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# PROFESSIONAL FOOTBALL CAREER LENGTH AND POSITION: POTENTIAL RISK FACTORS FOR CONCUSSIVE AND SUBCONCUSSIVE EXPOSURE OUTCOMES

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by Scott L. Rosenthal



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The thesis of Scott L. Rosenthal was reviewed and approved* by the following:

Semyon M. Slobounov
Professor of Kinesiology
Thesis Adviser

William J. Ray
Professor of Psychology

Karl M. Newell
Professor of Kinesiology and Biobehavioral Health

David E. Conroy
Professor of Kinesiology
Graduate Program Director

*Signatures are on file in the Graduate School.

# ABSTRACT

## Professional Football Career Length and Position: Potential Risk Factors for Concussive and Subconcussive Exposure Outcomes

Football is a high frequency and magnitude contact sport. Contact sports carry a higher rate of impacts to the head which are inherently associated with an increased risk of developing concussive injuries. Growing evidence indicates that subconcussive and concussive injuries can result in physiological changes which may lead to the development of cognitive, behavioral, and physical deficits. There is also evidence linking subconcussive and concussive injuries to neurodegenerative diseases like Chronic Traumatic Encephalopathy, Alzheimer's Disease, and Amyotrophic Lateral Sclerosis. Over the course of an athlete's career, concussive and subconcussive damage may accumulate and can result in permanent and devastating long-term dysfunction. Certain positions experience different types and frequencies of impacts, therefore, concussive and subconcussive-induced deficits may vary by position.

This study compared retired NFL players(n=24), similarly aged non-contact controls(n=15) and position matched collegiate players(n=24) using the VR HeadRehab 3 system in order to identify any potential long-term deficits. Players were tested on measures of balance, reaction time and spatial memory. Further analysis sought to identify any relationships or risk factors for the onset of these deficits. NFL players performed significantly worse than both control groups on all VR measures. This poorer performance was associated with player career length and position. Career length was significantly associated with longer reaction time. Players in positions that were more likely to receive concussive-type(less frequent but higher magnitude) impacts had poorer spatial memory, while players in positions that experience greater subconcussive(more frequent but lower magnitude) impacts were more likely to have poorer balance. Limited evidence suggests poorer VR performance at the collegiate level.

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# ABBREVIATIONS

1. 3D: Three-Dimensional
2. AD: Alzheimer’s Disease
3. ADHD: Attention Deficit Hyperactivity Disorder
4. ALS: Amyotrophic Lateral Sclerosis
5. ApoE4: Apolipoprotein E4
6. APP: Amyloid Precursor Protein
7. ATP: Adenosine Triphosphate
8. Ave: Average
9. BBB: Blood Brain Barrier
10. BBBD: Blood Brain Barrier Disruption
11. CBF: Cerebral Blood Flow
12. CG: College Control Group
13. CNS: Central Nervous System
14. COM: Center of Mass
15. COP: Center of Pressure
16. CTE: Chronic Traumatic Encephalopathy
17. DMN: Default Mode Network
18. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV
19. DTI: Diffusion Tensor Imaging
20. EEG: Electroencephalography
21. fMRI: Functional Magnetic Resonance Imaging
22. GABA: Gamma-Aminobutyric Acid

23. HC: Healthy Control
24. HFC: High Frequency Control Group
25. HFN: High Frequency NFL Group
26. ImPACT: Immediate Post-Concussion Assessment and Cognitive Testing
27. K+: Potassium
28. LFC: Low Frequency Control Group
29. LFN: Low Frequency NFL Group
30. LTD: Long-Term Depression
31. LTP: Long-Term Potentiation
32. Max: Maximum
33. MCI: Mild Cognitive Impairment
34. Min: Minimum
35. Min: Minutes
36. mTBI: Mild Traumatic Brain Injury
37. Na+: Sodium
38. NFL: National Football League
39. NFT: Neurofibrillary Tangle
40. NG: NFL Group
41. NMDA: N-Methyl D-Apsartate
42. OG: Older Non-Contact Control Group
43. P: p-value
44. PCS: Post-Concussion Syndrome
45. PD: Parkinson’s Disease

46. PTSD: Post-Traumatic Stress Disorder

47. R: Correlation Coefficient

48. rmTBI: Repetitive Mild Traumatic Brain Injury

49. ROS: Reactive Oxygen Species

50. S: Seconds

51. StDev: Standard Deviation

52. TBI: Traumatic Brain Injury

53. TDP-43: Tar DNA Binding Protein 43

54. VR: Virtual Reality

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# Chapter 1: Introduction

There is mounting evidence that repeated concussive and subconcussive blows can lead to long-term cognitive decline, psychiatric issues, behavioral disorders, and motor deficits. This is particularly concerning when one considers the high incident of concussive and subconcussive blows that individuals participating in athletics experience. This is even truer for the participants of contacts sports such as American football, boxing and ice hockey. Football players may experience on average more than 400 impacts per seasons and this number may even reach upwards of 2,000 impacts per season.[67] From 2002-2007, there were approximately 0.4 documented concussions per game in the NFL and approximately 142 concussions annually, with 152 players receiving more than one concussion.[68,69]

In the general population, there are 1.6 to 3.8 million concussions a year in the United States.[70] A concussion or mild traumatic brain injury(mTBI) is characterized by mostly transient neurological alterations resulting from the brain's absorption of damaging mechanical forces.

These mechanical forces result in axonal stretching and shearing that leads to a neurometabolic cascade that involves changes in ionic equilibrium, axonal permeability, neurotransmitter regulations and concentration, localized cerebral blood flow, and energy production and consumption. These neurological alterations often manifest as a constellation of symptoms involving affective, cognitive, sleep and physical domains. These may include, but are not limited to, confusion, memory loss, headaches, sleep disturbances and vestibular deficits.[5,7,71]

These clinical deficits typically resolve spontaneously within 1-2 weeks of injury; however, for some individuals, symptoms can last for months to years or remain subclinical in nature. The DSM-IV defines PCS as cognitive impairment in attention or memory and failure of

three or more concussive symptoms to spontaneously resolve after 3 months resulting in interference with social/occupational functioning.[56,57] Approximately 15 percent of those who receive a mTBI have lasting deficits and or symptoms.[54] The symptoms of PCS can be cognitive, affective, physical, or some combination thereof. Of the deficits reported, headache is the most commonly reported symptom.[72]

There is still much debate over the underlying mechanism of PCS and whether or not it is organic in nature stemming from pathophysiological changes or results from concurrent psychological and/or personality factors. One theory hypothesizes that an individual's personality predisposes them to a heightened sense of impairment and claims an association between neuroticism, depression, anxiety and PCS.[54] A different theory proposes a failure of organic changes to resolve and yet another theory sites a combination of both physiological and psychological factors.[55]

In addition to the overt development of PCS, concussive and repetitive subconcussive injuries may result in other serious long-term deficits and diseases. Recently, chronic traumatic encephalopathy(CTE), originally thought to present only boxers, has been identified post-mortem in retired NFL players as well as in a variety of other athletes including soccer players to circus performers.[73] CTE is a neurodegenerative disease characterized by a set of gross cerebral structural changes and a specific hyperphosphorylated tau deposition pattern that manifests clinically as executive dysfunction, memory impairment, suicidality, poor impulse control, and dementia. CTE appears to be distinct from PCS as its symptom presentation typically begins years after the most recent trauma and after original symptoms have subsided. CTE can only be confirmed via postmortem analysis. Unfortunately, the underlying pathophysiology of CTE remains unknown, but a strong link to repetitive brain trauma has been established.[74] There also

is limited evidence that repetitive impacts may increase the risk of developing Alzheimer's disease(AD) and Amyotrophic Lateral Sclerosis(ALS).[75]

While there is much unknown about both CTE, PCS, and the other potential long-term dysfunction resulting from concussions, it is clear that they carry life altering decrements and disruptions. For those suffering such impairments, treatment cannot wait for the underlying mechanisms and relationships to be determined. Currently there is no established treatment method that resolves the underlying pathology of concussions, CTE or PCS; however, unraveling the risk factors and mechanisms of neurological deterioration could lead to the development of treatment modalities that would prevent, stabilize or reverse an individual's deficits. The purpose of this thesis is to: 1) identify any long-term deficits in a sample of retired NFL players and 2) identify potential risk factors for deficit accumulation.

## Specific Research Questions

1. Do retired NFL players have deficits compared to controls on:
    a. Spatial Memory
    b. Reaction Time
    c. Balance
    d. Comprehensive Performance
2. What factors are associated with deficits:
    a. Age
    b. Career Length
    c. Position Type

## Specific Research Question Hypothesis

1. Retired NFL players will have deficits compared to controls on:
    a. Spatial Memory
    b. Reaction Time
    c. Balance
    d. Comprehensive Performance
2. The following factors will be associated with deficits:
    a. Age: Increased age will yield poorer performance on 1a-1d.
    b. Career Length: Career length will be inversely related to performance on 1a-1d.
    c. Position Type: Player positions will be related to poorer performance on 1a-1d.

## Generalized Hypothesis

The primary hypothesis of this thesis is that retired NFL players have accumulated deficits as a result of prolonged and repetitive exposure to concussive and subconcussive forces. Specifically, as a result of player position and career length. The justification for this hypothesis is based upon 1) the knowledge that increases in career length inherently increase the number of subconcussive and concussive impacts a player is exposed to, 2) certain football positions experience increased impact exposure, and 3) growing evidence is implicating subconcussive and concussive impacts in the development of long-term dysfunction and neurodegenerative disorders.

# Chapter 2: Literature Review

## Mechanism of Concussions

A concussion or mild traumatic brain injury(mTBI) encompasses the metabolic cascade that results from rapid accelerations of the brain resulting from external forces applied either directly or indirectly to the head. These rapid accelerations cause axonal stretching and sheering which is generally considered the initial or primary injury caused by a concussive impact.[1] This axonal deformation results in indiscriminate neurotransmitter release and unregulated ion flux which represents the onset of the secondary injury phase or the metabolic cascade of the concussion.

One of the key neurotransmitters released by the stretched axons is the excitatory amino acid glutamate. NMDA channels open in response to glutamate and allow the efflux of potassium and the influx of extracellular calcium and sodium. This leads to depolarization of the cell and widespread depolarization across the brain. It is hypothesized that this widespread depolarization, and subsequent neuronal excitation, is the underlying mechanism of a few key clinical symptoms of concussion such as confusion, vision problems, and vestibular dysfunction.[1,2]

In addition to glutamate, the affronted axons release large amounts of potassium. This is exacerbated by the potassium released by the activated NMDA channels. The large increase in the concentration of extracellular potassium coupled with the depolarization, prompts $Na^+/K^+$ ATP dependent pumps to work overtime in an attempt to return the cell to proper ion concentrations. This is represented by a period of hypermetabolism as the cells attempt to return to homeostasis. This can typically be witnessed 30 min after injury.[3,4] In an uninjured brain this would be difficult as $Na^+/K^+$ ATP dependent pumps are generally working close to maximum,

but in a concussed brain, this increase in ATP demand occurs in the presence of several mechanisms that act to reduce cerebral ATP reserves. The excess calcium that entered via the activated NMDA channels is typically sequestered in mitochondria which leads to mitochondrial dysfunction. This dysfunction results in reduced oxidative phosphorylation and, therefore, reduced ATP production.[7] This period of mitochondrial hypometabolism begins 5-6 hours after the initial hypermetabolism onset and can last up to 5 days.[5] An accompanying reduction in cerebral blood flow(CBF) is thought to also contribute to the reduction in available ATP. It is known that CBF is reduced following injury in more severe traumatic brain injuries and it has been shown that there is a 50 percent decrease in CBF in a rat models of concussion.[2] These events set the stage for an energy mismatch that is often referred to as an energy crisis. An insufficient supply of ATP clearly provides a large disadvantage for the recovering brain.

In addition to disrupting mitochondrial energy production, excess calcium leads to the production of reactive oxygen species(ROS), cellular damage, and possibly apoptosis. The accumulation of calcium inhibits proper reduction of molecular oxygen which results in the development of ROS. As ROS begin to accumulate, in a process known as oxidative stress, they overwhelm the antioxidant defenses present in the brain, leading to lipid peroxidation and oxidation of important biomolecules. This event has been shown to begin one minute after injury, continuing up to 48 hours, and can cause permanent damage.[6]

6-24 hours post injury, increased intracellular calcium levels can lead to microtubule disruptions which may play a role in inhibiting axonal transport. This may also contribute to axonal blebbing and, eventually, axonal disconnection.[5] Increased calcium may also over activate phospholipidases, protein kinases, nitric oxide synthase, endonucleases, calpains, and/or plasmalogenase which may result in initiation of programmed cell death, known as apoptosis.[7]

The mechanical stress induced by the concussive impact itself also causes axonal stretching which leads to deterioration through neurofilament compaction and swelling. The initial compaction occurs within 5 min and persists for 6 hours. This results in neurofilament collapse via phosphorylation-induced alterations of neurofilament stability or caplain-mediated proteolysis. Axonal swelling results via abnormal accumulation of organelles at the site of axonal damage and can result in the formation of axonal bulbs and secondary axotomy. Secondary axonal damage can be witnessed four hours post injury and can last for weeks. This accumulation is the result of continued transport from the still functional transport above the injury site.[7,5] These disruptions in axonal transport and integrity, along with the aforementioned calcium induced alterations, can result in the loss of neuronal communication and axonal connections which may underlie some of the cognitive symptoms of concussion.

The mechanical forces that cause axonal stretching also cause damage to the blood brain barrier(BBB). The blood brain barrier regulates the content of blood between the CNS and the rest of the body. The initial impact can cause damage to the BBB endothelium which can lead to changes in permeability and regulatory control.[8] Failure of the endothelium to recover can result in improper ionic flux, cerebral edema, and exacerbation of glutamate-induced dysfunctions. BBB damage has been identified one week post-injury and can last for months.[2]

For most individuals concussive symptoms disappear in first ten days following injury; however, some individuals continue to experience symptoms and deficits for weeks to years.[9] The first three days following injury are often referred to as the acute phase of injury/recovery. The metabolic and cellular events that occur during the first three weeks after the injury make up the subacute phase of injury. For most this is a period of natural recovery and repair; however, failure of the aforementioned disruptions to resolve contributes to the continuation of symptoms

and deficits. Approximately 15% of concussed individuals in the general population have symptoms that last beyond the standard 7-10 days of recovery.[54] The deficits and symptoms lasting beyond three weeks fall in the chronic phase of injury. It is possible that a disrupted BBB plays a role in the maintenance of the dysfunctions underlying the symptoms lasting beyond the initial week of injury.

There is evidence that disruptions of neuronal networks exist in the subacute to chronic phase of injury which strongly suggests that concussive symptoms and deficits are not only the result of cellular and ionic disruptions. It is believed that the damage incurred by axons affects the functional neural connectivity of the brain.[13] A recent study found that clinically asymptomatic individuals in the subacute phase of recovery had decreased connectivity of default mode network(DMN), specifically in the lateral parietal cortex. The lateral parietal cortex plays a role in processing spatial information, motor planning and control, and episodic memory.[10] The DMN plays a role in internal cognitive tasks like introspection and day-dreaming. It is deactivated when an individual focuses on external stimuli and plays a large role in proper shifting and allocation of attentional resources. Dysfunction of DMN has been hypothesized to participate in the mechanism of ADHD and likely contributes to the attentional deficits seen following concussions.[76] While the individuals in this study appeared asymptomatic, they still showed concussive-induced alterations in neural connectivity. This indicates that resolution of symptoms does not represent complete reversal of the underlying pathology of concussions. Other studies have also found disruption in of neural networks despite apparent asymptomaticity and performing equally to healthy controls on all diagnostic measures.[13,15] It is evident that some mechanism must compensate for the decreased functional connectivity and activation. Recent research supports the concept of cognitive reserve.

Cognitive reserve is the recruitment of additional brain resources in order to achieve the appropriate level of functioning. High levels of cortical recruitment have been observed in concussed individuals and it has been determined that concussive symptom severity is associated with increased hyperactivity in specific brain regions.[19,13,15,52,11] This heightened cognitive recruitment is also seen in the chronic phase which brings into question the time frame of cognitive reserve. Cognitive reserve may be a temporary mechanism to compensate until recovery can occur or, if full recovery does not occur , may be more representative of permanent functional reorganization.[52,12]

Whether increased neural activity in the presence of incomplete healing and clinical asymptomaticity is permanent or not, individuals at the subacute phase of healing are at increased risk for recurrent concussion. Repeat concussions are most likely during the first ten days following injury and deficits are often more pronounced.[9] Individuals often believe that resolution of their symptoms means that they are safe to return to their previous activities. If an individual receives an impact during this period they are at a higher risk for concussion as their brain is more vulnerable and still recovering. This means that a smaller impact may be sufficient to activate the concussive cascade or may produce a larger effect. Additionally, individuals at this stage of recovery have decreased mental stamina and fatigue sooner making them more likely to commit acts and experience environments that may place them at greater risk for another concussion.[14] With each re-occurring concussion an individual's symptom resolution time increases.[20] Consequently, this increased time for symptom resolution may increase concussion risk potentially leading to a reiterative cycle.

## Repetitive Concussions

There is mounting evidence that repetitive concussions, also known as repetitive mild traumatic brain injuries(rmTBI), exert a cumulative effect on the brain and can result in lasting deficits. Chronic cognitive impairments, such as reductions in memory and executive functioning, have become prominently observable in hockey players, boxers and football players as result of repetitive concussions. There is also strong evidence implicating multiple concussions in the onset and/or acceleration of neurodegenerative disorders.[21,22] Long-term visuomotor and vestibulomotor deficits as well impairments in motor learning have also been documented as a consequence of repetitive mTBI.[23,24,21]

While the complete mechanism underlying rmTBI is uncertain, several key characteristics have recently been identified. In several mice and rat models of multiple mTBI, it has been observed that additional concussive episodes result in significantly greater axonal and cellular damage.[21,25-27] It has been determined that cells exposed to repeated mTBI showed damage equivalent to that seen in moderate traumatic brain injuries.[22] This cumulative damage appears to be dependent upon the time between the initial and subsequent concussion. It was consistently shown that this increased damage only occurred when the additional concussive insult took place within one week with the most common time frame occurring 3-5 days post-injury.[25,26,27,21] Concussive insult outside this time frame resulted in damage equivalent to a single concussion. This indicates that there is a window of vulnerability during which the brain is significantly more susceptible to damage. During this window of vulnerability, increases in cognitive and behavioral deficits have also been seen and several studies have demonstrated an increased persistence of these deficits with cognitive deficits evident at one year post-injury.[25,21,27-29] Unfortunately, the time frame of the window of vulnerability for increased damage in humans

is still uncertain.

It has been proposed that these neuronal, behavioral, and cognitive deficits are the result of a separate cascade that differs from that seen following a single concussion.[22,30] One significant difference between a single concussion and repeated concussion is the level of metabolic disturbance. A single mTBI is characterized by a 22 percent reduction of ATP; however, a second mTBI demonstrates a 50 percent reduction, more than doubling that seen in a single mTBI. This level of ATP reduction was shown to be equal to that associated with severe TBI. There was also a 35 percent increase in ADP production witnessed 5 days post-injury while no increase was associated with a single injury. This implies that the mitochondria were not significantly damaged following single injury and that multiple injury causes greater mitochondrial damage and dysfunction, possibly to an irreversible level. This suggests that the brain is significantly more vulnerable to metabolic disruptions following the initial concussion and that these disruptions are much more significant.[26]

Another key mechanistic difference is increased astrocytosis and microglial activation.[29,27] This is typically associated with neuronal damage and deterioration. Astrocytes and microglia are both types of glia and are necessary for neuronal support and repair. It seems that increases in activated astrocytes may trigger the release of pro-inflammatory mediators and chemokines resulting in further damage by attracting inflammatory cells to the injury site.[31] Astrocytosis, also known as atrogliosis, is also associated with astocytic scarring which inhibits axonal regrowth and recovery.[32] Increased microglial activity is also associated with inflammatory responses and likely contributes to neuronal deterioration through the facilitation of the breakdown of the extracellular matrix.[25]

Caspace, a member of the protease family, also seems to participate in the inflammatory

mechanism seen following multiple concussions.[33] Proteases are the enzymes that play a role inflammation and apoptosis.[34] Significant increases in hippocampal and general neuronal neurite damage have been demonstrated *in vitro* following rmTBI.[33,22] The hippocampus is crucial for memory and proper neurite health is needed for successful memory encoding and retrieval. It has been suggested that caspace activation plays a role in mechanism underlying neurite damage and, potentially, memory deficits.[33]

Memory and learning is dependent upon long-term potentiation(LTP) and long-term depression(LTD) plasticity. A recent study of football players suffering from multiple concussion demonstrated decreased motor learning and increased gamma-aminobutyric acid(GABA) levels. GABA is an inhibitory neurotransmitter and it has been suggested that GABA-induced suppression of LTP and LTD-like synaptic plasticity underlie this decreased motor learning. There is evidence to suggest that GABA-induced blockage of NMDA-receptors contributes to this suppression.[24]

While the mechanisms underlying deficits resulting from repetitive mild traumatic brain injuries remains unclear, there is evidence indicating that the time between concussive impacts plays a large role in the severity of the resultant damage. There is also some evidence indicating that the severity of the repetitive injury also plays a role.[30,28] There is a strong relationship evolving between multiple concussions, long-term deficits, and neurodegenerative disorders. Increasing evidence is linking rmTBI with Chronic Traumatic Encephalopathy(CTE), Alzheimer's Disease(AD) and Amyotrophic Lateral Sclerosis(ALS).[75]

## Subconcussive Impacts

There is also mounting evidence that subconcussive impacts contribute to long-term deficits and are associated with an acceleration of neurodegeneration. They may also contribute to an increased risk of CTE and AD.[35]

While a formal definition of subconcussive impacts is currently unavailable, a reasonable description is biomechanical forces that are below the theoretical threshold for inducing a concussion. These impacts do not result in a diagnosable concussion based upon standard clinical grounds; however, evidence suggests that sub-clinical impairments may result.[35,37,45]

Individuals who participate in contact sports have an extremely high risk of exposure to repetitive subconcussive impacts and their potential consequences. Two particularly excellent examples include football and boxing. Several studies have sought to quantify the number of subconcussive blows football players experience and the finding are quite impressive. It is suggested that the number of subconcussive blows per season may range from around 400[47,45] to 2,500,[45] with the average player receiving approximately 800-1000 impacts.[45,48,36] One study found that high school players received an average of 15.5 collisions registering over 14.4g per organized activity.(Games, practices, pre-game warm-ups, etc.)[42] These numbers are higher for professional football players, receiving 30-50 impacts per game.[87] If one extrapolates the lower portion of the range, 400 impacts per season, to a four year career, that individual would be exposed to 1,600 collisions. When the average per season is considered, an individual could receive 3,200-4,000 subconcussive impacts. At the extreme, an individual could experience as many 10,000 subconcussive blows over a four year period. This represents only a short period of a player's career, similar to the length of a high school or collegiate career. If one were to consider an individual's total athletic career, these numbers would be significantly higher. These

numbers are higher for certain positions, such as linebackers, and much lower for others, like kickers.[49]

The evidence supporting a link between subconcussive impacts and cognitive deterioration is growing. A study of Long-Evans rats subjugated to a subconcussive blow resulted in acute neuroinflammation without any evidence of a concussion on behavioral assessments of cognition, sensorimotor function or social behavior. The neuroinflammation included increased microglia, macrophages and reactive astrogliosis.[46] An *in vitro* study demonstrated that sub-threshold stress that normally does not result in any neural changes caused damage when repeated over a short period.[30]

Several clinical studies have demonstrated neurocognitive changes in the absence of a clinically diagnosable concussion. It was recently found that a subset of football players demonstrated post-season decreases in learning compared to non-contact controls when assessed through cognitive screening and neuropsychological test batteries. It was also found that poorer performance was strongly correlated with an increase in measures of head impact exposure.[40] Similar findings have been found in soccer players. A study of professional soccer players demonstrated an association between increased heading frequency and poor memory, planning and visuoperceptual processing.[81] Two other studies have also found neurocognitive deficits in athletes without clinically diagnosable concussions.[44,37] One of which demonstrated that linebackers, the players who typical receive the most subconcussive collisions, had the highest incidence of neurocognitive deficits.[44] Globally, professional athlete exposure to subconcussive blows is likely greater due to increased intensity and career length.

There is also mounting evidence that these neurocognitive deficits are related to changes within the brain. A study using functional Magnetic Resonance Imaging(fMRI) and the ImPACT

neurocognitive exam found post-season neurophysiological alterations and neurocognitive deficits in football players in the absence of clinically observable symptoms associated with concussion. Alterations in activation were found in the dorsolateral prefrontal cortex which is associated with memory. These neurocognitive and neurophysiological alterations were also associated with a significantly higher incidence of head impacts.[42] Similar findings were demonstrated in an additional fMRI study.[38]

Other imaging studies have also demonstrated physiological changes in absence of concussive symptoms. A post-season Diffusion Tensor Imaging(DTI) study of hockey and football players found six individuals that had significant white matter changes compared to pre-season imaging. These changes were 3 times greater than those seen in controls. A significant relationship between the proportion of white matter changes and the number of impacts was found. It was discovered that these changes were similar to those seen in a clinically diagnosed concussion.[47] Similar white matter alterations were also found in another pre/post-season DTI study of asymptomatic players.[43] A third DTI study also found neural abnormalities and found evidence of blood-brain barrier disruption(BBBD) in the football players that received the highest number of subconcussive blows. BBBD increased following a single game and was also increased at the end of the season. The increase post-game was significantly correlated with the frequency of head impacts.[41]

It seems likely that subconcussive blows result in neurological changes. There is also growing evidence supporting a relationship between the number of subconcussive blows, deficits in cognition and changes in neurophysiology; however, the time course and long-term consequences of these changes remains unclear. A study examining the effects of repetitive subconcussive blows on overall football player performance found that the players were not

noticeably affected by the impacts.[36] Another study failed to detect and short-term neurological deficits following a single football season.[48] These findings are expected when one considers that even when cognitive deficits were seen on neurocognitive tests and when neural abnormalities were detected, no clinical concussive symptoms or deficits were observable. It seems likely that the effects of these changes are hidden by individuals' cognitive reserve and do not become clinically evident until sufficient damage has accumulated.[39] An electrophysiological study of the effects on repetitive subconcussive blows on measures of attentional allocation and reaction time has some evidence to support this theory. Changes in electrophysiological measures of attention were not found following a single season, but differences were found when comparing first year players to third and fourth year players. This theory may further be corroborated by the theory of normal aging's effect on cognition. Aging eventually results in changes in cognition. As age-induced deterioration accumulates, cognitive reserve is consumed leading to clinically evident deficits.[36]

If subconcussive blows do result in accumulated damage which slowly reduces cognitive reserve, then it seems logical that it may play a role the accelerated onset of neurodegenerative diseases, like CTE and AD. This would also explain any accelerated age-related changes in cognition.

The mechanism underlying the cognitive and neurophysiological changes associated with subconcussive impacts is still poorly understood and primarily speculative. *In vitro* evidence indicates that repetitive subconcussive stress in a short period of time can cause neural damage[30] and animal evidence indicates that this neural damage may be accompanied by an acute neuroinflammatory response which likely results in an inflammatory cascade.[46] There is also evidence of blood-brain barrier disruption.[41] It seems likely that as an individual experiences

repetitive subconcussive forces, small amounts of damage and physiological changes occur. As these changes are not significant enough to elicit clinical deficits, the individuals continues the activity exposing them to these forces. This allows for accumulation of further damage and changes.[42,43] The blood brain barrier may allow for the maintenance or exacerbation of these changes in manner similar to its hypothesized interaction in full blow concussive episodes. It may also contribute through permeability-induced alterations of important concentrations within the brain. These alterations and damage accumulate over time, reducing cognitive reserve. Additional neural deterioration occurs through natural aging which also depletes cognitive reserve.[39] Together, these mechanisms cause deterioration to accumulate until cognitive reserve can no longer accommodate the changes and clinical deficits become observable. This is potentially how accelerations of the effects of aging and neurodegenerative diseases arise.

Another potential mechanism suggests subconcussive blows as an underlying cause of neurodegenerative disease and not just an accelerator. In this model subconcussive blows result in deposition of amyloid-beta which are associated with neurodegenerative diseases like AD and CTE.[39] This theory draws support from the findings of amyloid precursor protein and increased microglia in mice models of subconcussive blows.[45,46] Amyloid precursor protein has been identified as a precursor of amyloid-beta and one theory of the development of CTE cites increased and abnormal microglia as a key factor.[51,50] If this mechanism is correct, it could help explain findings of CTE in football players without a history of concussion.[38]

Another hypothesized mechanism of neurodegeneration include an autoimmune response to molecules released following blood-brain barrier disruption,[41] and neuroinflammatory-induced lipid peroxidation and apoptosis.[46] Additional research is needed both on the long term consequences of subconcussive impacts and the mechanism underlying it. Future research

should also investigate the relationship between repetitive subconcussive impacts and repetitive concussions as the two might alter each others' rate of occurrence, mechanisms and outcomes.

## Chronic Phase

Concussed individuals with symptoms extending beyond the subacute phase of injury have been found to demonstrate increased neural activation on memory and attention tasks. It has been demonstrated that one month post-injury symptom severity is associated with activation changes during these tasks. Under increased working memory load, there was additional activation outside the working memory network. The ventrolateral prefrontal cortex, posterior parietal cortex, and the posterior cingulate gyrus are the key structures that exhibited this increased activation.[12] While these changes represent the minority individuals with symptoms a month post-injury, most individuals' concussive symptoms disappear after ten days.[9] It is often said that these individuals have “healed” and their symptoms have “spontaneously resolved”; however, there is evidence that full healing has not occurred even at 30 days post injury. Any residual damage or healing that occurs during this time can be referred to as the chronic phase of the injury.

Research is beginning to show that recently concussed but asymptomatic individuals have functional abnormalities. When scanned within 30 days post-injury, asymptomatic individuals(as of ten days post injury) found increased cortical activation while performing the same tasks as non-concussed controls. Increases in activation were seen in the hippocampus, dorsolateral prefrontal cortex and the parietal cortex. Interestingly, the asymptomatic subjects and the healthy controls both performed the tasks with the same success rates. This suggests that previously concussed individuals exert greater cognitive effort in order to match healthy

controls. The apparent asymptomaticity and increased cortical activity may be achieved through cognitive reserve or permanent reorganization of the brain.[52] This also suggests that some healing is still occurring at this point and that true complete recovery has not occurred.

Further evidence of incomplete healing was demonstrated in a study of gait 28 days post-mild traumatic brain injury. A dual task paradigm analysis of previously concussed subjects' gait found significant changes compared to healthy controls. The concussed subjects walked significantly slower, exhibited greater sway in the frontal plane, increased sway velocity, and decreased distance between center of mass(COM) and center of pressure(COP).[58] Similar findings have been witnessed two months post-injury in adolescents.[61] The decreased gait velocity and COP displacement suggest that concussed individuals adopted a more conservative gait strategy. The increased sway displacement and velocity may be the result of vestibular and/or motor deficits. This seems reasonable considering concussed individuals often demonstrate overt motor and vestibular impairment in the acute and sub-acute phase of concussions.[58] Considering these differences were only observable during the dual task paradigm, it is also possible that these alterations are the result of impairments in attentional resources. Attention is often diminished in the acute phase following concussion and attentional resources have been shown to be reduced months to years following concussion.[16,59,36,12,60] Finally, it is possible that these differences are the result of impaired learning. The healthy controls were able to adapt to the dual task by day 5, but the concussed individual were not.[58] This provides some indication that learning or memory deficits may be involved in these differences. Whether these gait changes are the result of decreased attentional resources, motor function, memory impairments or some combination thereof remains to be elucidated; however, it seems evident that individuals at this stage have not yet fully recovered.

While current understanding of the neural basis of these alterations is incomplete, there is some evidence from animal models that changes in axons and individual neuron activity may be involved. Mice in a recent study exhibited reduced spatial learning and memory at three weeks post-injury. This study also found axonal deterioration at four and six weeks post-injury. This damage was evident in the external capsule and dorsal thalamus.[63] A recent study analyzed individual hippocampal neuron activity during a test of memory and learning 30-90 days post-injury. This study found memory deficits and disorganized neural activity in the hippocampus. These findings occurred in the absence of overt histological changes to the neurons.[64] The authors hypothesized that the disordered firing result in network dysfunction. When the results of these studies are considered together, they provide some insight into the potential causes of the fMRI and gait changes mentioned above. It seems reasonable that deteriorated white matter tracts and disorganized neuronal firing would facilitate a need for increased activation as well as result in deficits. However, much more research into the chronic phase of injury is needed.

## Potential Long-Term Consequences and Outcomes

### Post-Concussional Syndrome

Individuals that reach the chronic phase of injury and still have symptoms typically suffer from Post-Concussional Syndrome(PCS). The DSM-IV defines PCS as cognitive impairment in attention or memory and three or more concussive symptoms that persist for three or more months, resulting in interference with social/occupational functioning.[56,57] Approximately 15% of concussed individuals suffer from PCS.[54] Individuals who receive rmTBI may be at a higher risk for developing PCS.[33] Post-Concussional Syndrome represents a significant consequence that can arise from a concussion.

There is still much debate over the pathophysiology underlying PCS and whether it is the result of physiological changes or psychological and personality factors. One theory hypothesizes that an individual's personality predisposes them to increased sensitivity to deficits and claims an association between neuroticism, depression, anxiety and PCS.[54] Another theory proposes a failure of physiological changes to resolve and yet another theory suggests combination of the two.[55] Recently, evidence has surfaced adding strength to the theory of physiological changes. A study comparing concussed but asymptomatic individuals to concussed sufferers of PCS found greater and wider structural impairment in the PCS group. It should be noted that both groups had structural impairment compared to non-concussed controls.[65] Further evidence was found by examining eye movements of PCS subjects in comparison to non-PCS mTBI subjects. This study found poorer eye function in the PCS group on anti-saccades, self-paced saccades, memory-guided sequences, and smooth pursuit. This suggests impairment in inhibition, memory and motor function; however, for those measures under conscious control, psychological influences could still be a factor. The self-paced, memory-guided and anti-saccades have components that evaluate subconscious eye responses. The poorer performance of the PCS groups on these measures strongly indicates physiological damage. This study also found an association between increased symptom load and poorer ocular performance.[66]

A more complex theory[53] hypothesizes a process known as immunoexcitotoxicity as part of the potential underlying mechanism of PCS. Concussions result in activation of microglia, the primary immune cells of the CNS, that cause massive efflux of the excitatory neurotransmitters glutamate and aspartame which, in turn, overstimulates glutamate receptors. These overstimulated receptors allow massive calcium influx which can lead to neuronal toxicity and death. In addition to the release of glutamate, microglia also release proinflammatory

prostaglandins, reactive nitrogen species, cytokines, chemokines, trophic factors, as well as several other immune factors. Following the removal of dead cells and inciting pathogens, microglia normally return to a neurorescue role to facilitate healing and recovery. It is hypothesized that combination of these immune factors and released excitatory neurotransmitters react with neuronal tissue, thus contributing to the prolonged cognitive deficits of PCS. It is also hypothesized that the failure of the activated microglia to return to their non-activated neurorescue role may contribute to the smoldering immune response that likely mediates the residual symptoms of PCS.[53]

While the mechanism of PCS still needs to be determined, individuals who suffer from this disorder experience significant disruptions to their daily life. Considering these individuals typically develop their symptoms immediately post-injury and suffer for months to years, developing successful treatments and inventions is absolutely crucial.

## General Cognitive Deficits

PCS is a fairly well documented potential long-term outcome of concussive injuries, but there is growing evidence that individuals develop impairments in memory, attention, reaction time, and executive functioning. A recent study found that 52.5% of individuals who had received a concussion 11 years earlier reported poor memory.[77] While this study was very small, another study containing 2,552 retired football players found that 17.6% reported a perceived significant and permanent deficit in memory eight years post-injury.[78] These studies, while limited by the subjective nature of self-reports, at least establish evidence of perceived memory deficits at more than eight years post-injury. These perceived deficits are strengthened by the finding that complaints of impaired memory, attention, and executive function in previously

concussed individuals were most strongly explained by impaired performance on neurocognitive measures.[54] More objective evidence has been discovered in comparing previously concussed individuals' performance on neurocognitive measures to healthy controls. Impairments in prospective memory were found 3 months post-injury in previously concussed adults when compared to those without a history of concussion.[80] Another study analyzing prospective memory found impairments 5 years post-injury when comparing previously concussed adolescents(age 10-19) to controls.[79] Prospective memory is planning and remembering to carry out an action at a future time.[80] Impairments in this domain are essentially impairments in both memory and planning(executive function).

Further evidence of impaired memory and planning has been demonstrated in professional soccer players as well. This study found an inverse relationship between the number of concussions and performance on of measures of memory, planning and visuoperceptual processing. A relationship between increased frequency of heading and poorer performance was also demonstrated.[81] These results are corroborated by a study of retired soccer players demonstrating memory, learning, and perception impairments in 32% of previously concussed players.[82] Cognitive impairments were demonstrated an average of 6 years post-mTBI in another comparison to non-concussed controls. Impairments of memory affected both long and short-term memory and the findings suggested dysfunction of encoding and recall. Deficits were also seen in executive function and attention.[83] It is extremely likely that these cognitive deficits are related to physiological changes within the brain. A diffusional kurtosis study found deterioration in the internal capsule and thalamus in mTBI individuals compared to controls. These changes were found over one year post-injury and, more importantly, were associated with cognitive impairments. The thalamic damage was correlated with impairments

on measures of attention, processing speed and working memory. [84] This corresponds with findings of cognitive impairment, thalamic deterioration, and internal capsule damage in a mouse model of mTBI.[63] When these results are taken in consideration with the findings of DTI changes following subconcussive blows, it seems likely that subconcussive and concussive blows result in white mater alterations that lead to changes in cognition.[43,47]

The aforementioned findings of attentional impairment are further strengthened by the results of EEG studies with healthy controls. A study examining mTBI individuals 7 years post-injury found decreased P3 amplitude compared to healthy controls. This was only evident whenever cognitive load was increased. P3 amplitude is believed to represent attention and attentional resources.[60] Decreased P3 was also found in an additional EEG study conducted at an average of 3.4 years post-injury. The decreased P3 was demonstrated in the absence of differences on the ImPACT.[59] These findings help to support the theory that previously concussed individuals have reduced attentional resources and may use greater cognitive resources to achieve equivalent performance and/or experience accelerated aging.

## Neurodegenerative Diseases

Whether these generalized impairments are the result of isolated dysfunction or part of more severe degenerative disorders is uncertain; however, it is clear that there is increasing evidence of an association between concussive/subconcussive impacts and an increased risk of neurodegenerative disorders. There is a significant amount of literature available that demonstrates an association between the more severe forms of traumatic brain injury and an increased likelihood of dementia.[85]

An association between concussion and Mild Cognitive Impairment(MCI), often

described as the intermediate stage between the results of normal aging and the onset of dementia, has been demonstrated in a study of 2,552 retired football players. Football players that received 3 or more concussions during their career were 5 times more likely to be clinically diagnosed with MCI.[78] Evidence of an association between full developed dementia and mTBI also exists. A nationwide study of the incidence of dementia in Taiwan analyzed 720,933 individuals with and without a history of mTBI. Of those 720,933 cases, 28,551 of the individuals had a history of at least one mTBI. This study then followed these cases for 5 years, looking for the onset of dementia. After controlling for outside variable such as age, socioeconomic status, alcohol use, and other confounders, this study found an increased risk of dementia even after a single mTBI. The incidence of dementia per 1,000 cases was 1.8 for individuals with a history of mTBI and only 0.3 for those without. This shows a significantly higher risk of the onset of dementia following a concussion.[86] While a mTBI may increase the risk of developing dementia, it is likely that genetic risks also contribute. Apolipoprotein E 4(ApoE4) allele over-expression is considered a major risk factor for dementia and is believed to be related to poorer outcome following TBI.[87] Carriers of ApoE4 that received a mTBI were found to have the greatest risk of developing dementia compared to those who either only had a mTBI or carried the allele. Furthermore, those with mTBI and the allele were 5 times more likely to develop dementia than those without either factor.[88]

Alzheimer's disease is a very common form of dementia and it is quite possible that the dementia of the previous studies is the result of AD. As general TBI is considered a large risk factor for dementia, it is also a large risk factor for AD.[90] A higher prevalence of AD was found in retired NFL players when compared to those of the same age,[78] and another study found a greater risk following mTBI with loss of consciousness.[89] Additionally, a few case reports have

found a rapid onset of AD following mTBI in individuals without cognitive changes prior to their concussion.[90-92] When considered together, the rapid onset and higher prevalence suggest mTBI as a risk factor for the earlier onset, or the development of, AD.[78]

There is mechanistic evidence supporting the link between concussions/subconcussive impacts and AD in human and animal studies. Amyloid-beta is a substrate deposited in AD brains and represents one of the key pathological changes. Amyloid-beta is believed to interfere with memory through inhibition of synaptic plasticity.[93] Increased production the precursor of amyloid-beta, APP, has been demonstrated in response to subconcussive blows in mice.[45,46] Oxidative stress is believed to interfere with proper APP metabolism, leading to amyloid-beta accumulation.[95] Several animal studies have found that rmTBI increases oxidative stress and amyloid-beta production.[94-96] Amyloid-beta deposition was also accelerated following a single mTBI but less severely. A significant positive correlation between mTBI episodes and amyloid-beta deposition has also been found.[94] In addition to amyloid-beta, neurodegenerative diseases have associated antibodies. A study of football players found blood-brain barrier dysruption following subconcussive impact exposure. In response to the increased BBBD, this study also found elevated levels of antibodies that have also been described in AD.[41]

Two other key pathological traits of AD are neurofibrillary tangles(NFTs) and cerebral atrophy. Greater cerebral atrophy has been demonstrated in retired soccer players when compared to controls. One third of the soccer players presented with cerebral atrophy and it was more common in those who headed the ball more frequently.[97] NFT accumulation has been found in young adults(age 23-28) following chronic repetitive head trauma.[90] These findings are supported by the findings of extensive cerebral atrophy and NFTs in a mice model of rmTBI.[96]

While cerebral atrophy and NFTS are a key finding of AD, they are also characteristic of

Chronic Traumatic Encephalopathy. The NFT's identified in the previously mentioned study are identical in CTE and AD.[96] While amyloid-beta is characteristic of AD, 44% of neuropathologically verified cases of CTE had amyloid-beta plaques.[73] AD and CTE can only be conclusively diagnosed post-mortem. Clinically diagnosed cases of AD have been neuropathologically identified post-mortem as CTE, therefore, caution must be used in clinical diagnosis of either disease.[98] CTE is differentiated from AD by its characteristic deposition of tau and NFTs in depths of sulci and in neocortical layers II and III. AD's deposition is typically in the deeper neocortical layers, V and VI. Microscopically, CTE is characterized by the accumulation of phosphorylated tau proteins as neurofibrillary tangles, neurites, and glial tangles(GT) throughout the frontal, temporal, and insular cortices. There are often accumulations of TAR DNA Binding Protein 43 (TDP-43) but these are usually more common in more severe tau pathology. Tau deposition is generally patchy and irregular with more concentrated regions in surrounding small blood vessels, in the depths of sulci, and superficially in the neocortex. This is another difference from AD. Alzheimer's disease tau NFT distribution is more uniform.[101] In advanced stages of CTE, there may be concentrated tau deposition in the amygdala, entorhinal cortex, and olfactory bulbs.[74]

Grossly, CTE is associated with cerebral atrophy, cavum septi pellucidi with and without fenestrations, shrinkage of the mammillary bodies, neocortical dropout, pallor of the substantia niagra, hippocampal atrophy, vermal atrophy, and widening of the ventricles.[109,73,74] CTE is clinically represented by a triad of cognitive, behavioral, and motor deficits. These deficits commonly manifest as executive dysfunction, memory impairment, depression, apathy, poor impulse control, suicidality, parkinsonism and dementia. CTE symptoms usually appear years after the athlete last received a concussive impact and have retired from play. Typically this

occurs in an individual's thirties to fifties.[74] After initial onset, CTE rapidly progresses to late manifestations within 2-3 years.[109]

CTE was originally identified in the boxing community under the term "punch drunk syndrome." This syndrome was first described in 1928 in boxers who demonstrated significantly impaired cognition, behavior, and motor skills. In 1937, "punch drunk syndrome" was renamed dementia pugilistica to add validity as a medically recognized disorder. In the 1960's, the term chronic traumatic encephalopathy was coined and, in 1973, CTE was identified neuropathologically in 15 retired boxers.[101] More recently in 2005, Omalu identified CTE in the brain of a retired NFL player post-mortem.[110] Since 2005, CTE has been identified in a variety of other sports and settings where there is a risk for repetitive head impacts. Such environments include ice hockey, rugby, horse racing, professional wrestling, as well as victims of abuse and sufferers of epilepsy.[74] Recently, incipient CTE was post-mortemly identified in an 18 year old amateur football player's brain who had only played football for 6 years. This implies that CTE pathology can appear rather early and after a relatively short exposure to repetitive brain trauma.[111] The best estimate of the prevalence of CTE comes from a random sample of 250 retired boxers. This study found that 17% of those sampled presented with CTE.[99] It is uncertain how representative this estimate is, however, some researchers have speculated a higher incidence.[73]

The current mechanism underlying CTE is still unknown; however, it is hypothesized that activated microglia play a role in combination with excitatory neurotransmitters in an excitoimmunotoxic reaction much like one of the mechanism hypothesized PCS. Aging may contribute to the onset of CTE by increasing the number of activated microglia and reducing the incidence of microglial return to their neurorescue mode. Additionally, there is some evidence

that genetic factors may preferentially predispose individuals to the development of CTE. APoE is associated with worsened neurological outcome following TBI and there is some suggestion that it may be associated with higher incidences of CTE.[74,101,73] Currently, the only commonality between all cases of diagnosed CTE are history of concussive and/or subconcussive impact exposure.[101,74]

There is some limited evidence suggesting a relationship between mTBI and subconcussive impacts with Amyotrophic Lateral Sclerosis and Parkinson's disease(PD). Football and soccer players were diagnosed with ALS four and 6.5 times more than the general population.[75,102] An association between mTBI with loss of consciousness and PD has been observed.[89] However, these findings need further examination as parkinsonism is associated with CTE and evidence of motor neuron disease has been found in some cases of CTE.[102] Cases of CTE with motor neuron disease may present clinically similar to ALS.[100] Research surrounding CTE is still in its infancy and much more investigation is needed. However, it seems quite evident that mTBI and subconcussive impacts carry a higher risk for the development of neurodegenerative disorders.

## Emotional and Psychiatric Consequences

CTE and AD both carry risks for personality changes and psychological comorbidities.[87,105] Additionally, mTBI carries a strong association with Post-Traumatic Stress Disorder(PTSD) and depression.[103,87,105] Although, PTSD is generally seen in mTBI received in combat and less frequently in other settings.[104,105] Emotional and psychological changes are important outcomes not only in and of themselves, but also due to their potential to increase the effects, duration and perception of other impairments.[105,106]

Major depressive disorder has been identified as a potential long-term outcome of mTBI in several studies.[107,108,83,75] A significantly greater risk of depression following mTBI compared to controls has been observed 5-17 months post-concussion.[107] Rates of 9-11% have been found and an association between recurrent concussions and depression have been demonstrated.[83,108,75] Those who have had 1-2 concussions are 1.5 times more likely to be diagnosed with concussion and 3 times more likely with a history of 3 or more concussions.[75,108] In addition to an increased risk of depression following mTBI, 25-50% of those suffering from dementia develop depression.[75] This is significant given the increased risk of dementia following mTBI and subconcussive impacts.

# Chapter 3: Methods

## Participants

This study examined a sample of 26 retired NFL football players, 24 currently active, Division I collegiate football players, and a convenience sample of 15 currently active non-contact older athletes. Of the 26 retired NFL players, 2 were excluded due to incomplete data, leaving 24 players for analysis. This group served as the population of interest having experienced a career latent with exposure to subconcussive and concussive impacts. The NFL players will be referred to as the NFL Group(NG). Retired NFL player demographic data are summarized in **Table 3.2.**

The 24 active collegiate football players served as position matched healthy controls. The football players were not age matched to the retired NFL players. Inclusion criteria for healthy control college players included no history of concussion within the last month, current football participation, and no overt abnormal cognitive or physical decrements. This group will be referred to as the College Control Group(CG). Player position and career length for both groups were obtained from internet databases. A summary of the career information of both football groups is available in **Table 3.1.**

The non-contact, active older subjects were included to provide a benchmark of older VR performance. These subjects participated in either swimming, running, cycling, dance, marathons, or triathlons. This group was comprised of both males and females. This group will be referred to as the Older Control Group(OG). See **Table 3.3** and **3.4** for a sport and demographic summary.

**Table 3.1 Football Participant Career Information**

| Position | Count | Group | Ave Pro Career | Ave NFL career | Ave College Career |
|---|---|---|---|---|---|
| DE | 4 | H | 4.25 | 9.5 | 3.5 |
| OG | 3 | H | 1.33 | 1.33 | 2.67 |
| TE | 2 | H | 8.5 | 8.5 | 3 |
| DT | 1 | H | 8 | 8 | 3 |
| OT | 1 | H | 5 | 7 | 4 |
| LB | 2 | H | 1.5 | 2 | 2 |
| QB | 2 | L | 2 | 5 | 2 |
| RB | 2 | L | 4.5 | 5 | 4 |
| DB | 2 | L | 3 | 3 | 3 |
| K | 3 | L | 9.67 | 9.67 | 3.33 |
| WR | 2 | L | 3 | 3.5 | 4 |
| Total | 24 | | 4.5 | 5.04 | 3.125 |

List of player position, grouping, and average career length by position. Average NFL career = Average career length of retired NFL players in NFL. Ave Pro Career = Total career length playing in any professional football league. Ave College Career = Collegiate career length of collegiate control group, H = High frequency group, L = Low frequency group. DE = defensive end, OG = offensive guard, TE = tight end, OT = offensive tackle, LB = linebacker, QB = quarterback, RB = running back, K = kicker, WR = wider receiver.

**Table 3.2 Retired NFL Group's Demographics**

| | Average | Standard Deviation | Median | Range |
|---|---|---|---|---|
| Age | 55.14 | 13.25 | 59.14 | 45.27 |
| NFL career | 4.50 | 4.30 | 3 | 16 |
| Total Pro Football Career | 5.04 | 4.33 | 4 | 16 |

Retired NFL player's demographics and career information. All demographics are in years.

**Table 3.3 Older Control Group Sport Participation**

| Gender | Swim | Cycle | Run | Dance | Triathlon | Marathon | Ave Career | StDev |
|---|---|---|---|---|---|---|---|---|
| Male | 2 | 1 | 2 | 1 | 2 | 1 | 13.22 | 4.67 |
| Female | 1 | 2 | 0 | 0 | 1 | 2 | 14.83 | 3.90 |

A summary of the older control group's sport participation. Ave Career=average sport participation length in years, StDev=standard deviation.

**Table 3.4 Older Control Group Demographics**

| Demographic | Average | Standard Deviation | Median | Range |
|---|---|---|---|---|
| Career Length | 13.87 | 4.14 | 12 | 13 |
| Age | 42.02 | 9.46 | 41.72 | 28.09 |

A summary of the age and sports participation of the older control group. Career Length=length of participation in that sport. Career length and age are in years.

## Contact-Based Frequency Groups

Players in both the NFL Group and the College Control Group were divided into one of four sub-groups based upon position played. These four groups were: 1) High Frequency NFL, 2) Low Frequency NFL, 3) High Frequency Control, 4) Low Frequency Control.

The High Frequency sub-groups included Line Backers, Defensive Ends, Defensive Tackles, Offensive Guard, Offensive Tackle, and Tight End. The Low Frequency sub-groups included Running Backs, Quarterbacks, Kickers, and Defensive Backs. See **Table 3.1** for a breakdown of group composition and **Table 3.3** for a summary of the groups' demographics.

Rationale for group classification was based upon the biomechanical findings reported in Head Impact Exposure in Collegiate Football Players by Crisco et al.[49] and Estimation of Head Impact Exposure in High School Football by Broglio et al.[117] The general basis of these classifications is that the positions of the High Frequency group receive lower magnitude but a higher frequency of impacts, suggesting subconcussive exposure. The positions comprising the Low Frequency groups were characterized as receiving less frequent but higher magnitude impacts, indicating a higher likelihood of concussive impact exposure. It should be noted that higher magnitude impacts are generally associated with a higher risk of concussion, but the

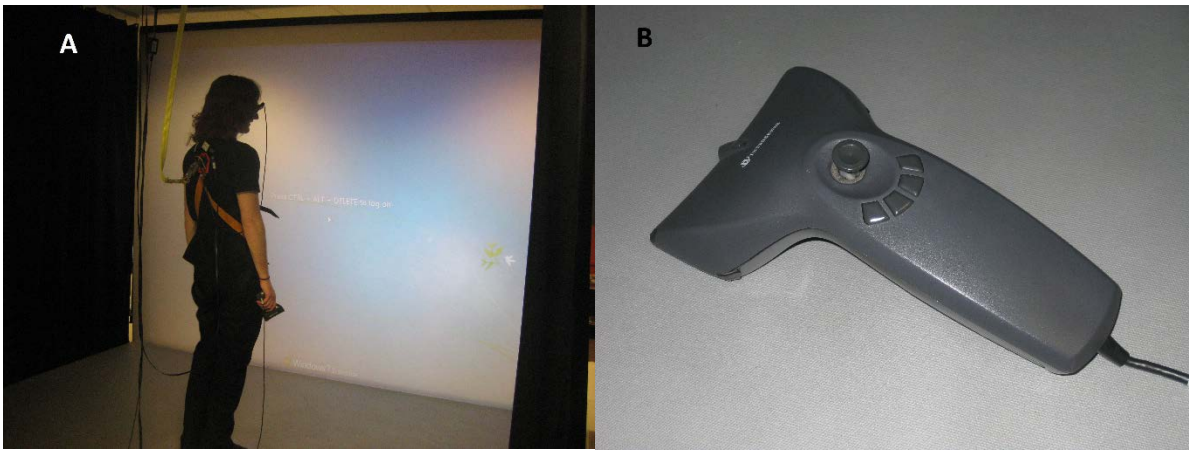
individual threshold for inducing concussion varies.[118,119]

## HeadRehab: Virtual Reality System

Participants were tested using the HeadRehab Virtual Reality system. This system virtually implants an individual inside a hospital. Within the virtual hospital, individuals see a room or hallway enclosed by a ceiling, three walls, and a floor. There are 3 potential ways of administering this system, all of which have been deemed equivalent through non-published, in-house validation. Each system demonstrated a high, significant correlation with the same subjects' performance output on the other systems.($R>0.9$, $p<0.001$)

One VR system utilized was the Virtual Reality Theater system. This system is comprised of a force plate(surface size: 18.5"x20"), large one wall screen and a motion tracking system. The one wall screen consists of a 92"x120" screen that generates the 3D virtual field via rear projection. The screen is synchronized with an AMTI force plate embedded in the floor(located 45" away from the screen) and an IS-900 micro motion tracking system attached to the subject's 3D glasses. This allows for subject manipulation of the VR world visual environment through their postural responses and head/body kinematics. VR world interactions were completed using a high resolution joystick. The floor containing the force plate and the screen containing the 3D virtual field are surrounded by two 92"x94" solid black curtains, creating a 3 walled virtual environment theater. See **Figure 3.1** for an image of this equipment set-up.

**Figure 3.1 Virtual Reality Theater System and Controller**



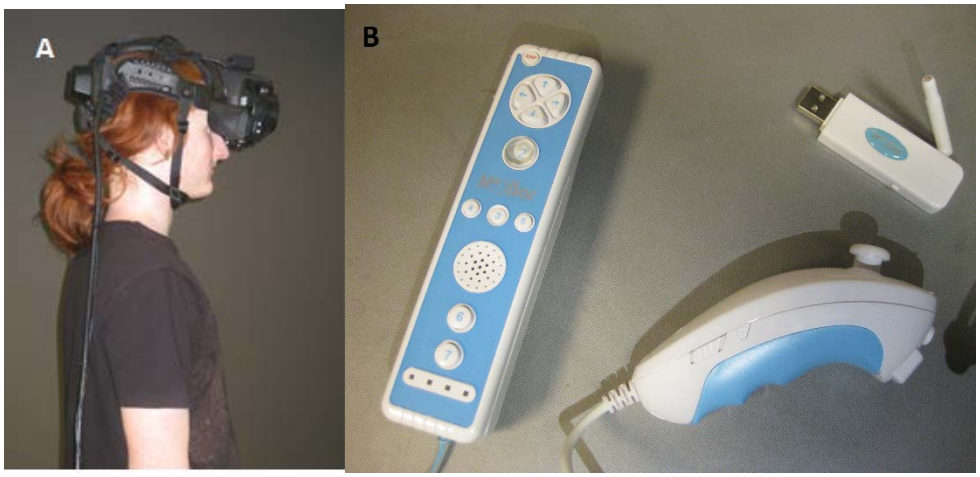

A) A subject standing in the Virtual Reality Theater. He is wearing the 3D glasses, a safety harness, and holding the high resolution controller. B) The high resolution controller used with the Virtual Reality Theater to complete in-world interactions.

The second VR system utilized was the 3D Television System. This system was comprised of a 51 inch 3D television, a head-mounted tri-axial accelerometer, and polarized 3D glasses. The tri-axial accelerometer was used to determine the subjects' COP and postural responses. The 3D television was mounted 63.5" above the ground and attached to the wall via an adjustable swivel. This permitted optimal alignment with the subjects' visual field. The subjects performed the assessments 45" away from the television while standing in alignment with the center of the television.

The third system utilized for VR assessment was the Head-Mounted Display system. This system has the benefit of portability. This system is comprised of two miniature screens aligned with each of the subject's eyes. The distance between the screens can be adjusted, allowing for proper alignment and complete virtual immersion. There is an accelerometer inside the Head-Mounted system that calculates the subject's COP. VR world interactions were completed using a wireless, MoBar Wii-PC controller. See **Figure 3.2** for an image of the head-

mount display set-up and controller.

**Figure 3.2 Head-Mounted Display VR System**




A) A subject wearing the Head-Mount Display System. B) The controllers and wireless receiver used to complete in-world interactions.

All 3 virtual reality systems employed the same 3 VR modules to assess spatial memory, reaction time, and balance. These modules were designed by the Penn State Center for Concussion Research utilizing the VTC Open GL developing kit. Each module automatically creates a final score based upon the raw data collected during each test. This final score can range from 0-10, with 0 representing the lowest score possible and very poor performance. Additionally, performance on the 3 VR modules are averaged to create a comprehensive, or total score. This score is also represented on a 0-10 scale.

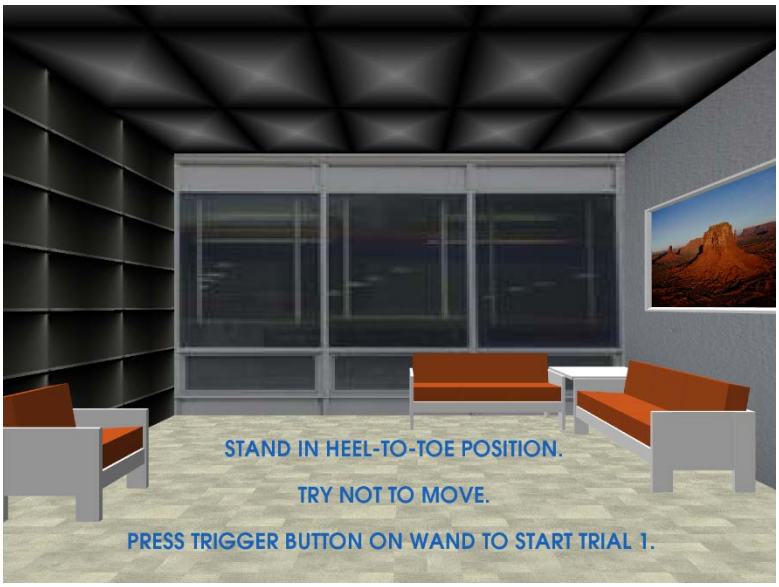
The balance VR module assessed the subjects' balance by destabilizing their visual field. It is well established that balance is disrupted immediately following concussions and that residual dysfunction can be observed up to 30 days post-injury even in clinically asymptomatic individuals.[112] This task challenges balance through visuo-kinesthetic conflict. This is accomplished by having the subject stand on the force plate in the Romberg position. The subject is then instructed to place their hands on their hips and try to stand perfectly still while

the virtual room moves. See **Figure 3.3** for an image of the balance module.

The preprogrammed virtual room movements consisted of 1) a stationary VR room; 2) forward and backward oscillations of the room within 18 cm displacement at 0.2 Hz; 3) VR room "Roll" around heading y-axis between 10-30 degrees at 0.2 Hz; 4) VR room "Pitch" between 10-30 degrees around the interaural x-axis at 0.2 Hz; 5) VR room "Yaw" between 10-30 degrees around the vertical z-axis at 0.2 Hz; 6) 18 cm VR room translation along the x-axis within 18 cm displacement at 0.2 Hz. Each VR room movement sequence lasted 30 s.

The COP was calculated using data from the force platform, sampled at 100 Hz, in conjunction with a special MATLAB program that estimates the subjects' postural response. This COP is then used to generate a normalized report of performance. This output is represented on a scale of 0-10. Zero represents extremely poor postural stability and 10 represents excellent postural control.

**Figure 3.3 VR Balance Module**




VR Balance module. Subjects were instructed to stand as still as possible while the room moved.

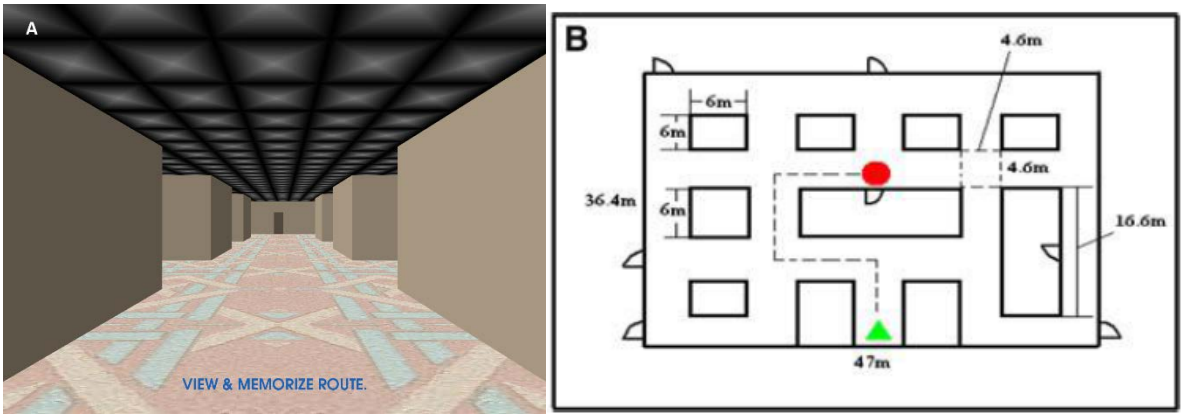
The reaction time VR module quantifies the timing of the subject's response to unpredictable room movements. Reaction time has been established as a measure of the integrity of a subject's executive functions which may be impaired due to previous concussive injuries.[21,22,83,114-116] The subject was instructed to sway in a manner that matched the movements of the virtual room. The room oscillated forward and backward at 0.2Hz for 30 seconds. At a randomized time point during each trial, the room would suddenly switch from the anterior-posterior oscillations to a roll in the medial-lateral direction. The subject would match this unpredictable roll with a whole body movement in the lateral direction. Reaction times ranged from greater than 800ms, scored as a zero on the output, to 250ms or less, scored as a 10. Zero represents long reaction time and poor performance, while 10 corresponds to excellent performance. See **Figure 3.4** for an image of the reaction time module.

**Figure 3.4 VR Reaction Time Module**


VR Reaction Time Module. Subjects were instructed to match the room's movements.

The Spatial Memory VR module assesses the subject's working memory by showing them a route to memorize. Impairments in memory have been observed in both the acute and chronic phase of concussion, and are common in neurodegenerative disorders.[7,57,74] The subjects were virtually placed inside a hallway and shown a randomly generated forward route to a door and then a return route back to their starting location. The return route is the forward route in reverse. The subjects were then instructed to repeat the forward and return route using the high resolution joystick. This joystick allowed them to freely navigate forward, backward, and side-to-side. Subjects were permitted 3 attempts to complete the tests. Following each failure, the subject was again shown the forward and return route. Performance was evaluated on a scale of 0 to 10. Zero represented a complete failure to navigate the forward and return route all three times. This score was calculated based upon task success(defined as ability to complete both routes), the number of trials necessary to complete the task(maximum of three attempts), and the time needed to complete the task(maximum of thirty seconds).

**Figure 3.5 VR Spatial Memory Module**




Spatial Memory VR module. A) The virtual hallway that subjects were instructed to navigate. B) An example of a randomized route that a subject would observe and navigate.

## Statistical Analysis

All statistical analyses were conducted using Minitab 16 statistical computing software. Correlations were calculated using Pearson's Product-Moment Correlation Coefficient. Between group and sub-group comparisons were computed using one-way Univariate Analysis of Variance(ANOVA). Post-hoc analysis into relationships were conducted using Tukey's Honest Significant Difference Test(HSD). Fischer's exact T-test was used to evaluate sub-group equality on demographic measures. All significance levels were set at $p<0.05$.

# Chapter 4: Results

## Retired NFL vs Control Groups

VR assessment of both control groups and the retired NFL players demonstrated consistent results across the various VR modules. The participants of both control groups performed significantly better($p<0.05$) than the retired NFL players on the balance, spatial memory, and reaction time modules. The controls also performed better on the total composite score. Summary of VR scores are available in **Tables 4.1-4.3.** For a graphical comparison of VR scores, see **Figures 4.1-4.4**

The retired NFL players performed the worst on the balance module, scoring an average of 3.15 out of 10. The college controls performed significantly better, averaging a 6.52.($F=16.32$, $p<0.001$) The second lowest VR average for the retired NFL players was the spatial memory module. The retired NFL players averaged a 3.85 out of 10. The college controls averaged a 7.88, which was again significantly better.($F=17.55$, $p<0.001$) The retired NFL players' next highest module of performance was the reaction time assessment. The NFL players averaged a 4.73 out of 10 and the college controls averaged a 6.44. This difference was also statistically significant.($F=4.24$, $p=0.045$) The comprehensive score was the NFL players' best score. It is based upon the subjects' performance on the three other modules and, therefore, the college controls again scored significantly better than the retired NFL players.($F=28.45$, $p<0.001$) The college controls averaged a 6.95 out of 10, while the retired NFL players scored a 4.30.

The Older Control Group significantly outperformed the NFL group on all VR measures. The Older Control Group averaged 8.44 on balance($F= 45.68$, $p<0.001$), 8.83 on spatial memory($F= 25.13$, $p<0.001$), 8.11 on reaction time($F= 21.61$, $p<0.001$), and 8.46 on

comprehensive(F= 83.79, p<0.001). The Older Control Group(average: 42.02 years) was statistically younger than then NFL group(average: 55.14 years).(T= -3.60, p=0.001) The Older Control group did not differ significantly in VR performance by gender.(T= -0.71, p=0.502)

The control groups were statistically different on 3 VR measures. The Older Control group was better on balance(F= 6.51, p=0.015), reaction time(F=4.70, p=0.037), and comprehensive score(F=10.98, p=0.002). There was no significant difference amongst control performance on spatial memory(F=1.68, p= 0.202).

**Table 4.1 College Control Group VR Assessment**

| Metric | Comprehensive | Spatial memory | Balance | Reaction time |
|---|---|---|---|---|
| Average | 6.95 | 7.88 | 6.52 | 6.44 |
| StDev | 1.73 | 2.79 | 2.83 | 2.96 |
| Median | 6.84 | 9.42 | 7.40 | 7.63 |
| Min | 4.12 | 1.26 | 1.76 | 0.01 |
| Max | 9.21 | 10.00 | 9.58 | 9.21 |
| Range | 5.09 | 8.74 | 7.82 | 9.20 |

The average, standard deviation (StDev), median, minimum(Min), maximum(Max)and range scores of the healthy control group. College career refers to collegiate training/playing experience in years.

**Table 4.2 Retired NFL Group VR Assessment**

| Metric | Spatial Memory | Balance | Reaction Time | Comprehensive |
|---|---|---|---|---|
| Average | 3.85 | 3.15 | 4.73 | 4.30 |
| StDev | 3.80 | 2.95 | 2.78 | 1.72 |
| median | 3.975 | 3.65 | 5.43 | 3.84 |
| Max | 9.54 | 7.52 | 8.71 | 7.39 |
| Min | 0 | 0 | 0 | 1.79 |
| Range | 9.54 | 7.52 | 8.71 | 5.6 |

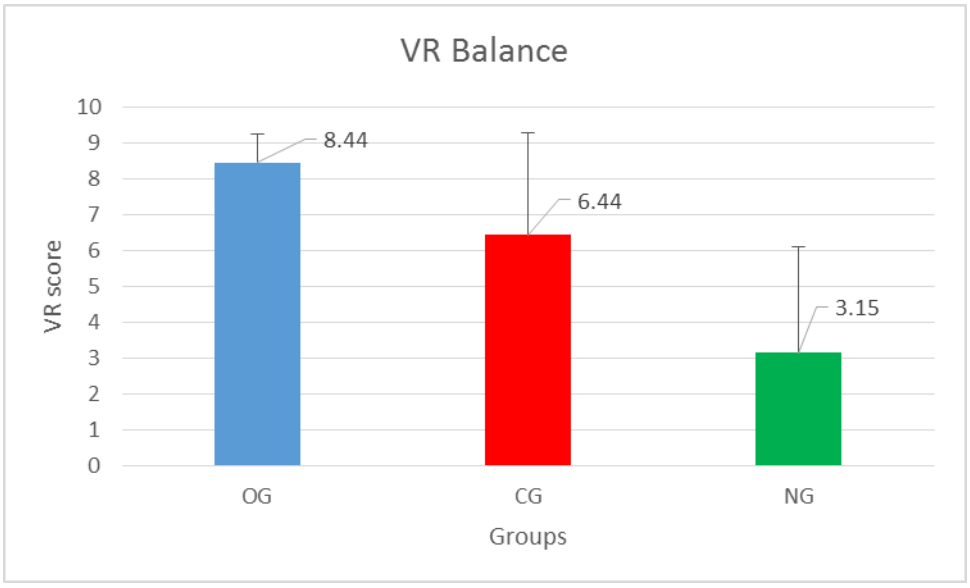
The average, standard deviation (StDev), median, minimum(Min), maximum(Max)and range scores of the retired NFL group.

**Table 4.3 Older Control Group VR Performance**

| Metric | Spatial Memory | Balance | Reaction Time | Comprehensive |
|---|---|---|---|---|
| Ave | 8.83 | 8.44 | 8.11 | 8.46 |
| StDev | 0.58 | 0.79 | 0.47 | 0.412 |
| Median | 9.11 | 8.57 | 8.13 | 8.55 |
| Min | 7.11 | 6.37 | 7.11 | 7.27 |
| Max | 9.32 | 9.18 | 9.23 | 8.97 |
| Range | 2.21 | 2.81 | 2.12 | 1.7 |

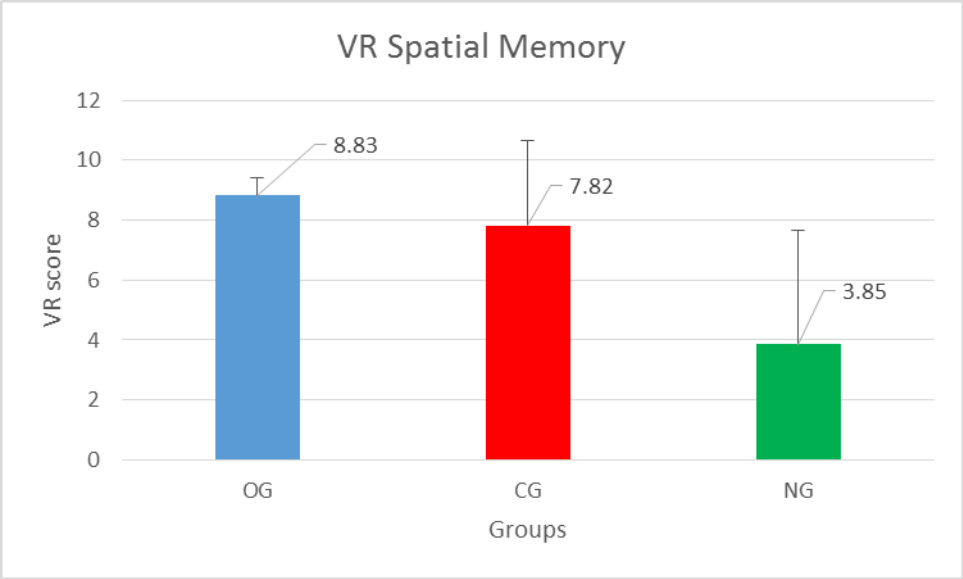
The average, standard deviation (StDev), median, minimum(Min), maximum(Max)and range scores of the Older Control group.

**Figure 4.1 VR Balance**



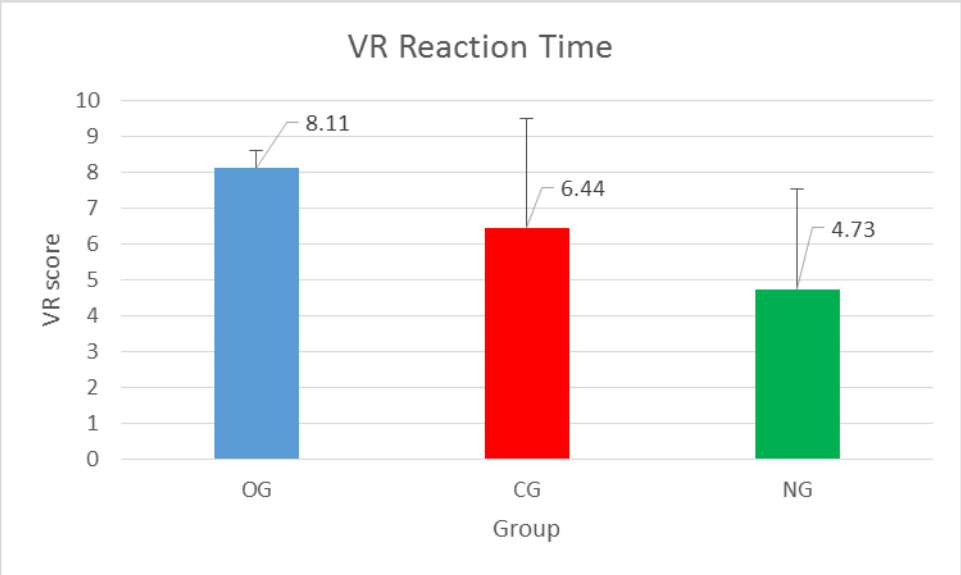

The value attached to each column correspond to the group's average. OG indicates Older Control group, CG indicates college control group, and NG indicates retired NFL group.

**Figure 4.2 VR Spatial Memory**



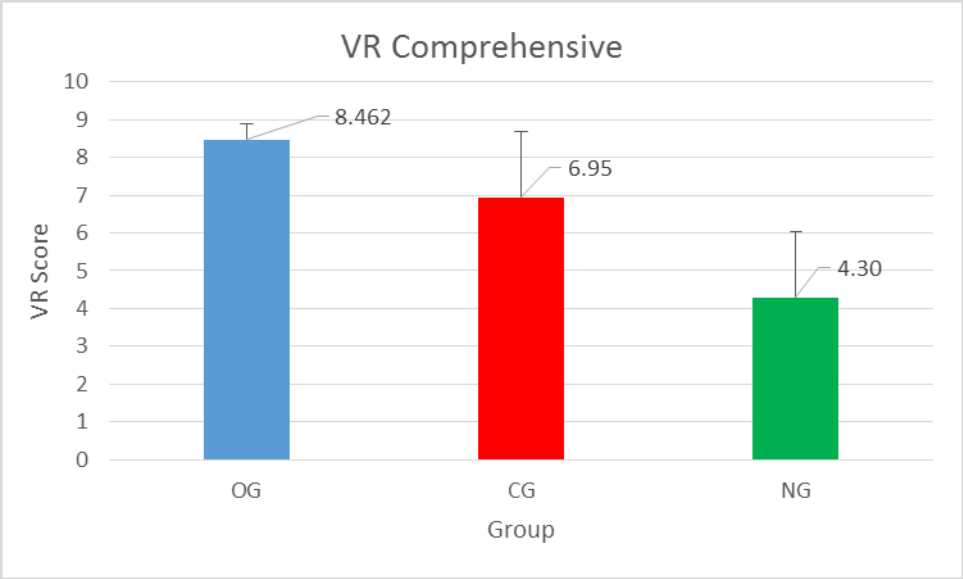

The value attached to each column correspond to the group's average. OG indicates Older Control group, CG indicates college control group, and NG indicates retired NFL group.

**Figure 4.3 VR Reaction Time**




The value attached to each column correspond to the group's average. OG indicates Older Control group, CG indicates college control group, and NG indicates retired NFL group.

**Figure 4.4 VR Comprehensive**




The value attached to each column correspond to the group's average. OG indicates Older Control group, CG indicates college control group, and NG indicates retired NFL group.

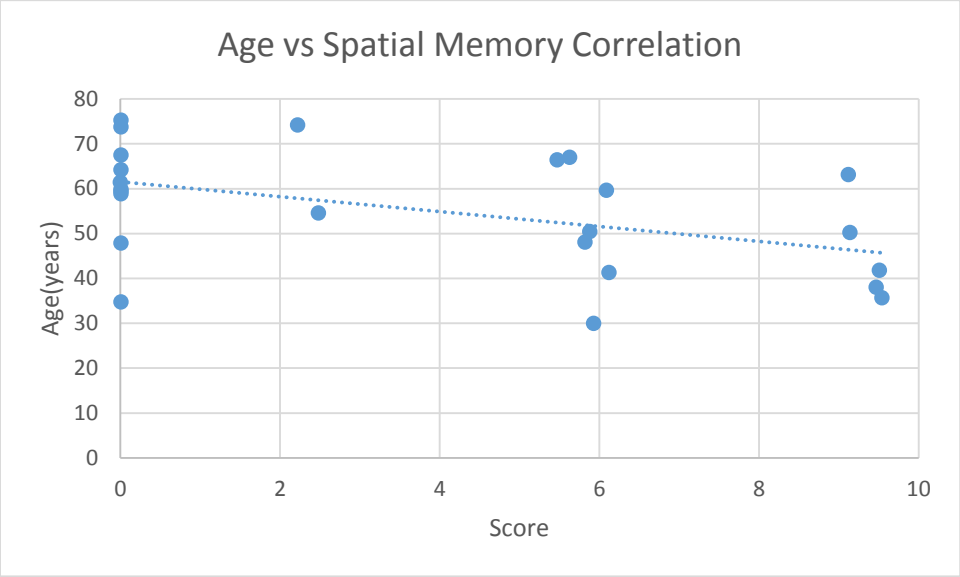
Correlational analysis of the retired NFL group revealed a few statistically significant relationships. For a summary of all correlational analysis see **Table 4.3** The retired NFL players demonstrated a moderate, significant inverse relationship between performance on the reaction time module and NFL career length.(R= -0.467; p=0.022) **Figure 4.6** This relationship was strengthened when career length was expanded to include all participation in professional football leagues.(R= -0.477; p=0.019) **Figure 5.7** Age demonstrated a moderate, significant inverse relationship with performance on spatial memory.(R= -0.524; p=0.009) **Figure 4.5** No other significant relationships were observed between the retired NFL players and the VR modules.

**Table 4.4 Group VR Correlations**

| Demographic | Balance | Spatial memory | Reaction time | Comprehensive |
|---|---|---|---|---|
| NFL career | 0.047; 0.826 | 0.203; 0.343 | **-0.467; 0.022** | -0.199; 0.351 |
| Pro Football | 0.106; 0.622 | 0.129; 0.548 | **-0.477; 0.019** | -0.211; 0.323 |
| NFL Age | -0.204; 0.339 | **-0.477; 0.018** | 0.032; 0.881 | -0.209; 0.163 |
| OG Age | 0.179; 0.523 | -0.352; 0.199 | 0.405; 0.134 | 0.108; 0.702 |
| OG Career | 0.379; 0.163 | -0.047; 0.869 | 0.156; 0.579 | 0.280; 0.311 |
| CG Career | 0.166; 0.437 | -0.055; 0.800 | 0.207; 0.332 | 0.182; 0.394 |

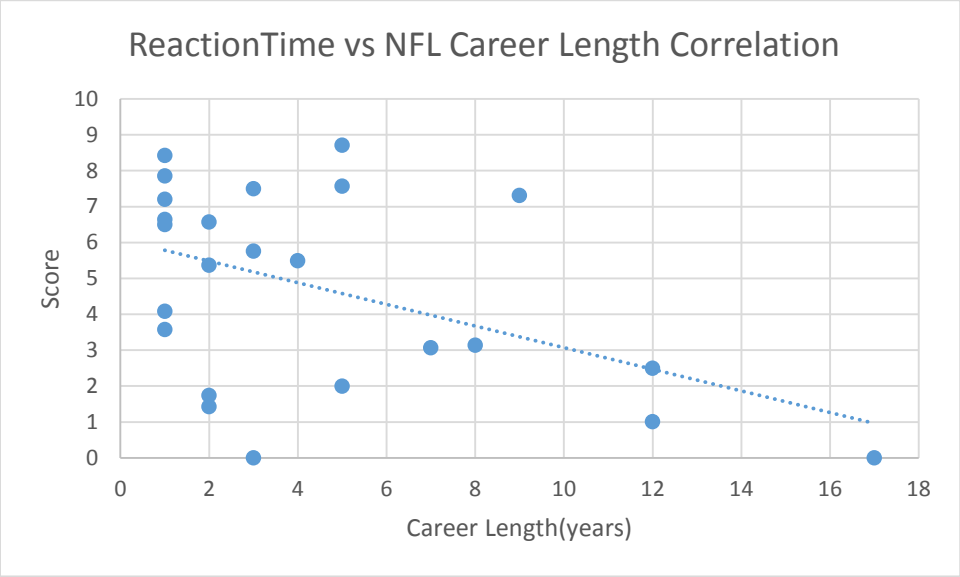
Correlational analysis of retired NFL players. Values are listed in R; p-value format. Significant correlations have been bolded. All demographic variables are measured in years. NFL career refers to NFL career length, Pro Football refers to total professional football career, NFL age refers to NFL group age, and OG age refers to Older Control group age. CG Career refers to the College Control group's career length.

**Figure 4.5 NFL Age vs Spatial Memory Correlation**



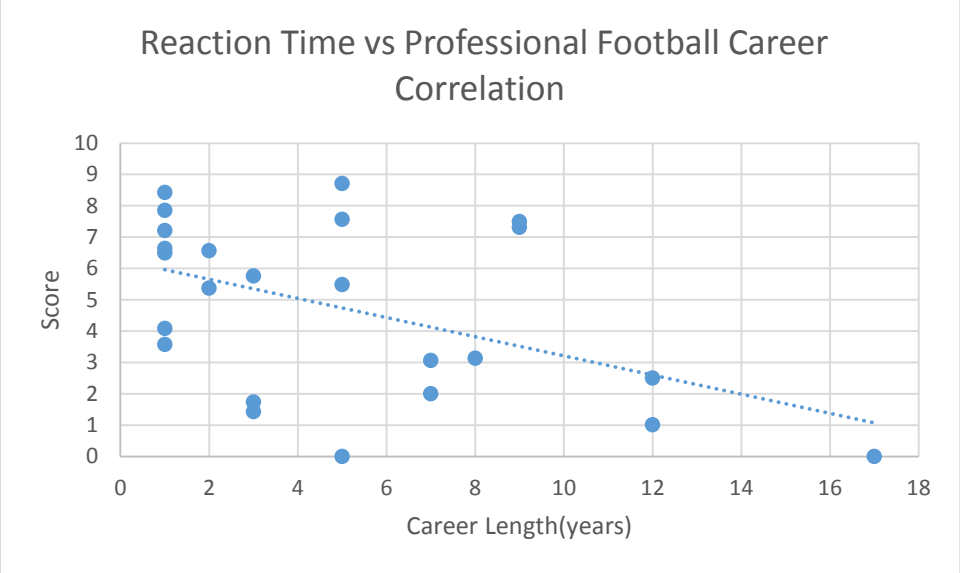

Correlation between retired NFL player age(in years) and spatial memory.

**Figure 4.6 Reaction Time vs NFL Career Length Correlation**




Correlation between NFL career length and Reaction Time

**Figure 4.7 Reaction Time vs Professional Football Career Correlation**




Correlation between reaction time and total professional football career length. Score is represented along the vertical axis and career length along the horizontal axis.

Correlational analysis of the control groups did not reveal any significant associations.

See **Table 4.4** for a summary. Neither career length nor age were significantly associated with

VR performance for the Older Control group. There were no significant correlations between the College Control group's career length and performance on the VR modules. Unfortunately, analysis of age-related relationships was excluded from this group due incomplete data.

## High Frequency and Low Frequency Results

The retired NFL and healthy control groups were broken into 4 sub-groups based upon their frequency of impact exposure, creating High Frequency NFL(HFN, n=13) and Low Frequency NFL(LFN, n=11), Low Frequency Control(LFC, n=11), and High Frequency Control(HFC, n=13) groups. The NFL groups were not statistically different in age(T=0.33, p=0.742), total professional career length(T=0.60, p=0.555), or NFL career length(T=-0.42, p=0.683) The High Frequency Control and Low Frequency Control groups were not statistically different in collegiate career length.(T= -0.69, p=0.499) See **Table 4.5** and **4.6** for a summary each group.

**Table 4.5 High Frequency Retired NFL Players Summary**

| Metric | Spatial Memory | Balance | Reaction-Time | Comprehensive | Age in Years | NFL career | Pro contact total |
|---|---|---|---|---|---|---|---|
| Ave | 5.06 | 2.13 | 4.48 | 4.38 | 54.30 | 4.15 | 4.54 |
| Med | 5.88 | 0.01 | 3.58 | 4.01 | 58.83 | 2 | 3 |
| StDev | 3.76 | 2.71 | 2.96 | 2.00 | 20.63 | 4.08 | 4.1 |

Ave indicates average. Med indicated median. StDev indicates standard deviation.

**Table 4.6 Low Frequency Retired NFL Players Summary**

| Metric | Spatial Memory | Balance | Reaction Time | Comprehensive | Age in Years | NFL career | Pro contact total |
|---|---|---|---|---|---|---|---|
| Ave | 2.43 | 4.36 | 4.36 | 4.36 | 56.13 | 4.91 | 5.64 |
| Med | 0.01 | 5.51 | 5.49 | 3.67 | 59.82 | 3 | 5 |
| StDev | 3.48 | 2.87 | 2.66 | 1.41 | 12.51 | 4.72 | 4.74 |

Ave indicates average. Med indicated median. StDev indicates standard deviation.

**Table 4.7 High Frequency Control Summary**

| Metric | Spatial Memory | Balance | Reaction Time | Comprehensive | CG Career |
|---|---|---|---|---|---|
| Ave | 7.58 | 5.86 | 6.33 | 6.59 | 3.00 |
| Med | 9.47 | 5.97 | 7.54 | 5.78 | 3.00 |
| StDev | 3.21 | 2.75 | 2.76 | 1.65 | 0.913 |

Ave indicates average. Med indicated median. StDev indicates standard deviation. CG Career indicates College Control group career length in years.

**Table 4.8 Low Frequency Control Summary**

| Metric | Spatial Memory | Balance | Reaction Time | Comprehensive | CG Career |
|---|---|---|---|---|---|
| Ave | 8.24 | 7.31 | 6.56 | 7.38 | 3.27 |
| Med | 9.40 | 8.91 | 7.86 | 8.22 | 4.00 |
| StDev | 2.28 | 2.84 | 3.31 | 1.79 | 1.01 |

Ave indicates average. Med indicated median. StDev indicates standard deviation. CG Career indicates College Control group career length in years.

For a summary of the statistical comparison of the frequency sub-groups, see **Table 4.9.** The High Frequency NFL group performed significantly worse than both the Low and High Frequency Control groups on balance, but was not statistically different from the Low Frequency NFL group. However, a noticeable trend towards significance was observed. The High Frequency NFL group scored an average of 2.13 out of 10 on the balance module, while the High and Low Control Frequency groups averaged 5.86 and 7.31, respectively. The Low Frequency NFL group average 4.36 out of 10. This difference between the NFL Frequency groups had a T-value of -1.95 and a p-value of 0.065. See **Figure 4.8** for graphical comparison.

The Low Frequency NFL group performed significantly worse than both of the Control Frequency groups on spatial memory(LFN average: 2.43, LFC: 8.24, HFC: 7.58), but was not significantly different from the High Frequency NFL group(average: 5.06). The High Frequency NFL group was not significantly different from the two Healthy Control Frequency groups. The

Low Frequency NFL group showed a slight trend towards significance(T=1.77, p-value= 0.091) when compared to the High Frequency NFL group. See **Figure 4.9** for a graphical comparison. The Control Frequency sub-groups did not differ on any VR modules.

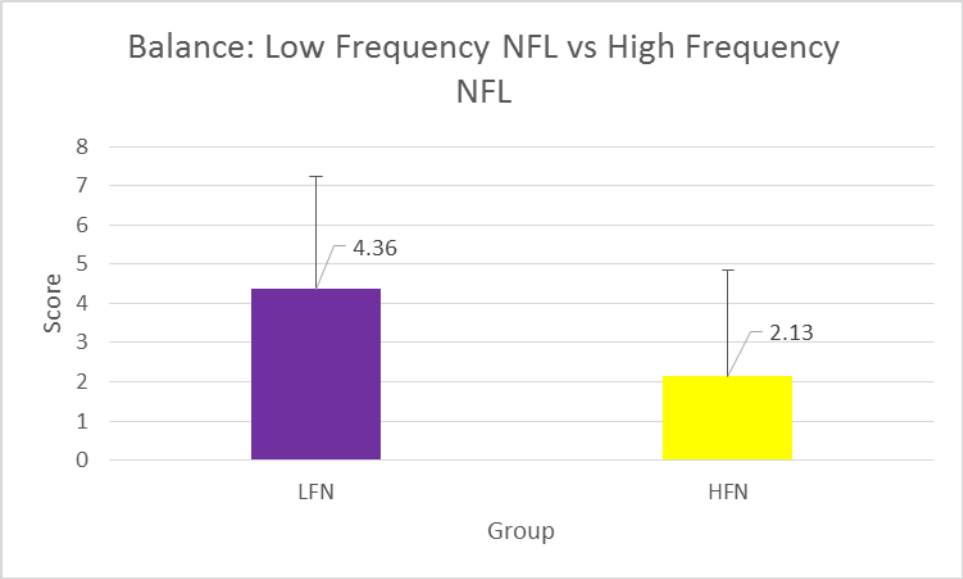
The four frequency sub-groups were not statistically different on the VR measure of Reaction Time(F=1.44, p-value=0.244). The HFN and LFN groups were significantly different from both of the Control Frequency groups but not each other.

**Table 4.9 Frequency Sub-Group VR Comparisons**

| VR Module | HFC | LFC | HFN | LFN | Significance Investigation |
|---|---|---|---|---|---|
| Spatial Memory | A; 7.58 | A; 8.24 | **A,B; 5.06** | **B; 2.68** | T=1.77, p=0.091 |
| Balance | A, 5.86 | A; 7.31 | **B; 2.13** | **A, B; 4.75** | T= -1.95, p=0.065 |
| Reaction Time | A; 6.33 | A; 6.56 | A; 4.48 | A; 4.95 | * |
| Comprehensive | A; 6.59 | A; 7.38 | B; 4.38 | B; 4.31 | * |

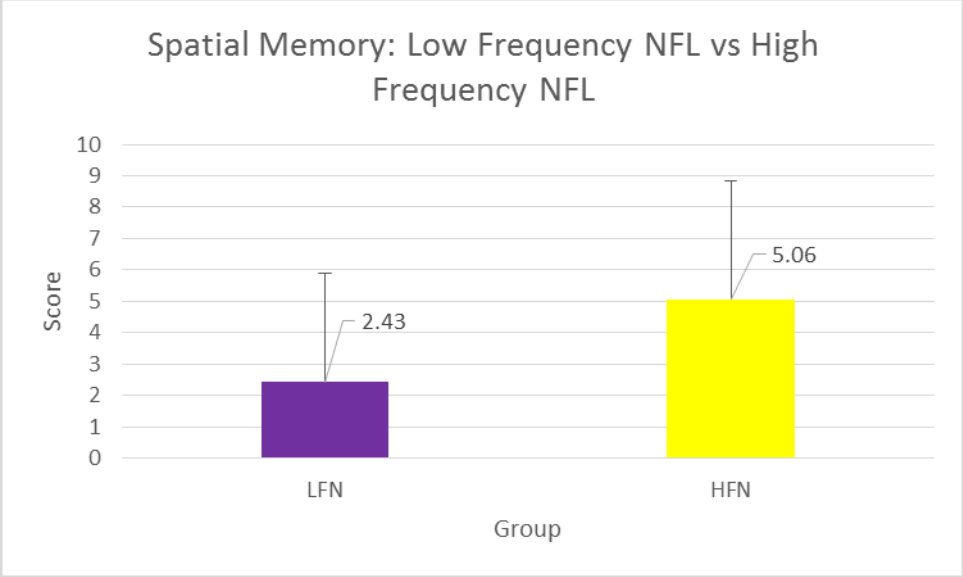
Groups that have the same letter are on a given VR module are not statistically different.($p>0.05$) Values are listed as significance letter, mean score. Bolded values were compared for significance trends. An asterisk indicates no investigation for significance trends. HFC=High Frequency Control group, LFC=Low Frequency Control group, HFN=High Frequency NFL group, LFN=Low Frequency NFL group

**Figure 4.8 VR Balance High Frequency NFL vs Low Frequency NFL**




The value attached to each column correspond to the group's average. LFN=Low Frequency NFL group, HFN=High Frequency NFL group.

**Figure 4.9 VR Spatial High Frequency NFL vs Low Frequency NFL**




The value attached to each column correspond to the group's average. LFN=Low Frequency NFL group, HFN=High Frequency NFL group.

# Chapter 5: Discussion

## Major Findings

The purpose of this thesis was to identify any long-term deficits in a sample of retired NFL players and identify potential risk factors for the accumulation of said deficits. As initially hypothesized, NFL players performed worse on VR measures than both control groups. The NFL players performed the worst on balance, then spatial memory, and the best on the reaction time module. Poorer reaction time was strongly associated with both NFL career length and total professional football career length. Spatial memory was inversely related to age in the NFL group. No significant correlations were found in either the Older Control group or the College Control group. Unexpectedly, the Older Control group outperformed the College Control group on VR measures of balance, reaction time, and comprehensive score. They were not different on the measure of spatial memory.

Sub-group analysis of the College Control group and the NFL group at the level of impact frequency yielded some important results and trends. The High Frequency NFL group had significantly poorer balance than both of the College Control Frequency groups but not the Low Frequency NFL group. However, a strong trend towards poorer performance was observed in the High Frequency NFL group when compared to the Low Frequency NFL group.($p=0.065$) A similar finding was observed when comparing the sub-groups' performance on spatial memory. The Low Frequency NFL sub-group performed significantly poorer than both of the College Control Frequency sub-groups but not the High Frequency NFL group; however, a moderate trend towards significantly poorer performance was observed.($p=0.091$) The College Control sub-groups had a significantly better comprehensive score than both of the NFL sub-groups but there was no difference within either the NFL or College Control group at the level of

impact frequency. Finally, reaction time was not significantly different amongst any impact frequency sub-group. Therefore, there reaction time did not differ by position type.

## Interpretation and External Support

The poorer performance of the NFL group on all VR measures indicates that as players continue their career at the professional level, they experience increased exposure to repetitive forces imparted to the head which cause deficits to develop. The generalized findings of this thesis are supported by a similar study conducted by Matser and colleagues[81] on professional soccer players. This study found poorer memory, planning, and visuoperceptual performance in professional soccer players when compared to healthy, non-contact controls. This study also found an inverse relationship between frequency of heading the ball and neuropsychological performance which is similar to the trends observed in this study's impact frequency sub-groups.[81]

Further support for this hypothesis of deficits due to increased professional career length is provided by biomechanical quantification of impact exposure in professional football players. At the college level players receive an average of 15.5 impacts per game[42] while NFL players receive 30-50 impacts per game.[87] Over the course of a single season, college players receive an average 800-1000 impacts,[45,48,36] and while the frequency of NFL player impact exposure is unknown, it is likely even higher. Considering the growing link between neural damage and concussive/subconcussive impacts alone,[13,15,38,42,43,46,47,59,60,63] increasing the number of seasons an athlete participates in will yield a large increase in the total number of impacts an individual experiences in their lifetime. This would indicate that the longer an individual's career, the more likely they are to receive impacts that will result in long-term and permanent deficits.

There is reason to believe that the deficits in spatial memory in the NFL players are due to increased concussive-type impact exposure of the Low Frequency NFL players. Players in the Low Frequency NFL sub-group are exposed to less frequent, but higher magnitude impacts.[49,117] Higher magnitude impacts are generally associated with a greater risk of concussion but large individual variation exists.[118,119] Additionally, many of the positions that comprised the Low Frequency sub-groups(Running backs, Kickers, Defensive backs) have been found to have the highest incidence of recurrent concussion in a 12 year study of the NFL.[69] Wide Receivers, also a member of the Low Frequency sub-group, have demonstrated an elevated incidence of recurrent concussions.[69] Finally, research indicates that skill position players(Quarter Backs, Running Backs, Wide Receivers) have a higher risk of concussions.[120] There is strong research evidence supporting a link between concussions and impairments in memory.[54,63,77-84]

Evidence that the spatial memory deficits are due to the Low Frequency NFL sub-group stems from sub-group comparisons. The Low Frequency NFL sub-group performed worse than the High Frequency Control and Low Frequency Control sub-group, but not the High Frequency NFL sub-group. However, the High Frequency NFL sub-group was not significantly different from the other two Control Frequency sub-groups. This indicates that the Low Frequency NFL group must have something driving this difference that the High Frequency NFL group does not. This difference is a combination of age and impact frequency/type. Career length can be ruled out as the two NFL frequency sub-groups were not different in career length. The Low Frequency NFL group is older than the Low Frequency Control group. The Low Frequency NFL group has likely experienced more concussive-type exposure than the High Frequency Control group. Together these difference indicate the Low Frequency NFL group is experiencing accelerated aging as result of concussion-induced depleted cognitive reserve. Cognitive reserve

is essentially the ability of the brain to allocate additional neural resources to offset cognitive impairments. Injured individuals with adequate cognitive reserve appear to be clinically normal but demonstrate recruitment of additional cognitive resources when analyzed with fMRI. Natural aging depletes cognitive reserve. Individuals with injuries that reduce cognitive resources, in addition to normal age-related depletion, demonstrate accelerated aging.[39] This is supported by findings of increased cortical recruitment in previously concussed individuals in both the subacute and chronic phase of concussion.[11-13,15,19,39,52]

Support for the theory of depleted cognitive reserve comes from NFL subjects' spatial memory being significantly correlated with age. If this relationship were part of normal aging we would expect to see a similar correlation amongst the Older Control group. However, no such association was present amongst these non-contact controls. While these groups differ both in age and gender these factors do not seem likely to explain this difference. Even though the Older Control group was younger than the NFL group, they are similar in age and one would still expect to see some correlation between age and spatial memory. Additionally, the difference in gender can be ruled out as a factor, as the males and females of this group did not perform significantly different. This indicates that the lack of impact exposure is a key difference between the Older Control group and the NFL group. This suggests that this association between age and poorer spatial memory is likely due impact exposure and subsequent accelerated aging.

Additional support stems from a comparison of the Low Frequency NFL and the High Frequency NFL group on spatial memory The Low Frequency NFL group performed poorer than the High Frequency NFL group and this difference demonstrated a trend towards significance.($p=0.091$). These groups were not significantly different in age or career length, therefore, this trend is likely due to the differences in impact exposure. This trend, the absence

of any significant correlation amongst the older non-contact group, the lack of significant difference between the High Frequency NFL group and both of the Control Frequency sub-groups, and the significantly poorer performance of the Low Frequency NFL group compared to both Control Frequency sub-groups provide strong evidence that cognitive reserve has been depleted and that these subjects are experiencing accelerated aging. It is entirely possible that the Low Frequency Control group has also experienced reduced cognitive reserve but it has not yet been depleted by aging sufficiently to demonstrate significant differences.[36]

The NFL group's poorer balance is likely due to the poorer performance of the High Frequency NFL sub-group. These individuals are exposed to lower magnitude, but more frequent impacts as a result of their position.[49,117] These lower magnitude impacts are thought to represent subconcussive impacts. There is growing evidence that repetitive subconcussive impacts result in physiological changes, long-term deficits, and may contribute to neurodegenerative diseases.[36-38,40-44,81]

The High Frequency NFL sub-group performed significantly worse than both the Low Frequency Control and High Frequency Control sub-groups on balance. The Low Frequency NFL group was not significantly different from either Control Frequency sub-group. Furthermore, the Low Frequency NFL sub-group demonstrated a trend towards better performance when compared to the High Frequency NFL sub-group.($p=0.065$) The High Frequency NFL sub-group differs from the High Frequency Control sub-group by career length and the Low Frequency Control sub-group by impact exposure. Therefore, the High Frequency NFL sub-group has likely had significantly greater subconcussive exposure resulting from position type and career length. The High Frequency NFL group was not significantly different from the Low Frequency NFL by career length and age, therefore, the trend towards poorer

balance is likely due to the differences in impact exposure. Further evidence that this difference is not the result of increased age is demonstrated by the lack of a significant correlation between balance and age for any group. These differences in impact exposure seem to have resulted from repetitive subconcussive injuries that accumulated over the High Frequency NFL sub-group's professional career. These accumulated injuries likely lead to the observed long-term decrements in balance.

There is evidence that poorer neuropsychological performance is associated with increased head impact exposure[40.44,37]. Diffusive Tensor Imaging has found greater white matter alterations in players with a higher incidence of subconcussive exposure.[41,43,47] There is also evidence that indicates greater blood brain barrier disruption in the football players that experience the highest incidence of subconcussive impacts.[41] The biomechanical research shows that the positions of the High Frequency sub-groups experience significantly more subconcussive blows than positions of the Low Frequency sub-groups,[49,117] therefore, it seems likely that these trends and risk factors apply to the members of the High Frequency NFL sub-group as well.

Additional support of a link between decreased balance and subconcussive exposure was demonstrated in a study that examined football players for deficits in the absence of a diagnosable concussion. This study found that, of all positions, Linebackers exhibited the poorest balance.[44] Further support was demonstrated in a DTI study of subconcussive exposure. In this study, greater head impact exposure was associated with increased measures of blood-brain barrier disruption and poorer balance.[41] When all this evidence is taken into consideration together, there is a strong indication that the NFL players' diminished balance is due to the increased subconcussive exposure of the High Frequency NFL sub-group. It is possible that the High Frequency Control group has also accrued damage as a result of subconcussive exposure,

but not at a level significant enough to result in observable clinical deficits.

The difference in reaction time between the NFL group and both control groups seem to be the result of generalized professional impact exposure. Evidence comes from the significant, moderate association between career length and poorer reaction time and the lack of any significant difference amongst the impact frequency sub-groups. Further evidence of this relationship was demonstrated when this association was expanded beyond the NFL to include all professional football career participation. In doing so, this relationship became marginally stronger and more significant. There is a multitude of research that supports slowed reaction time following mTBI in the acute to chronic phase of injury.[21,22,37,83,84,114-116,121] There is also some evidence that reaction time is also reduced following subconcussive injuries as well.[40,44] A study of 46 football players found the 35.7% of the players exhibited deficits in reaction time in the absence of a clinically diagnosed concussion[44], and another study found that poorer reaction time was significantly associated with measures of head impact exposure.[40] This seems to indicate that the reduced reaction time of the NFL players is likely due to subconcussive impact, concussive impacts, and a combination of the effects of both.

The comprehensive score is an average of an individual's performance on reaction time, spatial memory, and balance. Considering that the NFL group was significantly worse on all 3 of these measures, it is logical that the comprehensive score would be lower as well. The comprehensive score is, therefore, a redundant measure; however, it was included in this study to represent a summary of global functioning of the subjects. In other words, significantly lower comprehensive scores suggest overall poorer performance across multiple cognitive and physical domains.

The poorer performance of the College Control group on measures of balance, reaction

time, and comprehensive score when compared to the Older Control group was unexpected. It was also expected that the College Control group would be at least the same as the Older non-contact controls, or even better as they are younger. This could indicate that deficits are already present at the collegiate level. There is evidence within the literature that deficits and changes exist amongst college contact athletes as a result of both concussive and subconcussive injuries;[36,37,40,41,43,44,47,52] however, this interpretation must be considered cautiously within this study as these two groups differed greatly by age and size. The groups also differed by gender but this difference has been ruled out as the performance of the Older Control group was not significantly different by gender. If we continue to carefully speculate under this hypothesis, it is important to note that the no differences were observed amongst the High and Low Frequency Control sub-groups for any VR measure. Therefore, if any differences do exist as a result of subconcussive and concussive exposure at the college level, they are not yet significant enough to be seen. This would indicate that the differences amongst the NFL frequency sub-groups is the both the result of increased exposure and time, suggesting a delay between initial damage and the onset of permanent deficits. The time frame for the onset of the NFL player's deficit is uncertain and much research is still needed to unravel the timing between concussive/subconcussive-induced injury and permanent deficits.

Of particular interest is that the College Control group was not significantly different from the Older Control group on spatial memory. This, when considered with the lack of a difference amongst Control Frequency sub-groups, adds strength to the theory that the decreased NFL spatial memory performance is the result of accelerated aging. In other words, cognitive reserve has not been sufficiently depleted via impacts in the Older Control group or through aging in the College Control group to result in spatial memory deficits. To sufficiently examine

any deficits at the collegiate level, future studies should include non-contact, age matched athletes as healthy controls.

## Translational Significance

The findings demonstrated in his study carry some very significant implications. This research indicates that professional players' career length and position put them at risk for the development of negative long-term outcomes. This affects a large group of individuals as the NFL is comprised of 32 teams with 53 players per team. That means that each year 1,696 players are at risk for increased concussive and subconcussive exposure that may result in permanent damage. To combat such risks, players that have longer careers should be both informed of the potential risks and screened more frequently for the onset of any deficits. High frequency impact players, those exposed to subconcussive blows, should be informed of the increased risk of and observed for the development of balance deficits. Players that are more likely to experience concussive impacts, those in the low frequency impact positions, should be aware of the risk of spatial memory deficits and screened as well. Generally speaking it seems logical to suggest baseline evaluation upon entrance into the NFL and to periodically test players as they progress through their professional career with increased evaluation frequency as their career lengthens. This would allow both the NFL and players to identify any potential damage earlier, and make informed decisions. By informing players of the potential for deficits as well as screening for their onset, players are given the opportunity to seek preventative measures and/or treatment that may offset or delay later-life impairment.

Additionally, players with longer careers may need to consider playing less frequently. Considering players receive 30-50 impacts per game,[87] more veteran players may be able to

lengthen their career and reduce their risk of deficits by playing in fewer games. In line with this logic, the NFL may also want to consider reducing the total number of games per season or total season length to globally reduce concussive and subconcussive exposure.

Finally, if the analysis between the College Control group and the Older Control group is valid, then players are at risk for damage at the collegiate level. Therefore, players at the collegiate level need to be screened frequently as well. Again, a model of baseline assessment upon entrance into college football, coupled with frequent monitoring throughout their career, is highly recommended. Furthermore, if damage is indeed occurring at the collegiate level, players would likely benefit from reduced risk of impact exposure. It may be necessary to reduce the frequency in which players participate in games or practice. College football teams may also want to consider reducing the total number of games per season or season length. Additional benefits may be accrued by reducing the frequency of contact play within practices.

## Limitations

Unfortunately, this study has some rather large limitations. First, the sample size of the groups within this study were rather small and it is difficult to know if these groups are truly representative of their populations. Second, all groups lacked a history of their subjects' concussion exposure, drug and alcohol use, and clinical evaluation for neurodegenerative disorders/PCS. Third, the Older Control group was younger than the NFL group and contained a mixed gender. While statistically this group did not differ in performance by gender, it is difficult to be completely certain that there was no effect. This group was also smaller than both the NFL and College Control group. Additionally, this group was a convenience sample and, therefore, it is uncertain how representative this group is of older subject VR performance. Fifth,

the NFL group had orthopedic deterioration and a few individuals had difficulty standing or made use of a cane. It is unknown how much this affects VR measures of reaction time and balance. Sixth, there was incomplete data for analysis of the effects of age within the College Control group. Finally, this study lacked any means of imaging or establishing a direct neural source for the deficits demonstrated, therefore, items such as motivation and malingering cannot be completely ruled out.

## Future Studies

Given the significant trends between the development of deficits and career length, and the risk for the onset of deficits by position, further analysis into these relationships is warranted. Future studies would be strengthened by the inclusion of larger groups, imaging methods, subject history, and frequent follow up of both college and NFL football players to establish a time course for the onset of these deficits. Additionally, future studies should include players at the high school level to help strengthen evidence of risk factors and uncover the time-frame for the onset of these deficits. Future studies should be certain to include appropriate age and education matched, healthy controls.

## Conclusion

In conclusion, NFL players had significant deficits compared to position matched college controls and similarly aged non-contact controls. Player career length and position type are risk factors for the onset of balance, spatial memory, and reaction time deficits. Player career length is associated with increasing risk of reaction time deficits. Players exposed to less frequent, but higher magnitude impacts(impacts more likely to induce concussion) are more likely to develop

spatial memory deficits as a result of reduced cognitive reserve and accelerated aging. Players that are exposed to more frequent but lower magnitude subconcussive impacts, are more likely to develop balance deficits. There is also evidence that suggests that players at the collegiate level may already have accrued damage and experience reduced reaction time and balance. Limited evidence also suggests that collegiate players may have reduced cognitive reserve as well. Given such results, this author suggests increased screening for deficits and reduced exposure to subconcussive and concussive-type impacts. Further research into these relationships is strongly recommended.

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