition diagnosed as CTE has been quantified (McKee et al., 2009). It is also difficult to diagnose CTE

because of the latency period that occurs. The latency period can last different lengths of time depending on the person and the injuries they received. Therefore, symptoms for some individuals might begin to become noticeable to the patient a few weeks later, or many years, even decades later. After the patient passes away however, an autopsy can conclusively determine whether the individuals were suffering from CTE or not (Jordan, 2013). Risk factors for CTE have been determined to be continued sports involvement and an increase in age (Jordan, 2013). Several more factors contributing to CTE is the individual's head trauma history, the age at which the injury occurred, participating in collision and/or contact sports, being a member of the military, genetic variations, other health conditions such as epilepsy, and being the recipient of physical abuse (Saulle and Greenwald, 2012).

As time passes, many former athletes experience some small symptoms that gradually increase over time, becoming more and more severe. This is due to the neurological degeneration in the brain. The examination of individuals with CTE indicates that a reduction in the weight of the brain occurs and that an expansion in the ventricles of the brain, specifically the lateral and third ventricles, also occurs (McKee et al., 2009). Specific areas of the brain have been found to thin or shrink (atrophy) more frequently than other areas. Several areas commonly impacted are the frontal lobe, cerebral cortex, amygdala, and the hippocampus. However, this is not a comprehensive list, and many other brain structures undergo a significant amount of atrophy.

The symptoms resulting from CTE are not restricted to one aspect of mental functioning; instead, they invade multiple areas including cognition, mood, and behavior (Patel et al., 2013). Some examples of symptoms that fall beneath these three categories are memory and judgement impairment, decreased ability to concentrate, depression, aggression, and increased violence (Patel et al., 2013). The initial most common symptoms experienced by individuals suffering

from CTE are complications involving the memory, mood and executive functioning as well as the appearance of Parkinsonian signs (Gavett et al., 2010). Athletes that have experienced severe or multiple TBI's and/or CTE also have a higher likelihood of developing neurodegenerative diseases during their lifetime (Jordan, 2013). Some neurodegenerative diseases that have been associated with TBI's and CTE especially in athletes, are mild cognitive impairment, dementia, Alzheimer's disease, motor neuron disease (a couple common examples of which are ALS or Lou Gehrig's disease, PLS, and progressive muscular atrophy), as well as Parkinson's disease (Jordan, 2013). It is controversial whether the suicide attempts observed in many CTE-diagnosed individuals are a direct effect of the proteinopathy attributed to CTE (Iverson, 2013). Iverson (2013) stated that based upon the information divulged, in the only published source of epidemiological data, NFL players are actually at a decreased risk for suicide when compared to the risk for the general population. However, many others still believe that CTE is a valid explanation for the rate of suicide attempts amongst individuals living with CTE. In many of those who develop CTE, the behavioral and cognitive changes that occur contribute to this belief.

As described by Gavett et al. (2010), the symptoms associated with CTE result from the tangling of astrocytes, a type of glial cell that provides support and nutrition to the Central Nervous System (CNS) and aides in the removal of neurotransmitters from synaptic clefts, in addition to the tangling of neurofibrils throughout the frontal and temporal cortices of the brain. Next, they explained that these tangles typically organize themselves in a patch-like and superficial arrangement with their epicenters being located near the sulci of the brain. Gavett et al (2010) also mentioned that the patches tend to congregate in areas where small blood vessels are in higher concentration. Iverson (2013) added another common symptom of CTE by including the observance of abundant neuropil threads in the brains of those diagnosed with

CTE. These threads are composed of axons, dendrites, and glial cells and reside in the gray matter of the CNS. The three proteins that play an important role in the creation of the neurofibrillary tangles and neuropil threads are the tau protein, the amyloid-beta protein, and TAR DNA binding protein (Gavett et al., 2010).

Alzheimer's Disease

Alzheimer's disease (AD), is a progressive, neurodegenerative disease that typically presents itself in the elderly and always results in the death of the individual. It is responsible for more than half of the cases of dementia observed in elderly individuals. Common symptoms of AD include confusion, difficulty remembering newly acquired information as well as old

memories, disorientation, difficulty to keep track of place and time, alterations in mood, behavior, and independence level as the disease progresses. The neurodegenerative disease primarily affects memory and cognitive abilities, resulting in an alteration in the individual's exhibited behaviors. In addition, this disease is particularly devastating because the damage and progression of neural atrophy cannot be reversed. Symptoms as well as the features of the disease through which it develops are similar for the two main types of AD: sporadic and familial (Eckert et al., 2003). As explained by Eckert et al. (2003), the sporadic version of AD is the type most often observed as it is the type that is characterized by its presence in elderly individuals compared to the familial version of the neurodegenerative disease which is influenced by mutations in genetic material.

However, the symptoms associated with the neurodegenerative disease do not present themselves as soon as atrophy in the brain initiates. Instead, the symptoms gradually appear as the damage in the brain progresses and accumulates, a result of the gradual loss of synapses and neurons in the brain. However, in the beginning of the progression of AD, the deterioration that occurs in the brain is relatively slow, and does not increase until the middle stages of the disease has been reached (Ito et al., 2011). As stated by Zheng and Koo (2011), two main attributes of Alzheimer's disease, besides the characteristic decrease in functioning neurons and synapses in the brain are the neurofibrillary tangles and beta-amyloid accumulations in the brain. As noted by Andrade-Moraes et al. (2013), the initial symptoms of cognitive impairment are the result of the production of the amyloid-beta peptides from the amyloid precursor protein, as well as the phosphorylation of the tau proteins. These malformed proteins create the tangles and plaques commonly found in the brains of AD patients, and are the secondary named cause of the dementia-type symptoms that evolve from the disease.

The neural tissue is attacked from two fronts: the exterior of the cell as well as the interior. Plaques, composed of the sticky amyloid-beta peptides, compose the assault coming from the exterior of the cells. Tau, the main component of the tangles, is located on the interior of the cells as it is responsible for the transport of substances throughout the cells when properly formed. These plaques and tangles accumulate over time, even in individuals that are not diagnosed with AD, but as the amount and concentration increases, the atrophy and cognitive impairment resulting from the neurodegenerative disease ensue.

According to Eckert et al. (2003), there is evidence that the primary area of degeneration is in the synapse. As explained by the authors, this theory is supported by the fact that both glutamate and calcium receptors are highly concentrated in these regions and that the synapse is the recipient of elevated stress, both oxidative and metabolic. Oxidative stress, the disruption in balancing between free radical production and antioxidant defense, is high when neuronal membranes depolarize and action potentials are sent down the axons to the terminals and synaptic clefts (Eckert et al., 2003). Mitochondrial stress however, is when a lack of glucose causes a reduction in the rate of metabolism. Consequently, large numbers of mitochondria are needed in the synaptic clefts to control and provide sufficient amounts of energy so that the ion channels are able to work properly.

Eckert et al. (2003) went on to explain that apoptosis is a frequent occurrence in neurons with exposure to amyloid-beta deposits as it is correlated with oxidative stress, which in turn can allow and cause damage to the dendritic membrane of the postsynaptic neuron in the targeted synapse. In addition, the authors mentioned that caspases, which lead to DNA damage are activated, harmful substances such as nitric oxide and reactive oxygen species are produced and

inflammation occurs. All of these factors contribute to the damage and death of the neuron, the loss of which creates atrophy in the synapse and gaps in that particular neuronal pathway.

Most consider mild cognitive impairment to be the transition state between a normal or average cognitive state and a significantly impaired state that typically is found in dementia patients. The transitioning from the normal cognitive state, following deterioration and proteinopathy until a severe impairment is apparent, is explained by Jedynak et al. (2012). They explained a theory of AD progression proposed by Jack et al. (2010). The theory stated that the first protein to alter and accumulate in the brain is the amyloid-beta peptide. The next step in the model is the denaturation and tangling of tau proteins followed by structural changes and the reduction of gray matter in the brain. The development of the plaques, tangles, and changes that occur in the brains of those with AD lead to the transformation in memory, cognition, and overall functioning which is characteristic of the neurodegenerative disease (Figure 1).

Even though more significant and rapid degeneration occurs after these changes, Jedynak et al. (2012) noted that subtle declines in memory may be observed before the official diagnosis of the disease. This means that the reduction in brain function can transpire earlier on while the amassing of the harmful and abnormal amyloid-beta peptides and tau proteins and the structural changes are taking place. Once more of these factors have contributed to the deterioration and neuronal deaths, the noticeable and more drastic features of the disease are easily observed. These findings support the theory previously cited on the slow, initial progression followed by the increased rate of degeneration found in the middle stages of the disease mentioned by Ito et al. (2011).

Parkinson's Disease

Parkinson's is a disease marked by gradual atrophy and a progression of symptoms as the condition advances. However, in PD, impairment and death affects specific neurons, in particular those that are responsible for releasing the neurotransmitter known as dopamine. The symptoms

associated with PD are the result of the decrease in dopamine levels in the brain. Since dopamine is involved in both movement and emotional states, these two areas are most affected when low amounts of dopamine are available. As the most severe stages of the disease are reached, other parts of the brain are affected, since delusions and hallucinations can occur.

According to Huang et al. (2007), PD can differ in the rate of progression and its separation into two groups based upon which symptoms are predominantly displayed, and can be influenced by factors such as the age of the patient when onset of the disease transpired. The two subsections of PD mentioned by the authors are identified based upon whether tremor or gait complications are predominant. In fact, Huang et al. (2007), explained that these two subsections also differ from each other based upon how much cognitive impairment develops in the individual over time.

PD is considered to have five stages of development that most patients experience. As PD differs for each individual, however, the disease progression can travel through the various stages at a different pace, or evolves so quickly that it essentially jumps ahead and skips over a step. Khaindrava et al. (2011) stated that the time prior to the appearance of symptoms is known as preclinical or asymptomatic PD, but once symptoms begin to appear, the disease is considered to have entered the clinical (symptomatic) stages. The authors also stated that it typically takes about 20-30 years for the preclinical PD to advance enough that clinical PD is reached. Their data was able to support the statistic that by this time symptoms are displayed, approximately 70-80% of the dopamine neurons in the brain have been disturbed by abnormal α -synuclein collection or have died. The authors deduced that a reduction of 72% of the dopaminergic neurons in the substantia nigra occurred by the time locomotion related symptoms were observed; whereas a dopamine decrease in the brain of 45% occurred when neural plasticity was

the contributing factor. They conjectured that neural plasticity was the element that enabled other neurons to compensate for the massive loss of dopaminergic cells in the brain.

However, the five stages used to categorize the severity of PD observed in an individual only apply to those with clinical PD as the first stage is categorized by mild symptoms. The symptoms that develop begin as mild and over time, increase in severity. They include a slight stooping in posture, locomotion complications such as a reduction in balance and incomplete control over facial expressions as well as dementia. As the neurodegenerative disease advances, the symptoms become more apparent and the patient has difficulty taking care of his or herself. Walking is reduced to a shuffle while balancing, posture, coordination, speech and rate of movement decreases. In addition, some cognitive and personality changes may be observed.

A difference between the first and second stages of PD is that the symptoms present in the first stage are typically unilateral, but switches and is present in both sides of the body (bilateral) in the second stage. In the second stage, performing everyday activities begins to pose a challenge, and by the third stage, the patient may need a longer amount of time in which to complete them, or even some assistance. By the time the fourth stage is reached, the individual's independence is more significantly affected since many activities cannot be accomplished without help. Consequently, at this stage, the individual diagnosed with PD most likely will not be able to live alone.

The fifth stage is where the most severe symptoms is observed. In this stage, the individual cannot live alone and needs constant care as the muscle stiffness experienced to lesser degrees in previous stages is severe and can cause the individual to fall when attempting to stand or walk. In addition, it is not uncommon for hallucinations and delusions to occur at this point in the progression of the disease. As mentioned by Irwin et al. (2013), the majority of PD patients

develop dementia and show discrepancies in cognitive abilities for the greater part of the disease progression, with about a quarter of the patients displaying these deficiencies as early as their initial diagnosis of PD. The authors confirmed that the decline in the patients' cognition may impact their independence and prognosis negatively, leading to a precipitated mortality.

Motor Neuron Disease

A large subset of neurodegenerative diseases comprise the Motor Neuron diseases category, including Lou Gehrig's disease (ALS), bulbar-onset MND and primary lateral

sclerosis, although many consider ALS and MND to be synonymous. Motor Neuron diseases all have one common theme: the neurodegeneration that progressively occurs is selective for all motor neurons. Consequently, motor neurons in both the CNS and the peripheral nervous system (PNS) may be affected by the disease. The upper level of motor neurons typically refers to those that originate in the brain and pass through the medulla down to the spinal cord, while those in the lower levels typically consist of those that travel down and innervate the muscle cells. Symptoms found in these two levels of motor neurons help diagnose MND since there are no definitive tests that can be performed.

As mentioned by Winhammar et al. (2005), the upper level signals that aid diagnosis of MND include spasticity, stiffness of muscles due to continued contractions, weakness and hyper-reflexia when the autonomic nervous system is hypersensitive. The authors also specified that lower body signs include fasciculation, quick muscle contractions like twitches, wasting or atrophy of muscle cells, weakness, and hyporeflexia, a reduction in the functioning of the autonomic nervous system, the opposite of hyper-reflexia. As motor neurons are responsible for muscle contractions, the symptoms that result from the atrophy that occurs affects movement, but also affect swallowing, speech and breathing. As a result, the patients' independence is affected as their muscles become atrophic and their eventual inability to perform essential tasks requires them to ultimately need full care. The highest cause of death in individuals diagnosed with MND is complications involving the heart (Winhammar et al., 2005).

As with many other neurodegenerative diseases, the symptoms do not become apparent until a significant number of motor neurons have degenerated. In MND, as motor units are lost by a reduction in the number of properly functioning and healthy motor neurons, other motor neurons re-innervate those muscles fibers (Winhammaer et al., 2005). This enables the units to

keep functioning as normally as possible until a larger number of motor neurons have been lost, causing the symptoms to become increasingly noticeable. In addition, as the progression of neurodegeneration indicates, the length of the time since an individual's diagnosis is positively correlated with the severity of atrophy or neurodegeneration in the precentral gyrus and the corticospinal tract (Winhammar et al., 2005).

Tar DNA binding protein is commonly found in the brains of those who were diagnosed and lived with MND. In addition, this type of proteinopathy is observable extending from the brain down to the spinal cord, which is consistent with the findings that MND affects both the upper level and lower level motor neurons, not just those in the upper level that originates in the brain. This is unlike the other neurodegenerative diseases and proteinopathies such as amyloid-beta and AD. However, like the other neurodegenerative diseases previously discussed, there are only treatments that can delay the progression of the disease and alleviate some symptoms, but there is no current cure for MND, and death is the outcome for those who are diagnosed. It was mentioned by Carra et al. (2012), that the length and polarization of the motor neurons contribute to the way they are affected by various threats, especially the deposition of the malformed proteins formed or accelerated by oxidative damage in the neuronal tissues. The misfolded proteins are harmful to the motor neurons and affect them in a fashion similar to the way the abnormal formations and aggregates of amyloid-beta, tau, and alpha-synuclein affect the cells. These abnormal formations block transports of nutrients and signals, as well as inducing oxidative stress thereby causing harm to mitochondria and other parts of the cell necessary for proper functioning.

Psychological Changes

Emotional stability and personality changes have been identified in many individuals post-TBI. Some of these changes may be small enough that only close family and friends may notice the differences, while other changes may be large and obvious to many people. Some

differences that are typically observed are depression, anger, and anxiety. These, along with the physical abilities of the individual, influence social interactions. Lezak and O'Brien (1988) completed a longitudinal study by examining each participating TBI patient six times over a five-year interval.

When studying the identified emotional, social and physical changes, they found that a few patterns emerged. The first pattern noted in seven different categories, the difficulties many of the individuals voiced did not abate, but rather remained consistent. These categories included problems with anger, anxiety, significant relationships, social contacts, work/school, driving, and appropriate social interactions. While a trend of significant improvement in categories such as independence of living and initiative over time was identified, there were also other categories where the trend of improvement was much slower or changed over time, but did not necessarily decrease. The authors mentioned that inappropriate social interaction was one of the categories that decreased at a slow but relatively constant rate while anxiety and depression problems, which were evidenced following the injuries, also increased in severity before it improved and even had a difference that was statistically significant.

Lezak and O'Brien (1988) also mentioned that the reactions of the TBI patient's family for the first four years after the injury, influences the patient's rate of recovery or improvement in dealing with emotional, behavioral, physical, social and cognitive difficulties. In addition, they mentioned that anger problems were long-lasting as 40% of the observed individuals still had moderate or higher difficulties when the TBI incident was five years prior.

Anger, apathy and aggression issues are one of the more prevalent psychiatric complications experienced by TBI patients. These issues also tend to exacerbate or lead to other complications since they indirectly affect life satisfaction. Aggression and anger can prevent

proper and healthy interactions with other people, can affect the individual's career, independence and social life (Conneeley, 2002). Consequently, over time, the TBI patient can become isolated and more dependent on family members. However, there are many other factors at play including the stability of the patient's family and the strength of their relationship, in addition to changes in memory, physical ability, as well as beliefs and quality of life before the brain injury.

Another complication that has a high prevalence rate amongst TBI patients is depression. Due to the many conflicting experimental results linking damage to a specific area of the brain to depression, a theory has been formed stating which brain structures, when injured, might influence the development of depression. These brain structures, as specified by Schwarzbald et al. (2008), include the prefrontal cortex, amygdala, hippocampus, thalamus, and the basal ganglia. The damage to the neurons during and after the TBI are blamed for the changes in temperament in addition to the development of various psychological and psychosocial complications since synapses, the release of neurotransmitters, and the communication between neurons and areas of the body are compromised. It was also mentioned by Schwarzbald et al. (2008) that alcohol and anxiety addictions or issues are two frequently observed problems that are comorbid with depression. Similar to aggression and anger control issues, these problems can have a significant and negative impact on the patient's life satisfaction.

Recovery and Injury Factors

Numerous modifications occur in the body and the nervous system from the time a person is born, until they are elderly. The short and long-term injuries received after a TBI as well as the length of the recovery period following the injury and the extent of the recovery may be influenced and explained by different age-related factors. If a head injury disrupts or inhibits proper brain development including the modification of the neurons and synapses in the brain that occurs as children progress through adolescence and teenage years, then this could cause serious implications for their future. The brain is an essential organ that is responsible for countless aspects of a person's life from their personality and sense of humor to their abilities to remember past events, move, recognize faces, and acquire new information. Consequently, when there is a disruption in the development of neural tissue or development of certain areas of the brain, the individual could face large consequences. These changes include the pruning and amendment of neurons and synapses, the anatomy of the body and the head, and the abilities and development of the brain.

Neural Plasticity

Neural plasticity is the ability of the brain to form new neurons plus new pathways and connections between neurons that were not previously linked. These synaptic changes, or the re-mapping of the brain, therefore, have implications for memories and learning. The plasticity of the brain is a quality that lasts throughout an individual's lifetime, but was previously believed to primarily occur in children, adolescents, and teens. This theory is based upon the knowledge that many changes in the synapses are due to learning and memorization of new information. There is evidence supporting the concept that neurogenesis and the formation of new synapses or connections between neurons can still occur in adults and in the elderly even though it is known that neural plasticity is a large and important event in the young.

It was previously believed that all neurons present in the brain were formed prior to birth since neuronal cells, unlike glial cells, are post-mitotic, meaning that no new neurons could be formed after birth. This, if true, would cause serious implications for those that sustained head injuries. However, recently, evidence has been found to the contrary, that some neurons, in particular those that are found in the subventricular zone of the lateral ventricles as well as the subgranular zone of the hippocampus's dentate gyrus can actually be formed during an individual's lifetime from neural stem cells (Zhao et al., 2014). This process, the creation of new neuronal cells, is known as neurogenesis, and has three main steps: cell proliferation, cell migration, and cell differentiation. The first of the three steps, proliferation, is when progenitor cells divide horizontally, producing another progenitor cell as well as a new neuron. This new neuron already has been given its function, but waits until it is in the proper location to differentiate, develop and begin working.

The synapses between two neurons are formed after the axons of the new neurons grow with the help of growth cones and the axon guidance molecules that direct where the axon

travels. After this step is completed, the synapse can be formed. This occurs when the dendrites of a neuron reach out towards and contact the axon of another neuron. This results in the surge of synaptic vesicles and active zone proteins the axon of the latter neuron, forming the presynaptic component of the new synapse. The neuronal cell that approached the axon of the second neuron, forms the postsynaptic component when receptors form and accumulate. The large number of neurons that are present in the brains of babies and children undergo a reduction process where many neurons are removed. This modification process is normal and is essential for proper brain function. The neurons that are more active and therefore have stronger synapses and connections to other neurons are favored over those that are weak and used either very little or hardly at all. Another method of neuronal refinement is when certain neurons are pre-programmed to die at a certain age. Lastly, some neurons are chosen based upon how much of a limited supply of nutrients or neurotrophic factors they receive, such as nerve growth factor; those that are able to obtain sufficient amounts of the nutrients live while those that are not able to attain the nutrients die.

Plasticity of the brain is defined as the formation of new neurons and synapses to form new pathways and connections in neural tissue leading to the ability to learn new information, retain memories and adapt from life experiences. The strength of some of these pathways depends on how often that particular pathway is utilized; the more often a synapse is used, the stronger the signaling between the two neurons become. This reinforcement process is known as long term potentiation (LTP). The changes that are made to the synapse primarily occur on the post-synaptic component and result in increasing the speed and the efficiency of the communication between the two neurons, and therefore as learning and experiences. The cellular and molecular changes that occur enabling the LTP process are with the two glutamate receptors:

AMPA and NMDA. As stated by Bliss and Collingridge (1993), the NMDA receptor has a voltage dependent magnesium block which can be removed, allowing an influx of sodium and calcium ions, if glutamate binds to the AMPA receptor and triggers an influx of sodium. In the earlier phases of calcium influx, an insertion of AMPA receptors occurs allowing a faster response and strengthening for a period lasting about a few hours. However, as the synapse is used more repeatedly and calcium influxes more often (late phase), alterations are made to protein synthesis via the influence of transcription factors. This change can last a long time, anywhere from 24 hours to a lifetime.

The decline noted and previously believed to be linked to an inability for neurogenesis to occur was, in reality, the functional decline primarily noticed in those over the age of 65 (Cai et al., 2014). However, the authors stated that neural plasticity has a close and interconnected relationship with both motor skill attainment and cognitive capabilities in elder adults, as evidenced by the increase in the amount of gray matter in particular areas of the brain being used during different types of activities. They mentioned that when testing activity-dependent plasticity by performing a novel, complicated task involving the visual system and motor skills, an increase in excitability and size of the gray matter in the parts of the brain used in performing the task was observed in both younger and older participants.

Greenwood and Parasuraman (2010) mentioned that if an elderly person is successful and healthy, then they can still adapt to various stimuli that come their way using different plasticity factors such as promoting neurogenesis in a specific location of the brain based upon where more synapses or neurons are needed. They mentioned that in an experiment studying the brain plasticity of rats, those that were exposed to novel stimuli more frequently or on a day-to-day basis displayed a larger response to new stimuli and situations. Therefore, they were able to learn

and remember better than those that did not explore as much. This ability can be linked to the resilience of children. Since, as a whole, they have learned and experienced less than adults and elderly individuals, it can be inferred that the children have a better ability to absorb and retain new concepts and information as well as adapt to new situations and stimuli than adults who do this less frequently.

Brain Development

Brain development roughly follows the same timeline in different individuals even though the stages of neuronal development and the health of the neural tissue produced is influenced by many factors, primarily, genetics and the environment. Studies of the development of the brain using MRIs and other brain-imaging techniques have found that different areas of the brain have unique developmental rates (Lebel et al., 2008). It was also mentioned by Lebel et al. (2008) that MRI studies have provided evidence that the volume of certain brain tissues alters throughout an individual's life even though the overall brain volume remains constant.

Brain development begins approximately four weeks after conception, but the majority of brain development occurs after birth. Neurogenesis is one of the stages that occurs during the pre-natal stage with the help of progenitor cells. This means that almost all of the neurons the individual is born with are already present at birth. The progenitor cells are also involved in the formation of the neural tube that evolves into the spinal cord and the brain. The rostral end of the neural tube that contributes to the formation of the brain then divides into three brain regions: the forebrain, midbrain and hindbrain (Houston et al., 2014). As the majority of the neurogenesis and migratory stages occur during pre-natal development, some neurogenesis and neural migration still occurs after birth and throughout post-natal life, contributing to brain development and plasticity.

The glial cells that contribute to the health, myelination, and the organization of neurons, are not post-mitotic and consequently, divide throughout the post-natal life of the individual. The myelination of neurons by oligodendrocytes and schwann cells continues throughout adolescence and teenage years into adulthood, and does not stop until the individual has reached their twenties or thirties (Lebel et al., 2008). This results in an increase in white matter over time. In

addition to brain-wide alteration in both gray and white matter, post-natal development is characterized by the evolution of brain structures. In fact, Lebel et al. (2008) mentioned that the results of their experiment provided support of brain structural maturation and discrepancies amongst the developmental rates of various structures, and explained that these results indicated that areas of the brain with connections via white matter tracts, and areas with gray matter, to the frontal and temporal regions, took a longer time to mature than other areas.

Adolescence was not always associated with changes in the brain as a result from synaptic pruning and brain rewiring. In fact, the realization that brain development occurs past birth and extends throughout adolescence occurred within the past 50 years. When describing the history behind the awareness and knowledge regarding brain development during adolescence, Blakemore and Choudhury (2006) stated that at that time, research revealed that many alterations occur within the prefrontal cortex during this stage in life. Supporting the conclusions of Lebel et al. (2008) regarding the increase in white matter and decrease in gray matter during adolescence, Blakemore and Choudhury (2006) mentioned that myelination, the wrapping of the neurons in a fatty layer providing both insulation for the neuron and an increase in the speed of the conduction of action potentials, occurred in the frontal region of the brain both before and during adolescence, and can continue during adulthood as far as ages between twenty or thirty. However, in other areas of the brain devoted to the senses and motor abilities, the myelination transpired during the years following birth.

In addition, Blakemore and Choudhury (2006) explained that the discovery of adolescent brain development did not just involve the process of myelination of neurons. They explained that the other change in brain matter was synaptic pruning, or the elimination of synapses. It is known that the density of synapses in children greatly exceeds the density in adult brains. The

high level of neurons in the brain of a child is due to synaptogenesis, the stage where synapses are created. Following this stage is the elimination of those neurons that are weak or not often utilized. According to Blakemore and Choudhury (2006), there are two waves of synaptogenesis in the prefrontal cortex that transpire during childhood and later during puberty. However, they explained that following both periods of synapse creation, there is a short pause where there is no net creation or destruction of synapses, and then neuronal pruning begins, a process associated with increasing the efficiency of the CNS.

Blakemore and Choudhury (2006) focused on development of the brain in regards to executive function and social cognition. After stating that the prefrontal and parietal cortexes are the two regions of the brain that have consistently been found to undergo changes after puberty, they discussed how executive functioning forms in individuals of this age group as well as what the term executive functioning includes. As they explained, this is an umbrella term encompassing many different skills including decision-making, attention, working memory, multitasking as well as designing and carrying out plans. The other component, social cognition, covers higher-level cognitive abilities including the formation of beliefs and desires, and can be influenced by different experiences. As a whole, the formation of the brain and the changes that occur over time all play a role in the variability found between individuals (Lenroot and Giedd, 2006).

Experiences, knowledge gained, pathways formed and removed, and the development of various regions of the brain all influence these differences even though the same overall processes occur in the brain throughout life during the same age ranges. This was mentioned by Lenroot and Giedd (2006) when they provided an example of how London taxi drivers tend to have larger hippocampi than the average person who does not require as extensive of a mental

map as the taxi drivers do. They stated that the resulting brain structures often used in an individual's life, depending on the sports or instruments they play, the job they have, and other different activities, are typically larger than when compared to someone who does not commonly partake in those activities. This demonstrates how vital brain development is to the creation of an individual's identity as well as being the key to a functioning mind and body. If this process is disrupted, any range of negative effects on the individual in the short and long-term could develop.

As stated by Ewing-Cobbs et al. (2008), TBIs are responsible for causing much damage to both white and gray matter in the brain. Broglio et al. (2012) stated that youth athletes playing contact sports have an increased risk in sustaining a TBI compared to adult athletes. The authors hypothesized that while aging, those with a history of TBIs would display a more extreme, and quicker decline in addition to the deterioration occurring at an earlier age than those without a TBI history. Not only were these trends observed, but the authors also noted the occurrence of neuronal death in specific brain areas in those individuals with TBI histories. The brain structures Broglio et al. (2012) specifically mentioned displaying cell death after injury was the pyramidal region and the hippocampus. The occurrence of abnormal protein deposits commonly found in the cerebral cortex, within sulci and around the vasculature located in the cerebrum leading to a wide variety of neurodegenerative disease and symptoms was also mentioned.

Broglio et al. (2012) discussed that in normal aging, structural changes occur in the brain such as a reduction in synaptic plasticity and calcium homeostasis in addition to alteration in the expression of neurotrophic factors, and changes in the levels of dopamine, serotonin, acetylcholine and glutamate resulting from changes in the neural pathways involving and utilizing these neurotransmitters. The authors, when studying the effects of concussions on the

brain and normal functioning, determined that there were decreases and complications in both cognition and motor skills displayed in those individuals that sustained the head injury. However, they mentioned that there is evidence that young individuals with a history of a single concussion have displayed minute, but noticeable declines in cognition and motor skills. They asserted that some have progressed to develop severe symptoms and mental declines over time while others show few to no negative effects over time. However, it was acknowledged that in either case, those in early adulthood have the ability to uphold or sustain an increased level of functioning that could essentially hide or dampen the decline observed. However, high functioning wears off with age, and many symptoms from sustaining head injuries do not present themselves until a later period.

The brain's ability to retain high functioning through brain plasticity despite the existing and accumulating damage, due to the nature of malformed proteins and the cascade of brain damage, was one reason why it was previously believed that children and young athletes were to have a better prognosis than an adult who received the same injury (Daneshvar et al., 2011). However, Daneshvar et al. (2011) hypothesized that the damage to a young developing brain from a TBI is different, if not more severe than that which occurs to an adult brain in the same condition. A comparison of long-term consequences in young versus adult athletes who sustained TBIs would take many years to complete, especially considering that in many cases, the long-term symptoms and conditions sometimes take decades before they become apparent.

Hypothesis and Conclusion

Developing a generalized theory on brain injuries in different age groups is difficult since many factors compose and influence a single individual's situation and condition (Table 1). In addition, it is difficult to assess the extent of damage resulting from a TBI because of the latency period that may last any number of years before the long-term consequences and symptoms begin to appear. The goal of this review of literature regarding TBI's, long-term consequences and their development, as well as normal brain development and activity, was to hypothesize as to whether the consequences of a TBI is more severe for young and adolescent athletes as opposed to adult athletes.

The information collected and assessed indicated that young athletes were previously believed to have a better prognosis compared to adult athletes who were also thought to have a longer recovery in addition to a worse prognosis. This theory was based upon young athletes having more neurons and increased neural plasticity enabling them to compensate for their injuries compared to adults with already developed brains, longer persistence of initial symptoms, and observed complications later in life even though they have less susceptibility for these types of injuries than young athletes. The study of brain development from childhood to adulthood revealed that both high levels of brain plasticity and brain development primarily occur throughout childhood and adolescence, but do extend, in some aspects, into early adulthood. This indicates that if a brain injury were to impair these important processes, the

individual and the individual's quality of life could suffer as a result. However, the fact that the brain's plasticity and level of functioning is at its highest in younger individuals, enables those who are young to show resilience and a quicker recovery to baseline compared to an older athlete. This does not necessarily mean that the older athlete incurs more damage and consequences from the injury. It might mean that the recovery leading to the latent period occurs at a faster rate in young athletes, but if damage is done to brain structures and interferes with brain development, the athletes could face more severe consequences in the long-term. It could also mean that the higher level of functioning in the younger athletes makes the injury and symptoms less apparent. As a result, it is hypothesized that the injuries have the potential to be more severe for young athletes than for adults whose majority of brain development has been completed without interruption. Even so, the injuries all athletes face are severe, and minimization of these injuries would be beneficial in both the short and long-term, not to mention, improving their quality of life by preventing events that could potentially disrupt their lives by affecting their health, mental state and independence.

It is currently difficult, if not impossible to test or provide enough evidence to either refute or support this hypothesis as sports-related TBIs are a relatively recent discovery and topic of interest with information relating to the brain being challenging to obtain. These factors inhibit the identification of undiscovered concepts that are integral to the hypothesis. In order for it to be tested, more information about the brain, the impact to the brain from TBIs as well as the significance of age on TBIs must be collected. In addition, more knowledge must be gained pertaining to the pathways involved in the misfolding and aggregation of proteins, in the development and activity of the brain and in neural plasticity. In order to specifically determine whether young athletes potentially have more severe long-term consequences as a result of their

sport-related TBIs, longitudinal studies must be completed. However it will take many years to collect sufficient data for this type of study as decades will have to be spent tracking and analyzing the lives of the athletes who participate in the studies. In the meantime, sports and organizations should take as many precautions as possible to aid in the prevention of Traumatic Brain Injuries amongst their players in all age groups as well as develop ways of ensuring that symptoms have dissipated before re-entry into play.

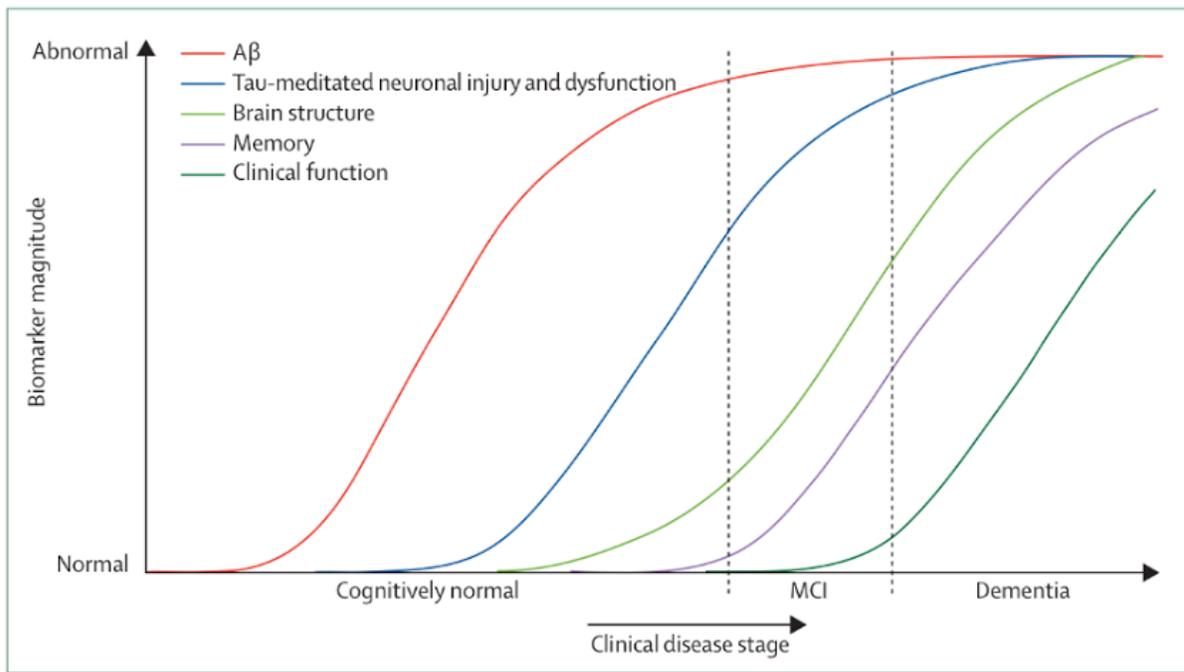


Figure 1. Biomarkers in the cascade leading to the onset and presentation of Alzheimer's disease (Jack et al., 2010)

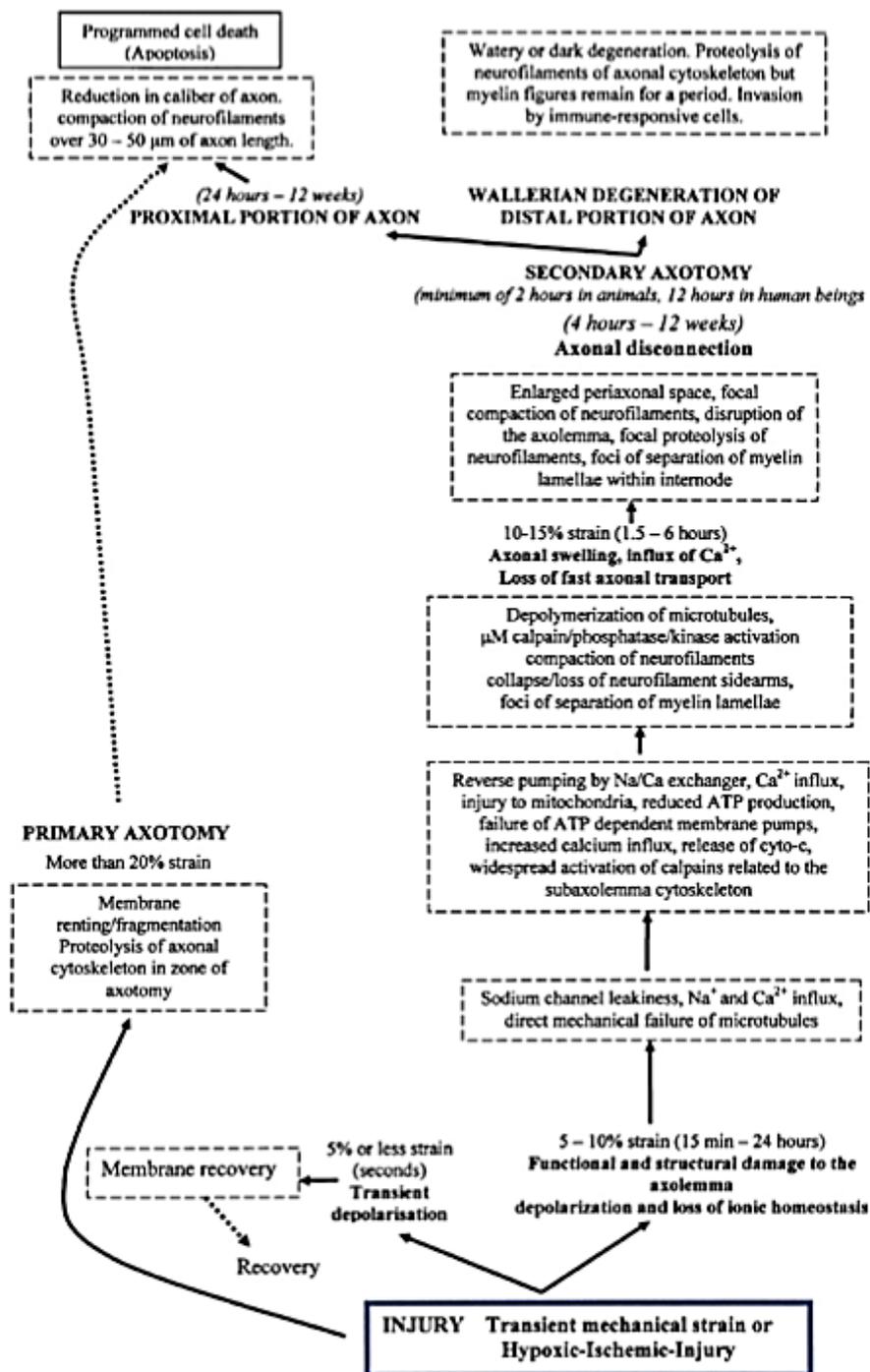


Figure 2. Diagram explaining theory on axonal injury, neuronal degeneration, and the cascade of proteinopathy. (Bigler and Maxwell, 2012)

Table 1. Summary and Comparison of Qualities in Young and Adult Athletes that Influence Injuries, Recovery and Prognosis Following a TBI

Young Athlete	Adult Athlete
Previously believed to have better prognosis	Believed to have longer recovery and worse prognosis
Developing Brains	
Increased risk of sustaining TBI	Developed brains
More neurons	Post-synaptic pruning
Increased neural plasticity	Less plastic abilities
Increased level of functioning	Lower level of functioning

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