DOES GENOTYPE MODERATE THE EFFECTS OF CONCUSSION HISTORY AND CONTACT EXPOSURE ON WORKING MEMORY PROCESSES IN RETIRED FOOTBALL PLAYERS?

Eleanna Martha Lyman Varangis

A thesis submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Arts in the Department of Psychology.

Chapel Hill
2015

Approved by:

Kelly S. Giovanello

Joseph B. Hopfinger

Kevin M. Guskiewicz

ABSTRACT

Eleanna Martha Lyman Varangis: Does Genotype Moderate the Effects of Concussion History and Contact Exposure on Working Memory Processes in Retired Football Players?
(Under the direction of Kelly Giovanello)

Recent studies have linked concussions earlier in life and later memory problems, but little is known about neurocognitive long-term effects of concussion, and whether a genetic risk factor for Alzheimer's Disease, Apolipoprotein-ε4 (APOE-ε4), might play a role in these long-term effects. In the present study, participants between 50-65 (N=63) were grouped based on concussion history (0-1 or 3+), football exposure (college or college+NFL), and APOE-ε4 status (APOE-ε4+ or APOE-ε4-). Participants completed two batteries of neurocognitive tasks, and performed an fMRI-adapted N-back task. Neurocognitive results revealed selective deficits in memory across all sub-groups, but no differences between the groups. Functional connectivity results suggested that APOE-ε4 genotype interacted with concussion and exposure history in accounting for differences in connectivity within a fronto-parietal working memory network. Thus, while there are no behavioral differences between groups, functional connectivity may be altered by the interaction between concussion history, football exposure, and APOE-ε4 status.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ALS	Amyotrophic Lateral Sclerosis
ANOVA	Analysis of Variance
APOE	Apoliprotein-E
BDI	Beck Depression Inventory
BOLD	Blood Oxygen Level Dependent
CDR	Clinical Dementia Rating
CNSVS	CNS Vital Signs
COWAT	Controlled Oral Word Association Test
CTE	Chronic Traumatic Encephalopathy
fMRI	Functional Magnetic Resonance Imaging
LDLPFC	Left Dorsolateral Prefrontal Cortex
LIPL	Left Inferior Parietal Lobule
LIPS	Left Intraparietal Sulcus
MANOVA	Multivariate Analysis of Variance
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
mTBI	Milt Traumatic Brain Injury
NFL	National Football League
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RDLPFC	Right Dorsolateral Prefrontal Cortex
RIPL	Right Inferior Parietal Lobule
RIPS	Right Intraparietal Sulcus
ROI	Region of Interest

WAIS	Wechsler Adult Intelligence Scale
WTAR	Wechsler Test of Adult Reading

CHAPTER 1: INTRODUCTION

The long-term effects of sport-related concussion have become increasingly pertinent as former football players age and experience a growing number of cognitive concerns. Rates of concussions in high school through professional football remain high (CDC, 2007; Gessel, Fields, Collins, Dick, & Comstock, 2007; Guskiewicz et al., 2003; McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004; Prevention, 2011), and research concerning the mechanisms by which concussive injury results in long-lasting psychological (Gavett, Stern, & McKee, 2011; Guskiewicz et al., 2007; Hart et al., 2013), neurological (Gavett et al., 2011; Hart et al., 2013; McKee et al., 2009; Omalu et al., 2005; Tremblay et al., 2013), and cognitive (De Beaumont et al., 2009; Ford, Giovanello, & Guskiewicz, 2013; Guskiewicz et al., 2005; Hart et al., 2013) effects may provide valuable insight into the potential for mitigation of these long-term consequences.

While many psychological and neurological later-life effects of concussion are have been noted, one of the most frequently reported long-term effects of repeated concussion is changes in memory (Baugh et al., 2012; De Beaumont et al., 2009; Guskiewicz et al., 2005; McKee et al., 2009; Omalu et al., 2005). Since such memory changes are also common in clinical populations with neurodegenerative disorders, the focus of research now aims to determine whether individuals who sustained multiple concussions earlier in life have sub-clinical memory impairments, or if they may be suffering from some sort of neurodegenerative disorder as a result of this earlier repetitive neural trauma. As such, recent research efforts aim to bridge four critical areas to identify the unique effect of concussions on long-term memory outcomes: (1) general

patterns of memory impairment in aging; (2) memory impairment in neurodegenerative disorder (e.g., early Alzheimer's disease); (3) long-term effects of concussions on memory; and (4) the relationship between concussion and the development of neurodegenerative disorders.

Memory in Aging

It is a commonly held belief that, in general, memory impairments tend to increase with advancing age (F. Craik & Jennings, 1992). More specifically, older adults tend to show impairments in episodic memory (i.e., memory for day to day events) and working memory (i.e., short-term store and rehearsal processes) relative to younger adults. Several theories of aging have attempted to account for the cognitive mechanisms underlying these impairments. Such theories include: (1) Craik's theory of reduction in attentional resources (1982), and (2) Hasher and Zacks' theory of a failure of inhibitory control (1988). Each theory is discussed in detail below as a theory of aging that might be used to explain some accelerated patterns of cognitive aging in concussion.

Attentional resource reduction. One prominent theory regarding age-related memory changes is the Attentional Resource Reduction theory (F. I. M. Craik & Byrd, 1982). This theory suggests that limited cognitive resources in aging stem from an underlying reduction in attentional resources. Craik and Byrd posit that as attentional resources become scarce, mental energy is reduced, resulting in age-related memory impairments on more "controlled" tasks, yet leaving "automatic" task performance relatively preserved (Anderson, Craik, & Naveh-Benjamin, 1998; Castel & Craik, 2003). Thus, in older adults, performance may be spared on tasks that tap relatively automatic processing resources (i.e., language-based working memory tasks), but may exhibit poorer performance on tasks that tap into more controlled processing resources (i.e., more difficult or abstract working memory tasks).

One way in which the proponents of this theory test it is through tests that divide or stress attentional resources in younger adults to see whether younger adults in a divided attention condition show similar patterns of performance to older adults in a full attention condition. For instance, one of the original studies on the effects of this theory of reduced attentional resources in aging on memory performance looked at encoding of contextually-rich information in old and young adults (Rabinowitz, Craik, & Ackerman, 1982). The authors suggested that since older adults showed spared performance in general knowledge about the studied items, but impaired context-specific knowledge about the items, that aging was reducing the availability of controlled processing resources to support more elaborate, semantic encoding of novel scenes or items. In order to test whether this reduction in attentional resources in aging was acting via a similar mechanism as divided attention in young adults, the authors showed that by dividing attention during the encoding task in young adults, they found a similar pattern of impairment on the retrieval tasks as older adults who had no divided attention manipulation. Thus, it seems as if this reduction in attentional resources in aging is of a similar magnitude as dividing attention in a younger population.

In a more recent study on this effect, researchers examined memory encoding in both younger (full and divided attention conditions) and older adults (full attention condition only) during study of unrelated word pairs (Castel & Craik, 2003). The authors found that both older adults in the full attention condition and young adults in the divided attention condition performed significantly worse on the task that young adults in the full attention condition, and that this deficit was most pronounced in both groups in their associative memory performance. However, the authors found an even larger deficit in older adults in associative recall than that in young adults in the divided attention condition; while older adults generally perform similarly to

younger adults in the divided attention condition, their performance on associative recall is even worse. Thus, the theory of an attentional resources deficit in aging seems to be a consistent finding that predicts a general reduction in available resources to perform a given task, resulting in impaired performance on tasks requiring more controlled or elaborate processing (i.e., associative recall tasks, executive control tasks).

Failure of inhibitory control. A later theory that also attempts to explain cognitive patterns in aging that are immediately relevant to working memory performance is the Failure of Inhibitory Control hypothesis (Hasher & Zacks, 1988). This theory suggests that older adults' cognitive impairment is due to a general reduction in ability to inhibit irrelevant information. As such, in cognitive tests that require refreshing or updating of information (i.e., working memory), older adults have difficulty inhibiting a previously relevant but now irrelevant stimulus. By not being able to "forget" or inhibit this now irrelevant information, older adults significantly reduce the capacity of their working memory systems, making cognitive tasks that involve a high degree of working memory load more difficult for them to perform.

One study that directly tested this failure of inhibitory control theory of aging looked at responses to previous distractor items in the context of negative priming (suppression or slowing of response to memory items that were previously distractor items) in both older and younger adults (Hasher, Stoltzfus, Zacks, & Rypma, 1991). The authors found that while younger adults were slowed in later responses to previous distractor items (the classic "negative priming effect"), older adults showed no such differences in responses to previously relevant or distractor items. These results are taken as support for a failure of inhibitory control in that older adults never showed inhibition to these previous distractor items, suggesting that they did not show this tendency to inhibit or slow responses to previously irrelevant material. Similarly, in another

study targeting effects of aging on inhibitory control, researchers found that older adults showed difficulty inhibiting retrieval of words generated earlier by participants, but known to not be target words (Hartman & Hasher, 1991). Thus, independent of the mode of measurement of inhibition, older adults tend to show reductions in the ability or propensity to inhibit irrelevant information.

While these theories predict somewhat differing patterns of cognitive impairment in aging, and differential mechanisms behind such impairments, they do not necessarily extend their hypotheses into predictions about neural activity. Though cognitive theories on their own are important in conceptualizing mechanisms behind impairments in aging, functional neural theories are also important in distinguishing underlying functional network differences that arise in aging that may be associated with these cognitive impairments.

The Brain in Aging

Although the exact source of these behavioral deficits is disputed, differences in functional neural activation patterns between younger and older adults provide some insight into the age-related differences in task performance. While several theories have been proposed to explain these functional neural differences, two of the most prominent standing theories are the dedifferentiation hypothesis (Li & Lindenberger, 1999) and the HAROLD model (Cabeza, 2002). While both models predict differences in functional activation patterns between younger and older adults, they predict different hemispheric patterns underlying these differences.

Dedifferentiation hypothesis. The dedifferentiation hypothesis (Li & Lindenberger, 1999) asserts that while older adults "over-recruit" neural regions relative to younger adults, such recruitment reflects a difficulty in efficiently recruiting task-relevant regions. Thus, older adults may show reductions in the typical asymmetrical pattern of recruitment during a memory task,

but this may reflect the fact that they are recruiting more extraneous regions to perform the task that younger adults would not recruit. Proponents of this view cite the fact that cognitive tests tend to correlate more with each other with age (Babcock, Laguna, & Roesch, 1997; Baltes & Lindenberger, 1997) which is indicative of the fact that while performing each task, older adults are recruiting a similar degree of task-irrelevant regions to complete the task. Thus, similar decrements should occur across all cognitive tasks since recruitment of task-irrelevant neural regions during a memory task results in decrements in memory performance; recruitment of task-irrelevant neural regions during an attention task results in decrements in attention; thus, memory and attention performance tend to follow similar trends, and thus are likely to correlate with each other.

HAROLD model. In contrast, the Hemispheric Asymmetry Reduction in Old Adults (HAROLD) Model (Cabeza, 2002) suggests that the reduction in the traditional asymmetrical recruitment pattern in aging represents older adults increasingly recruiting more frontal and bilateral regions in a compensatory manner (Cabeza, Anderson, Locantore, & McIntosh, 2002; Cabeza et al., 2004). Specifically, Cabeza et al. (2002) showed that these recruitment patterns are associated with successful performance of the task, as high-performing older adults tend to show this hemispheric asymmetry reduction during the task, while low-performing older adults tend to show similar patterns of hemispheric asymmetry to younger adults. Since successful task performance seems to be associated with this reduction in hemispheric asymmetry, it is suggested that this "over-recruitment" of bilateral and frontal regions might be reflective of a compensatory pattern of activation underlying task success. The authors propose this model in opposition to the dedifferentiation hypothesis, suggesting that rather than the over-recruitment of task-irrelevant regions suggesting an inability to recruit task-relevant regions, the specific pattern

of over-recruitment implied in the HAROLD model suggests a compensatory recruitment of extra neural regions to successfully complete the task (to a similar level of success as younger adults). Thus, instead of resulting in an overall memory deficit, such over-recruitment might mediate task success in older adults.

Theories of reserve. One set of theories that somewhat bridges the gap between cognitive and functional neural theories of impairment in aging are the reserve theories. These theories are typically thought of as falling into two main categories: neural or brain reserve (passive) theories, and cognitive reserve (active) theories. Brain reserve theories (or "neuronal reserve theories") couch impairments in aging as related directly to neural damage that an individual sustains either through natural cell atrophy in aging, or through neural trauma (i.e., stroke), and suggest that measures of brain volume or synaptic integrity are indicative of level of impairment in aging (Katzman, 1993; Mortimer, Schuman, & French, 1981). A related theory posited by Satz (1993), the Brain Reserve Capacity theory, directly ties these individual differences in brain size and number of synapses to functional impairments. Satz (1993) suggests that there is some theoretical threshold that exists, at which point impairments will begin to occur. For instance, a certain degree of loss of brain volume and loss of synapses would have to reach a certain threshold in order for functional changes to occur. These types of passive models completely implicate neural health as indicators of risk for impairment in aging, and are indicative of some degree of inevitability in cognitive decline.

More recent theories, however, have focused on active conceptualizations of this degree of "reserve" by incorporating non-neural sources of influence on reserve. As such, Stern (2002) proposed a type of "cognitive" reserve to account for the individual differences in cognitive impairment at similar levels of neural healthy/atrophy. In his theory of cognitive reserve, Stern

suggests that individual factors such as education level, exercise frequency, sociability, and cognitive engagement over the life span might account for some of the variability in cognitive response to neural damage in aging. Thus, individuals with a greater degree of this cognitive reserve (i.e., well-educated individuals who exercise regularly, interact with members of their community, and read frequently), might be somewhat insulated against impairment resulting from neural damage, and thus might have somewhat of a higher threshold for impairment than individuals with lower cognitive reserve. This theory, though not necessarily making direct predictions about cognitive domains that might be impaired in aging, is a nice bridge for some neural theories of functional impairment, and how they might interact with more cognitive aspects of impairment. However, while these cognitive and neural theoretical models are informative in examining memory performance in healthy older adults, their extension into clinical populations may prove informative in characterizing neural recruitment patterns during impaired or inefficient memory task performance.

Memory in Neurodegenerative Disease

As a hallmark disorder of memory, Alzheimer's Disease (AD) has long been associated with a spectrum of memorial impairments including, but not limited to, impairments in semantic memory (Hodges, Salmon, & Butters, 1990, 1992), episodic memory (Greene, Hodges, & Baddeley, 1995; Hodges et al., 1990; Perry & Hodges, 1996), and working memory (A. D. Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Greene et al., 1995; R. G. Morris & Baddeley, 1988). While the disorder is known to be a progressive neurodegenerative disorder, research is increasingly focusing on the precursor to AD, Mild Cognitive Impairment (MCI). MCI is characterized as a disorder entirely dissociable from AD in which the patient reports generally normal cognitive and daily-life functioning but with a disproportionate deficit in

memory performance (Petersen et al., 1999). While able to be identified and diagnosed entirely distinctly from AD, MCI still shows a high conversion rate to AD based on genetic (Mosconi et al., 2004), neurological (Misra, Fan, & Davatzikos, 2009; Okello et al., 2009; Risacher et al., 2009), and cognitive risk-factors (Wagner et al., 2012). In fact, more recently, this diagnosis has been updated to reflect its causal relationship with AD, such that it is now conceptualized as MCI-AD, or MCI due to AD (Albert et al., 2011). As such, some of the classic AD-like genetic components (presence of apoliprotein-E ε4 allele), neuropathological features (such as hippocampal volume decreases and presence of amyloid-beta and tau deposits), and memory impairments (such as associative memory) also indicate risk for conversion from MCI to AD.

A crucial feature of AD is its genetic link. Though AD may not be perfectly heritable, it does tend to co-occur to a great degree in monozygotic (67% concordance) as compared to dizygotic (22% concordance) twins, suggesting that there is a substantial role that genetics plays in the development of the disease (Gatz et al., 1997). As such, researchers have identified a genotype associated with an increased risk for the development of AD: specifically the type 4 allele of APOE (Strittmatter et al., 1993). By looking at this allele within a sample of AD patients, researchers found that it is associated with a late-onset, familial variant of AD and that it was significantly more prevalent among an AD population than a healthy population. Though this allele still does not perfectly predict development of AD, it does suggest an increased risk for development of the disease and can therefore be conceptualized as a biomarker for AD risk, especially in older populations within the age range of 65-75 years old (Chang et al., 2013).

APOE status is directly linked to risk for development of AD in its role in the propensity towards metabolism and deposition of tau (Leoni, Solomon, & Kivipelto, 2010), a neuropathological hallmark of the progression from MCI to AD (Wagner et al., 2012), that

shows an affinity for Medial Temporal Lobe (MTL) structures (such as the hippocampus). Leoni et al. (2010) found that among a group of participants classified as "cognitively-impaired" (MCI and AD), levels of tau and p-tau (hyperphosphorylated tau) were correlated with APOE-ε4 and 240HC (a form of neural cholesterol). The authors offer that this correlation suggests a direct influence of APOE-ε4 status on tau expression, such that polymorphisms in the APOE genotype could induce either scavenging of tau from neurons (such as in healthy individuals) or accumulation of tau in neurons (such as in neurodegenerative disorder). Thus, APOE status may be directly related to neural damage associated with cognitive impairments seen in neurodegenerative disorders.

However, one of the striking aspects of the role of APOE-ε4 is that it has an effect on cognition that is independent of neurodegenerative disorder. While it is most strongly associated with risk for development of AD, among samples of healthy older adults, presence of the ε4 allele has been associated with poorer episodic memory performance (De Blasi et al., 2009), specifically as it relates to amyloid-beta burden (Lim et al., 2013). Surprisingly, even among a sample of young adults carrying the ε4 allele, these individuals (relative to non-ε4 young adults) showed a greater degree of bilateral medial temporal lobe (MTL) activity during a subsequent memory paradigm, and an overall reduction in functional connectivity across anterior and posterior cortices (Dennis et al., 2010). As such, even if an ε4-carrier does not ultimately develop a neurodegenerative disorder, just the presence of the allele suggests the possibility for disproportionate deficits in episodic memory performance with advancing age.

One other suggested factor that might impact development of or conversion to AD is cognitive reserve (Stern, 2002). In a review of studies on AD, Stern (2006) found that risk for development of AD might be reduced for individuals high in cognitive reserve (i.e., high IQ,

high degree of educational and occupational attainment, etc.). As such, he proposes that two different aspects of neural functionality might underlie differential functional patterns of recruitment during a cognitive fMRI task. First, Stern suggests that a higher degree of neural reserve in individuals with higher cognitive reserve may result in stronger neural pathways and networks, such that a significantly greater degree of disruption must occur to result in impairment within these networks. Alternatively, he suggests that these individuals may also exhibit a greater degree of neural compensation in being able to draw on alternate existing networks to compensate for damage in primary networks due to a greater degree of plasticity. Thus, not only can neurological, cognitive, or genetic factors play a role in risk for development of AD, but cognitive reserve may also explain some individual differences in impairment profiles in individuals at greater risk for development of AD.

While concussions may seem to be relatively unrelated to the gradual and progressive neural damage associated with neurodegenerative disease such as AD and MCI, its underlying long-term symptom profile, the age of onset of these symptoms, and some aspects of its neurobiological signatures appear remarkably similar to those of AD and MCI. As such, questions about cognitive outcomes following injury, neural mechanisms involved in response to injury, and genetic risk factors for damage expression in injury may be relevant for a better understanding of disease/damage progression and potential for mitigation of symptoms in both populations.

Concussions and Memory

While concussions may be the result of myriad activities and are all characterized by a similar acute symptom profile, for the purposes of this review athletic mild traumatic brain injuries (mTBIs) will be the focus. Due to the unique circumstances under which they occur, and

their association with repetitive exposure to head impacts or trauma, sport-related concussions are a special type of mTBI, and thus are more relevant to the current study that the broader scope of mTBI.

Concussions are inextricably linked to memory, as one of the defining features of an acute concussion is amnesia surrounding the concussive event. Though not required for the diagnosis of a concussion, the presence of amnesia or memory impairment following concussion is a common complaint among individuals who have sustained a concussion, and is an important marker of the concussion's severity. However, up until recently, the long-term effects of these concussive episodes were largely unknown. The study of the long-term effects of concussions has been gaining ground within the past ten years as retired football players begin to approach their 50s and 60s, and they and their family members begin to notice changes in their cognitive abilities. Now, not only do we know that memory is impaired in the short-term following a concussion (Bruce & Echemendia, 2003; Sim, Terryberry-Spohr, & Wilson, 2008), but that it may also be impaired decades afterwards as former athletes who received concussions earlier in life continue to age (Ford, Giovanello, & Guskiewicz, 2013).

One of the first studies to identify the types of cognitive impairments present in retired professional football players (Guskiewicz et al., 2005), utilized questionnaires to target general health (i.e., number of concussions, number of surgeries, number of depressive episodes, etc.) and memory-related (specifically, clinically-relevant symptoms of MCI) outcomes within a sample of retired National Football League (NFL) players. Results from the health questionnaires showed that retired football players overall had an increased incidence of AD, and an earlier potential onset of AD (unrelated to number of concussions previously sustained). Additionally, results from the memory scale included in the health questionnaire showed that,

although retired football players showed no overall memory impairments when compared to the general population, individuals who had sustained multiple concussions previously did, in fact, show impairments relative to healthy older adults. In analyzing the responses from the memory and MCI questionnaire, the authors also found that diagnosis of MCI and self-reported memory impairments tended to be associated with concussion history, whereby retired NFL players who had sustained more than three concussions had a fivefold prevalence of MCI diagnosis and a threefold prevalence of self-reported significant memory impairment when compared to age-matched individuals with no history of concussion. Thus, the authors were able to suggest that multiple concussions sustained as an adolescent or young adult were associated with memory impairments and MCI later in life.

Similarly, another study by De Beaumont and colleagues (2009) utilized neurocognitive testing to test the cognitive capabilities of retired athletes who had sustained concussions in early adulthood. Results from the neurocognitive tests indicated that individuals who had received concussions earlier in life showed significant impairments compared to controls on both immediate and delayed recall. The authors suggest that since they were able to find impairments in episodic memory and in other tasks associated with frontal lobe functioning (i.e., flanker task, auditory oddball paradigm), that these impairments might be comparable to those seen in MCI and early-onset AD. Additionally, the authors point out that in their sample only two individuals reported three or more concussions, meaning that this pattern of impaired episodic memory and frontal lobe functioning can occur even after only one or two concussions earlier in life.

Both studies on memory function in retired athletes showed how memory impairments associated with concussion occur not only at an acute level but also impact retired players decades after these concussions occur. As such, memory impairment can be both an acute, as

well as a long-term symptom of concussive injury. In order to gain a more complete understanding of the effects of this type of neural injury on memory, however, both structural and functional neuroimaging analyses are crucial to analyze any links between neuroanatomy/function and memory impairments.

In a study by Tremblay et al. (2013), the authors collected neuroimaging, genetic, and cognitive data on former athletes who had sustained concussions at least three decades prior to enrollment in the study. Results from the study showed a general trend towards larger lateral ventricles in individuals who had a history of concussion, that this enlargement correlated positively with episodic memory impairment, and also that it interacted with age such that the enlargement was further exacerbated with advancing age in the concussion history group. Additionally, the authors noted significant cortical thinning that was associated with age, exacerbated by concussions (such that individuals with a history of concussion showed greater cortical thinning), and also correlated with episodic memory deficits in individuals with a history of concussion (such that individuals with a history of concussion showed a marked correlation between cortical thickness and episodic memory ability). Since the results suggest a general trend towards abnormal aging in individuals who have sustained concussions previously, they are crucial towards gaining a better understanding of the mechanisms by which these neurocognitive and neurodegenerative long-term symptoms of repeated concussion occur, and in determining when they might begin to result in functional impairments in these individuals. As episodic memory impairment appears to correlate with ventricle enlargement and cortical thinning, therefore, there appears to be a general relationship between memory functioning and neurological health within this sample of retired athletes.

Another study looking at neurobiological and neurocognitive changes resulting from multiple concussions focused less on neurovascular components and their association with memory performance and instead on white matter integrity and its association with memory performance and mood disturbance (Hart et al., 2013). Overall the results showed that former football players classified as "cognitively impaired" (those showing specific cognitive deficits, diagnosed with MCI, or diagnosed with dementia; 41% of the sample) were distinguished from former football players without cognitive deficits and controls based on measures of visual and verbal memory as well as measures of naming and word finding but performed similarly on other cognitive tests. Additionally, the authors found that there were significant diffuse differences in white matter integrity between cognitively impaired or depressed former players and controls. The authors further found that differences in regional blood flow between the cognitively impaired group and controls corresponded to regions found to be associated with performance on memory, naming, and word finding cognitive tasks (i.e., superior temporal gyrus). As such, these data show further evidence for structural and functional neural differences associated with concussion history.

Based on the research reviewed here, there is a clear link between history of concussion and likelihood of presentation of memory impairments later in life. The link between these factors and underlying differences in neural vasculature, white matter integrity, and regional blood flow provides more concrete evidence for long-term changes in memory and cognitive functioning that are associated with having received multiple concussions earlier in life. As the defining feature of this initial cognitive impairment in aging of former football players, memory plays a crucial role in identification of individuals who might be at an increased risk of developing neurodegenerative complications as a result of concussions, and also provides

somewhat of a behavioral indicator for potential underlying changes in neural structure and function.

Concussions and Neurodegenerative Disorder

Such memory impairments as described above are of utmost concern because they are potential clinical signs of underlying neurodegenerative disorder. As mentioned previously, retired NFL players tend to have an elevated prevalence of AD and MCI, exhibit an earlier onset of AD symptomology, and show increasing MCI risk with greater numbers of reported concussions (Guskiewicz et al., 2005). As such, a finer examination of the relationship between repeated concussions earlier in life and mechanisms of neurodegenerative disorder would illuminate a potential spectrum of cognitive effects of this type of neural injury.

A recent study by Lehman et al. (2012) examined neurodegenerative causes of death within a sample of former NFL players. Since past studies had implicated repeated concussions in early development of memory impairment, MCI, and AD, the authors were interested in how these inclinations towards neurodegenerative disorders in this population might influence causes of death. Initial results showed that overall, mortality within this sample was reduced compared to the general population, however mortality due to neurodegenerative causes was significantly elevated. As the authors hypothesized, the most common neurodegenerative causes of death within this sample were AD and amyotrophic lateral sclerosis (ALS). Additionally, among speed position players (who typically receive the greatest number of concussions), neurodegenerative causes of death were significantly elevated for both AD and ALS as compared to the general population and non-speed position players. Though the authors were not able to collect data on concussion history in the study, their results provide support for the notion that former football players who received more concussions or head impacts (i.e., speed players) are at a greater risk

for development of neurodegenerative disorders (such as MCI, AD, and ALS) characterized by memory impairment, as well as more generalized cognitive impairment. The novel finding that former football players are also more likely to die from these later-life concussive effects further informs the need to continue to study the trajectory of these memory impairments and their underlying neurobiological profiles in order to better understand the true impact of concussion on later-life neurocognitive outcomes.

While many researchers acknowledge that concussions might be directly linked to neurodegenerative disorders like MCI, AD, and ALS, some researchers posit that these cognitive and psychological effects of repeated concussion might instead be representative of a unique disorder called Chronic Traumatic Encephalopathy, or CTE (Omalu et al., 2005), associated directly with head impacts sustained earlier in life. Proponents of this view assert that the post-mTBI neural (increased deposition of tau neurofibrillary tangles diffusely throughout the cortex) and behavioral changes (i.e., memory impairments, depression, paranoia, attentional difficulties) are a function of a biological cascade that is triggered by the repeated mild brain injury associated with concussions. Though the cascade is induced by events that begin decades before the symptoms manifest, the neural injury produced with each concussion results in a pattern of delayed neuronal and behavioral changes over time, such that the true effect of the injury is not realized until much later (Gavett et al., 2011; McKee et al., 2009). However, since these researchers are only able to diagnose CTE during autopsy, it is somewhat unclear as to how the presence of this disease manifests clinically and how it progresses (Gavett et al., 2011) and also whether it is indicative of a wholly new disorder or just a different manifestation/expression of an already-established neurodegenerative disorder (i.e., MCI, AD, ALS).

To target the question of whether these later-life effects are representative of a unique disorder (CTE), or reflect symptoms of existing neurodegenerative disorders, Randolph et al. (2013) examined the prevalence and characteristics of MCI within a sample of former NFL players and outlined two competing accounts for the behavioral and cognitive changes observed: CTE or the hypothesis of diminished reserve. With their diminished cerebral reserve hypothesis, the authors suggest that perhaps these repeated head traumas result in a diminished cerebral reserve, which potentially leads to an earlier expression of neurodegenerative disease (like AD or Parkinson's disease). The authors suggest that, if CTE is a truly unique pathology, individuals who have sustained multiple head impacts earlier in life should present with a unique clinical symptom profile that could not be better accounted for by any existing neurodegenerative disorder. Additionally, if their diminished cerebral reserve hypothesis were true, the individuals who sustained multiple concussions should show the exact symptom profile as that of an existing neurodegenerative disorder but at a much earlier age of onset. To test this, the authors examined the prevalence and symptom profiles of individuals who had played professional football and were considered "probable MCI" and those who had been diagnosed with MCI from the general population. They found that overall the performance for both MCI groups across all domains tested in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) followed the same trend; the only difference being that the former football players were younger in showing these patterns. More specifically, MCI participants and former football players who had sustained multiple concussions showed the same trend in sub-test scores such that memory sub-test scores (immediate and delayed memory indices) were selectively depressed relative to other sub-test scores (visuospatial/constructional, language, and attention). As such, the authors suggested that, since this symptom profile appears nearly identical, CTE might not, in fact, be its

own unique diagnosis but rather might be an earlier-onset expression of an existing neurodegenerative disorder.

While the link between concussions and later-life cognitive impairment or neurodegenerative disease seems to be firmly established, what remains unknown is the mechanism by which the neural damage associated with concussion plays a role in the development of neurodegenerative disorder. One way of examining this link is by looking at the role of genetics in the relationship between repeated concussions and later-life neurodegenerative disorder. In doing so, research can investigate whether traditional risk-factors for neurodegenerative disease (i.e., APOE-ε4 allele) are also risk-factors for development of cognitive impairment with repeated concussions.

Kutner and colleagues (2000) investigated the presence of APOE-ε4 in a sample of active football players to see whether genetic risk for AD was also a risk-factor for the presence of memory and cognitive impairments within this sample. Results from genotypic and cognitive testing showed that there was an interaction between age and APOE-ε4 status such that older players who possessed the ε4 allele performed significantly worse on memory and attention tasks than younger players who possessed the ε4 allele and players who did not possess the ε4 allele. Additionally, the authors noted that the ε4 allele seemed to specifically affect the domains of attention and memory and showed no association with tests of reasoning or spatial ability, suggesting that this genotype seems to specifically predispose carriers towards impairment in those two domains. This evidence suggests that not only do former football players possess a risk for developing impairments in the future, but that active football players who are at an elevated risk for AD might begin to express impairments in memory and attention from an early age, independent of current AD or MCI diagnosis. This line of research is crucial for the study of

memory impairment in retired football players who had sustained multiple concussions, in that it adds neurobiological validity to the existing behavioral data on memory processes affected by concussion. Thus, the question of what other components might underlie these risk factors becomes crucial to successfully target at-risk athletes or patterns of behavior.

Role of subconcussive impacts in aging. Despite these results of consistent memory or cognitive impairments associated with repeated concussions, researchers question whether such findings are indicative of an actual association between repeated concussion and memory impairments or if a measure of repeated concussion serves as a proxy for the cumulative effect of more minor, subconcussive hits sustained by football players on a daily basis (Baugh et al., 2012; Gavett et al., 2011). Some researchers suggest that these subconcussive hits result in incremental minor brain damage that accumulates over time to produce some of the long-term effects on memory and cognitive health related to concussion history in previous studies. They suggest that concussion history itself, thus, may be a sort of proxy for subconcussive hits, since it may just be that these individuals with a history of repeated concussions also are exposed to a greater number of hits to the head overall. However, without a way to measure the cumulative impact of these subconcussive hits retrospectively in those retired football players presenting with these cognitive impairments, it is difficult to disentangle the effects of repeated concussive events from those of repeated contact exposure to subconcussive hits.

In order to develop a measure to capture potential exposure to these subconcussive hits, our team developed an interview to capture total hours of exposure to football from high school through professional football experience (Kerr et al., 2015). This raw number of hours is then weighted to reflect differences in contact frequency and severity by position and type of exposure (full-pads practice, post-season game, etc.), and thus represent a weighted measure of

total contact exposure from participation in high school, college, and professional football. This measure was created such that any exposure to subconcussive hits should be reflected by this weighted number of "contact exposure" hours calculated for each individual and thus can be conceptualized as a proxy for potential exposure to subconcussive hits. As such, data from the current study can target questions about risk-factors for later-life cognitive impairment based on three potentially important factors: genetic risk, concussion history, and contact exposure history.

The Current Study

The current study examined the unique roles of concussion history, contact exposure history, and genotype, as well as their interaction, on patterns of cognitive performance as assessed by cognitive tasks, as well as their effect on functional connectivity during an in-scanner working memory task. The analysis of these factors (concussion history, exposure history, and genetics), all thought to independently affect cognition, represents the first study to investigate the potential relationship among these risk-factors of cognitive impairment and functional inefficiencies while performing a memory task.

Previous research on memory in aging provides some theoretical framework from which we can view the results from the current study. Specifically, neuropsychological test performance patterns can be compared to those posited by existing cognitive theories of aging to determine which theory of aging might best account for cognitive changes associated with multiple concussions. Additionally, functional neural connectivity patterns can be examined to assess if they follow a dedifferentiated-type pattern of recruitment wherein participants have difficulty selectively recruiting task-relevant regions (Li & Lindenberger, 1999) or a compensatory-type pattern wherein participants recruit additional bilateral and frontal regions to aid in task performance (Cabeza, 2002). Testing these models of cognitive impairments and

neural recruitment patterns in aging may have implications for how cognitive impairments and functional recruitment differences in older individuals with a history of repeated concussions are viewed, and potentially whether these individuals can be classified as engaging in compensatory or inefficient patterns of cognitive aging.

While effects of acute sport-related concussion on working memory are well-documented (Dettwiler et al., 2014; Mayers, Redick, Chiffriller, Simone, & Terraforte, 2011; Pardini et al., 2010), fewer studies have looked at more persistent effects of repeated concussion on working memory (Terry et al., 2012; Theriault, De Beaumont, Tremblay, Lassonde, & Jolicoeur, 2011), and no studies other than the prior study on this data set have focused on long-term effects of repeated sport-related concussion on working memory. As a form of memory concerned with the retention and manipulation of information over short time-courses (A. Baddeley, 1992a, 1992b; A. Baddeley & Della Sala, 1996), working memory is a crucial domain of cognition for successful engagement in most everyday activities. In fact, research has found working memory abilities to be related to and dependent upon myriad domains of cognition, spanning areas of attention, executive control processes, memory, and even intelligence (Conway & Engle, 1996; Conway, Kane, & Engle, 2003; Engle, Tuholski, Laughlin, & Conway, 1999; Kane & Engle, 2002). Therefore, a more complete picture of the long-term effects of concussion on working memory task performance and functional connectivity would prove necessary to shed more light on mechanisms underlying patterns of cognitive impairment in aging within this sample, and on the overall effects of repeated concussion on cognitive function.

However, previous research on the long-term effects of concussion allows us to place the findings from the current study in the context of existing research on contributors toward cognitive decline in individuals who have a history of multiple concussions. While most previous

studies only examined the role of concussion history (Baugh et al., 2012; De Beaumont et al., 2009; Ford et al., 2013; Gavett et al., 2011; Guskiewicz et al., 2005; Hart et al., 2013; Theriault et al., 2011; Tremblay et al., 2013), concussion history and contact exposure history (see preliminary findings), or concussion history and genotype (Kutner et al., 2000) on cognitive later-life outcomes, this will be the first to incorporate all three measures in examining neural substrates of working memory performance in a sample of former NFL and college football players. Based on the results of prior analyses on the data, a further examination of genetic influences on neural inefficiencies would contribute towards a more complete understanding of risk factors for later-life cognitive impairment within this sample.

Specific aims. The goals of the present study were two-fold: (1) To delineate the genetic modulations of concussion and exposure history in neurocognitive processes supporting working memory; and (2) To delineate the genetic modulations of concussion and exposure history in neural processes supporting working memory. To test these two aspects of neurocognitive function in retired football players, two experiments will be conducted. The first experiment assessed patterns of cognitive impairment in former athletes through a battery of neuropsychological tests (targeting domains such as memory, attention, executive function, and language) to determine how neuropsychological profiles of former athletes differ based on concussion history, contact exposure history, and genotype, and what types of overall neurocognitive deficits are present in the sample. The second experiment examined how these same factors (concussion history, contact exposure history, and genotype) influence patterns of functional connectivity during working memory task performance.

CHAPTER 2: METHODS

Participants

Participants in this study (see Table 1) were thirty-one former professional (NFL) players who played a minimum of five seasons of professional football ("PRO"; M_{age}=58.12; SD=3.74; all male) and thirty-two former college football players who played a minimum of three years of college football ("COL"; M_{age}=58.63; SD=3.663; all male). An additional former professional football player (from the high concussion group) underwent all neuropsychological and genotyping assessments, but his functional magnetic resonance imaging (fMRI) data were invalid due to excessive movement in the scanner and cessation of the scan prior to completion. Before participating in the study, all participants gave written informed consent in accordance with the requirements of the Institutional Review Board at the University of North Carolina at Chapel Hill.

Participants in both the former college and professional football player groups were further divided into two additional groups based on self-reported concussion history (see Table 1 for sample demographics). The two concussion history groups were stratified based on previous research that indicated an elevated risk of later-life cognitive impairments among individuals who have sustained three or more sport-related concussions (Guskiewicz et al., 2005). The "low concussion" group was comprised of individuals who had sustained no more than one concussion during their football careers (either professional or college; n=32), and the "high concussion" group was comprised of individuals who had sustained three or more concussions during their careers (n=31). As a result, four groups were created based on football exposure and

concussion history: former professional players with no more than one concussion (PRO-LOW; *n*=16), former professional players with more than three concussions (PRO-HIGH; *n*=15), former college players with no more than one concussion (COL-LOW; *n*=16), and former college players were more than three concussions (COL-HIGH; *n*=16). Within both the "low" and "high" concussion groups, former NFL and former college players were matched on self-reported number of concussions, position(s) played, and age at the time of the visit. For certain analyses, some participants in the study either had incomplete data for some of the measurements included, or did not meet performance criteria for tasks, and thus were excluded from analyses on a case-by-case basis (see Table 2).

Recruitment of former professional and college football players. All retired professional football player subjects were recruited from our database of approximately 3,000 retired National Football League players that has been developed over the past nine years, in conjunction with the National Football League Players' Association. This database includes results from a self-reported general health survey (Appendix B- Health Survey of Retired NFL Players) that included information about the retired player's football history (exposure), medical history (including neurological conditions such as depression, Alzheimer's disease, and Parkinson's disease, etc.), history of mTBI (including number of mTBI during high school, college and professional playing career), and general health status. A subsequent questionnaire focusing on memory and issues related to mild cognitive impairment (Appendix B- MCI Survey) was sent to those retirees age 50 and older. From within this group (and based upon mTBI status), retired players were randomly selected and contacted by telephone regarding their willingness to participate in this study.

Former collegiate football players were recruited from the tri-state area surrounding Chapel Hill, NC. The recruitment process for this cohort began after the demographics had been collected on the retired NFL cohort. The process for identifying former college football players (age 50+) entailed contacting the sports information directors and athletic trainers from Division I football programs in North Carolina, Virginia, and South Carolina to identify graduates of their respective programs who were living in the area. These individuals were then sent a letter from our research team, inquiring if they would be interested in participating in our research study. These study participants were then assessed on the same screening instruments as the retired NFL cohort and eventually were invited to campus for the full test battery. Matching the retired college subjects was accomplished by matching as best as possible to age, education level, and position played. We excluded any subjects with a history of stroke or any central nervous system disease (e.g., multiple sclerosis and amytrophic lateral sclerosis). Subjects were also excluded if they have any condition that makes MRI unsafe (e.g., cardiac pacemaker, epicardial pacemaker leads, or cochlear implants).

Design

The present study was set up as two experiments assessing different aspects of cognitive function. Experiments 1a and 1b were comprised of neurocognitive tasks assessing various aspects of cognitive function from both a more global level (experiment 1a), as well as a more specific level (experiment 1b). Experiment 2 was a functional neuroimaging study in which functional MRI data were acquired in the context of a working memory task.

Measures and Procedures

Global neuropsychological assessment (Experiment 1a). An extensive battery of neuropsychological tests was conducted in order to obtain a full neuropsychological profile for

all participants. The following tests were administered to all participants: two general tests of cognitive functioning (Mini-Mental State Examination or MMSE (Folstein, Folstein, & McHugh, 1975), Clinical Dementia Rating or CDR (J. C. Morris, 1993)), two generalized tests of intelligence and neuropsychological function (Wechsler Adult Intelligence Scale or WAIS (Wechsler, 2008), Repeatable Battery for the Assessment of Neuropsychological Status or RBANS (Randolph, Tierney, Mohr, & Chase, 1998)), three tests of language function (Controlled Oral Word Association Test or COWAT (Benton, Hamsher, & Sivan, 1983), Boston Naming Test or BNT (Kaplan, Goodglass, & Weintraub, 1983), Wechsler Test of Adult Reading or WTAR (Holdnack, 2001)), and one test of executive function (Trail Making Test parts A & B or Trails A and Trails B (Reitan & Wolfson, 1985)). Additionally, as a measure of depression, all participants completed the Beck Depression Inventory (BDI-II)(Beck, Steer, & Brown, 1996). For the purposes of this set of analyses, only the data from the RBANS sub-scale scores for each participant will be utilized.

Specific neurocognitive assessment (Experiment 1b). A focused battery of neurocognitive tests, CNS vital signs (Gualtieri & Johnson, 2006, 2008), was also conducted in order to obtain a more discrete view of cognitive function and impairment within the sample. The following cognitive tests were administered as part of this battery: immediate verbal memory, delayed verbal memory, immediate visual memory, delayed visual memory, the finger tapping test (motor processing speed), the symbol-digit coding test (processing speed and executive function), the stroop test (information processing speed), the shifting attention test (cognitive flexibility), and the continuous performance test (sustained attention).

For the purposes of this set of analyses, the following variables will be utilized: immediate memory corrected recognition (average corrected recognition on visual and verbal

immediate memory), delayed memory corrected recognition (average corrected recognition on visual and verbal delayed memory), symbol-digit coding accuracy, shifting attention accuracy, immediate memory correct reaction time (average correct reaction time on visual and verbal immediate memory), delayed memory correct reaction time (average correct reaction time on visual and verbal immediate memory), shifting attention correct reaction time, and Stroop effect (reaction time to incongruent stimulus – reaction time to congruent stimulus).

Contact exposure index (Experiments 1 & 2). Research staff conducted structured oral interviews with participants on their football career history, beginning at the high school football level and continuing through college and professional football (Kerr et al., 2015). For each year of their football career, participants provided information on their: primary position played (i.e., quarterback, offensive line, running back, defensive line, defensive back, linebacker, wide receiver, special teams); number of games in the pre-season, regular season, and post-season; percent of time that they played in games; number and length of contact practices. From this information, we created the exposure history variable.

For each year, we first calculated the number of practice contact hours using the following formula:

> (# pre-season practice sessions/week * # pre-season weeks * # hours/pre-season practice session) + (# regular season practice sessions/week * # regular season weeks * # hours/regular season practice session) + (# post-season practice sessions/week * # post-season weeks * # hours/post-season practice session)

Next, we calculated the number of game hours using the following formula:

(# pre-season games * % of time active in pre-season games * 1 hour) + (# regular season games * % of time active in regular season games * 1 hour) + (# post-season games * % of time active in post-season games * 1 hour)

The sum of the number of practice contact and game hours for each year was summed throughout one's high school, college, and professional career to create their total contact exposure.

Because we were concerned with the differences in the frequency and the severity of impacts that occur in games compared to practice, we then created adjusted totals that applied a weight to the total unique to each position. These weights were based from previous findings that compared the frequency and severity (i.e., linear acceleration) of hits in games and practices (Crisco et al., 2010).

fMRI Design and Procedure (Experiment 2)

The in-scanner working memory paradigm utilized in this study was an N-back task (Kirchner, 1958). The stimuli for this task included both upper- and lower-case letters that appeared on the screen one at a time for 3 seconds each. Letters were mixed upper- and lower-case to avoid responses based on purely perceptual features of the stimuli, and to encourage a deeper level of working memory processing associated with task success. These stimuli were presented in six blocks, with seventy-two letters appearing in each block. Prior to beginning the scanning sessions, participants were familiarized with the task, provided with verbal instructions for the task and given a practice session for each of the three variants of the N-back task used in the scanner. Participants were not permitted to begin the fMRI scan unless they could successfully complete all three tasks outside of the scanner.

The experimental task was divided into three tasks defined by working memory load: zero-back, one-back, and two-back. Each task was presented over two consecutive blocks within the scanner, and task order was randomized across participants. Prior to beginning each block, participants were provided with written instructions for the upcoming task to re-familiarize them with response criteria and task instructions. For each task, participants were told to respond "yes" or "no" with their dominant hand for each letter that appeared on the screen. During the zero-back task (low working memory load), participants were told to respond "yes" every time the letter "d" (or "D") appeared on the screen, and "no" for every other letter. During the one-back task (moderate working memory load), participants were told to respond "yes" any time the current letter on the screen was the same as the previous letter, and "no" for any letter that was not the same as the previous letter. During the two-back task (high working memory load), participants were told to respond "yes" to any letter that was the same as the letter that had appeared two letters before it, and "no" to any letter that was not the same as the letter that had appeared two letters before it.

fMRI data acquisition. Magnetic resonance images were acquired using a Siemens Trim-Trio 3-T scanner. Participants' heads were held in place using cushions and a headrest. An initial localizing scan was followed by a high resolution T1 weighted structural scan for anatomical visualization (160 1mm slices, TR=1750ms, TE=4.38ms). Next, functional scans were collected during all six BOLD runs. Whole brain, gradient-echo, echo planar images (fifty interleaved 3mm slices, TR=3s, TE=30ms, Flip angle=90º, 3 x 3 x 3 mm) were acquired at an angle parallel to the long axis of the hippocampus, identified during the T1 scan.

Following T1-weighted and functional scans, a resting-state scan, a profusion scan, a T2-weighted sagittal scan, and a DTI series were collected. However, the analysis in the current paper focuses exclusively on the data from the task-based functional scans.

Generalized Neuropsychological Task Data Analysis (Experiment 1a)

In order to gain a better understanding of patterns of cognitive impairment in a sample of retired football players, a one-way repeated-measures ANOVA was conducted on sub-tests within the RBANS to examine any consistent trends in cognitive task performance within this sample (such as those observed in Randolph et al., 2013). Additionally, individual RBANS scores were z-transformed relative to controls in the Randolph (2013) sample to test whether the current sample of participants performed significantly worse than controls from a separate study using the same task.

Specific Cognitive Task Data Analysis (Experiment 1b)

To further probe any trends found in the aforementioned ANOVA analysis, regressions were conducted in which the score of each of the specific cognitive tests was regressed independently on weighted hours of contact exposure, number of concussions sustained, a dichotomous variable representing APOE-ε4 status, as well as their interactions. As such, the following equation was the model for the data:

$$\text{Cognitive test score} = \beta_0 + \beta_1(\text{number of concussions sustained}) + \beta_2(\text{weighted hours of contact exposure}) + \beta_3(\text{APOE status}) + \beta_4(\text{number of concussions sustained})*(\text{weighted hours of contact exposure}) + \beta_5(\text{number of concussions sustained})*(\text{APOE status}) + \beta_6(\text{weighted hours of contact exposure})*(\text{APOE status}) + \beta_7(\text{number of concussions sustained})*(\text{weighed hours of contact exposure})*(\text{APOE status}) + \varepsilon$$

The moderation effect in this model was tested via the parameter estimates for the interaction variables between APOE status and concussion, and exposure, and the three-way interaction variable of APOE status by concussion history by exposure. In order to correct for multiple comparisons, a p-value of .00625 was used as a cut-off for significance of parameter estimates (p=.05 divided by 9 regression analyses performed).

fMRI Univariate Analysis (Prior Analyses Experiment 2)

Before examining more fine-grained differences in fMRI data from raw number of concussions, weighted hours of exposure, and APOE status, a more traditional univariate analysis of the fMRI data was first conducted to test for expected effects of concussion grouping and exposure grouping on BOLD signal change across the whole brain. All functional runs were initially analyzed based on pre-specified univariate contrasts comparing activity between functional runs. The three main contrasts were: 1-back>0-back, 2-back>0-back, and 2-back>1-back in order to capture any differences in recruitment based on working memory load manipulations. These contrasts were compared at the random effects level in an ANOVA design in which participants were stratified into their four groups (COL-0/1, COL-3+, COL+PRO-0/1, COL+PRO-3+) in order to isolate the unique effects of exposure history and concussion history, and also to test for the effect of any interaction between concussion and exposure. Whole-brain images were used in order to capture differences in recruitment across the cortex, resulting in a statistical cut-off for significance of $p<0.001$, and $k>5$. Univariate analyses aided in establishing whether or not there were baseline differences in fMRI signal by group before engaging in more specific fMRI analyses of connectivity.

fMRI Connectivity Analysis (Experiment 2)

A goal of the current study was to examine functional neural differences in working memory task performance based on the interactions among weighted hours of contact exposure, concussion history, and genotype (APOE-ε4 status). To examine these interactions, whole brain images were collected every three seconds throughout all six functional runs, capturing the average hemodynamic response for each task block. The use of fMRI was crucial to the study design in order to localize functional recruitment during working memory performance within this sample of retired football players.

Images were preprocessed and analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK) software implemented as a suite of commands in MATLAB (MathWorks, USA). Images were co-registered with each person's anatomical scan, slice-time corrected, realigned, normalized and smoothed using a Gaussian 8mm kernel.

ROI specification. In order to examine task-relevant functional connectivity during N-back task performance, regions of interest (ROIs) were created from a fronto-parietal network known to be implicated in working memory performance (Dosenbach et al., 2007). Based on this network identification, coordinates for 11 ROIs within the network were used for the following set of analyses. To account for differences in regional specification, masks for frontal ROIs were created as spheres with a 10mm radius, and masks for parietal and midbrain regions were created as spheres with a 3mm radius in AFNI in native participant space (Cox & Hyde, 1997). Following mask creation, preprocessed time-series data was drawn from each ROI per participant for use in connectivity analyses.

Graph theory analyses. In order to examine differences in fronto-parietal network efficiency during n-back task performance, the graph theory metric of "strength" was utilized as

a measure of strength of the network during each level of the task (Sporns, 2011). This measure was generated by first creating unique participant correlation matrices of BOLD time-series data across the 11 fronto-parietal network ROIs, per task type (0-back, 1-back, and 2-back). Strength of each ROI was representative of the total correlation strength of each of its connections to other regions within the network (see Figure 1). Strength of the network was created by adding each participant's unique ROI strengths to generate one single measure representing the strength of all possible connections within the fronto-parietal network.

Additionally, to examine task-related modulation of network strength, each participant's network strength at each level of the task was used to generate a regression line that was representative of that participant's change in network strength as a function of working memory load. As such, in addition to having strength variables representing total network strength at each level of the task, each participant also had a unique slope and intercept representing the trajectory of their network strength as working memory load increased.

Parametric connectivity regression analyses. To gain a better understanding of the overall relationship between actual number of concussions, actual hours of contact exposure, genotype status (and their interactions) and functional connectivity during the working memory task, a regression was conducted in which modulation of network connection strength across levels of the N-back task was regressed on concussion history and exposure history, the dichotomous variable of APOE status, and their interactions. In order to analyze the interaction effect of APOE status with the other variables, APOE status was coded such that a value of "1" indicates that an individual carries at least one APOE-ε4 allele (heterozygous or homozygous), and a value of "0" indicates that an individual does not possess any APOE-ε4 alleles (non-carrier). As such, the following equation was the model for the data:

Slope of strength= β_0 + β_1(number of concussions sustained) + β_2(weighted hours of contact exposure) + β_3(APOE status) + β_4(number of concussions sustained)*(weighted hours of contact exposure) + β_5(number of concussions sustained)*(APOE status) + β_6(weighted hours of contact exposure)*(APOE status) + β_7(number of concussions sustained)*(weighed hours of contact exposure)*(APOE status) + ε

The moderation effect in this model was tested via the parameter estimates for the interaction variables between APOE status and concussion, and exposure, and the three-way interaction variable of APOE status by concussion history by exposure.

Task-level connectivity analyses. In order to assess whether the variables of interest also affected strength at each level of the task, a series of regressions were also conducted in which network connection strength at each level of the N-back task was regressed on concussion history and exposure history, the dichotomous variable of APOE status, and their interactions. As such, the following equation was the model for the data:

Task-level strength = β_0 + β_1(number of concussions sustained) + β_2(weighted hours of contact exposure) + β_3(APOE status) + β_4(number of concussions sustained)*(weighted hours of contact exposure) + β_5(number of concussions sustained)*(APOE status) + β_6(weighted hours of contact exposure)*(APOE status) + β_7(number of concussions sustained)*(weighed hours of contact exposure)*(APOE status) + ε

The moderation effect in this model was tested via the parameter estimates for the interaction variables between APOE status and concussion, and exposure, and the three-way interaction variable of APOE status by concussion history by exposure. In order to correct for multiple comparisons, a p-value of .0125 was used as a cut-off for significance of the regression parameters (p=.05 divided by 3 regressions performed).

ROI-level connectivity analyses. In order to assess whether connectivity strength of each ROI was modulated by the variables of interest, ROI connection strengths were included as the dependent variables in 3 separate MANOVA analyses (all including participant ID as a covariate to account for random effects due to individual differences): (1) a 2x2x3 MANOVA examining the separate and combined effects of concussion history, APOE status, and n-back level on connectivity strength, (2) a 2x2x3 MANOVA examining the separate and combined effects of exposure history, APOE status, and n-back level on connectivity strength, and (3) a 2x2x2x3 MANOVA examining the separate and combined effects of concussion history, exposure history, APOE status, and n-back level on connectivity strength.

Hypotheses

Cognitive test data (Experiment 1). I hypothesized that: (1a) former athletes will have significantly lower scores on tests of memory (both immediate and delayed) and executive function (more controlled processes), but relatively spared performance on tasks of simple attention and language (relatively automatic processes); and (1b) significant proportions of the variance in tests of memory and executive function will be explained by APOE-ε4 status, concussion and contact exposure history, as well as the interaction between concussion/contact exposure history and APOE-ε4 status. If hypothesis (1a) were to be confirmed, it would provide support for the Attentional Resource Reduction theory in cognitive aging, suggesting that these individuals showing deficits in controlled processes are showing significant depletion in attentional resources impacting performance on controlled cognitive tasks relative to performance on more automatic cognitive tasks (F. I. M. Craik & Byrd, 1982). Additionally, if hypothesis (1b) were to be confirmed, it would support the idea that the damage associated with concussion, and cognitive changes in aging associated with APOE-ε4 status are directly and

indirectly related to discrete cognitive measures indexing memorial and executive function processes.

Functional connectivity (Experiment 2). I hypothesized that: (2a) significant proportions of the variance in functional connectivity strength during working memory task performance will be explained by APOE-ε4 status, concussion history, as well as the interaction between concussion history and APOE-ε4 status; (2b) patterns of functional connectivity in individuals with a higher number of repeated concussions and those who are APOE-ε4 positive will follow a generally dedifferentiated pattern, associated with a general trend of correlations in performance across regions. If hypothesis (2a) were to be supported, it would confirm the idea that APOE-ε4 status plays some role in moderating the effects of neural damage associated with concussion history on functional patterns of activation during a working memory task (Dennis et al., 2010). Further, support for hypothesis (2b) would indicate that these patterns of functional recruitment might not just differ by group, but might also be indicative of a general pattern of decreases in neural efficiency across the board within APOE-ε4 positive and high concussion individuals, such that impairments in correlated recruitment of one region are also associated with similar-magnitude impairments in recruitment of other networked regions due to a similar degree of functional neural inefficiency (Li & Lindenberger, 1999).

CHAPTER 3: RESULTS

Generalized Neuropsychological Tasks (Experiment 1a)

A one-way repeated measures ANOVA on RBANS task performance, revealed a significant difference among the sub-tests within the sample ($F(4)=15.538$, $p<.001$). Post-hoc tests revealed that delayed memory showed the lowest level of performance ($M=91.52$, $SD=12.83$; lower than immediate memory, $p=.039$, visuospatial, $p<.001$, language, $p=.028$, and attention subtests, $p<.001$), followed by immediate memory ($M=96.22$, $SD=14.08$; lower than attention, $p=.001$) and language ($M=96.94$, $SD=6.77$; lower than visuospatial, $p=.045$, and attention, $p<.001$), followed by visuospatial ($M=102.22$, $SD=12.3$) and attention ($M=105.73$, $SD=13.17$; see Figure 2). Additionally, when comparing RBANS scores from the present sample to healthy control participants from a previous study's sample (Randolph et al., 2013) using z-scores, participants from the present study did not show significant differences in cognitive measures from the control group either looking at overall means (regardless of recruitment grouping), or looking at recruitment group-level means (see Table 3).

Specific Cognitive Tasks (Experiment 1b)

Regression analyses on CNS Vital Signs sub-tests showed no predictive validity of concussion history, exposure history, APOE status, or their interactions in 7 of the 8 regressions (see Table 4). The only regression in which the included variables significantly predicted the cognitive test outcome was in the regression of shifting attention reaction time. In this regression, the interaction between concussion history, exposure history, and APOE status was significant such that for those participants who were APOE-ε4+, those with greater concussion and

exposure histories showed lower reaction times than those with lower concussion and exposure histories, while those who were APOE-ε4- showed no such trend.

fMRI Univariate Analysis (Prior Analyses Experiment 2)

Univariate analyses of the fMRI data revealed an overall main effect of concussion history at each contrast, a main effect of exposure only at the 2-back>0-back contrast, and no interaction between concussion history and exposure (see Table 5). A main effect of exposure was found to be significant in one of the three univariate contrasts. During high (2-back), relative to low (0-back) working memory load, the low exposure groups showed greater levels of activation than the high exposure groups in clusters within the superior temporal gyrus and fusiform gyrus.

A main effect of concussion was found to be significant in each of the three univariate contrasts. During moderate (1-back), relative to low (0-back) working memory load, we observed several regions that significantly differed between groups. More specifically, the low concussion groups showed greater levels of activation than the high concussion groups in clusters within the orbital frontal gyrus, caudate, fusiform gyrus, nucleus accumbens, and lingual gyrus. During high (2-back), relative to low (0-back) working memory load, the high concussion groups showed greater levels of activation then the low concussion group in clusters within the cuneus, supramarginal gyrus, and superior temporal gyrus. During high (2-back), relative to moderate (1-back) working memory load, the high concussion groups showed greater levels of activation in clusters diffusely spread throughout the cortex, including regions such as the superior temporal gyrus, orbital gyrus, cingulate gyrus, fusiform gyrus, and precentral gyrus.

fMRI Connectivity Strength (Experiment 2)

Regression analyses on the modulation of network strength showed no predictive validity of concussion history, exposure history, APOE status, or their interactions in accounting for variance in parametric modulation of network strength as a function of working memory load (see Table 6; Figure 3).

Task-level regression analyses on the strength of the network during each level of the n-back task showed no predictive validity of concussion history, exposure history, APOE status, or their interactions in predicting 0-back or 1-back strength. However, exposure history, APOE status, and their interaction significantly predicted some of the variance in *2-back* network strength (see Table 6). Further examination of the interaction revealed that for individuals who were APOE-ε4-, network strength was greater for those with more hours of contact exposure than those with fewer hours of contact exposure, but for individuals who were APOE-ε4+, there was no difference in network strength based on contact exposure history (see Figure 4).

ROI-specific MANOVA analyses on the strength of each node examined the combined and unique effects of concussion history and APOE status, and exposure history and APOE status separately, then ROI-specific MANOVA analyses were used to examine 3-way interactions among the three variables. In a 2x2x3 MANOVA comparing the effects of concussion history, APOE status, and n-back level on node-level strength, only the LIPL ROI showed a significant main effect of concussion, and only the LIPS and RIPL ROIs showed a significant interaction between APOE status and concussion history. No other regions showed any significant differences in strength based on the factors included. The main effect of concussion in the LIPL suggested that individuals with higher concussion history show less connection strength within this ROI than individuals with lower concussion history (see Table 7).

The interaction effect between concussion history and APOE status in the LIPS and RIPL suggested that individuals who are APOE+ with low concussion history show greater connection strength than individuals who are APOE+ with high concussion history, while individuals who are APOE- show no difference in connection strength based on concussion history.

In a second 2x2x3 MANOVA comparing the effects of exposure history, APOE status, and n-back level on node-level strength, only the LIPS, L precuneus, and R precuneus showed a significant interaction between APOE status and exposure history (see Table 7). In each of these three regions, the interaction effect suggested that individuals who are APOE- with low exposure history show weaker connection strength than individuals who are APOE- with high exposure history, while individuals who are APOE+ show no difference in connection strength based on exposure history (see Table 8).

Finally, in a 2x2x2x3 MANOVA integrating both previous MANOVA models into one omnibus model (including concussion, exposure, and APOE status) yielded several interactions of interest. Specifically, an interaction between concussion and APOE status (RIPL), an interaction between exposure and APOE status (Lprecuneus, midcingulate, Rprecuneus), and an interaction between concussion, exposure, and APOE status (LIPS) emerged (see Table 9). The interaction between concussion and APOE status in the RIPL, and the interaction between exposure and APOE status in the Lprecuneus and Rprecuneus showed similar patterns of results as reported previously. The novel 2-way interaction between exposure and APOE status in the midcingulate suggested that individuals with low exposure history show no difference in connection strength based on APOE status, but individuals with high exposure history who are APOE+ show weaker connection strength than individuals with high exposure history who are APOE- (see Table 8). Additionally, the 3-way interaction between concussion, exposure, and

APOE status in the LIPS suggested that low concussion individuals do not differ in LIPS connection strength difference based on exposure history, but for individuals with high concussion history, those are are APOE+ show lower connection strength with high exposure history than APOE- individuals (see Figure 5).

CHAPTER 4: DISCUSSION

Overall results from the present study are unique in their ability to simultaneously examine the specific and interactive effects of concussion history, weighted hours of contact exposure, and genotype on aging patterns. Specifically, they expand upon past research in the ability to examine these factors simultaneously in one study, in the utilization of these measures in a matched sample of former college and professional athletes, and also in the focus on applicability of current theories of cognitive aging to patterns of aging in concussion. Additionally, the results from this study are unique in that they focus on specific aspects of cognitive function in aging (i.e., working memory, attention, delay memory, etc.) as opposed to assessing cognition as a more globally-defined construct calculated based on performance on a wide variety of cognitive tasks.

Neurocognitive Tasks - RBANS

Based on the neurocognitive task results from RBANS data analyses, it is clear that the sample in the present study exhibited a deficit in memory, and also possibly a deficit in language (relative to performance on attention and visuospatial tasks). These results partially support the hypothesis that this sample would show selective deficits in measures of memory, but spared performance on measures of language and attention. However, when RBANS data from the present study were compared with that from Randolph's prior studies in healthy control and MCI participants (2013; 1998) the present sample's means did not significantly differ from those of the slightly older control population (see Table 3), but generally fell closer to the cognitive profile of Randolph and colleagues' (2013) MCI participants, rather than the control participants

(see Figure 6). The trend from the current study reflects the pattern the authors observed in their sample of retired NFL players (Randolph et al., 2013), but in a much younger population of retired NFL players. As such, the present results may be compared to his suggestion that this profile of cognitive performance in this sample may reflect more of an early onset of MCI-like deficits, instead of representing a unique cognitive deficit profile that might suggest the presence of a unique neurodegenerative disorder within this sample. While the present data may not speak perfectly to such an interpretation, they do extend the findings of Randolph and colleagues into a younger sample of retired NFL players, and may suggest that such a trend of selective impairment in measures of memory (like that of an MCI sample) in retired NFL players emerges quite early (around 50-62 years old).

Neurocognitive Tasks - CNSVS

However, in more discrete analyses of neurocognitive task performance on the CNSVS tasks, none of the hypothesized patterns of results emerged. Specifically, neither exposure hours nor concussion history interacted with genotype to explain the variance in accuracy or reaction time for measures of memory or executive function. The only task for which these measures partially explained some of the variance was shifting attention reaction time, and the effect was the opposite of what one might expect. As such, the present analysis cannot fully explain why this pattern of results emerged, nor whether the observed data pattern may be due to chance variation in this outcome measure.

Since none of the expected predictors significantly predicted variance in these measures of memory or executive function, the present data do not suggest any patterns of accelerated cognitive aging in this sample based on the predictors included within the models. Thus, the data do not support the notion that individuals with higher exposure hours/concussion history have

accelerated patterns of: reduction in attentional resources as evidenced by no difference in performance on measures of memory and attention (F. I. M. Craik & Byrd, 1982), or failure of inhibitory control as evidenced by no differences in performance on tasks of executive control (Hasher & Zacks, 1988). While this may be contrary to the expected pattern of results, there may be several explanations for the lack of differences in patterns of cognitive aging observed in this sample. First, considering the results from RBANS and CNSVS analyses, it may be the case that everyone in the sample showed similarly lower performance on cognitive measures of memory, even if these lower scores were not significantly different from controls', and thus the predictors included in the models did not account for any differences in impairment. Second, it may be the case that the RBANS measures of memory are more sensitive to within-subject impairment than CNSVS measures of memory, and thus any differences in memory performance that might truly exist are not being measured by the tasks used. Third, it may be the case that the RBANS tasks are just sensitive enough to observe some early deficits, but more specific cognitive tasks may not show any impairment yet. This relates to the pilot behavioral data within this sample showing equivalent levels of performance on an n-back task; maybe the CNSVS tasks utilized were similarly subject to this equivalence in task performance based on the predictors included. However, ultimately all three factors could be influencing the results observed in this study – it may just be the case that everyone in the sample shows relatively lower performance on measures of memory, but that it is too early to use the tasks in this study to distinguish those at greater risk of impairment from those with lesser risk of impairment based on exposure hours, concussion history, and genotype.

Regardless of what factors account for the lack of difference in memory/executive function/attention in this sample, the results observed here are not in line with those from

previous studies showing memory impairment in individuals with high vs. low concussion histories (De Beaumont et al., 2009; Guskiewicz et al., 2005), or those showing memorial and attentional impairments in former football players who were APOE-ε4+ (Kutner et al., 2000). While we did see a general trend towards lower memory performance within our sample, we did not observe any differences in memory performance based on concussion history or genotype.

fMRI Analyses - Univariate

Preliminary analyses on the data in the current study comparing concussion history and exposure history, and their effect on neural recruitment during a working memory task, revealed an overall critical role of concussion history in accounting for neural recruitment differences between the four groups (former professional and college football players with either low or high concussion history). The results suggested that, while concussion history and contact exposure both accounted for some functional differences during memory task performance, concussion history consistently played a larger role in accounting for the observed neural inefficiencies than did exposure history. Overall, across each set of fMRI analyses, concussion history accounted for more variability in neural response than exposure history. Considering that there were no behavioral differences in accuracy on the working memory task utilized in the scanner, all neural differences occurred in the absence of behavioral differences.

fMRI Analyses - Functional Connectivity

Functional connectivity analyses of fronto-parietal network strength somewhat supported the hypothesis that concussion history would interact with APOE status in predicting differences in patterns of functional connectivity within this task-specific network. Results from parametric analyses of network strength showed no difference in the modulation of strength based on the predictors included, and results from task-level analyses of network strength showed an

interaction between exposure history and APOE status in accounting for variance in strength. Specifically, individuals who are APOE-ε4- show greater network strength when they have greater history of exposure hours, but individuals who are APOE-ε4+ do not show any difference in network strength as a function of exposure hours. This may suggest that individuals who are APOE-ε4- are able to compensate for subconcussive neural injury through increased network strength during performance of the hardest level of the task, while those who are APOE-ε4+ do not show this type of compensation.

Additionally, when the analysis instead focused on ROI-specific differences in strength based on concussion history, exposure history, and APOE status, regions in the parietal lobe showed modulation of strength based on concussion history, the interaction between concussion history and APOE status, the interaction between exposure history and APOE status, and the interaction between concussion history, exposure history, and APOE status. While network-based approaches were not able to detect these more subtle effects, it does suggest that when narrowing in on node-level aspects of connectivity, genotype might affect the brain's ability to compensate for accrued neural injury (either by concussive or subconcussive events). Thus, concussive or exposure history alone might not have an effect on task-related functional connectivity, but genotype may affect the way in which the brain compensates for this neural injury. Given the mechanism of concussive injury and subconcussive injury, and the effect of APOE on the ability to deposit and metabolize tau protein, this connectionist approach may imply that individuals with accrued injury who are APOE+ are more vulnerable to neural injury that results in difficulty integrating brain regions into an effective network. As such, these individuals may be less able to utilize synchronized recruitment of task-relevant regions to perform a task efficiently. While in the context of this study this was not associated with any

behavioral differences, deficits in functional connectivity could imply underlying structural damage that may eventually result in behavioral impairment. However, while these analyses were intended to be used to test for differences in neural patterns of cognitive aging within this sample, analyses showed that this network was far too dense to test whether observed connectivity patterns provided evidence for more of a HAROLD (Cabeza et al., 2002) or dedifferentiated (Li & Lindenberger, 1999) pattern of network recruitment in cognitive aging.

In discussing results from parametric strength analyses, it is important to consider the degree of heterogeneity in slope observed in the data (see Figure 3). While none of this variation in slope was predicted by exposure hours, concussion history, or APOE status (or their interactions), there is clear variation in the magnitude and direction of modulation of strength. As such, this may suggest that modulation of strength is governed by some variable not included in our model; maybe some other factor is proving more influential in predicting this modulation than the variables included in the present study. Additionally, and importantly, preliminary analyses on this fronto-parietal network data revealed a high degree of heterogeneity in fMRI BOLD data within this sample (Lane et al., 2014). While it may still be the case that the results here are subject to missing variable problems, it may also be the case that neural data within this sample is just highly variable overall.

Limitations

Though the results of the study may provide insight as to the neurocognitive processes of aging within a sample of retired football players, they may also be subject to several limitations in the design of the study. Most critically to the present results, the uneven sample size of APOE-ε4+ (n=18) and APOE-ε4- (n=45) participants may have contributed towards the present study's risk of both Type I and Type II error. However, since p-values in each set of analyses were

adjusted, and since only one set of analyses showed an effect of APOE status on outcome measures, it may be more likely that the present results were subject to Type II error than to Type I. Additionally, while it is unfortunate that sample sizes in each genotype category were not equivalent, the prevalence of APOE-ε4 in our sample (28.6%) is nonetheless higher than that of the general population (13.7%), making this study slightly better able to characterize this group than if it had been done in a more representative sample of the overall population (Farrer et al., 1997).

Another concern lies in the estimation of concussion history. While past studies have suggested that overall, self-report concussion history may be a fairly accurate measure of number of concussions sustained (Kerr, Marshall, & Guskiewicz, 2012), recent evidence has suggested that this estimate may not be quite as reliable as previously thought (Z. Y. Kerr et al., 2015). Thus, since the present study utilized a self-report measure of number of concussions, this reported number might not be a perfectly accurate representation of actual history of concussions received. Additionally, when data on concussion history was collected, former college players were asked to report any concussions sustained during their college football careers, and former NFL players were asked to report any concussions sustained during their professional football careers. As such, both estimates overlook concussions sustained prior to the athlete's most recent football experience, and thus are likely to underestimate total concussions sustained by the athlete. Clearly this is a limitation in establishing an accurate estimate of concussions sustained by the participants, and could significantly contribute to the lack of effect of concussion history observed in the present study. However, given that the present study was conducted on previously collected data, this limitation was unfortunately unavoidable given the design of the study.

Relating to more specific limitations of the measurements utilized in the present study, aspects of the neurocognitive and functional connectivity data may also have limited our ability to observe an effect of the predictors of interest. Specific to neurocognitive task data, it may have been the case that analyzing these more general tasks included in a neuropsychological battery of tasks (CNSVS or RBANS) may have been a slightly cruder estimation of cognitive ability than had the present study utilized more sensitive measures of cognitive function (i.e., relational memory, attentional control, and reversal learning tasks). However, since overall trends towards selective deficits in memory were observed in the RBANS sub-test data, this limitation may not have significantly impacted results. Additionally, results from functional connectivity analyses may have been limited by the fact that such a small, dense network was used in analyses. Since all participants showed a great degree of correlated activity in this fronto-parietal network, it may be the case that few differences were found due to the fact that participants were effectively recruiting this network at "ceiling". However, since some differences were observed at the 2-back level, and there was clearly heterogeneity in parametric modulation of the network, the density of this network may not have affected results significantly. In that vein, the high degree of heterogeneity within this sample may have also affected the present study's results, however since the heterogeneity in itself may be informative, it may not be a limitation so much as an important consideration in studies on individuals with a history of neural trauma.

Implications

The results from the present study may have important implications about the role of subconcussive exposure, concussion history, and genotype on cognitive aging in retired athletes. First, regarding the results of the cognitive tasks, the finding that overall retired athletes in the present study showed relatively lower performance on measures of memory suggests that

regardless of degree of exposure to head trauma, retired football players may be at risk for memory complaints later in life. Since this sample was relatively young compared to traditional samples of older adults, these trends of selective deficits in memory may be important to monitor as this population ages. However, since the present sample's cognitive performance did not significantly differ from that of controls, this sample may not show any degree of observable memory impairment – but they may show slightly lower performance on tasks of memory relative to other tasks of cognition (unlike control participants). Second, the findings that there were no differences in more specific measures of memory, executive function, and attention based on exposure, concussion history, or genotype could also affect what types of populations we consider "at risk". While at present individuals with high concussion histories, or exposure to repeated subconcussive impacts may be considered most at risk for accelerated patterns of cognitive aging, it could be the case that at the 50-65-year-old age window there are no observed impairments based on those risk factors. While popular opinion may suggest that football players with concussions are all at risk of an early death and early onset of memory impairments, results from the present study indicate that at least by age 65 these individuals perform just as well as control participants on these tasks. Thus, these individuals are not by any means globally impaired, nor are they showing signs of neurodegenerative disorder yet.

Beyond differences in cognitive task performance, functional connectivity results also might help illuminate what neural processes might be at risk of dysfunction. The finding that exposure hours and APOE status only affect functional connectivity at the hardest level of the n-back task suggests that it might be the case that APOE status affects participants' ability to compensate for neural trauma when task demands are high. This finding may be crucial towards gaining a better understanding of how neural trauma (exposure) and a genetic marker

representing propensity to accrue damage from neural trauma (APOE) might interact in affecting neural efficiency during a cognitive task. Additionally, since ROI-specific analyses suggested that genotype moderates the effect of concussion and exposure at an ROI level in parietal regions, it may be the case that neural damage affects connectivity at the local as well as the network level. While participants did not show any behavioral differences on this task, the fact that these "at risk" individuals are showing a lesser ability to engage in compensatory recruitment of the task-specific network might make these individuals more vulnerable to impairments in cognitive function over time as they become less able to compensate for accruing damage.

Future Directions

Future studies on this topic might employ a variety of different techniques to gain a better understanding of the unique and combined effects of exposure to subconcussive impacts, concussion history, and genotype in predicting patterns of neurocognitive impairment in aging athletes. In particular, one of the assumptions made in the present study was that APOE status was associated with a biological propensity to metabolize proteins associated with accrued neural damage (Leoni et al., 2010), however we were unable to assess tau deposition in the context of the present study. As such, future studies should employ techniques such as FDDNP-PET (Small et al., 2013) in order to directly link aspects of cognitive function to patterns of neural damage within this sample.

Additionally, the present study utilized the graph theory metric of strength to measure strength of connections among regions within a working memory network during task performance. While some differences in connectivity strength were observed in the context of this study, future studies should examine larger-scale brain networks to assess how individuals

with varying levels of neural trauma (i.e., subconcussive impacts and concussions) are able to engage in segregation of networks and integration of networks as per demands of a task. While the metric of "strength" worked well within the present study, since the network utilized was small and quite dense, other graph theory metrics looking at more specific types of network organizational properties were not employed (Sporns, 2011). If other networks were included along with a fronto-parietal task-relevant network, or if the network was broadened to include less task-specific regions, future studies might be able to greatly build upon our understanding of how large-scale functional connectivity is affected by trauma. Further, these findings could be combined with an analysis of DTI white matter integrity to see how white matter perturbations implicated in concussive injury (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012; Cubon, Putukian, Boyer, & Dettwiler, 2011; Zhang et al., 2010) might influence connectivity.

Most importantly, all of these aspects must be in some way linked together to develop a comprehensive theory of the influence of concussive and subconcussive injury on cognitive aging. Based on results from the current study, there is no existing theory of cognitive aging that might account for the deficits observed in this sample, so future studies must probe more specific aspects of cognition in tandem with more comprehensive evaluations of neural integrity in order to develop a more complete picture of the effects of earlier-life neural injury on cognitive aging. The present study suggests that individuals with exposure to football may be at a greater risk for memory impairments, and that those who are APOE-ε4+ might be less able to compensate for neural trauma, but future studies should delve more into what aspects of memory might be specifically vulnerable to trauma (i.e., associative memory, visual working memory, etc.), and attempt to link those patterns of impairment to types of neural damage.

APPENDIX 1: TABLES AND FIGURES OF RESULTS

Table 1

Demographics and neurological/psychological test results. MMSE=Mini-Mental Status Exam; CDR=Clinical Dementia Rating; BDI=Beck Depression Inventory

	College (n=32)		PRO (n=31)			
	Low Concussion (n=16)	High Concussion (n=16)	Low Concussion (n=16)	High Concussion (n=15)	*Overall*	ANOVA p-value
Age	59 (4.02)	58.19 (3.43)	58.75 (3.87)	57.87 (3.74)	58.46 (3.71)	0.831
%Nonhispanic White	87.5	100	81.3	86.7	88.9	n/a
Number of Concussions	0.63 (0.5)	7.19 (6.88)	0.44 (0.51)	7 (6.96)	3.76 (5.79)	<.001
Years of Football Played	3.97 (0.64)	4.16 (0.63)	13.69 (2.43)	13.92 (3.86)	6.86 (3.51)	<.001
Weighted Exposure Hours	1048.91 (310.94)	1332.67 (263.55)	3246.86 (1238.6)	3041.72 (1609.35)	2153.66 (1408.66)	<.001
MMSE (total)	29.31 (1.08)	29.19 (0.91)	29 (1.37)	28.8 (1.32)	29.08 (1.17)	0.646
APOE	5	6	2	5	18	n/a
BDI	5.06 (5.6)	9.88 (6.63)	5.69 (7.1)	5.47 (5.34)	6.54 (6.39)	0.112
CDR (#>0)	5	3	1	6	15	n/a

±Concussions reported for the PRO Group include only the concussions sustained during National Football League career, while concussions reported for the COL Group include only the concussions sustained during college career.

Table 2

Total number of participants per analysis with reasons for exclusion of data (if applicable).

Test	Number of Participants	Reason for Exclusion
RBANS Subtests	63	n/a
CNSVS - memory	61	Invalid data for participants 1569 and 2119
CNSVS - Stroop	61	Invalid data for participants 1569 and 2079
CNSVS - attention	62	Invalid data for participant 1569
CNSVS - symbol digit	62	Invalid data for participant 1569
Connectivity	62	Negative connection weights for 1533 not appropriate for strength analysis

Table 3

RBANS subtest z-scores relative to Randolph et al. (2013) Healthy Control data overall and by concussion/exposure/APOE status grouping. In order for the z-score to be considered significant, it had to be at least ±1.695.

Model	APOE Status		Immediate Memory	Visuospatial	Language	Attention	Delay Memory
APOE & Concussion	APOE-	Low Concussion	-0.45	0.05	0.01	0.54	-0.55
		High Concussion	-0.63	0.04	-0.13	-0.01	-0.90
	APOE+	Low Concussion	-0.90	-0.18	-0.20	-0.13	-0.95
		High Concussion	0.49	-0.10	0.08	0.08	-0.52
APOE & Exposure	APOE-	Low Exposure	-0.81	0.06	-0.07	0.07	-0.81
		High Exposure	-0.28	0.04	-0.04	0.49	-0.61
	APOE+	Low Exposure	0.32	0.02	0.10	-0.05	-0.39
		High Exposure	-0.65	-0.37	-0.24	0.08	-1.16
OVERALL			-0.39	-0.01	-0.05	0.21	-0.70

Table 4

CNSVS regression analysis results.

Model	DV	Coefficient							Adjusted R-squared
		Exposure Hours (E)	Number of Concussions (C)	APOE (A)	ExA	ExC	CxA	ExCxA	
Accuracy	Delay Memory	<.01 (.15)	<.01 (.67)	0.22 (.02)	<.01 (.05)	<.01 (.28)	0.01 (.71)	<.01 (.61)	0.12
	Immediate Memory	<.01 (.74)	<.01 (.84)	-0.04 (.66)	<.01 (.69)	<.01 (.88)	0.02 (.35)	<.01 (.54)	-0.04
	Symbol Digit	<.01 (.84)	0.65 (.03)	-0.23 (.96)	<.01 (.52)	<.01 (.07)	0.01 (.99)	<.01 (.93)	.08
	Shifting Attention	<.01 (.20)	0.45 (.22)	1.87 (.75)	<.01 (.28)	<.01 (.19)	-0.36 (.79)	<.01 (.62)	-0.04
Reaction Time	Delay Memory	0.23 (0.13)	-1.41 (.75)	52.11 (.47)	0.01 (.67)	<.01 (.14)	22.52 (.18)	-0.01 (.07)	0.11
	Immediate Memory	<-.01 (.86)	-3.72 (.44)	7.3 (.92)	0.01 (.76)	<.01 (.16)	21.75 (.22)	<-.01 (.3)	-0.02
	Shifting Attention	-0.02 (.45)	-12.12 (.06)	-119.69 (.24)	0.07 (.14)	0.01 (.09)	62.13 (.01)	-0.03 (.005)*	0.07
	Stroop Effect	<-.01 (.42)	-4.5 (.16)	-30.76 (.55)	<.01 (.69)	<.01 (.05)	15.17 (.2)	<-.01 (.13)	<.01

*Significant at p<.00625 level

Table 5

Univariate fMRI Analysis Results.

			MNI coordinates				
Region of Interest	Hemisphere	BA	x	y	z	t-value	p-value
1-back>0-back: Low Concussion Group > High Concussion Group							
Orbital Frontal Gyrus	R	11	18	26	-8	4.49	<0.001
Orbital Frontal Gyrus	L	11	-16	48	-14	4.16	<0.001
Caudate	L	n/a	-14	24	-6	3.80	<0.001
Fusiform Gyrus	R	37	42	-50	-22	3.71	<0.001
Nucleus Accumbens	R	n/a	10	8	-2	3.68	<0.001
Orbital Frontal Gyrus	L	11	0	40	-16	3.53	<0.001
Lingual Gyrus	R	19	32	-58	2	3.46	0.001
2-back>0-back: Low Exposure Group > High Exposure Group							
Superior Temporal Gyrus	L	21	-56	-14	-4	4.17	<0.001
Fusiform Gyrus	R	37	34	-44	-16	3.45	0.001
2-back>0-back: High Concussion Group > Low Concussion Group							
Cuneus	R	19	14	-82	32	4.09	<0.001
Supramarginal Gyrus	L	40	-48	-40	26	3.93	<0.001
Superior Temporal Gyrus	L	22	-52	-40	18	3.73	<0.001
2-back>1-back: High Concussion Group > Low Concussion Group							
Superior Temporal Gyrus	R	22	68	-26	8	5.04	<0.001
Insula	R	n/a	36	-10	12	3.99	<0.001
Inferior Parietal Lobule	R	40	38	-44	26	4.29	<0.001
Inferior Parietal Lobule	R	40	44	-48	30	3.56	<0.001
Orbital Gyrus	L	11	-20	26	-12	3.27	0.001
Superior Occipital Gyrus	R	19	20	-90	32	4.02	<0.001
Amygdala	L	34	-20	-2	-14	4.00	<0.001
Fusiform Gyrus	L	37	-40	-46	-8	3.89	<0.001
Middle Temporal Gyrus	R	22	52	-62	12	3.84	<0.001
Superior Temporal Gyrus	R	39	56	-58	22	3.64	<0.001
Middle Temporal Gyrus	R	21	50	-48	-2	3.48	<0.001
Inferior Frontal Gyrus	R	45	50	36	0	3.84	<0.001
Posterior Cingulate	L	30	-20	-54	14	3.80	<0.001
Superior Occipital Gyrus	L	19	-20	-88	30	3.72	<0.001
Cuneus	L	19	-12	-88	26	3.30	0.001
Fusiform Gyrus	R	37	38	-48	-22	3.68	<0.001
Posterior Cingulate	R	30	8	-52	10	3.64	<0.001
Cingulate Gyrus	L	31	-14	-46	26	3.59	<0.001
Orbital Gyrus	R	11	22	32	-14	3.57	<0.001
Orbital Gyrus	R	11	26	36	-8	3.43	0.001
Inferior Frontal Gyrus	R	47	34	40	-10	3.32	0.001
Middle Occipital Gyrus	R	19	42	-78	14	3.52	<0.001
Orbital Gyrus	L	11	-14	48	-14	3.45	0.001
Fusiform Gyrus	R	37	38	-52	-6	3.36	0.001

Table 6

Strength connectivity regression results with predictors of number of concussions (C), contact exposure hours (E), and APOE status (A).

Model	DV	Intercept	Coefficient							Adjusted R-squared
			E	C	A	ExA	ExC	CxA	ExCxA	
Parametric Modulation of Network Strength	Slope of Strength (0-1-2-back)	-6.4 (.03)	<.01 (.05)	.08 (.83)	6.48 (.25)	<-.01 (.3)	<-.01 (.99)	-0.95 (.53)	<.01 (.7)	-0.01
Network Strength	0-back	66.54 (<.01)	<.01 (.74)	.34 (.55)	11.49 (.2)	<-.01 (.09)	<-.01 (.82)	-2.71 (.25)	<.01 (.29)	-0.04
	1-back	64.1 (<.01)	<.01 (.17)	.44 (.46)	8.53 (.36)	<-.01 (.34)	<-.01 (.14)	-2.95 (.24)	<.01 (.22)	<.01
	2-back	53.73 (<.01)	.006 (<.01)*	.5 (.31)	24.45 (<.01)*	-0.01 (<.01)*	<-.01 (.77)	-4.6 (.03)	<.01 (.08)	.17

*Significant at p<.0125 level

Table 7

2x2x3 MANOVA analysis results illustrating the effects of concussion history (C), exposure history (E), and APOE status (A) on ROI-level connectivity. Results are comprised of F-values (all with df_{error}=174) with p-values in parentheses.

	Concussion & APOE MANOVA			Exposure & APOE MANOVA		
	C	A	CxA	E	A	ExA
LDLPFC	0.07 (.79)	0.06 (.80)	0.10 (.76)	0.07 (.80)	<.01 (.98)	3.24 (.07)
Lfrontal	<.01 (.95)	0.04 (.85)	0.15 (.70)	0.16 (.70)	0.15 (.70)	1.29 (.26)
LIPL	4.02 (.05)*	1.53 (.22)	2.08 (.15)	0.01 (.93)	2.77 (.10)	1.75 (.19)
LIPS	6.39 (.01)**	0.01 (.92)	4.88 (.03)**	1.88 (.17)	0.64 (.43)	3.99 (.05)*
Lprecun	0.38 (.54)	0.11 (.74)	0.03 (.87)	<.01 (.95)	0.50 (.48)	5.52 (.02)**
midcingulate	0.18 (.67)	1.15 (.29)	1.07 (.30)	0.78 (.38)	2.16 (.14)	3.57 (.06)
RDLPFC	1.47 (.23)	1.13 (.29)	0.54 (.47)	0.90 (.35)	1.23 (.27)	0.11 (.74)
Rfrontal	0.53 (.47)	1.47 (.23)	0.67 (.41)	3.24 (.07)	0.99 (.32)	0.04 (.84)
RIPL	2.44 (.12)	0.55 (.46)	4.29 (.04)**	0.18 (.67)	1.63 (.20)	3.04 (.08)
RIPS	0.29 (.59)	0.07 (.80)	2.82 (.10)	0.58 (.45)	0.01 (.92)	1.79 (.18)
Rprecun	0.02 (.88)	0.69 (.41)	0.33 (.57)	0.57 (.45)	1.44 (.23)	5.63 (.02)**

*p=.047
**p<.05

Table 8

Means (standard deviations in parentheses) for main effect and interaction effects observed in Table 7.

	ROI	Interaction	Low Concussion	High Concussion
2x2x3 MANOVA: Concussion & APOE	LIPL	n/a	5.97 (1.34)	5.59 (1.68)
	LIPS	APOE-	6.06 (1.33)	5.98 (1.37)
		APOE+	6.65 (0.85)	5.44 (2.42)
	RIPL	APOE-	6.24 (1.38)	6.37 (1.14)
		APOE+	6.58 (1.19)	5.66(2.43)
			Low Exposure	High Exposure
2x2x3 MANOVA: Exposure & APOE	L precuneus	APOE-	6.03 (1.17)	6.48 (1.04)
		APOE+	6.35 (1.31)	5.88 (1.22)
	R precuneus	APOE-	6.38 (1.06)	6.67 (0.95)
		APOE+	6.59 (1.13)	6.04 (1.08)
	LIPS	APOE-	5.94 (1.41)	6.10 (1.29)
		APOE+	6.25 (1.68)	5.36 (2.45)
2x2x2x3 MANOVA	Midcingulate	APOE-	5.56 (1.41)	5.82 (1.45)
		APOE+	5.42 (1.52)	4.95 (2.19)

Table 9

2x2x2x3 MANOVA analysis results illustrating the unique and interactive effects of concussion history (C), exposure history (E), and APOE status (A) on ROI-level connectivity. Results are comprised of F-values (all with df_{error}=162) with p-values in parentheses.

	C	E	A	CxA	ExA	ExC	CxExA
LDLPFC	0.02 (.90)	0.06 (.81)	<.01 (.98)	0.12 (.73)	2.93 (.09)	<.01 (.96)	0.04 (.85)
Lfrontal	0.04 (.84)	0.15 (.70)	0.16 (.69)	0.08 (.79)	1.22 (.27)	<.01 (.98)	0.04 (.84)
LIPL	3.74 (.06)	0.16 (.69)	1.45 (.23)	2.05 (.15)	1.07 (.30)	0.02 (.88)	0.68 (.41)
LIPS	7.73 (.01)***	0.45 (.50)	0.01 (.94)	6.01 (.02)**	1.95 (.16)	0.85 (.36)	4.25 (.04)**
Lprecun	0.04 (.84)	0.03 (.86)	0.51 (.48)	0.01 (.91)	5.51 (.02)**	0.43 (.51)	0.25 (.62)
midcingulate	<.01 (.95)	1.39 (.24)	2.47 (.12)	1.90 (.17)	4.00 (.05)*	0.19 (.66)	1.29 (.26)
RDLPFC	1.19 (.28)	0.91 (.34)	0.74 (.39)	0.53 (.47)	0.05 (.83)	0.00 (.99)	0.11 (.74)
Rfrontal	0.58 (.45)	3.28 (.07)	0.58 (.45)	0.92 (.34)	0.09 (.76)	0.02 (.90)	0.01 (.94)
RIPL	3.09 (.08)	0.01 (.93)	0.46 (.50)	5.51 (.02)**	1.39 (.24)	2.37 (.13)	0.98 (.32)
RIPS	0.18 (.67)	0.73 (.40)	0.09 (.79)	2.83 (.09)	1.26 (.26)	0.33 (.57)	0.19 (.66)
Rprecun	0.75 (.39)	1.36 (.25)	2.34 (.13)	1.39 (.24)	7.34 (.01)***	2.05 (.16)	2.03 (.16)

*p=.047
**p<.05
***p<.01

Figure 1

Example of connectivity strength calculation for LDLPFC: each line between regions represents a correlation computed, and the sum of all lines represents LDLPFC strength.

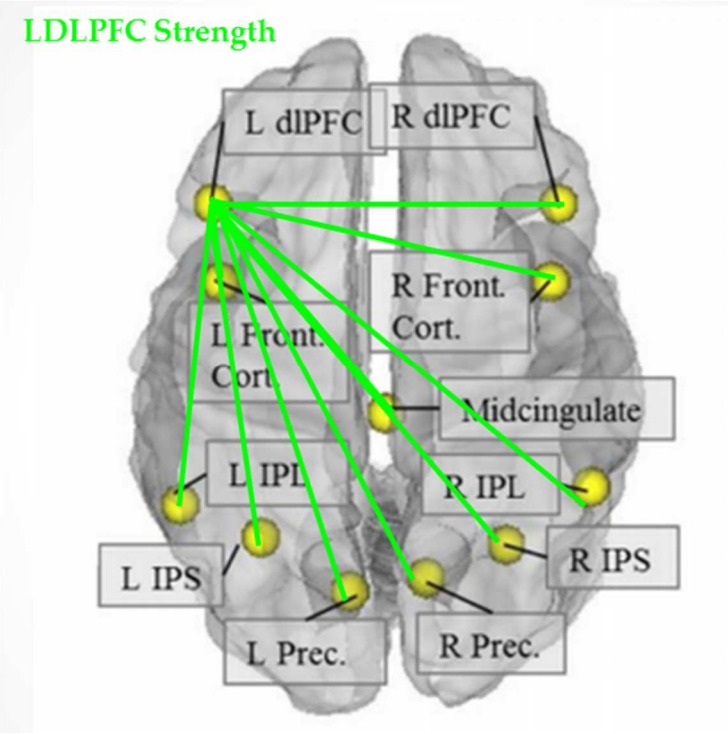


Figure 2

RBANS graph of subtest means.

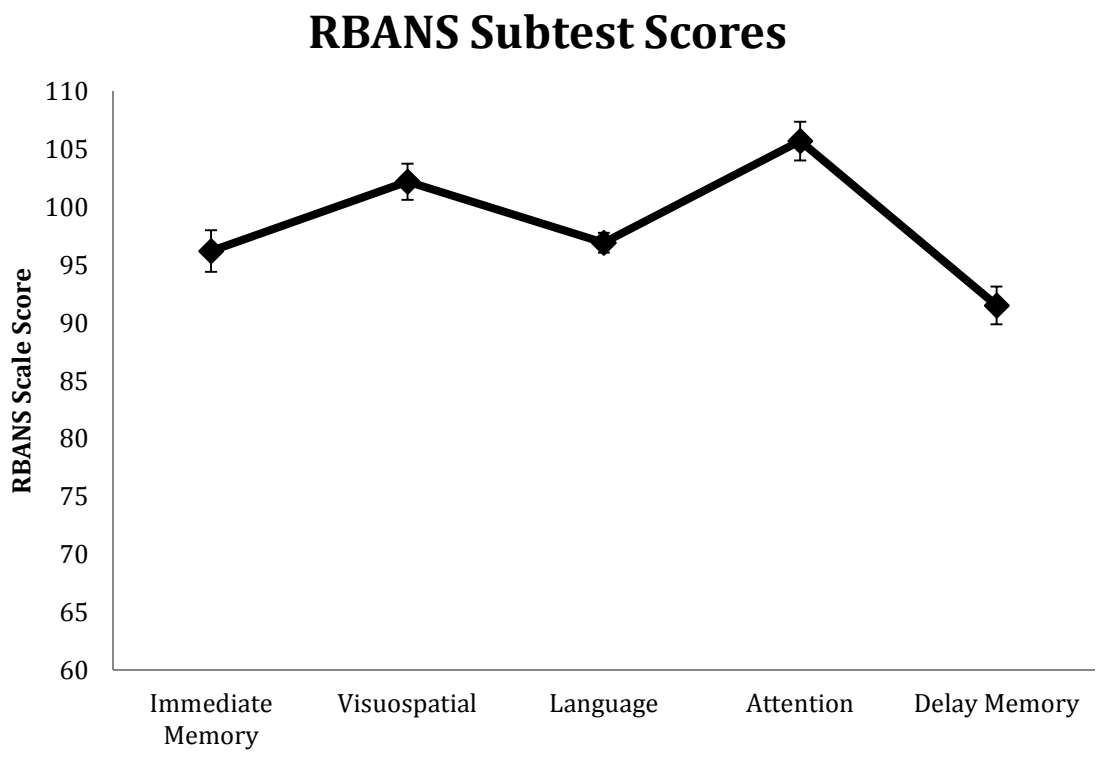


Figure 3

All participant connectivity strength slopes.

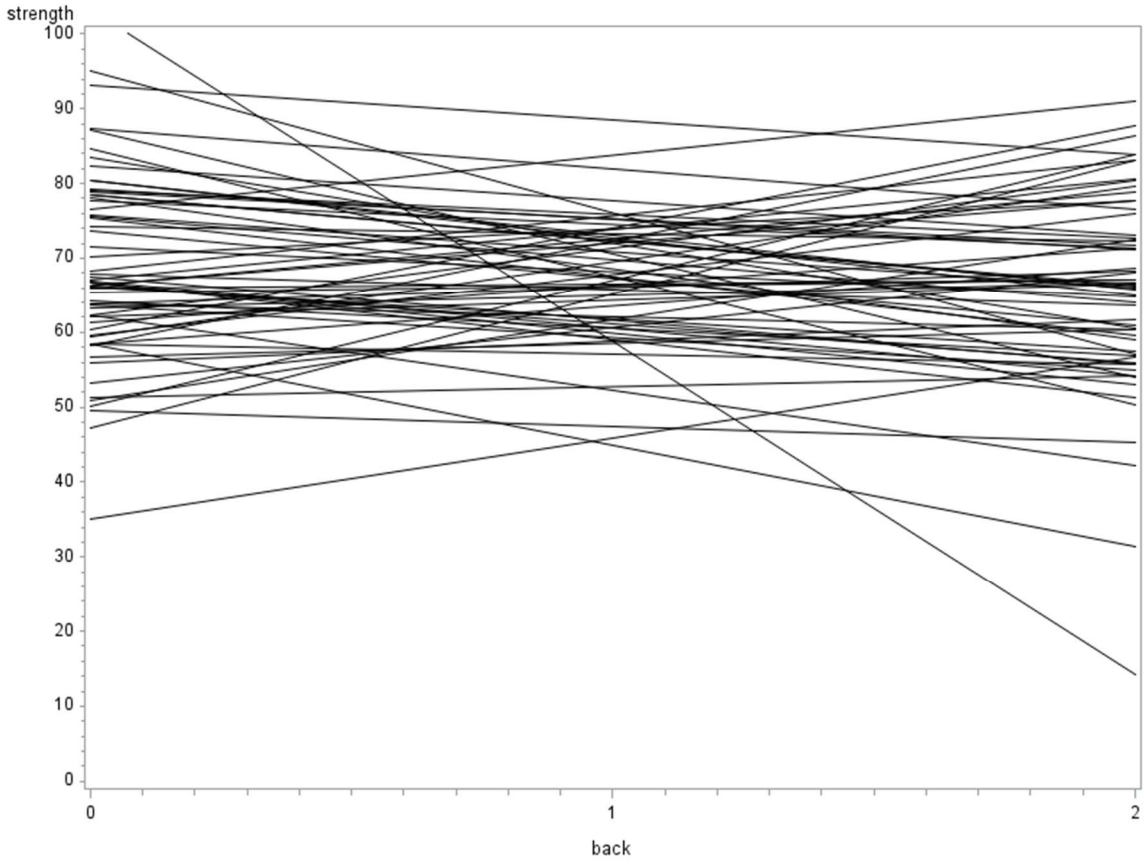


Figure 4

Graph of 2-back strength interaction between exposure and APOE status.

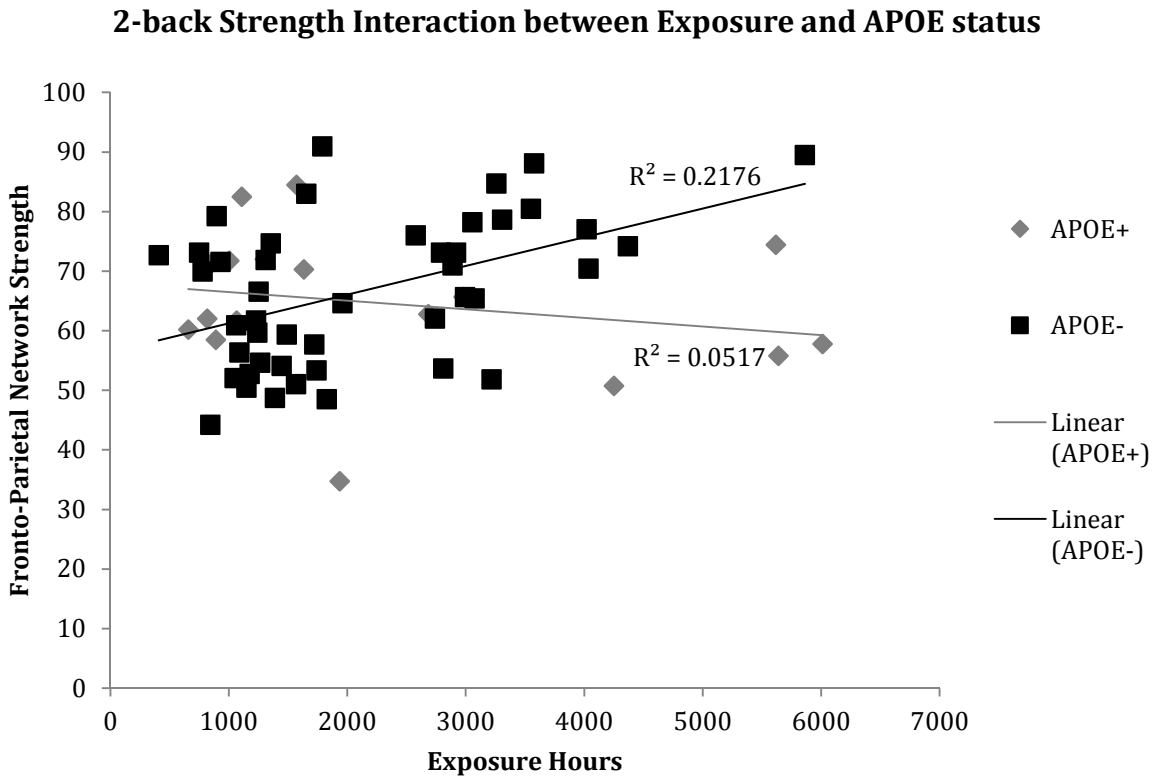


Figure 5

3-way interaction between concussion history (C), exposure history (E), and APOE status (A) on connection strength in the LIPS.

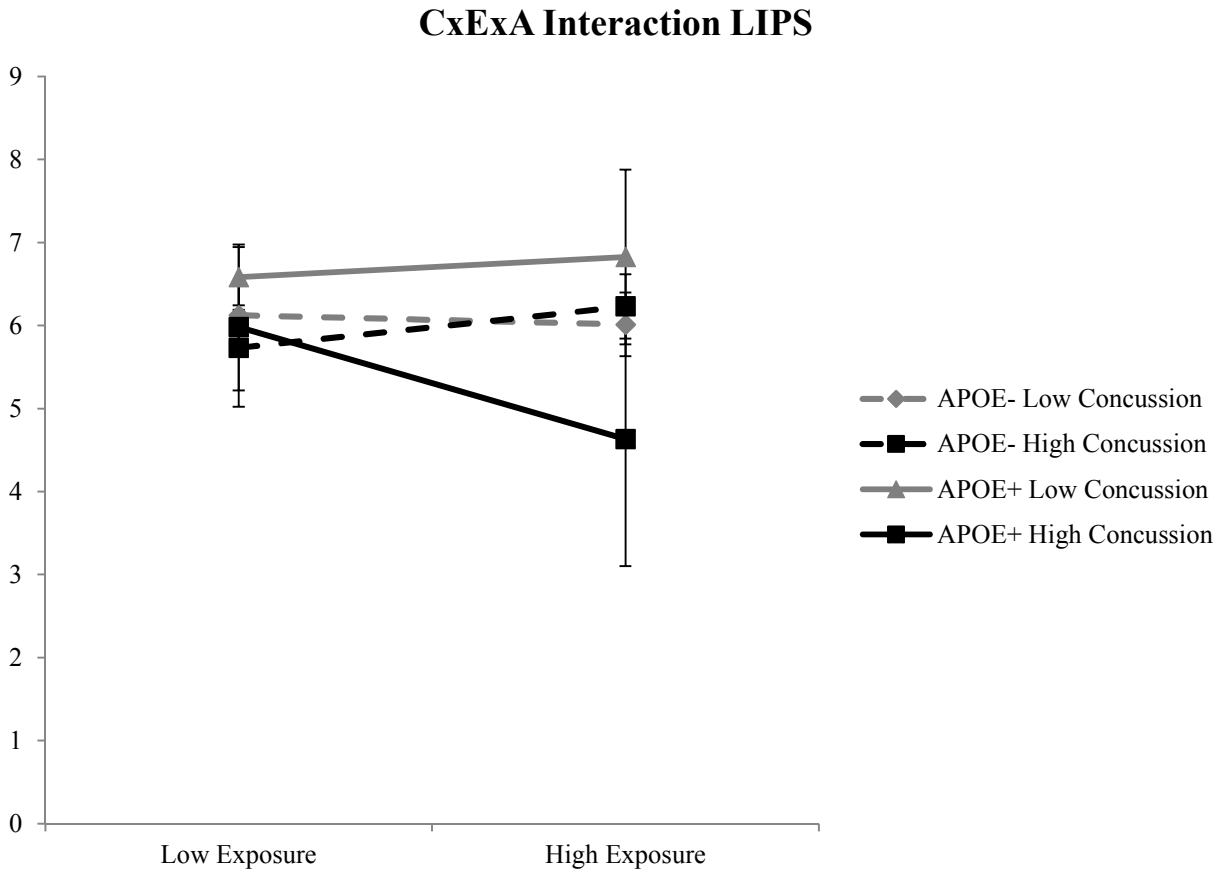
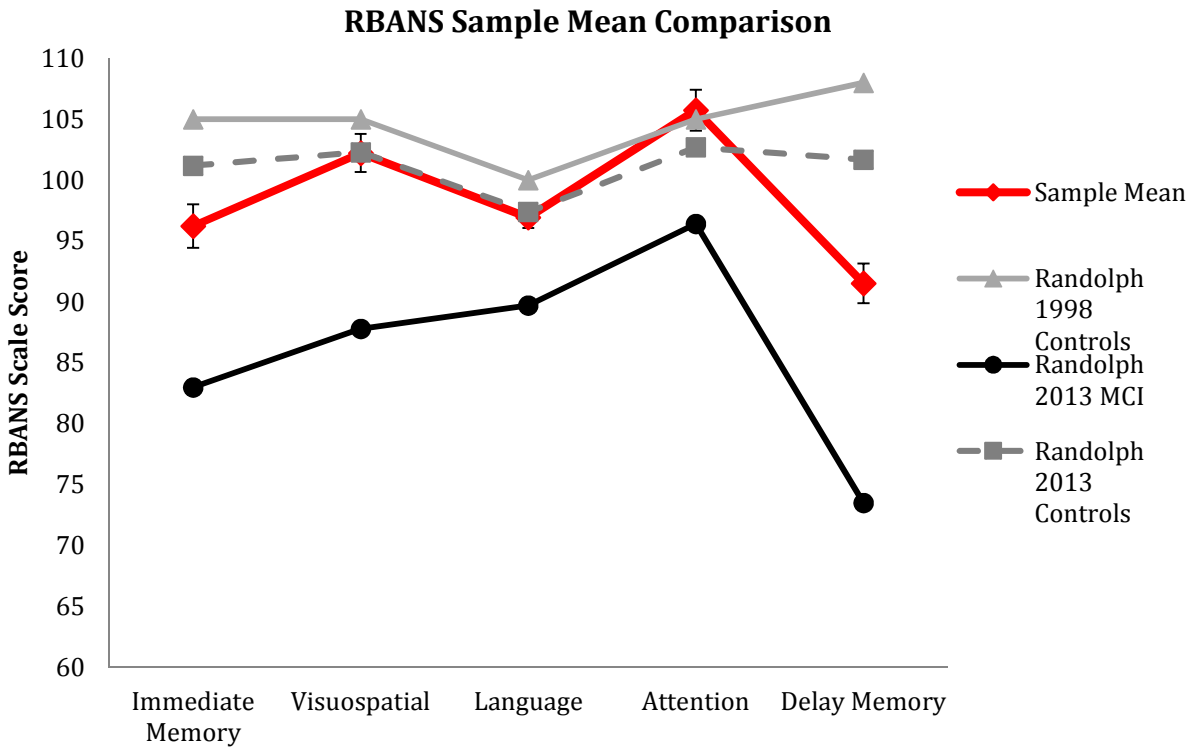


Figure 6

RBANS subtest scores as compared to data from Randolph (1998) and Randolph (2013) data.



REFERENCES

CDC, C. f. D. C. a. P. (2007). Nonfatal traumatic brain injuries from sports and recreation activities--United States, 2001-2005. *MMWR Morb Mortal Wkly Rep, 56*(29), 733-737.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 270-279. doi: 10.1016/j.jalz.2011.03.008

Anderson, N. D., Craik, F. I., & Naveh-Benjamin, M. (1998). The attentional demands of encoding and retrieval in younger and older adults: 1. Evidence from divided attention costs. *Psychol Aging, 13*(3), 405-423.

Babcock, R. L., Laguna, K. D., & Roesch, S. C. (1997). A comparison of the factor structure of processing speed for younger and older adults: testing the assumption of measurement equivalence across age groups. *Psychol Aging, 12*(2), 268-276.

Baddeley, A. (1992a). Working memory. *Science, 255*(5044), 556-559.

Baddeley, A. (1992b). Working Memory: The Interface between Memory and Cognition. *J Cogn Neurosci, 4*(3), 281-288. doi: 10.1162/jocn.1992.4.3.281

Baddeley, A., & Della Sala, S. (1996). Working memory and executive control. *Philos Trans R Soc Lond B Biol Sci, 351*(1346), 1397-1403; discussion 1403-1394. doi: 10.1098/rstb.1996.0123

Baddeley, A. D., Bressi, S., Della Sala, S., Logie, R., & Spinnler, H. (1991). The decline of working memory in Alzheimer's disease. A longitudinal study. *Brain, 114 (Pt 6)*, 2521-2542.

Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol Aging, 12*(1), 12-21.

Baugh, C. M., Stamm, J. M., Riley, D. O., Gavett, B. E., Shenton, M. E., Lin, A., . . . Stern, R. A. (2012). Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging Behav, 6*(2), 244-254. doi: 10.1007/s11682-012-9164-5

Bazarian, J. J., Zhu, T., Blyth, B., Borrino, A., & Zhong, J. (2012). Subject-specific changes in brain white matter on diffusion tensor imaging after sports-related concussion. *Magn Reson Imaging, 30*(2), 171-180. doi: 10.1016/j.mri.2011.10.001

Beck, A. T., Steer, R. A., & Brown, G. (1996). Manual for the Beck Depression Inventory-II. San Antonio, TX: The Psychological Corporation.

Benton, A. L., Hamsher, K., & Sivan, A. B. (1983). Multilingual aphasia examination (3rd ed.). Iowa City, IA: AJA Associates.

Bruce, J. M., & Echemendia, R. J. (2003). Delayed-onset deficits in verbal encoding strategies among patients with mild traumatic brain injury. *Neuropsychology, 17*(4), 622-629. doi: 10.1037/0894-4105.17.4.622

Cabeza, R. (2002). Hemispheric asymmetry reduction in old adults:The HAROLD Model. *Psychology and Aging, 17*, 85-100. doi: 10.1037/0882-7974.17.1.85

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., & Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb Cortex, 14*(4), 364-375.

Castel, A. D., & Craik, F. I. (2003). The effects of aging and divided attention on memory for item and associative information. *Psychol Aging, 18*(4), 873-885. doi: 10.1037/0882-7974.18.4.873

Chang, Y. L., Fennema-Notestine, C., Holland, D., McEvoy, L. K., Stricker, N. H., Salmon, D. P., . . . Initiative, f. t. A. s. D. N. (2013). APOE interacts with age to modify rate of decline in cognitive and brain changes in Alzheimer's disease. *Alzheimers Dement*. doi: 10.1016/j.jalz.2013.05.1763

Conway, A. R., & Engle, R. W. (1996). Individual differences in working memory capacity: more evidence for a general capacity theory. *Memory, 4*(6), 577-590. doi: 10.1080/741940997

Conway, A. R., Kane, M. J., & Engle, R. W. (2003). Working memory capacity and its relation to general intelligence. *Trends Cogn Sci, 7*(12), 547-552.

Cox, R. W., & Hyde, J. S. (1997). Software tools for analysis and visualization of fMRI data. *NMR Biomed, 10*(4-5), 171-178.

Craik, F., & Jennings, J. M. (1992). Human Memory. In F. I. M. Craik & T. A. Salthouse (Eds.), *The Handbook of Aging and Cognition* (pp. 51-110). Hillsdale, NJ, England: Lawrence Erlbaum Associates, Inc.

Craik, F. I. M., & Byrd, M. (1982). Aging and cognitive deficits: The role of attentional resources. In F. I. M. Craik & S. Trehub (Eds.), *Aging and Cognitive Processes* (pp. 191-211). New York: Plenum Press.

Crisco, J. J., Fiore, R., Beckwith, J. G., Chu, J. J., Brolinson, P. G., Duma, S., . . . Greenwald, R. M. (2010). Frequency and location of head impact exposures in individual collegiate football players. *Journal of athletic training, 45*(6), 549.

Cubon, V. A., Putukian, M., Boyer, C., & Dettwiler, A. (2011). A diffusion tensor imaging study on the white matter skeleton in individuals with sports-related concussion. *J Neurotrauma, 28*(2), 189-201. doi: 10.1089/neu.2010.1430

De Beaumont, L., Théoret, H., Mongeon, D., Messier, J., Leclerc, S., Tremblay, S., . . . Lassonde, M. (2009). Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain, 132*(Pt 3), 695-708. doi: 10.1093/brain/awn347

De Blasi, S., Montesanto, A., Martino, C., Dato, S., De Rango, F., Bruni, A. C., . . . Passarino, G. (2009). APOE polymorphism affects episodic memory among non demented elderly subjects. *Exp Gerontol, 44*(3), 224-227. doi: 10.1016/j.exger.2008.11.005

Dennis, N. A., Browndyke, J. N., Stokes, J., Need, A., Burke, J. R., Welsh-Bohmer, K. A., & Cabeza, R. (2010). Temporal lobe functional activity and connectivity in young adult APOE varepsilon4 carriers. *Alzheimers Dement, 6*(4), 303-311. doi: 10.1016/j.jalz.2009.07.003

Dettwiler, A., Murugavel, M., Putukian, M., Cubon, V., Furtado, J., & Osherson, D. (2014). Persistent differences in patterns of brain activation after sports-related concussion: a longitudinal functional magnetic resonance imaging study. *J Neurotrauma, 31*(2), 180-188. doi: 10.1089/neu.2013.2983

Dosenbach, N. U., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A., . . . Petersen, S. E. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci U S A, 104*(26), 11073-11078. doi: 10.1073/pnas.0704320104

Engle, R. W., Tuholski, S. W., Laughlin, J. E., & Conway, A. R. (1999). Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. *J Exp Psychol Gen, 128*(3), 309-331.

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., . . . van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA, 278*(16), 1349-1356.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Ford, J. H., Giovanello, K. S., & Guskiewicz, K. M. (2013). Episodic memory in former professional football players with a history of concussion: an event-related functional neuroimaging study. *J Neurotrauma, 30*(20), 1683-1701. doi: 10.1089/neu.2012.2535

Gatz, M., Pedersen, N. L., Berg, S., Johansson, B., Johansson, K., Mortimer, J. A., . . . Ahlbom, A. (1997). Heritability for Alzheimer's disease: the study of dementia in Swedish twins. *J Gerontol A Biol Sci Med Sci, 52*(2), M117-125.

Gavett, B. E., Stern, R. A., & McKee, A. C. (2011). Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clin Sports Med, 30*(1), 179-188, xi. doi: 10.1016/j.csm.2010.09.007

Gessel, L. M., Fields, S. K., Collins, C. L., Dick, R. W., & Comstock, R. D. (2007). Concussions among United States high school and collegiate athletes. *J Athl Train, 42*(4), 495-503.

Greene, J. D., Hodges, J. R., & Baddeley, A. D. (1995). Autobiographical memory and executive function in early dementia of Alzheimer type. *Neuropsychologia, 33*(12), 1647-1670.

Gualtieri, C. T., & Johnson, L. G. (2006). Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsychol, 21*(7), 623-643. doi: 10.1016/j.acn.2006.05.007

Gualtieri, C. T., & Johnson, L. G. (2008). A computerized test battery sensitive to mild and severe brain injury. *Medscape J Med, 10*(4), 90.

Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Cantu, R. C., Randolph, C., & Jordan, B. D. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery, 57*(4), 719-726; discussion 719-726.

Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Harding, H. P., Matthews, A., . . . Cantu, R. C. (2007). Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc, 39*(6), 903-909. doi: 10.1249/mss.0b013e3180383da5

Guskiewicz, K. M., McCrea, M., Marshall, S. W., Cantu, R. C., Randolph, C., Barr, W., . . . Kelly, J. P. (2003). Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA, 290*(19), 2549-2555. doi: 10.1001/jama.290.19.2549

Hart, J., Kraut, M. A., Womack, K. B., Strain, J., Didehbani, N., Bartz, E., . . . Cullum, C. M. (2013). Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: a cross-sectional study. *JAMA Neurol, 70*(3), 326-335. doi: 10.1001/2013.jamaneurol.340

Hartman, M., & Hasher, L. (1991). Aging and suppression: memory for previously relevant information. *Psychol Aging, 6*(4), 587-594.

Hasher, L., Stoltzfus, E. R., Zacks, R. T., & Rypma, B. (1991). Age and inhibition. *J Exp Psychol Learn Mem Cogn, 17*(1), 163-169.

Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and aging: A review and a new view. In G. H. Bower (Ed.), *The Psychology of Learning and Motivation* (Vol. 22, pp. 193-225). San Diego, CA: Academic Press.

Hodges, J. R., Salmon, D. P., & Butters, N. (1990). Differential impairment of semantic and episodic memory in Alzheimer's and Huntington's diseases: a controlled prospective study. *J Neurol Neurosurg Psychiatry, 53*(12), 1089-1095.

Hodges, J. R., Salmon, D. P., & Butters, N. (1992). Semantic memory impairment in Alzheimer's disease: failure of access or degraded knowledge? *Neuropsychologia, 30*(4), 301-314.

Holdnack, H. A. (2001). Wechsler Test of Adult Reading: WTAR. San Antonio, TX: The Psychological Corporation.

Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. *Psychon Bull Rev, 9*(4), 637-671.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). Boston Naming Test. Philadelphia, PA: Lea & Febiger.

Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology, 43*(1), 13-20.

Kerr, Z., Littleton, A., Cox, L., Varangis, E., DeFreese, J., Lynall, R. C., . . . Guskiewicz, K. K. (2015). Estimating contact exposure in football using the Head Impact Exposure Estimate (HIEE). *J Neurotrauma*. doi: 10.1089/neu.2014.3666

Kerr, Z. Y., Marshall, S. W., & Guskiewicz, K. M. (2012). Reliability of concussion history in former professional football players. *Med Sci Sports Exerc, 44*(3), 377-382. doi: 10.1249/MSS.0b013e31823240f2

Kerr, Z. Y., Mihalik, J. P., Guskiewicz, K. M., Rosamond, W. D., Evenson, K. R., & Marshall, S. W. (2015). Agreement Between Athlete-Recalled and Clinically Documented Concussion Histories in Former Collegiate Athletes. *Am J Sports Med*. doi: 10.1177/0363546514562180

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *J Exp Psychol, 55*(4), 352-358.

Kutner, K. C., Erlanger, D. M., Tsai, J., Jordan, B., & Relkin, N. R. (2000). Lower cognitive performance of older football players possessing apolipoprotein E epsilon4. *Neurosurgery, 47*(3), 651-657; discussion 657-658.

Lane, S. T., Varangis, E., Henry, T., Giovanello, K., Guskiewicz, K., & Gates, K. (2014). *Quantifying heterogeneity in functional connectivity across a sports-related concussed sample*. Paper presented at the Organization for Human Brain Mapping, Hamburg, Germany.

Lehman, E. J., Hein, M. J., Baron, S. L., & Gersic, C. M. (2012). Neurodegenerative causes of death among retired National Football League players. *Neurology, 79*(19), 1970-1974. doi: 10.1212/WNL.0b013e31826daf50

Leoni, V., Solomon, A., & Kivipelto, M. (2010). Links between ApoE, brain cholesterol metabolism, tau and amyloid beta-peptide in patients with cognitive impairment. *Biochem Soc Trans, 38*(4), 1021-1025. doi: 10.1042/BST0381021

Li, S.-C., & Lindenberger, U. (1999). Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems dedifferentiation of cognitive abilities in oldage. In L.-G. Nilsson & H. J. Markowitsch (Eds.), *Cognitive Neuroscience of Memory* (pp. 103–146). Seattle: Hogrefe & Huber.

Lim, Y. Y., Ellis, K. A., Ames, D., Darby, D., Harrington, K., Martins, R. N., . . . Group, A. R. (2013). Aβ amyloid, cognition, and APOE genotype in healthy older adults. *Alzheimers Dement, 9*(5), 538-545. doi: 10.1016/j.jalz.2012.07.004

Mayers, L. B., Redick, T. S., Chiffriller, S. H., Simone, A. N., & Terraforte, K. R. (2011). Working memory capacity among collegiate student athletes: effects of sport-related head contacts, concussions, and working memory demands. *J Clin Exp Neuropsychol, 33*(5), 532-537. doi: 10.1080/13803395.2010.535506

McCrea, M., Hammeke, T., Olsen, G., Leo, P., & Guskiewicz, K. (2004). Unreported concussion in high school football players: implications for prevention. *Clin J Sport Med, 14*(1), 13-17.

McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., . . . Stern, R. A. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol, 68*(7), 709-735. doi: 10.1097/NEN.0b013e3181a9d503

Misra, C., Fan, Y., & Davatzikos, C. (2009). Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. *Neuroimage, 44*(4), 1415-1422. doi: 10.1016/j.neuroimage.2008.10.031

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology, 43*(11), 2412-2414.

Morris, R. G., & Baddeley, A. D. (1988). Primary and working memory functioning in Alzheimer-type dementia. *J Clin Exp Neuropsychol, 10*(2), 279-296. doi: 10.1080/01688638808408242

Mortimer, J. A., Schuman, L., & French, L. (1981). Epidemiology of dementing illness. In J. A. Mortimer & L. M. Schuman (Eds.), *<div data-angle="0" data-canvas-width="79.61725841712952" data-font-name="g_font_49_0" dir="ltr" style="font-size: 11.9736px; font-family: serif; left: 87.8044px; top: 269.735px; transform: rotate(0deg) scale(1.03916, 1); transform-origin: 0% 0% 0px;">The Epidemiology of Dementia: Monographs in Epidemiology and Biostatistics* (pp. 323-333). New York: Oxford University Press.

Mosconi, L., Perani, D., Sorbi, S., Herholz, K., Nacmias, B., Holthoff, V., . . . Pupi, A. (2004). MCI conversion to dementia and the APOE genotype: a prediction study with FDG-PET. *Neurology, 63*(12), 2332-2340.

Okello, A., Koivunen, J., Edison, P., Archer, H. A., Turkheimer, F. E., Någren, K., . . . Brooks, D. J. (2009). Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. *Neurology, 73*(10), 754-760. doi: 10.1212/WNL.0b013e3181b23564

Omalu, B. I., DeKosky, S. T., Minster, R. L., Kamboh, M. I., Hamilton, R. L., & Wecht, C. H. (2005). Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery, 57*(1), 128-134; discussion 128-134.

Pardini, J. E., Pardini, D. A., Becker, J. T., Dunfee, K. L., Eddy, W. F., Lovell, M. R., & Welling, J. S. (2010). Postconcussive symptoms are associated with compensatory cortical recruitment during a working memory task. *Neurosurgery, 67*(4), 1020-1027; discussion 1027-1028. doi: 10.1227/NEU.0b013e3181ee33e2

Perry, R. J., & Hodges, J. R. (1996). Spectrum of memory dysfunction in degenerative disease. *Curr Opin Neurol, 9*(4), 281-285.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol, 56*(3), 303-308.

Prevention, C. f. D. C. a. (2011). Nonfatal traumatic brain injuries related to sports and recreation activities among persons aged ≤19 years--United States, 2001-2009. *MMWR Morb Mortal Wkly Rep, 60*(39), 1337-1342.

Rabinowitz, J. C., Craik, F. I. M., & Ackerman, B. P. (1982). A Processing Resource Account of Age Differences in Recall. *Canadian Journal of Psychology, 36*(2), 325-344.

Randolph, C., Karantzoulis, S., & Guskiewicz, K. (2013). Prevalence and characterization of mild cognitive impairment in retired national football league players. *J Int Neuropsychol Soc, 19*(8), 873-880. doi: 10.1017/S1355617713000805

Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol, 20*(3), 310-319. doi: 10.1076/jcen.20.3.310.823

Reitan, R. M., & Wolfson, D. (1985). The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and clinical interpretation Tucson, AZ: Neuropsychological Press.

Risacher, S. L., Saykin, A. J., West, J. D., Shen, L., Firpi, H. A., McDonald, B. C., & (ADNI), A. s. D. N. I. (2009). Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. *Curr Alzheimer Res, 6*(4), 347-361.

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology, 7*(3), 273-295. doi: 10.1037/0894-4105.7.3.273

Sim, A., Terryberry-Spohr, L., & Wilson, K. R. (2008). Prolonged recovery of memory functioning after mild traumatic brain injury in adolescent athletes. *J Neurosurg, 108*(3), 511-516. doi: 10.3171/JNS/2008/108/3/0511

Small, G. W., Kepe, V., Siddarth, P., Ercoli, L. M., Merrill, D. A., Donoghue, N., . . . Barrio, J. R. (2013). PET scanning of brain tau in retired national football league players: preliminary findings. *Am J Geriatr Psychiatry, 21*(2), 138-144. doi: 10.1016/j.jagp.2012.11.019

Sporns, O. (2011). *Networks of the Brain*. Cambridge, Massachusetts: The MIT Press.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc, 8*(3), 448-460.

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord, 20*(2), 112-117. doi: 10.1097/01.wad.0000213815.20177.19

Strittmatter, W. J., Saunders, A. M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G. S., & Roses, A. D. (1993). Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A, 90*(5), 1977-1981.

Terry, D. P., Faraco, C. C., Smith, D., Diddams, M. J., Puente, A. N., & Miller, L. S. (2012). Lack of long-term fMRI differences after multiple sports-related concussions. *Brain Inj, 26*(13-14), 1684-1696. doi: 10.3109/02699052.2012.722259

Theriault, M., De Beaumont, L., Tremblay, S., Lassonde, M., & Jolicoeur, P. (2011). Cumulative effects of concussions in athletes revealed by electrophysiological abnormalities on visual working memory. *J Clin Exp Neuropsychol, 33*(1), 30-41. doi: 10.1080/13803391003772873

Tremblay, S., De Beaumont, L., Henry, L. C., Boulanger, Y., Evans, A. C., Bourgouin, P., . . . Lassonde, M. (2013). Sports concussions and aging: a neuroimaging investigation. *Cereb Cortex, 23*(5), 1159-1166. doi: 10.1093/cercor/bhs102

Varangis, E., Giovanello, K., Foster, C., Kerr, Z., DeFreese, J., Marshall, S., & Guskiewicz, K. (Under Review). Effects of concussion history and football exposure on working memory performance in National Football League and college football players. *Journal of Neurotrauma*.

Wagner, M., Wolf, S., Reischies, F. M., Daerr, M., Wolfsgruber, S., Jessen, F., . . . Wiltfang, J. (2012). Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease. *Neurology, 78*(6), 379-386. doi: 10.1212/WNL.0b013e318245f447

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale-Fourth Edition: Administration and scoring manual*. San Antonio, TX: Pearson.

Zhang, K., Johnson, B., Pennell, D., Ray, W., Sebastianelli, W., & Slobounov, S. (2010). Are functional deficits in concussed individuals consistent with white matter structural alterations: combined FMRI & DTI study. *Exp Brain Res, 204*(1), 57-70. doi: 10.1007/s00221-010-2294-3