NEUROPSYCHOLOGICAL FUNCTIONING IN AGING NATIONAL FOOTBALL LEAGUE RETIREES

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NEUROPSYCHOLOGICAL FUNCTIONING IN AGING NATIONAL FOOTBALL LEAGUE RETIREES

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Concussive and sub-concussive head impacts sustained over a National Football League (NFL) career have been proposed to increase risk for later cognitive impairment. However, research is generally limited on the neuropsychological functioning among NFL retirees, and no studies to date have investigated the cognitive performance of NFL retirees over time. Study One was a critical review of research on neuropsychological functioning among NFL retirees. Findings were mixed, but studies suggested some NFL retirees have lower verbal memory, confrontation naming, and executive functioning abilities compared to control groups. Investigations of dose-response relationships between cognition and head-injury exposure also generated mixed findings which may be related to small samples, sampling bias, small effect sizes, and the measurement of different head-injury exposure variables. Study Two was a prospective cohort design investigating neuropsychological functioning and head-injury exposure in NFL retirees aged 50 and up. Retirees underwent baseline (N = 53) and follow-up (N = 29) comprehensive

neuropsychological evaluations. Cognitively normal retirees (n = 26) were age, education, and IQ-matched to healthy controls (n = 26). Retirees diagnosed with MCI or dementia (n = 27) were matched as closely as possible to a clinical sample of patients with MCI and dementia by age, education, and diagnosis (n = 22). Independent samples t-tests and repeated measures ANCOVAs were used to evaluate neuropsychological scores between groups. Pearson correlations, partial correlations, and quadratic regressions were used to examine relationships between head-injury exposure and neuropsychological scores. Head-injury exposure variables included concussions, number of concussions with loss of consciousness, years playing professionally, games played, games started, and age beginning tackle football. Overall, NFL retirees did not significantly differ on the majority of measures at baseline or on any measures over time compared to their respective control groups. Furthermore, the vast majority of neuropsychological scores were not significantly related to head-injury exposure, regardless of cognitive diagnosis. In totality, findings suggest that NFL retirees do not have lower cognitive functioning compare to non-athlete controls later in life, and that head-injury exposure obtained over an NFL career is not related to cognitive functioning later-in-life.

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AD8	AD8 Dementia Screening Interview
AFE	Age of first exposure
ALS	Amyotrophic lateral sclerosis
AMNART	American National Adult Reading Test
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
B-SIT	Brief Smell Identification Test
BAI	Beck Anxiety Inventory
BDHI	Buss Durkee Hostility Inventory
BDI	Beck Depression Inventory
BHS	Beck Hopelessness Scale
BIS	Barret Impulsivity Scale
BMI	Body mass index
BNT	Boston Naming Test
BRIEF-A	Behavior Rating Inventory of Executive Function – Adult Version
BVMT-R	Brief Visuospatial Memory Test-Revised
CFL	Canadian Football League
COWAT	Controlled Oral Word Association Test
CSP	Cavum septi pellucidum
CTE	Chronic traumatic encephalopathy
CVLT	California Verbal Learning Test

DETECT	Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests
DKEFS	Delis-Kaplan Executive Functioning System
DTI	Diffusion tensor imaging
DWI	Diffusion weight imaging
FA	Fractional anisotropy
FLAIR	Fluid attention inversion recovery
fMRI	Functional magnetic resonance imaging
GDS	Geriatric Depression Scale
HAM-D	Hamilton Depression Rating Scale
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing
IQ	Intelligence quotient
LOC	Loss of consciousness
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
NAB	Neuropsychological Assessment Battery
NFL	National Football League
NHL	National Hockey League
PAI	Personality Assessment Inventory
PET	Positron emission tomography
PHQ-9	Patient Health Questionnaire-9 Item
RAVLT	Rey Auditory Verbal Learning Test

RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCFT	Rey Complex Figure Test
RVDLT	Rey Visual Design Learning Test
SDMT	Symbol Digit Modalities Test
SORT	Semantic Object Retrieval Test
SRC	Sports-related concussion
SWI	Susceptibility weighted imaging
TCST	Texas Card Sorting Test
TDP-43	Transactive response DNA binding protein of approximately 43 kd
TMT	Trail Making Test
TOMM	Test of Memory Malingering
TSPO	Translocator protein
UPDRS	Unified Parkinson's Disease Rating Scale
UTSW	University of Texas Southwestern
VA-BU-CLF	Veterans Administration Boston Health Care System-Boston University-Concussion Legacy Foundation
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sorting Test
WM	White matter
WMSA	White matter signal abnormality
WRAT	Wide Range Achievement Test
WTAR	Weschler Test of Adult Reading

GENERAL DISSERTATION OVERVIEW

Evidence and Rationale

The long-term outcome of sports-related concussion (SRC) is a rapidly growing topic of scientific study. Recent discovery of the neuropathological condition chronic traumatic encephalopathy in former National Football League (NFL) players has led to a surge of scientific and public interest long-term cognitive outcomes of SRCs, specifically in NFL players. However, despite the increase in interest, long-term cognitive outcomes are largely unknown and there continues to be debate whether single or repetitive SRC increases risk for later-in-life neurodegenerative conditions, cognitive impairment, or late-life cognitive decline.

SRC is defined by the International Conference on Concussion in Sports as "a traumatic brain injury caused by biomedical forces" sustained during the course of athletic play (McCrory et al., 2017). SRCs do not typically involve observable neurostructural injury and are characterized by an acute set of symptoms that may include mental fogginess, reduced reaction time, emotional lability, irritability, loss of balance, and sleep/wake disturbance that typically peak within 24 to 72 hours and abate within a month (McCrory et al., 2017), with athletes often returning to play within 10 days after injury (Iverson et al., 2017). According to the 2019 NFL safety report, there were 224 concussions sustained during the NFL preseason and regular season, equating to approximately .70 concussions per game. However, despite their frequency and well-characterized acute recovery pattern, the long-term cognitive impact of repetitive and cumulative SRCs is unclear, and it is unknown whether cumulative SRCs are associated with long-term cognitive impairment, neurodegenerative disorders, and/or dementia.

Only four investigations have evaluated the prevalence of mild cognitive impairment (MCI) and dementia in former NFL players. Two studies utilizing survey data from the NFL Player's Association found higher rates of self-reported MCI and memory decline in NFL players compared to rates in the general population (Guskiewicz et al., 2005; Randolph, Karantzoulis, & Guskiewicz, 2013). In an additional 2009 survey, telephone interviews of a stratified random sample of 1,063 retired NFL players using questions from the National Health Interview Survey compared responses from this NFL sample to the U.S. Census responses matched by age and race (Weir, Jackson, & Sonnega, 2009). Self-reported or proxy-reported "diagnosis of dementia, Alzheimer's, or other memory-related disease" were significantly higher for younger retired athletes (ages 30-49) than their peers in the general population (1.9% vs. .1%), and rates of self or informant-reported dementia in the older retirees (age 50+) were noted to be almost 6 times higher than reports in the general population (6.1% versus 1.2%; Weir et al., 2009). However, all three of these studies were limited to survey data and self or informant-reported diagnoses, which are prone to recall and misattribution bias. In the only non-survey investigation evaluating risk of dementia and neurodegenerative conditions in former NFL players, Lehman and colleagues evaluated mortality rates of former NFL players who played at least 5 years in the league (N=3,439) by linking their pension records to the National Death Index. Findings suggested NFL players had a reduced mortality rate overall compared to men in the U.S., but mortality rates were higher from neurodegenerative disease, Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS), although findings were based on a very small number of neurodegenerative cases (10 underlying and 17 contributing causes of death), which led the authors to conclude their results were highly imprecise because of their limited sample size (Lehman, Hein, Baron, & Gersic, 2012).

In addition to MCI and dementia, a neuropathological condition known as chronic traumatic encephalopathy (CTE) has been linked to repetitive SRCs and "sub-concussive" hits (McKee, Alosco, & Huber, 2016), which gathered worldwide attention after its discovery in several popular deceased NFL players. CTE is a neuropathological condition characterized by irregular perivascular collections of hyperphosphorylated tau predominantly found within the depths of the cerebral sulci (McKee et al., 2016). Some have speculated that CTE is common in former NFL players based on convenience samples found in brain banks (Mez et al., 2017), although the extent to which these frequencies generalize to all past or present NFL athletes (~25,000 players) is unknown. In the most recent investigation on CTE prevalence to date, 750 brains were retrospectively linked to amateur sport participation by obituaries or high school yearbooks (N=300 athletes vs. N= 450 non-athletes) and examined for CTE pathology at the Mayo Clinic Tissue Registry (Bieniek et al., 2019). In total, 5.6% of the sample either showed features (2.8%) of CTE pathology or met consensus neuropathological criteria for CTE (2.8%), all but one of which were male, with the highest frequency (~15%) of CTE pathology found in former football players. In a small subsample of football players who played past high school, 47% (7 of 15) were found to have at least some CTE pathology, though it also important to note that approximately 37% of individuals with CTE pathology also had comorbid AD pathology (Bieniek et al., 2019), which raises questions about the specificity between post-high school football participation and CTE pathology per se. This is consistent with other neuropathological studies, as a high frequency of comorbid CTE pathology has been found in other brain banks as well (Mez et al., 2017) and is of unknown clinical or mechanistic significance. Additionally, how these most recent results may apply to former NFL players, however, remains unknown. Furthermore, the course and clinical features of CTE are yet to be established, although it has

been suggested that symptoms likely develop years after a playing career ends, and progressive memory, executive functioning, and explosive mood/behavioral changes may accompany the pathology (Stern et al., 2013).

Despite the rising concern over SRCs and participation in football leading to long-term cognitive decline, there has been a paucity of data characterizing the degree and pattern of cognitive impairments in retired NFL players. The literature to date on the neuropsychological performances in retired NFL players is in the early stages, as studies have only been published within the last 6 years, exclusively utilized convenience samples and cross-sectional designs, and generated mixed findings (Baker et al., 2018; Casson, Viano, Haacke, Kou, & LeStrange, 2014; Hart et al., 2013; Stamm et al., 2015; Strain et al., 2015). In 2013, Hart et al. found cognitive impairments in 41% (14 of 34) of players, including 4 with fixed cognitive deficits (12%), 8 with MCI (24%) and 2 with dementia (6%) in a small sample of retired players (aged 41 to 79) recruited from the NFL Player's Association in North Texas. Cognitively impaired players, compared to healthy controls and non-cognitively impaired players, performed worse on measures of verbal learning and memory, confrontation naming, and non-verbal delayed recall. In another small sample of retired players recruited from the NFL Player's Association (N=45) aged 30 to 60, Casson et al., found impairments in 24% of players, with the most frequent area of impairment in verbal memory, though there was no control group for comparison or reporting of mean performances and standard deviations, making it difficult to draw firm conclusions. In a recent 2018 study comparing the neuropsychological performance (i.e., measuring processing speed, attention, language, memory, and executive functioning) of 21 retired NFL and National Hockey League (NHL) players to non-contact professional athlete controls, NFL and NHL players had significantly worse performance on measures of naming, phonemic fluency, and

verbal memory (Baker et al., 2018). Additionally, a higher frequency of MCI (defined according to Jak et al., 2009 criteria) was found in contact sport retirees (38%) compared to non-contact controls (14%), though this difference was non-significant (p = .08). However, despite impairments being found in some players in these studies (Hart et al., 2013, Casson et al., 2014, Baker et al., 2018), as a group, neuropsychological performances of retired players have largely fallen within the average range (Baker et al., 2018, Hart et al., 2013, Casson et al., 2014, Alosco et al., 2017). In contrast to the above studies which suggest that some former NFL players score lower on neuropsychological tests later in life, two recent studies suggest that former professional football players are *not* at greater risk for cognitive impairment. Tarazi and colleagues (2018) compared 45 retired Canadian Football League (CFL) players to education-matched controls. They found that CFL players reported significantly more cognitive dysfunction on a self-report measure than controls, but as a group performed in the average to above average range measures of processing speed, verbal memory, and motor speed. Additionally, the only significant difference found between groups on neuropsychological measures was that CFL players scored higher on a visuospatial sequencing task (Tarazi et al. 2018). In a similar investigation of former NFL and NHL players (N=22), no differences were found in immediate and delayed verbal memory, visuospatial abilities, or executive functioning compared to professional non-contact athlete controls, despite former NFL and NHL players self-reporting significantly more cognitive difficulties than former non-contact elite athletes (Willer et al., 2018). Due to these mixed results from relatively small convenience samples of retired players, further research is needed to determine whether concussive and sub-concussive impacts are associated with lower neuropsychological functioning later in life.

To evaluate the impact that concussions and/or head-injury exposure can have on neurocognitive functioning later in life among former NFL players, several studies have attempted to discern a dose-response relationship between cognitive impairment and cumulative head-injuries and/or head injury exposure. Perhaps the most well-known investigation was published in 2015 using data from the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) cohort which compared age of first exposure to tackle football (before or after 12 years old) and neuropsychological functioning in symptomatic NFL retirees (Stamm et al., 2015). They found that retired NFL players who began playing tackle football prior to age 12 exhibited significantly worse performance on one task measuring executive functioning, one task measuring verbal memory, and one task measuring word-reading abilities than those who began playing after age 12. However, this study had several limitations, including the absence of a non-NFL player control group, failure to control for learning disabilities found in the >12 group, only evaluating symptomatic NFL retirees, and the exclusion of other neuropsychological measures, despite their availability within the DETECT cohort (Stamm et al., 2015). Due to the above limitations, a similar study attempted to replicate their findings. Solomon and colleagues evaluated 45 players (aged 30 to 60) and found no significant relationship between years of pre-high school football and neuropsychological functioning, neuroradiological findings, or neurological exam findings (Solomon et al., 2016). In a 2019 investigation of 35 former NFL players, Fields and colleagues sought to examine if a linear relationship existed between years played in the NFL, total number of concussions, and number of concussions resulting in loss of consciousness, and neuropsychological functioning later-in-life. On composite neuropsychological indices of attention/speed, language, memory, and overall functioning, no linear relationship was identified, suggesting that there is not a clear linear dose-

response relationship between cumulative SRCs, head-injury exposure, and late-life neuropsychological functioning.

When evaluating the literature in totality, findings from investigations of the neuropsychological performance in retired professional football players have been mixed, with several finding group level cognitive impairments in areas of memory, language, and executive functioning in some retired players (Hart et al., 2013, Casson et al., 2014, Alosco et al. 2017), while others have found no significant differences in neuropsychological performance compared to education matched controls (Tarazi et al., 2018) and retired non-contact professional athletes (Willer et al., 2018). Furthermore, no clear dose-response between concussions/head-injury exposure and post-retirement cognitive functioning has been established. These mixed findings could be due to various methodological differences among studies. First, the age range of retired players in the literature has been wide, ranging from age 30 to 79 across studies. Age is the greatest known risk factor for neurodegenerative conditions and cognitive decline (Alzheimer's Association, 2017; L.E. Hebert et al., 2010; Liesi E. Hebert, Weuve, Scherr, & Evans, 2013), and it is possible that exclusively examining older retirees may yield different patterns, severities, and frequency of cognitive impairment than when examining both young and old NFL players. Second, studies have varied widely regarding sampling and inclusion criteria. That is, some studies have required cognitive/psychiatric complaints for greater than 6 months prior to entering the study (e.g., Alosco et al., 2017), whereas others have included players with and without cognitive complaints (e.g., Hart et al., 2013, Casson et al., 2014, and Solomon et al., 2016). Third, studies have differed in their use of comparison groups, including retired non-contact professional athletes (Baker et al., 2018, Willer et al., 2018), age-matched healthy controls (Hart et al., 2013, Alosco et al., 2017), education-matched controls (Tarazi et al., 2018), and no

comparison group (Casson et al., 2014). Utilizing appropriate comparison groups (i.e., comparing healthy NFL players to healthy controls, and impaired NFL players to impaired older adults) may help elucidate the impact that an NFL career may have on long-term cognitive functioning. Finally, perhaps the biggest limitation to the literature to date is the absence of a single longitudinal examination of neuropsychological functioning in NFL players. As such, it is unknown if any observed effects between neuropsychological functioning and head-injury exposure are static, or may be related to abnormal cognitive changes over time. Serial evaluations measuring change over time would help determine whether cognitive changes are static or progressive, and if patterns of cognitive decline may be associated with different degrees of head-injury exposure. This research would also serve to generate additional research hypotheses about cognitive functioning following an NFL career.

Study Design

Although several investigations suggest former NFL players may be at greater risk of cognitive impairment, no research to date has examined neuropsychological functioning in an exclusively older group of aging players or examined their performances longitudinally. The results of investigations evaluating dose-response relationships between head injury exposure variables (e.g., number of years played, games played, and concussions) are largely mixed, with very few studies examining whether differences found between players and controls are related to cumulative concussions or head-injury exposure over an NFL career. There are also no published literature reviews examining long-term neuropsychological outcomes among NFL retirees. As such, this dissertation has three primary aims: **(1)** conduct a critical review of the literature on neuropsychological performance in aging NFL retirees, and **(2)** compare the

neuropsychological performance of an aging group of NFL retirees (i.e., aged 50 and older) both cross-sectionally and longitudinally, and **(3)** assess if neurocognitive functioning may be related to head-injury exposure in the NFL. This proposed project will fulfill dissertation path "Option 3" and will result in two related first-authored journal articles, a critical literature review (Study 1) and a report of related original research (Study 2).

Prior to Study 1, there had not been a published literature review on neuropsychological performance on NFL retirees. This review examined the current evidence on neuropsychological functioning in retired NFL players, and identified gaps and limitations within the current literature. The findings from Study 1 served to identify the aims, hypotheses, and design of Study 2, which examined neuropsychological performance both cross sectionally and longitudinally in older NFL retirees. Study 1, designed to present a critical review of the literature on the neuropsychological performance of aging retired NFL athletes as it relates to risk of late-life cognitive impairment and/or risk of neurodegenerative disease from cumulative head injury, has been published in the *International Review of Psychiatry* (Schaffert et al., 2019). The review included 22 articles (using PubMed, Scopus, Google Scholar, and reference sections from searched articles) identified using search terms such as: neuropsychological functioning/assessment/performance, neurocognitive functioning/assessment/performance, cognitive functioning/assessment/performance, national football league, professional football, dementia, mild cognitive impairment, and chronic traumatic encephalopathy. Only studies utilizing standard clinical neuropsychological measures were included, i.e., studies exclusively using global cognitive screening measures, computerized measures not routinely used in clinical practice to assess cognitive decline, and/or functional magnetic resonance imaging tasks were not evaluated. As expected, findings within the literature were largely mixed, were generated out

of a handful of NFL cohorts, and included numerous methodological issues, the most notable of which included extremely wide age ranges of NFL retirees, but surprisingly the absence of a single examination of former NFL players over time. Despite the largely mixed findings, several patterns of cognitive performance emerged across different cohorts. Lower verbal memory performance (Hart et al., 2013; Strain et al. 2015; Casson et al. 2014; Alosco et al., 2017; Wright et al., 2016; Koerte et al. 2017) and confrontation naming (Hart et al., 2013; Wright et al., 2016; Alosco et al., 2017; Koerte et al. 2017) were found in several studies, though most studies did not find NFL cohorts to have impaired verbal memory or confrontation naming as a group. Additionally, performance on measures of executive functioning were also found to be lower in former NFL players in some studies (Alosco et al., 2017; Wright et al. 2016), with one study suggesting a dose-response relationship between age of tackle football exposure and executive functioning impairment (Stamm et al., 2015). However, no clear dose-response relationship between concussions/head-injury exposure was identified in two other larger investigations (Solomon et al., 2016; Fields et al., 2019).

STUDY 1: NEUROPSYCHOLOGICAL FUNCTIONING IN AGING RETIRED NFL PLAYERS: A CRITICAL REVIEW

Abstract

Recent discovery of chronic traumatic encephalopathy in former National Football League (NFL) players has led to a surge of papers investigating cognitive functioning in these former athletes. This critical review of the literature focused on the neuropsychological functioning in these aging athletes, and included 22 articles published between 2013 and 2019, of which 13 reported on neuroradiological imaging and four focused on dose-response relationships of repetitive head injury on cognitive outcomes. Four studies suggest higher prevalence of MCI and neurodegenerative disease among NFL retirees, although a quantifiable risk and prevalence of cognitive impairment and dementia in these players remains unknown. Decreased verbal memory has been found in some players across multiple studies, though with unknown clinical significance due to small sample sizes, unreported effect sizes, and absence of longitudinal data. Studies investigating a dose-response relationship between cognitive decline and head injury have generated mixed findings utilizing various measures of head-injury exposure. Neuroradiological findings are inconsistent, but suggest that some NFL players may be at greater risk for reduced white matter integrity. Future research is needed to understand the relationship between sport-related concussions and the risk of long-term cognitive decline and neurodegenerative disease in aging NFL players.

Introduction

The long-term impact of sports-related concussion (SRC) continues to be an area of great scientific intrigue, and debate continues as to whether single or repetitive mild traumatic brain injury (mTBI) increases risk for later-in-life neurodegenerative conditions. Recent research using large database record reviews has found evidence suggesting that mTBI increases the risk of dementia (Barnes et al., 2018; Gardner et al., 2014; Lee et al., 2013; Nordstrom & Nordstrom, 2018), but have several limitations including the use of a restricted age-sample, a short time from injury to dementia diagnosis, and injuries that are atypical of SRC, such as prolonged loss of consciousness (LOC) and intracranial injuries (Barnes et al., 2018; Gardner et al., 2014). SRC is best defined as a subtype of mTBI, sustained during the course of athletic play, and often do not result in more serious sequelae such as significant post-traumatic amnesia or LOC. It is estimated that 1.6 to 3.8 million SRCs occur each year (Langlois, Rutland-Brown, & Wald, 2006), but this may be a vast underestimate as many go unreported (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). In recent years, reporting of concussions has been on the rise due to a combination of factors, such as increased awareness and recent legislation requiring reporting and removal from play, but it is still estimated that a considerable number of SRCs (~20%) go unreported (LaRoche, Nelson, Connelly, Walter, & McCrea, 2016).

In 2012, the International Conference on Concussion in Sports defined SRC as "a traumatic brain injury caused by biomedical forces," typically including absence of structural neuropathology and a brief graded set of clinical symptoms, such as cognitive fogginess and/or slowed reaction time, emotional lability and irritability, loss of balance, and sleep/wake disturbance (McCrory et al., 2017). The majority of symptoms occur within 24 to 72 hours after injury and clinical recovery within the first month post-injury is expected for most SRCs

(McCrory et al., 2017). This pattern of acute recovery has been seen across all sports, including in National Football League (NFL) players. In a 2004 study evaluating active NFL players who sustained a SRC, no changes on neuropsychological functioning pre- vs post-injury were found days after a SRC (Pellman, Lovell, Viano, Casson, & Tucker, 2004). However, despite typical acute recovery after SRC, the long-term cognitive impact of repetitive and cumulative SRCs remains unclear.

Risk of Mild Cognitive Impairment and Dementia in NFL Players

Several investigations have suggested that NFL retirees may be at greater risk of mild cognitive impairment (MCI; Guskiewicz et al., 2005; Randolph, Karantzoulis, & Guskiewicz, 2013) and neurodegenerative conditions such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS; Lehman, Hein, Baron, & Gersic, 2012). MCI is thought to be an intermediate stage between normal aging and dementia. It is defined as: evidence for a concern regarding cognition, lower than expected performance in one or more cognitive domains, and essentially intact functional abilities without evidence of dementia (Albert et al., 2011). A 2005 study by Guskiewicz and colleagues sent surveys to 2,552 NFL retirees and a follow-up survey to 758 retired players and their spouses (based on initial data that identified them at higher risk of cognitive impairment). This questionnaire asked players and their spouses about cognitive complaints in addition to ever receiving an MCI or AD diagnosis by a physician. They found that the frequency of self-reported MCI and earlier onset (before age 70) AD was higher in NFL retirees at least 50 years old. Those with 3 or more concussions were 5 times more likely to report having a diagnosis of MCI and 3 times more likely to have memory complaints compared to players without history of concussion. Despite these findings, only 3% (N = 22 of 758) of

NFL players self-reported a physician diagnosis of MCI, and 10% (N=77 of 758) self-reported difficulty with memory. Importantly, 3 of those with reported MCI also had a history of stroke, and it is unknown if results would remain significant with these individuals excluded given the small number of MCI diagnoses reported (N = 22). In a follow-up survey in 2013, Randolph and colleagues sent the AD8 (Galvin et al., 2005), an informant-completed questionnaire designed to detect late-life cognitive impairment, to the spouses of 908 players at least 50 years old (mean age=64.2) who were affiliated with the NFL Players Association. It was noted that 35.1% of players had clinically significant cognitive impairment based on these informant ratings (defined as an AD8 cut-score ≥ 2), which was significantly higher than the general population based on epidemiological estimates (<5% of men under 75). However, the authors found no association between the number of years played in the NFL (a proxy for repetitive head injury) and reported cognitive impairment. In addition, the authors identified a subsample of NFL players with probable MCI (N = 41) through clinical screening (i.e., Modified Telephone Interview for Cognitive Status) and compared their neuropsychological profiles (based on brief testing) to a well-characterized non-athlete clinical sample with amnestic MCI (N = 81) recruited from two university medical centers. They found no significant differences in their neuropsychological profiles, leading the authors to suspect it was unlikely that this NFL group was suffering from a distinct tauopathy like chronic traumatic encephalopathy, and that it was more likely that repetitive head trauma lowered cognitive reserve (Randolph et al., 2013). It is unclear why frequencies of MCI were so much higher in the follow-up study by Randolph and colleagues, but a reliance on spouse/informant report of cognitive difficulty compared to self-reported physician diagnoses of MCI may have influenced results. In sum, survey data suggests NFL players who sustain more concussions may be at higher risk of MCI and/or cognitive impairment (13% to

35%), but the overall frequency of cognitive impairment and definitive MCI in this population remains unknown.

Only two investigations to date have attempted to estimate the frequency of dementia in former NFL athletes. In 2009, Weir and colleagues from the University of Michigan conducted phone interviews of a stratified random sample of 1,063 retired NFL players with at least 3 years in the NFL. The authors matched questions used in the National Health Interview Survey used by the U.S. Census Bureau, and weighted the general population responses to match the NFL sample by age and race. Rates of self-reported or proxy-reported "diagnosis of dementia, Alzheimer's, or other memory-related disease" were significantly higher for younger retired athletes (ages 30-49) than their peers in the general population (1.9% vs. .1%). Similarly, rates of dementia in the older retirees (age 50+) were almost 6 times higher than reports in the general population (6.1% versus 1.2%) (Weir, Jackson, & Sonnega, 2009). Another study examining risk of neurodegenerative disease specifically in NFL players was a 2012 study by Lehman et al., who evaluated mortality rates of former NFL players who played at least 5 years in the league (N=3,439) by linking their pension records to the National Death Index, which provided information regarding underlying and contributing causes of death. Findings suggested that NFL players had an overall reduced mortality rate compared to men in the U.S., but mortality rates were higher from neurodegenerative disease, AD, and ALS. Interestingly, these findings were only significant in those who played speed positions, and no association was found in defensive or offensive linemen, who are arguably exposed to more head impacts overall. Also, the findings were based on a small number of neurodegenerative cases (10 underlying and 17 contributing causes of death), which led the authors to caution that their "results were highly imprecise because of the small numbers" (Lehman et al., 2012).

Overall, the literature on the frequency of dementia and cognitive impairment in this population is limited and restricted to survey data and retrospective record linkage. The limitations of survey data are well-known, and are prone to reporting, recall, and sampling bias which may artificially inflate estimates of the prevalence of cognitive impairment. Still, findings suggest that some former NFL players may be at increased risk of dementia and certain neurodegenerative conditions, warranting future large prospective cohort studies to examine risk factors. To date, there have been no carefully controlled longitudinal studies on risk of MCI and/or dementia in retired NFL athletes.

Chronic Traumatic Encephalopathy

A neuropathological condition known as chronic traumatic encephalopathy (CTE) has been putatively linked to repetitive SRCs and "sub-concussive" hits (McKee, Alosco, & Huber, 2016), which has garnered worldwide attention after its discovery in several popular deceased NFL players. Neuropathologically, CTE is characterized by irregular perivascular collections of hyperphosphorylated tau predominantly found within the depths of the cerebral sulci (McKee, Alosco, et al., 2016). Additional neuropathology has also been associated with CTE, including transactive response DNA-binding protein of approximately 43 kd (TDP-43)(McKee et al., 2010), AD pathology (Mez et al., 2017), and Lewy body disease pathology (Adams et al., 2018). In fact, although a substantial focus has been on CTE neuropathology, early reports out of the Veteran Administration Boston Health Care System – Boston University – Concussion Legacy Foundation (VA-BU-CLF) collaborative brain depository found that 11 of 34 (32%) autopsied professional football players with CTE also met criteria for a comorbid neurodegenerative disease such as AD, Lewy body disease, and/or frontotemporal lobar degeneration (McKee et al.,

2013). In perhaps the most highly publicized study to date, varying degrees of CTE pathology (i.e., staging) was found in 110 out of 111 donated brains of former NFL players (Mez et al., 2017), leading some to speculate that CTE is not rare in NFL players. Although the frequency of CTE within this brain depository is striking, little attention has been paid to the extent to which these results may or may not generalize to the larger population of football players, and thus, the prevalence of CTE in past or present NFL players (~25,000) remains unknown. Some studies suggest that sub-concussive blows, rather than repetitive SRCs, influence risk of CTE, as supported by a positive correlation between proxy measures of sub-concussive hits (years played in contact sports, games played, etc.) and severity of CTE pathology (McKee et al., 2013). However, sub-concussive hits are difficult to quantify with the lack of any clear threshold, as by definition any strike, bump, or impact to the head or body that does not result in clinical symptoms meets criteria for a sub-concussive hit. Furthermore, data examining the association between cognitive functioning and objective measurable hits (e.g., helmet sensor data) accumulated over many years in NFL players has yet to be reported. Although there is some evidence to suggest that exposure to repetitive head injury may be associated with CTE pathology, a quantifiable risk of CTE in NFL players has not been established and this is an area that future research will need to address.

At present, CTE can only be diagnosed post-mortem, and no consensus clinical criteria are available. In 2013, two clinical phenotypes (behavioral versus cognitive) of CTE were proposed using data collected via retrospective informant interviews for 36 cases of neuropathologically confirmed CTE (Stern et al., 2013). The proposed behavioral phenotype (n = 22) was characterized by early onset (mean age = 35) of explosivity, impulsivity, and aggression, with most reportedly progressing to cognitive impairment (Stern et al., 2013). In contrast, the

cognitive phenotype was described in 11 of the remaining participants, highlighted by a later age of onset (mean age = 57), with initial symptoms of cognitive decline involving episodic memory and executive dysfunction, as well as a progressive clinical course. The cognitive phenotype also had more severe CTE neuropathology than the behavioral phenotype at autopsy (Stern et al., 2013). All 36 subjects had severe CTE pathology, but only 10 subjects were clinically diagnosed with dementia, and 3 subjects with CTE were asymptomatic. Frequencies of suicide were high (18.2%) in both phenotypes from this sample, which is consistent with the high frequency of suicide (10%) in the larger (N=111) descriptive study of the VA-BU-CLF brain depository (Mez et al., 2017). It is worth noting that earlier mean ages of death in the behavioral phenotype group may have resulted in failure to detect later cognitive changes that may accompany the pathology. In addition, neither phenotype was necessarily mutually exclusive, as features of behavioral and cognitive changes were present within both groups. Nonetheless, episodic memory difficulties and executive dysfunction, along with extreme behavioral changes have also been reported in larger samples of cases with CTE pathology in the same VA-BU-CLF brain depository (McKee, Cairns, et al., 2016; McKee et al., 2013; Mez et al., 2017), suggesting additional study is needed to determine whether there is a relationship between clinical presentation and these neuropathological findings.

Despite these efforts, CTE cannot be diagnosed *in-vivo,* and the current literature examining the clinical presentation of CTE has several limitations. First, all studies to date have relied on retrospective telephone interviews, which are prone to reporting and recall bias. Second, it has been assumed that CTE pathology causes these clinical symptoms, when cognitive and psychiatric symptoms have many potential causes such as other medical conditions, psychosocial stressors, and various psychiatric diagnoses. Third, neuropathological findings may

or may not correlate to clinical presentation. For example, in one community-based study, cognitively normal individuals were routinely (36%) meeting pathological criteria for AD at autopsy (Bennett et al., 2006). When the limitations are considered in concert, i.e., using retrospective report of family/friends following a player's death to correlate CTE pathology to non-specific multifactorial cognitive and psychiatric symptoms, hypothesized prevalence rates of CTE and the validity of the proposed clinical presentation of CTE become questionable at best. Thus, more research is needed to determine the impact that CTE neuropathology may have on clinical presentation, and *in-vivo* prospective studies are needed prior to establishing meaningful clinical criteria for CTE.

Review Aims

Although a link between late-life cognitive decline and repetitive SRCs has been suggested, the mechanism remains unclear. It has been proposed that the accumulation of head impacts over an NFL career may initiate a neurodegenerative process (e.g., CTE, AD, ALS, Lewy body pathology). Alternatively, repetitive brain injury may result in lowering of cognitive reserve and lead to earlier expression of cognitive impairment. It is also possible that most NFL players are not at an increased risk of cognitive decline, but perhaps a minority may be at greater risk due to other and/or additive risk factors (e.g., genetic, vascular, etc.). Despite a great deal of scientific interest in cognitive decline following an NFL career, research utilizing comprehensive neurocognitive examinations of NFL players is lacking. A comprehensive neuropsychological examination is commonly used in clinical settings to assess cognitive abilities as they relate to brain function, assist in differential diagnosis of neurodegenerative conditions, and track disease progression; thus, neuropsychological assessment may be useful to assist in characterizing the

degree, pattern, and course of cognitive impairment of NFL athletes. The studies to date that have evaluated neuropsychological functioning in retired NFL athletes have yielded mixed results. The majority of research on neuropsychological functioning in NFL retirees is generated out of a handful of NFL player cohorts in various academic medical center settings and has largely focused on comparing neuropsychological performance to normative data or control groups, along with correlating neuropsychological performance to repetitive head injury exposure and neuroradiological findings. Sampling procedures, inclusion criteria, and methodology have varied widely, and the primary aim of this paper was to present a critical review of the literature on the neuropsychological performance of aging retired NFL athletes as it relates to risk of late-life cognitive impairment and/or risk of neurodegenerative disease from cumulative head injury.

Method

Articles selected for this review were obtained from PubMed, Scopus, Google Scholar, and reference sections from searched articles using search terms such as: neuropsychological functioning/assessment/performance, neurocognitive functioning/assessment/performance, cognitive functioning/assessment/performance, national football league, professional football, dementia, mild cognitive impairment, and chronic traumatic encephalopathy. Only journal articles published in English were considered. In addition, because this review was focused on long-term neuropsychological performance in retired professional football players, studies and findings exclusively using global cognitive screening measures, computerized measures not routinely used in clinical practice to assess cognitive decline, and/or functional magnetic resonance imaging (fMRI) tasks were not included. This review included 22 articles published

between 2013 and 2019, of which 4 focused on dose-response relationships of repetitive head injury on cognitive outcomes and 13 reported on neuroradiological correlations with cognitive performances in former NFL players (for a complete list of all reviewed studies and their key findings, see Table 1).

Table 1

Studies reviewed investigating neuropsychological performance in retired NFL players

Study: Hart et al., 2013, *Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: a cross-sectional study* **Method** • Cross-sectional examination of 34 retired NFL players (ages 41-79) recruited from the Dallas retired players association (ages 41-79) compared to 26 age-matched healthy controls • Imaging consisted of DTI, MRI, Hemosiderin Scan • An NP battery consisted of WASI, WAIS-IV Digit Span and Coding, TMT parts A & B, COWAT, BNT, CVLT-II, RCFT, SORT, and BDI-II **Key findings** • 10 of 22 NFL players were impaired (either MCI or dementia) • NFL players with cognitive impairment had worse performance in in CVLT learning, SORT, BNT, and RCFT delayed recall • 8 of 22 players were diagnosed with depression based upon consensus diagnosis and the BDI-II, 6 of which had no reported previous diagnosis or treatment of depression • Regional (left temporal pole, inferior parietal lobule, and superior temporal gyrus) blood flow reductions were found in cognitively impaired players
Study: Randolph et al., 2013, *Prevalence and characterization of mild cognitive impairment in retired national football league players* **Method** • A 2008 survey characterizing memory problems using the AD8 was sent to 908 retired NFL players, with a 70% response rate (N=633) • Of these, 81% had an available spouse report, yielding a final sample of 513 • 41 players through telephone interviews were identified to have probable MCI were recruited and underwent a brief neuropsychological battery consisting of the RBANS and the WAIS-III short-form, and compared to 81 individuals with amnestic MCI and 41 age-matched healthy controls **Key findings**

- Spousal data suggested that 35.1% of the sample displayed clinically significant cognitive impairment (AD8 ≥ 2)
- As expected, the RBANS Total Score in both NFL players with MCI (M = 92) and amnestic MCI (M = 81.7) was significantly worse than controls (M = 1.6)
- The NFL MCI sample was significantly younger compared to those with amnestic MCI (M_{age} = 64.2 vs. 77.3)
- No significant interaction was found between RBANS domains and group (NFL MCI vs. Amnestic MCI), suggesting no significant differences in neuropsychological performance
- NFL players with MCI followed a very similar pattern of neuropsychological performance across domains when compared to those with amnestic MCI

Study: Casson et al., 2014, *Is There Chronic Brain Damage in Retired NFL Players? Neuroradiology, Neuropsychology, and Neurology Examinations of 45 Retired Players*

Method

- 45 retired NFL players aged 30-60 were recruited from the NFL Players Association
- Players underwent a neurological examination, along with MRI, SWI, and DTI
- Players completed a NP battery consisting of TOMM, CVLT, BVMT-R, COWAT, Category Fluency, TMT part B, WAIS-III Digit Symbol Coding, WTAR, BDI-II, MMSE, ImPACT, and PHQ-9.
- Mean scores on most NP measures were not reported, and instead broken into ordinal categories

Key findings

- 75% of sample reported experiencing 3+ concussions (Mean = 6.9)
- 15 players were at least mildly depressed on BDI-II and 9 players met criteria for MDD on the PHQ-9
- No players met study criteria for dementia (2+ domains of NP impairment and functional decline)
- 62% of players had no impairments on NP testing, 24% of players had impairments on 1 to 2 NP tests, and 13% of players had borderline or impaired performance on 1 test, but had low verbal IQ and/or performance validity concerns as measured by the TOMM
- NP measures were "statistically associated" with BMI and alcohol use, but strength of this association and the definition of excessive alcohol use were not defined
- Concussions were associated positively associated with FA levels and abnormal CNS examination findings
- 34 players had evidence of cavum septi pellucidum (CSP), but only 3 of 34 had enlarged ventricles and cavum vergae

Study: Coughlin et al., 2015, *Neuroinflammation and brain atrophy in former NFL players: An in vivo multimodal imaging pilot study*

Method

- 9 former players (aged 57 to 74) were compared to 9 age-matched healthy controls
- Subjects underwent MRI and PET to identify levels of translocator protein (TSPO)
- An NP battery consisted of MMSE, WTAR, TMT parts A & B, SDMT, phonemic fluency, category fluency, RCFT, CVLT-II, BVMT-R, modified WCST, and HAM-D

- However, only CLVT-II performance was reported

Key findings

- Increased TSPO was observed in the supramarginal gyrus and right amygdala in NFL players
- Significant atrophy in the right hippocampus was observed in the NFL players
- NFL players had variable performance on the CVLT-II, although all mean percentile scores were in the average range
- 2 players had mild depression on the HAM-D

Study: Stamm et al., 2015, *Age of first exposure to football and later-life cognitive impairment in former NFL players*

Method

- Subjects consisted of 42 former NFL players aged 41-65 out of the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) cohort
- Subjects were age-matched and dichotomized (n=21) into age of first exposure to tackle football (AFE) <12 or ≥12
- No control group was analyzed, although methods report one was available
- NP battery consisted of WCST, NAB-LL, and WRAT-4

Key findings

- Mixed-effects linear model revealed that those with AFE < 12 had worse performance on WCST (errors, perseverations, non-perseverations, and conceptual level responses), NAB List Learning (immediate, short, and long delay recall), and WRAT-4 Word Reading standard score
- Number of WCST categories completed was not reported

Study: Strain et al., 2015, *Imaging Correlates of Memory and Concussion History in Retired National Football League Athletes*

Method

- 20 cognitively intact former NFL players recruited from the Dallas, TX retired players association were compared to 21 healthy education and IQ-matched controls
- 8 NFL players with MCI were compared to 6 amnestic MCI controls recruited from the University of Texas Southwestern Alzheimer's Disease Center
- Age range of NFL players was 36-79
- All subjects underwent NP testing (CVLT-II, RCFT, BNT, and SORT), neurological examination, and fMRI to compare hippocampal volume after being divided into age quintiles

Key findings

- Age, CVLT-II total score, and number of grade 3 concussions (i.e., with LOC) predicted bilateral hippocampal volume in NFL players without MCI
- Lower scores on CVLT-II (albeit still non-impaired) were observed in cognitively intact NFL players compared to controls

- Regression models revealed that among former athletes with at least one G3 concussion had lower hippocampal volumes bilaterally after age 57
- Athletes with ≥120 games played had lower left hippocampal volumes after age 62
- Former NFL players without MCI had worse raw score performance on the CVLT-II learning trials after age 57
- No differences on the NP measures were found between athletes with and without G3 concussions in any age quintile

Study: Koerte et al., 2016, *Cavum Septi Pellucidi in Symptomatic Former Professional Football Players*

Method

- 72 symptomatic former NFL players out of the DETECT cohort, aged 40-69, and were compared to 14 controls who participated in elite-level non-contact sports without a history of concussion
- All subjects underwent MRI to evaluate size and presence of CSP in addition to a NP battery consisting of NAB List Learning, NAB Map Reading, NAB Naming, RCFT, TMT parts A and B, WAIS-R Digit Symbol, WRAT-4, WCST, HAM-D, Brown-Goodwin Lifetime History of Aggression, BIS, Modified Scale for Suicidal Ideation, BRIEF-A, BDI, BHI, and BDHI

Key findings

- NFL players exhibited worse performance on verbal learning, visuospatial abilities, nonverbal memory, and reading, although mean scores were not impaired.
- NFL players exhibited higher related to depression, impulsivity, aggression, , and hopelessness compared to controls
- CSP was present in 92% of NFL players compared to 57% of controls, and CSP was associated with reduced NAB list-learning immediate recall and WRAT-4 reading scores in NFL players
- Players also had greater length of CSP and a larger ration of CSP length to septum length

Study: Multani et al., 2016, *The association between white-matter tract abnormalities, and neuropsychiatric and cognitive symptoms in retired professional football players with multiple concussions*

Method

- 18 CFL players and 17 age-matched healthy male controls without history of neurological disease, psychiatric illness, developmental disorders, or migraines completed neurological examination, neuropsychological testing, and neuroimaging (DWI, DTI, Tract-based spatial statistics, and probabilistic tractography)
- NP battery included the RVDLT, WTAR, and the PAI (depression, aggression, mania, and paranoid scores were computed into a composite)

Key findings

- CFL players had significantly more cognitive complaints (memory, executive functioning, and language) and other complaints (sensory, behavioral, constitutional, headaches) than healthy controls

- CFL player's RVDLT total learning z score correlated positively with FA in the right superior lateral fasciculus

Study: Solomon et al., 2016, *Participation in Pre-High School Football and Neurological, Neuroradiological, and Neuropsychological Findings in Later Life: A Study of 45 Retired National Football League Players*

Method

- 45 retired NFL players aged 30-60 were recruited from the NFL Players Association underwent a neurological examination, along with MRI, susceptibility weighted imaging, and DTI
- Players completed a neuropsychological battery consisting of TOMM, CVLT, BVMT-R, COWAT, Category Fluency, TMT part B, Digit Symbol Coding (WAIS-III), WTAR, BDI-II, MMSE, ImPACT, and PHQ-9
- Relationship between outcomes on neuroradiological, neurological, and neuropsychological examination and years of pre-high school (PreYOE) were assessed

Key findings

- After applying corrections for multiple comparisons, the authors found no association between PreYOE and any outcome variable
- However, authors report some analyses were underpowered, and associations with neuropsychological measures and PreYOE were at least trending toward significance, i.e., TMT part B (p=.045), BVMT-R delayed recall (p=.017), and CVLT-II delayed free recall (p=.067), warranting examination in future studies

Study: Wright et al., 2016, *An index predictive of cognitive outcome in retired professional American Football players with a history of sports concussion*

Method

- 40 retired NFL players aged 30 to 65 who participated in the Center for Study of Retired Athletes in collaboration with the NFL Player's Association
- NP performance, measures of cognitive reserve (estimated verbal intelligence, occupational attainment, and education), concussion history, and play history were used to generate an index designed to predict cognitive outcome
- NP battery consisted of the AMNART, CVLT-II, RCFT, TMT, SDMT, COWAT, and category fluency and were categorized into domains of global cognition, attention and processing speed, verbal memory, nonverbal memory, and executive ability

Key findings

- NFL players were on average, 47 years old and 20 years retired
- At least mild deficits (> 1 SD below average) were observed in attention and processing speed (20%), verbal memory (22.5%), nonverbal memory (37.5%), and executive ability (37.5%)
- 35% of the sample displayed deficits in two or more cognitive domains
- Concussion factors explained 9% of the variance in global cognition, whereas cognitive reserve increased the variability explained by 25%, bringing the total variance explained to 34%

Study: Alosco et al., 2017, *Olfactory Function and Associated Clinical Correlates in Former National Football League Players*

Method

- 96 symptomatic former NFL players (DETECT cohort) were compared to 28 healthy controls in NP measures and olfactory performance as measured by the B-SIT
- NP battery consisted of TMT parts A & B, WAIS-R Digit Span, WAIS-R Digit Symbol Coding, WCST, COWAT, DKEFS Color Word Interference, RCFT, and NAB Story Learning, List-Learning, Map Reading, and Naming, along with several mood measure screening for depression, hopelessness, suicidality, aggression, and impulsivity
- NP measures were collapsed into domains as created by principle component analyses

Key findings

- NFL players performed significantly worse on all measures except on a measure of selective attention and response inhibition (DKEFS Color-Word Interference) and verbal fluency (COWAT)
- Only 6 players exhibited impaired olfaction, although had significantly lower scores compared to healthy controls
- B-SIT scores had small correlations with component measures of behavioral/mood and psychomotor speed/executive functioning, but not measures of memory

Study: Coughlin et al., 2017, *Imaging of Glial Cell Activation and White Matter Integrity in Brains of Active and Recently Retired National Football League Players*

Method

- 4 active and 10 retired NFL players (Mean age = 31) were age, sex, education, and BMI-matched to 16 healthy controls
- Subjects underwent an NP battery and MRI, DTI, and PET imaging to identify TSPO signal and white matter changes
- The total NP battery consisted of WTAR, MMSE, TMT, WAIS-IV Coding, WAIS-IV Digit Span, phonemic fluency (letters “s” and “p”), and CVLT-II

Key findings

- NFL players performed slightly worse on MMSE, Coding, and Trials 1 through 5 on the CVLT-II, although only raw scores were reported
- NFL players showed higher distributions of TSPO in multiple brain regions with comparatively little change FA and mean diffusivity, and no regional differences in brain volume

Study: Kuhn et al., 2017, *Interrelationships Among Neuroimaging Biomarkers, Neuropsychological Test Data, and Symptom Reporting in a Cohort of Retired National Football League Players*

Method

- 45 retired NFL players aged 30-60 were recruited from the NFL Players Association underwent a neurological examination, along with MRI, susceptibility weighted imaging, and DTI

- Players completed an NP battery consisting of TOMM, CVLT, BVMT-R, COWAT, Category Fluency, TMT part B, Digit Symbol Coding (WAIS-III), WTAR, BDI-II, MMSE, ImPACT, PHQ-9
- This study evaluated the correlation between NP measures between the presence of CSP, global mean FA, and presence of microhemorrhages

Key findings

- There were no statistically significant ($p < .05$) correlations between NP measures, mood questionnaires, and neuroradiological findings

Study: Strain et al., 2017, *White Matter Changes and Confrontation Naming in Retired Aging National Football League Athletes*

Method

- 25 former NFL players aged 41 to 79 were compared to 22 cognitively normal male controls
- Subjects underwent an NP battery (though BNT was the focus of the study) and DTI to compare mean FA and mean diffusivity
- Athletes with BDI-II scores >11 were excluded

Key findings

- NFL players had worse performance on BNT compared to controls
- BNT was a significant predictor of white matter integrity
- FA along forceps major and minor tracts significantly correlated to BNT in retired NFL players

Study: Alosco et al., 2018, *White matter signal abnormalities in former National Football League players*

Method

- 86 symptomatic former NFL players (DETECT cohort) and 23 healthy controls underwent MRI to identify white matter signal abnormalities (WMSA) and NP testing, and correlated these outcomes to a composite cumulative head injury index (Montenigro et al., 2017).
- The DETECT NP battery consisted of TMT A & B, WAIS-R Digit Span, WAIS-R Digit Symbol Coding, WCST, COWAT, DKEFS Color Word Interference, RCFT, and NAB Story learning, list-learning, map reading, and naming tests, along with several mood measure screening for depression, hopelessness, suicidality, aggression, and impulsivity

Key findings

- Volume of WMSA correlated positively with cumulative head trauma ($p = .043$) and predicted worse performance on psychomotor speed/executive measures (index derived from factor analysis reported in Alosco et al., 2017)
- Overall volume of WMSA was higher in African American players in addition to exhibiting lower performance on the index of psychomotor speed/executive function
- Controlling for race, volume of WMSA was still significantly associated with cumulative head trauma ($p = .021$) but was no longer significantly associated with psychomotor speed/executive measures ($p = .061$)

- Greater WMSA volumes in symptomatic NFL players were found when compared to healthy controls (p = .046)

Study: Baker et al., 2018, *An Exploratory Study of Mild Cognitive Impairment of Retired Professional Contact Sport Athletes*

Method

- 21 NFL and NHL players were recruited from local alumni associations (M_{age} = 57 years) and compared to healthy noncontact athletes (N = 21, M_{age} = 55 years)
- MCI was defined according to Jak et al. (2009) criteria, i.e., at least 2 test scores below 1 SD from the mean within 1 cognitive domain or at least 1 test score below 1 SD in 3 cognitive domains
- All subjects completed an NP battery consisting of WAIS-III Digit Span and Digit Symbol, TMT A & B, NAB List Learning and Story Learning, COWAT, NAB Naming, WCST, DKEFS Color-Word Interference, WRAT-4, BDI-II

Key findings

- Significant lower NP performance were found in contact athletes in NAB Naming, phonemic fluency, and list B interference trial, but only list B interference and phonemic fluency were significant after adjustments for estimated IQ
- 8/21 (38%) and 3/21 (14%) met criteria for MCI, which was not significantly different (p = .083)
- Contact athletes had higher frequency of vascular risk factors (1+ versus 0) and HDL cholesterol
- BDI-II scores were significantly higher in contact athletes (p = .04), but frequency of depression was not significantly different (p = .078)

Study: Clark et al., 2018, *Effects of Career Duration, Concussion History, and Playing Position on White Matter Microstructure and Functional Neural Recruitment in Former College and Professional Football Athletes*

Method

- 61 former college and NFL players (age range 52-65) underwent a brief NP battery, along with fMRI (with an in scanner working memory task) and DWI
- Groups were stratified by career duration (college vs. NFL), playing position (speed vs. nonspeed), and concussion history (1 vs. 3+)
- NP battery consisted of MMSE, RBANS, WAIS-III, Zung Anxiety Scale, and BDI

Key findings

- No significant differences were found in neuropsychological measures or mood measures between the stratified groups, although subtests of RBANS and WAIS-III were not evaluated statistically
- In college players, 3+ concussions was associated with lower mean FA, but unexpectedly the opposite finding was observed in NFL players
- In nonspeed players, 3+ concussions was associated with lower mean FA, but not in speed players
- No differences were observed between groups on the fMRI working memory task

Study: Tarazi et al., 2018, *Motor Function in Former Professional Football Players with History of Multiple Concussions*

Method

- 45 CFL players with 2+ concussions and 25 age and education matched healthy controls underwent neurological examination using the Unified Parkinson's Disease Rating Scale (UPDRS) and NP battery
- NP battery consisted of grooved pegboard, TMT parts A & B, RAVLT, SDMT, and PAI (Depression and Anxiety subscales)

Key findings

- No differences between groups were found on the UPDRS (p = .260)
- No differences were found on the PAI Anxiety and Depression subscales between groups
- Former CFL players reported significantly more subjective concerns in memory (78% vs 16%), executive problems (53% vs. 8%), and behavioral symptoms (67% vs 20%)
- However, former CFL players actually performed better (high average range) on Trails A (p = .023) and better performance on Trails B was approached significance (p = .051)

Study: Willer et al., 2018, *Evaluation of Executive Function and Mental Health in Retired Contact Sport Athletes*

Method

- 22 NFL and NHL players were recruited from local alumni associations (M_{age} = 56 years) and compared to healthy noncontact athletes (N = 21, M_{age} = 55 years)
- All subjects completed an NP battery consisting of WAIS-III Digit Span and Digit Symbol, TMT A & B, NAB List Learning and Story Learning, COWAT, NAB Naming, WCST, DKEFS Color-Word Interference, WRAT-4, BDI-II, BAI, Personality Inventory for the DSM-5, and BRIEF-A
- Informants also provided executive function ratings on the BRIEF-A

Key findings

- NFL players perceived themselves to have difficulty in executive functioning as measured by the BRIEF-A, specifically in working memory and initiation
- No significant differences were found in any NP measures
- NFL and NFL players endorsed significantly more depressive symptoms on the BDI-II and more anxiety symptoms on the BAI

Study: Fields et al., 2019, *No Linear Association Between Number of Concussions or Years Played and Cognitive Outcomes in Retired NFL Players*

Method

- 35 retired NFL players (aged 50+) with at least one concussion underwent clinical interview and neuropsychological testing
- A neuropsychological battery consisted of WASI, WAIS-IV Digit Span and Coding, TMT parts A & B, COWAT, BNT, CVLT-II, RCFT, SORT, and BDI-II

- Composite measures were created of Attention/Processing Speed, Memory, Language, and Overall cognitive functioning and correlated to total number of concussions, concussions with LOC, and years played in the NFL

Key findings

- 14/35 players were identified as cognitively impaired
- After Bonferroni correction, no cognitive performances were significantly correlated with total number of concussions, concussions with LOC, or years played in the NFL
- However, the Memory and Overall composite approached significance (set at $p < .01$) after correction ($p = .023$ and $p = .025$)
- BDI-II scores were not significantly correlated with head injury exposure variables

Study: Stern et al., 2019, *Tau Positron-Emission Tomography in Former National Football League Players*

Method

- 26 former NFL players (from the DETECT cohort) and 31 healthy controls without history of TBI underwent NP testing and PET imaging to measure *in-vivo* beta-amyloid and tau accumulation
- NP battery used and assessed included the MMSE, TMT part B, semantic fluency, and NAB List Learning test, along with the BDI-II, BHS, and BIS

Key findings

- A percentage of NFL players showed deficits (T<35, i.e., <7th percentile) in NAB List Learning delayed recall (35%), TMT part B (27%), and category fluency (12%)
- Depression rates were very high (81%) with >50% of sample endorsing severe depressive symptomatology on the BDI-II (Median = 31.5)
- Symptomatic NFL players had worse MMSE scores compared to controls (Mean = 27.2 vs. 29.06)
- Greater tau deposition was observed in former players in the bilateral superior frontal and medial temporal regions, in addition to the left parietal lobe
- Increased beta-amyloid deposition was not observed in NFL athletes
- Small to moderate positive correlations between years played of tackle football and tau deposition in the bilateral superior frontal ($r = .58$), bilateral medial temporal ($r = .45$), and left parietal lobe were reported ($r = .50$), but not correlations were observed between tau deposition and NP measures

Study: Taghdiri et al., 2019, *Elevated cerebrospinal fluid total tau in former professional athletes with multiple concussions*

Method

- CSF biomarkers, white matter integrity, NP measures were compared between 24 former professional athletes with concussion histories (12 CFL players, 9 NHL players, and 1 professional snowboarder), 5 healthy controls, and 12 individuals with AD
- Players were classified into high or low total tau (t-tau) groups (+/- 300 pg/ML)
- NP battery consisted of TMT parts A & B and written SDMT

Key findings

- Athletes were more likely to have elevated total-tau (t-tau) and worse performance on TMT part B compared to controls
- No difference was found between healthy controls and athletes in beta-amyloid or phosphorylated tau
- Higher levels of t-tau were associated with reduced WM integrity in athletes

Note:

Organizational abbreviations: NFL = National Football League, NHL = National Hockey League, CFL = Canadian Football League

Disease/Health abbreviations: MCI = mild cognitive impairment, MDD = major depressive disorder, BMI = body mass index, CSP = cavum septi pellucidum, CNS = central nervous system, HDL = high density lipoproteins, CSF = cerebrospinal fluid

Neuropsychological abbreviations: NP = neuropsychological

Global*:* MMSE = Mini-Mental State Examination, WAIS = Wechsler Adult Intelligence Scale, WASI = Wechsler Abbreviated Scale for Intelligence, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, AD8 = AD8 Dementia Screening Interview, ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing, NAB = Neuropsychological Assessment Battery, WRAT = Wide Range Achievement Test, B-SIT = Brief Smell Identification Test

Processing Speed/Attention: TMT = Trail Making Test, SDMT = Symbol Digit Modalities Test

Executive Functioning: WCST = Wisconsin Card Sorting Test, BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version, DKEFS = Delis-Kaplan Executive Functioning System

Language: COWAT = Controlled Oral Word Association Test, BNT = Boston Naming Test, WTAR = Wechsler Test of Adult Reading, SORT = Semantic Object Retrieval Test, AMNART = American National Adult Reading Test

Memory: BVMT-R = Brief Visuospatial Test-Revised, CVLT = California Verbal Learning Test, RCFT = Rey Complex Figure Test, RVDLT = Rey Visual Design Learning Test; RAVLT = Rey Auditory Verbal Learning Test

Mood/Behavioral: GDS = Geriatric Depression Scale, BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, BHS = Beck Hopelessness Scale, BIS = Barrett Impulsivity Scale, PHQ-9 = Patient Health Questionnaire, HAM-D = Hamilton Depression Rating Scale, BDHI = Buss Durkee Hostility Inventory, PAI = Personality Assessment Inventory

Effort: TOMM = Test of Memory Malingering

Motor: UPDRS = Unified Parkinson's Disease Rating Scale

Neuroradiological abbreviations: MRI = magnetic resonance imaging, fMRI = functional magnetic resonance imaging, SWI = susceptibility weighted imaging, DTI = diffusion tensor imaging, FA = fractional anisotropy, DWI = diffusion weight imaging, PET = positron emission tomography, TSPO = translocator protein, WMSA = white matter signal abnormalities, WM = white matter

Neuropsychological functioning in NFL players

Do retired NFL players display impaired neuropsychological performances?

Following a surge in scientific interest in CTE, several studies have evaluated the neuropsychological functioning of retired NFL players in an attempt to ascertain risk of cognitive decline. In 2013, 34 NFL retirees aged 47-71 were recruited from the Dallas-Fort Worth area Players Association and word-of-mouth among players and were compared to 28 healthy age-matched non-athletes (Hart et al., 2013). All players underwent a comprehensive battery of neuropsychological tests and a neurological examination, with clinical diagnoses determined by a blinded-consensus panel consisting of a behavioral neurologist and two neuropsychologists. Fourteen players demonstrated cognitive deficits (41%), including 8 who met criteria for MCI and 2 for dementia. The frequency of MCI and depression (8 of 22 players) were slightly higher among athletes than typically seen in this age population; however, no players under age 60 were cognitively impaired, suggesting that increased age was a significant risk factor for impairment. Also notable was that most players (approximately 66%) did not show evidence of cognitive impairment. Compared to age-matched healthy controls and cognitively intact NFL players, cognitively impaired NFL players displayed deficits in verbal learning and memory, nonverbal memory, confrontation naming, and word retrieval (Hart et al., 2013), suggesting memory and language may be at greater risk of decline in former NFL players,

although the small sample (n = 14) of cognitively impaired players makes it difficult to draw firm conclusions.

A larger study in 2014 consisted of 45 NFL players ages 30 to 60 recruited from the NFL Players Association, with no history of alcohol/drug abuse, major medical/neurological conditions (e.g., stroke, brain tumor, seizure, cancer, etc.), or concussion following their NFL career (Casson, Viano, Haacke, Kou, & LeStrange, 2014). Restricting the age of former players to 30 to 60 did not have a reported rationale, and a control group was not included for comparison. Instead, the authors elected to group 10 neuropsychological measures into ordinal categories by clinical degree of impairment (i.e., Normal: T-scores ≥ 38 or scaled scores ≥ 7, Borderline: T = 33-37 or scaled score 5-6, and Impaired; T ≤ 32 or scaled score ≤ 4), and mean scores were not reported. Twenty-four percent of the sample were in the "impaired" category on at least 1 or 2 tests. Only descriptive statistics of these categories (i.e., 0 = Normal, 1 = Borderline, 2 = Impaired) were reported in the published supplement, limiting the ability to compare patterns of neuropsychological test performance. Based solely on these ordinal averages, the worst performance was in verbal memory. However, breaking down linear neuropsychological normative performances into impairment categories limits the range of scores seen in the moderate and severely impaired groups, thus limiting clinical interpretation. Depression was significant within the sample, as 15 (33%) of players endorsed at least mild depressive symptomatology and 9 (20%) players met criteria for major depressive disorder based on self-report questionnaires. Interestingly, an association between excessive alcohol use with divided attention/mental flexibility and working memory was found, along with an association between body mass index and verbal fluency, working memory, and fine motor speed. However, what constituted "heavy" alcohol consumption was unclear, and the strength of these

associations was not reported. Although 24% of NFL players in this sample (n =11) displayed deficits on neuropsychological testing, the absence of a control group, reporting impairments in ordinal categories, and paucity of statistical reporting make it difficult to generate any clear conclusions from these data.

A 2017 investigation by Alosco and colleagues examined neuropsychological functioning in NFL players in the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) study. In the DETECT study, former NFL players were age 40-69, with at least 12 years of lifetime tackle football exposure, and self-reported complaints of cognitive, behavioral, and/or mood symptoms for at least 6 months. The primary aim of the study was to examine olfactory functioning and its cognitive correlates in 94 "NFL players presumably at high risk for CTE" using the Brief-Smell Identification Test (B-SIT). The authors found that NFL players had reduced olfaction compared to controls, which correlated with composite neuropsychological behavioral/mood measures and processing speed/executive measures. However, only 6 out of 94 players actually obtained abnormal olfactory scores. Because the author's considered NFL players to be at high risk for CTE, they speculated that impaired olfaction "may be an early marker of CTE-related neurodegeneration, analogous to AD" (Alosco et al., 2017). However, heavy alcohol use is also associated with reduced olfaction (Rupp et al., 2004), which was present in >50% of the former NFL players, indicating that these conclusions may be misattributed. In additional analyses, NFL players performed significantly worse compared to healthy controls ($p < .05$), controlling for age and education, on measures of visuospatial scanning speed, visuomotor processing speed, visuospatial construction, and verbal memory (both story memory and list-learning). Despite these differences, as a group, the majority (63%) of mean test scores fell within the average range, 27% fell in the low average range, and only

immediate story recall (1%) fell in the borderline to mildly impaired range, with a mean T-score of 39 (13th percentile). Thus, although statistical differences were found between former NFL players and a well-educated control group, most neuropsychological scores appeared normal. NFL retirees as a group exhibited at least mild levels of depression (Beck Depression Inventory-II mean score = 16; Hamilton Depression Scale mean score = 9) and had significantly higher rates of excessive alcohol use (52%), hypertension (51%), and high cholesterol (53%) than controls, which were not controlled for in between-group analyses. Overall, the study reported lower scores on olfactory performance and most neuropsychological measures across domains, in addition to greater depression in the former NFL players. However, despite the NFL players having a persistent cognitive or psychiatric subjective complaint, most olfactory and neuropsychological performances were within normal limits and the authors did not statistically account for group differences in alcohol/drug abuse, depression, or vascular factors, which could have contributed to findings.

Several recent studies have examined cohorts similar to NFL players, and they are worth mentioning due to having similar risk of exposure to repetitive head injury and SRC. An investigation of 45 retired Canadian Football League (CFL) players (Mean age = 53) revealed significantly higher rates of self-reported memory (77%), executive function (53%), and behavioral complaints (67%) compared to an age-matched control group. However, no differences were found in performance on assessments of emotional (anxiety and depression), motor, or neuropsychological functioning, with the exception of above average and significantly better performance on a test of visuospatial scanning speed in the former CFL players (Tarazi et al., 2018). In a series of papers out of the University of Buffalo, 21 retired NFL and National Hockey League (NHL) players (age 36 to 72) were compared to age-matched elite non-contact

athlete controls. General findings were that no players met criteria for early onset dementia nor the hypothesized clinical profile for CTE, as outlined earlier (Willer, Zivadinov, Haider, Miecznikowski, & Leddy, 2018). Frequencies of MCI (defined according to Jak et al., 2009 criteria) were higher (albeit not statistically significant) in contact athletes (38%) compared to controls (14%), and contact athletes had lower estimated IQ scores (Baker et al., 2018). After adjusting for IQ, all NFL and NHL players had significantly better verbal fluency performance but worse performance on an interference trial of a verbal memory task (i.e., difficulty learning multiple sources of information). Despite this, all mean scores for athletes were in the average range except immediate story recall, which was in the low average range. Similar to previous studies (Alosco et al., 2017; Hart et al., 2013), this cohort also exhibited higher ratings of depression than controls (Baker et al., 2018). In another investigation focusing on executive functioning, NFL and NHL athletes reported more subjective difficulty, but did not demonstrate any significant differences in neuropsychological performance as measured by tasks related to concept formation and problem solving, response inhibition, divided attention, and phonemic fluency (Willer, Tiso, et al., 2018). Of these studies, NFL and NHL players on average had better verbal fluency performance, only one score in the low average range (verbal memory), and only one significant difference between athletes and controls was found on an interference trial of a verbal memory task, although performances were still in the average range. Clinically, 1 or 2 impaired scores within different cognitive domains in a comprehensive neuropsychological examination is considered normal and is not typically considered clinically relevant. Overall, little to no differences were found in these cohorts of CFL, NFL, and NHL players when compared to a healthy control group.

Neuropsychological performance and degree of head injury exposure

Many studies have examined a dose-response relationship between head impacts and neurocognitive functioning, hypothesizing that a greater degree of head injury exposure results in greater cognitive difficulties. In perhaps the most well-known study examining this relationship, Stamm and colleagues (2015) evaluated the association between age of first exposure to tackle football (AFE) and three neuropsychological measures within the DETECT cohort described earlier. The authors reported that after adjusting for age and duration of play, 21 NFL players with AFE < age 12 had worse neuropsychological performance on measures of concept formation and problem-solving, word-reading, and verbal memory than 21 NFL players with AFE ≥ age 12 (Stamm et al., 2015). Word-reading is generally an index of premorbid cognition and resistant to cognitive decline, and thus it is unclear why the groups differed on this measure. The authors suggest this may relate to brain damage in the prefrontal cortex impacting subsequent neurodevelopment, but an alternative possibility was the inclusion of 3 individuals with learning disabilities in the AFE < 12 group skewed the results. Others have also suggested this limitation to their findings, in addition to pointing out that higher rates of substance use and steroid use were reported in the DETECT cohort overall (Solomon et al., 2016), although significant differences in substance/steroid use were not found between the <12 and >12 AFE groups. The authors also suggested that higher rates of depression were found in a previous analysis, but did not report depression rates in this study. Last, a major limitation of this study was the absence of a healthy control group, despite data on a cohort of elite non-contact athletes seemingly available within the DETECT study (Stamm et al., 2015).

Subsequent studies have failed to replicate the finding of worse neuropsychological functioning in individuals with earlier exposure to tackle football using various proxy measures

for head injury exposure. In 2016, Solomon and colleagues evaluated 45 retired players recruited from the NFL Players Association (same cohort as Casson et al., 2014). The authors utilized regression models to assess the relationship between years of pre-high school football exposure and neuropsychological measures, neuroradiological findings, or neurological functioning, while accounting for age, body mass index, learning disability, years of NFL experience, number of NFL concussions, and position (lineman versus other). No association between number of years of pre-high school football and any neuropsychological, neuroradiological, or neurological measure was found. However, the authors utilized a very conservative interpretive approach. In their list of limitations, the authors noted their study was marginally underpowered, though they corrected for multiple comparisons. This led them to conclude null findings, though some differences between measures approached statistical significance, i.e., delayed visual memory (p = .017), divided attention (p = .045), and delayed verbal memory (p = .067). Though this study exhibited several methodological strengths, these results were found in the context of a small underpowered sample and identify delayed recall and divided attention as areas for further investigation.

In the most recent investigation to date, Fields and colleagues (2019) evaluated 35 NFL retirees (age 52-78) with a history of at least one concussion. They examined correlations between neuropsychological functioning and total number of concussions, number of concussions with LOC, and years played in the NFL. Neuropsychological domain composite scores were created to limit the number of statistical comparisons, and consisted of attention/processing speed, language, and memory, which together created an overall cognitive composite score. To correct for multiple comparisons, the authors *a priori* set $p < .01$ as the level of significance. With a priori corrections for multiple comparisons, no statistically significant

linear relationships were found between composite neuropsychological scores and exposure variables (total concussions, concussions with LOC, years played in the NFL). Though not statistically significant, years played in the NFL correlated with memory (r = -.388, p = .023) and global composite scores (r = -.389, p = .025), suggesting avenues for future investigation. Similar null findings were found when analyses were separated by players who were cognitively intact (n = 21) and those that were cognitively impaired (n = 14) based on a consensus diagnosis of MCI or dementia. Exposure variables were also not significantly correlated with depression ratings. The authors concluded that these results put prior findings into context, suggesting that any possible relationship between SRC and later-life cognitive impairment does not appear to be simple, linear, or dose-response in nature, calling for future studies to consider additional factors that may explain why some athletes experience cognitive dysfunction later in life.

Others have taken different methodological approaches to examine the relationship between head injury exposure and neurocognitive functioning. A 2018 study by Clark and colleagues examined neuroradiological findings and neuropsychological performance in a sample of former division I college (n= 31) and NFL players (n= 30) ages 55-65, stratified by high versus low frequency of concussion (0-1 versus 3+), position (speed versus non-speed), and career duration (college versus NFL). No mean differences in depression, intellectual, or global neuropsychological measures were observed between concussion groups when broken down by position or career duration. However, discrete cognitive domains and subtests were not examined, sample sizes were limited by classification into career and position (N ~15), and years of exposure to football was essentially restricted to a dichotomous variable due to career duration (average years played for college athletes = 8; NFL athletes = 17) (Clark et al., 2018).

Neuropsychological performance and neuroradiological findings

Several studies have evaluated the association between neuropsychological performance and neuroimaging findings, with one of the more frequent findings being reduced white matter integrity. In the first published study examining neuroradiological differences in retired NFL players, cognitive dysfunction and depression were correlated with reduced white matter integrity on diffuse tensor imaging (DTI), in addition to white matter lesions observed on fluid-attenuated inversion recovery (FLAIR) signals among retired NFL players with cognitive impairment (Hart et al., 2013). A follow-up investigation in 2017 found reduced confrontation naming in 25 NFL retirees (ages 41-79) compared to non-athlete controls (N = 22), which was correlated with decreased white matter integrity (Strain et al., 2017). A 2018 study out of the DETECT cohort also found that a cumulative head impact index score (Montenigro et al., 2017) and a factor analysis derived index of psychomotor speed/executive function correlated with abnormal white matter signal (Alosco et al., 2018). Other studies have also found mean diffusivity and fractional anisotropy (FA) changes in younger (mean age = 31 years) NFL retirees (Coughlin et al., 2017), in addition to neuroinflammation (Coughlin et al., 2017; Coughlin et al., 2015) and hippocampal volume loss (Coughlin et al., 2015) in retired players compared to age-matched controls, although sample sizes were too small to compare neuropsychological performances.

In addition to white matter signal, temporal lobe function is of particular interest in investigations of SRC in aging, due to hippocampal involvement in episodic memory function, AD, and dementia. In a 2015 study, Strain and colleagues found that NFL retirees (N= 17) who sustained at least one grade 3 concussion (i.e., concussion with LOC) were significantly more likely to have lower verbal learning and memory performance, as well as reduced hippocampal

volumes in comparison to healthy age- and IQ- matched controls (N = 21). Older retirees (over age 63) with a history of concussion with LOC were more likely to have MCI than those without concussion with LOC. Additionally, retirees who played in more games (at least 120 games) had lower hippocampal volumes, but were less likely to have a history of concussion with LOC, compared to those who played fewer than 120 games (Strain et al., 2015).

In contrast, Casson and colleagues (2014) reported an association between reduced white matter integrity on DTI and number of NFL concussions and years of high school football but did not find an association between fractional anisotropy (FA) and neuropsychological measures. However, as mentioned before, neuropsychological measures were broken down into ordinal categories that could have reduced variance, especially in the impaired ranges (Casson et al., 2014). The follow-up study by Solomon and colleagues (2016), which evaluated the same cohort using a different statistical approach, found no associations between neuropsychological measures, neuroradiological findings, or years of pre-high school football. However, a very conservative approach was taken, accounting for many potential confounding factors, including age, BMI, learning disability, years of NFL football, number of NFL concussions, and position, in which the authors acknowledged that analyses were underpowered. (Solomon et al., 2016). Findings were replicated one year later in a follow-up investigation using a slightly different design, with no correlations found between neuroradiological findings (i.e., microbleeds, cavum septum pellucidum, and FA) and neuropsychological measures (Kuhn, Zuckerman, Solomon, Casson, & Viano, 2017). Furthermore, some reported findings have shown a pattern that is counter or opposite to what would be expected if SRC negatively affected brain integrity. For example, in the aforementioned study that compared NFL and collegiate players by concussion history (Clark et al., 2018), reduced FA was seen in former college players with 3 or more

concussions compared to those with no concussions or only one concussion, whereas NFL players with fewer SRCs, curiously, showed the opposite finding. In fact, FA levels in the highest exposure group (NFL players with 3+ concussions) did not differ from the lowest exposure group (former college players with 0 to 1 concussions).

Examing the Cavum septi pellucidi (CSP) in former NFL players has been the focus of several neuroradiological investigations. CSP is a reported neuropathological feature of CTE (McKee & Daneshvar, 2015), and has been investigated in both the DETECT cohort and the Casson et al., 2014 cohort. In a 2016 study investigating if CSP was present, and if so the length of CSP in symptomatic former football players (i.e., DETECT cohort), CSP was found in 66 of 72 (92%) former NFL players compared to 8 out of 14 (57%) noncontact athlete controls (Koerte et al., 2016). CSP was significantly longer in NFL players compared to controls, and a greater than 6 mm CSP length was associated with reduced verbal learning and word reading in NFL players, but none of the other 22 neuropsychological or mood measures (Koerte et al., 2016). In the Casson cohort, CSP was also a common finding, occurring in 35 of 45 (78%) former NFL players, although the vast majority (32) were rated as "small" qualitatively by the authors (Kuhn et al., 2017). Unlike previous findings by Koerte et al., however, there were no neuropsychological or mood (depressive) measures that correlated with CSP in this cohort, suggesting that additional investigation of the clinical significance of CSP in NFL players is warranted (Kuhn et al., 2017).

Advances in imaging and biomarker technology have allowed researchers to evaluate *in-vivo* markers of neuropathological processes, and recent studies evaluated the presence of tau pathology in former NFL players. For example, tau and beta-amyloid levels (measured by PET) along with several neuropsychological measures (divided attention/mental flexibility, semantic

fluency, and episodic memory) in 26 former NFL players out of the DETECT cohort and 31 healthy controls were compared in a recent study by Stern and colleagues (2019). Greater tau deposition was observed in former players in the bilateral superior frontal and medial temporal regions, in addition to the left parietal lobe. Increased beta-amyloid deposition was not observed in the NFL athletes. Small to moderate positive correlations between years played of tackle football and tau deposition in the bilateral superior frontal (r = .58), bilateral medial temporal (r = .45), and left parietal lobe were reported (r = .50), but there was no association with neuropsychological measures and tau deposition, despite 35% of the sample showing episodic memory impairment (Stern et al., 2019). Another recent study compared cerebrospinal fluid biomarkers, white matter integrity, and neuropsychological measures between 24 cognitively normal former professional athletes with self-reported concussion histories (12 CFL players, 9 NHL players, and 1 professional snowboarder), 5 healthy controls, and 12 individuals with AD (Taghdiri et al., 2019). The tau levels of former athletes were divided into high and low groups (+/- 300 pg/ML). Overall, former athletes had higher levels of CSF-derived total tau, but not phosphorylated tau (p-tau) or beta-amyloid compared to controls, whereas AD subjects had greater levels of p-tau, total tau, and beta-amyloid compared to both former athletes and controls. Compared to younger athletes, older athletes were significantly more likely to have higher levels of total tau and worse performance on a measure of divided attention and mental flexibility, albeit similar to previous studies, the mean score was in the average range. The high t-tau group also had fewer concussions on average (4.0 versus 6.3) and began playing contact sports at a later age (age 11.4 versus 8.8), although these differences were not statistically significant. Although both of these studies suggest that tau deposition may be more frequent in former contact athletes, several questions remain unanswered. First, although it is suspected that the

increase in tau is related to cumulative head injury, neither study found a strong dose-response relationship between head injury and tau levels. Second, the clinical significance of their findings is unclear, as only one of the studies found a relationship between tau and a single neuropsychological measure, in which the former athletes as a group still performed in the average range. Lastly, it is unknown if tau levels found in these studies will correlate to neurodegenerative changes over time, as both studies measured tau at only one time point. Without longitudinal investigation, it is possible that these levels of tau are static and may have plateaued decades prior, and thus are of unknown significance in terms of increasing risk for neurodegenerative changes over time.

Limitations, Future Directions, and Conclusions

Limitations of the current literature

Despite a substantial increase in scientific interest and studies in the cognitive performance of retired NFL athletes over the last six years, wide-ranging methodological differences make it difficult to draw firm conclusions regarding the risk of long-term cognitive dysfunction in NFL athletes in relation to SRC and/or head injury exposure. The few prior attempts to identify the prevalence or risk of MCI and dementia in NFL players have largely relied upon survey data, retrospective record review, and/or only one time point rather than prospective investigations or detailed surveillance methods typically used in epidemiological studies. This has likely produced the wide-ranging estimates of MCI (12% to 35%) between studies (Guskiewicz et al., 2005; Randolph et al., 2013) and, combined with small sample sizes, has produced “highly imprecise” estimates of neurodegenerative disease risk in a single study

(Lehman et al., 2012). Despite the scientific interest in CTE, there have been no *in-vivo* neuropsychological studies of individuals identified with CTE at autopsy, there are no well-accepted clinical criteria for CTE, and research thus far has relied exclusively on retrospective studies utilizing donated brains to attempt to identify clinical symptoms, which can be prone to recall bias.

When evaluating the cognitive profiles of living NFL players using gold-standard clinical assessments (i.e., clinical neuropsychological evaluation), the literature has produced largely mixed results which vary significantly with regard to methodology. First, group comparisons have been inconsistent. Some studies elected to not use a control group, limiting the ability to determine if NFL athletes differ from a healthy aging population. Others have compared an "at-risk" sample of NFL players with cognitive and psychiatric complaints to a healthy control group, when a more appropriate control group would be a non-SRC exposure clinical sample with similar complaints, such as those with major depressive disorder and/or subjective cognitive concerns related to aging. This would help determine if symptomatic aging NFL players differ from the general population with cognitive or psychiatric complaints. Second, most studies have included wide age ranges (spanning 30+ years in many cases), which most likely influences the risk and degree of cognitive decline seen in these athletes, considering age is the largest risk factor for dementia and related conditions. Additionally, inclusion and exclusion criteria have varied substantially across studies. For example, some investigators have elected to include those with a history of substance use, while others have not. It is possible that cognitive impairment may be associated with substance abuse, and cognitive impairment may not be attributable to repetitive head injuries sustained over a playing career. Alternatively, it is plausible that persistent substance use is a result of psychiatric symptomatology (e.g., depression) related or

unrelated to repetitive head injury or a combination of head injury and other factors, and the exclusion of these individuals may remove those who are experiencing more severe psychiatric symptoms. Third, small sample sizes in nearly all of the published studies limit statistical power for detecting effects of SRC on neuropsychological functioning, subgroup examination (e.g., examining for differences in older versus younger retirees), and may produce unreliable or unstable findings. Fourth, an additional limitation with current samples within the literature is the potential for a "survivor bias" that include only more resilient players, as perhaps those with persistent post-concussive symptomatology or more vulnerability to head injuries had their playing career cut short and did not make it to the NFL. Fifth, in studies with limited power and small sample sizes, efforts to correct for multiple comparisons may be overly conservative, increasing the risk of missing subtle findings (i.e., Type-2 error). Sixth, few studies report effect sizes, and when statistical differences have been reported between NFL retirees and controls, mean performances are often in the normal range, suggesting that these differences may not be clinically meaningful or could reflect premorbid group differences. Seventh, the measurement of severity of concussive injuries (e.g., LOC versus no LOC) has not been consistent, and may be impacting the mixed findings regarding a dose-response relationship between head injury and cognitive decline. Another limitation not yet addressed by the literature may be a possible "ceiling effect" that occurs after a few concussions, where the impact of multiple concussions reaches a maximum threshold thus limiting impact of future concussions in some individuals. Lastly, and perhaps the biggest limitation of the literature to date, relates to the absence of a single longitudinal investigation of neuropsychological functioning in NFL retirees over time, which could provide crucial evidence to determine if NFL players are at greater risk for

cognitive impairment and generate additional research hypotheses on potential long-term impacts of SRC.

Future Directions

Future studies should aim to recruit large numbers of NFL retirees in a systematic, randomized fashion, with efforts to reduce sampling bias and without requiring cognitive or psychiatric complaints. Because age is the most significant risk factor for cognitive impairment related to neurodegenerative conditions, studies ideally would recruit players from all ages, and include stratified analyses to determine differences in risk of cognitive decline by various age brackets. Longitudinal surveillance with serial evaluations to measure change over time is desperately needed and will help identify which players may be more at risk for cognitive decline over time. Neuropsychological evaluation, at the time of retirement and longitudinal surveillance, in a large sample of NFL players would serve to determine risk of cognitive decline, patterns of aging/cognitive decline, the nature of a potential relationship between SRC and cognitive decline, and epidemiological estimates of MCI and dementia among this population. High rates of depression have also been seen in some NFL samples within the literature, which may be due to a host of factors including adjustment to post-retirement. Thus, careful documentation of psychiatric symptomatology and history is also needed and could be contributing to rates of cognitive complaints and neuropsychological performance. Comparing neurocognitive profiles in those with MCI and dementia without a history of SRC exposure is also warranted to continue to better understand whether SRC may be associated with a different pattern of neuropsychological functioning than is typically seen in cognitively impaired individuals in the general population. Brain donations and *in-vivo* biomarker studies (e.g.,

imaging, cerebrospinal fluid) are necessary to correlate clinical symptoms and cognitive data with pathology. Although it can be argued that similar to CTE, other neurodegenerative dementias cannot be diagnosed *in-vivo*, though other neurodegenerative dementias (e.g., AD) have well-characterized neurocognitive and neurobehavioral profiles based on decades of longitudinal studies. Only one validation study has been completed on CTE pathological criteria (McKee, Cairns, et al., 2016), whereas other neurodegenerative conditions like AD have had numerous revisions with clear pathologic and clinical criteria (for a recent review specific to this topic, see Brett et al., 2019). Thus, carefully controlled longitudinal prospective studies on players is needed to correlate neurobehavioral symptoms to autopsy-based pathology data.

Conclusions

In total, 22 studies pertaining to retired NFL players and neuropsychological performance were reviewed for the purposes of this manuscript. Although evidence is limited, some studies suggest a higher prevalence of cognitive impairment in NFL retirees, which suggests at least some players may be at greater risk for cognitive decline after repetitive head injury. However, research to date has not established a quantifiable risk or prevalence of MCI, dementia, neurodegenerative disease, or CTE in NFL players. Neuropsychological performance data among NFL players generally have been mixed, but decreased verbal memory has been seen in some players across multiple studies (Baker et al., 2018; Casson et al., 2014; Hart et al., 2013; Stamm et al., 2015; Strain et al., 2015). However, the clinical significance of prior findings is unclear due to small sample sizes, unreported effect sizes, and absence of longitudinal data. Although a dose-response relationship between cognitive decline and head injury exposure has been suggested by some, findings have been mixed, with various proxy measures of head-injury

exposure examined categorically versus linearly and no clear linear or non-linear relationship has been established. Future research is needed to understand the relationship between SRCs, an NFL career, and the risk of long-term cognitive decline and neurodegenerative disease in aging NFL players.

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STUDY 2: NEUROPSYCHOLOGICAL FUNCTIONING IN AGING RETIRED NFL ATHLETES: A CROSS-SECTIONAL AND LONGITUDINAL INVESTIGATION

Introduction

The influence of sports-related concussion (SRC) on long-term cognitive outcomes is an area of expanding scientific interest, and is not without controversy following the relatively recent discovery of chronic traumatic encephalopathy (CTE) in former National Football League (NFL) players. According to the 2019 NFL safety report, there were 224 concussions sustained during the preseason and regular season, equating to approximately .70 concussions per game. However, despite their frequency, the long-term cognitive impact of repetitive and cumulative SRCs is unclear, and debate continues whether cumulative head impacts are associated with long-term cognitive impairment, neurodegenerative disorders, and/or dementia.

NFL Players and Risk of Neurocognitive Impairment

Research evaluating the risk of mild cognitive impairment (MCI) and dementia in former NFL players is limited, and has been mostly restricted to retrospective self or informant report survey data. In three survey studies, higher rates of self-reported cognitive impairment, (i.e., either mild cognitive impairment [MCI] or dementia) were reported by NFL retirees or their spouses (Guskiewicz et al., 2005; Weir, Jackson, & Sonnega, 2009; Randolph, Karantzoulis, & Guskiewicz, 2013). In a highly cited study by Guskiewicz and colleagues, survey data from the NFL Players Association (N=2,552) suggested higher rates of self-reported MCI and memory decline in NFL players compared to rates in the general population in those who sustained recurrent concussions during their playing career (Guskiewicz et al., 2005). A 2013 follow-up

led by Randolph et al. (2013) also found higher rates (i.e., 35%) of spouse-reported (N=513) cognitive impairment based on the AD8 questionnaire than expected for the age of their sample (Mage=64.2). In a systematic survey by Weir and colleagues in 2009, telephone interview data of a stratified random sample of 1,063 retired NFL players were compared to age-matched data from the U.S. Census. Findings suggested self-reported or proxy-reported "diagnosis of dementia, Alzheimer's, or other memory-related disease" were significantly higher for younger retired athletes (ages 30-49) than their peers in the general population (1.9% vs. .1%), and rates of self or informant-reported dementia in the older retirees (age 50+) were noted to be approximately 5 times higher than reports in the general population, i.e., 6.1% versus 1.2% (Weir et al., 2009). However, all three of these studies were limited to survey data and self or informant-reported diagnoses, which are prone to recall and misattribution bias. In a 2012 non-survey study, Lehman and colleagues evaluated mortality rates of deceased former NFL players (N=3,439) by linking pension records to National Death Index data. Findings suggested NFL players had reduced mortality rates overall compared to men in the U.S., but mortality rates were higher from neurodegenerative disease, Alzheimer's disease (AD), and amyotrophic lateral sclerosis (Lehman, Hein, Baron, & Gersic, 2012). However, a major limitation of these data was the very small number of neurodegenerative cases (10 underlying and 17 contributing causes of death), which led the authors to conclude their findings may have been "unstable" (Lehman et al., 2012). Despite findings being limited to survey data or small statistical samples, the increased risk of dementia in former NFL players has been propagated forward by the mainstream media, mainly due to an increased focus on CTE research and findings generated out of a limited set of brain banks.

Chronic Traumatic Encephalopathy

Although some researchers have suggested CTE is an established neurodegenerative disease, others have cautioned that CTE research is just beginning (Randolph, 2018; Iverson, Keene, Perry, & Castellani, 2018), especially when compared to the research standards of other neurodegenerative disorders (for a review see Brett et al., 2019). CTE is currently defined as a neuropathological condition characterized by irregular perivascular collections of hyperphosphorylated tau predominantly found within the depths of the cerebral sulci, and has been linked to repetitive SRCs and "sub-concussive" hits (McKee, Alosco, & Huber, 2016). CTE's status as a public health-risk rapidly increased and garnered worldwide attention after the discovery of CTE pathology in several popular deceased NFL players.

While some have speculated that CTE is common in former football players based on convenience samples found in some brain banks (e.g., Mez et al., 2017), the extent to which these findings generalize to all past or present football players or NFL players (~25,000 players) is yet to be determined. In the most recent post-mortem investigation of CTE prevalence to date, 750 deceased individuals (N=300 former amateur athletes vs. N= 450 non-athletes) underwent neuropathological examination at the Mayo Clinic Tissue Registry. CTE was found to be rare overall, with consensus diagnosis guidelines being achieved in only 21 cases, with 21 additional cases showing "CTE features." Despite rarity of CTE pathology, the authors found CTE pathology was nearly twice as common in athletes (N=27) than non-athletes (N=15), and the highest frequency (~15%) of CTE pathology was found in former football players (Bieniek et al., 2019). However, it also important to note that approximately 37% of individuals with CTE pathology also had comorbid AD pathology, and 80% of the entire sample had at least one tau

immunoreactive lesion, suggesting the link between participation in contact sports and hyperphosphorlated tau may not be specific to CTE.

The cause of CTE pathology, while more frequent in some brain banks of those with high rates of head injury exposure (Mez et al., 2017), is not fully understood. A recent study, using donated brains from the VA-BU-CLF and Framingham Heart Study, found a dose-response relationship between years of football played and CTE pathology, and reported an odds ratio of 2.6 for every year of football played (Mez et al., 2020). However, brain-bank samples are a select and unique group, with a high likelihood of selection bias due to their extreme frequencies of individuals already suspected of having CTE or neurodegenerative disease. Other brain-bank studies have found CTE is present in individuals without any history of head injury but with other psychiatric and neurological diseases, including alcohol (Noy et al., 2016) and opiate users (Anthony et al., 2010), epilepsy (Puvenna et al. 2016), amyotrophic lateral sclerosis (Walt et al., 2018), and multiple system atrophy (Koga, Dickson, and Bienek, 2016), suggesting there may be multiple mechanisms leading to CTE pathology. In addition, the relationship between CTE pathology and exposure to head-injury is not unique to CTE, and other studies have reported that head-injury is a risk for several neurodegenerative diseases, including AD, Lewy body disease, and Frontotemporal dementia (LoBue et al., 2019). As such, the literature has not conclusively provided evidence to date that CTE is directly linked to concussions, head-injuries, or sub-concussive hits. To further complicate this relationship, CTE does not have established clinical criteria to differentiate the pathology from other neurodegenerative diseases during life, and the course and clinical features of CTE are not well-defined.

The course and clinical features of CTE are ambiguous and non-specific. Initial research using retrospective informant-report interviews developed initial phenotypes that proposed CTE

symptoms begin years after a playing career ends, and that progressive memory, executive functioning, and explosive mood/behavioral changes accompany the pathology (Stern et al., 2013). However, retrospective informant-report interviews present several methodological problems. First, informants and next-of-kin may have differing perspectives and recall of patient's behavior and symptoms. Second, these report's may be additionally influenced by increased media attention, particularly for NFL retirees. Third, clinically differentiating between neurodegenerative conditions later-in-life is difficult, as memory and behavioral changes associated with several neurodegenerative diseases (e.g., AD and Frontotemporal dementia), and neurodegenerative disorders may present similarly in individuals in late stages of dementia. Lastly, misattribution over the cause of symptoms in clinical populations is frequently seen when performing clinical evaluations (e.g., memory "impairment" may be attributed to attention difficulties or depression). Despite these limitations, several clinical research criteria for diagnosing CTE *in-vivo* have been published and involve a wide array of vague and non-specific clinical and cognitive symptoms (Jordan, 2013; Montenigro et al., 2014; Reams et al., 2016; Victoroff, 2013), and combined have reported at least 56 potential symptoms of CTE. As such, the literature to date has not conclusively defined the specific course or symptoms of CTE, and systematic prospective *in-vivo* studies of those who are later confirmed to have CTE are desperately needed. In a recent study by LoBue and colleagues (2020), archived neuropsychological and clinical data for autopsied CTE positive patients were obtained from the National Alzheimer's Coordinating Center. Findings suggested there were no significant differences in neuropsychological, neurobehavioral, neuromotor, or neuropsychiatric presentation between a small sample of patients with co-occurring Alzheimer's and CTE (n=6) and age-matched patients with Alzheimer's disease (N=25). Although sample sizes were small,

their results question whether CTE contributes meaningfully to clinical presentation among those with well-established neurodegenerative diseases.

Neuropsychological Functioning in NFL Retirees

Despite the rising concern over SRCs and participation in football leading to long-term neurocognitive decline, there is limited and mixed data characterizing the degree and pattern of cognitive impairments in retired NFL players. In a recent paper, Schaffert and colleagues published a critical review of the available research up to 2019 on the neuropsychological performance of retired NFL players (Schaffert et al., 2019). Twenty-two studies were reviewed since 2013, with 13 reporting on neuroradiological findings, and 4 specifically focused on examining a dose-response relationship between neuropsychological functioning and aspects of head-injury exposure (i.e., number of concussions, games played, age started playing football, etc.). This review noted that several investigations found worse NFL player performance in tests measuring verbal memory (Hart et al., 2013; Strain et al. 2015; Casson et al. 2014; Alosco et al., 2017; Wright et al., 2016; Koerte et al. 2017; Baker et al., 2018), confrontation naming (Hart et al., 2013; Strain et al., 2017; Wright et al., 2016; Alosco et al., 2017; Koerte et al. 2017, Baker et al., 2018), and executive functioning (Alosco et al., 2017; Wright et al. 2016), though most group level performances were not in the impaired range and some studies did not find any differences in neuropsychological functioning compared to controls (Willer et al., 2018; Tarazi et al., 2018). Regarding a dose-response relationship between head-injury exposure and neuropsychological performance, head-injury exposure variables were examined both categorically and linearly, and yielded mixed findings. One well-cited study found that beginning tackle football prior to age 12 was significantly associated with executive dysfunction later-in-life (Stamm et al., 2015) while

others have failed to find a statistically significant linear relationship between various head-injury exposure variables (i.e., number of concussions, years of football played, games played) and neuropsychological performance among retired players (Solomon et al., 2016; Fields et al., 2019). Mixed findings can likely be attributed to a host of methodological differences and limitations across the literature, including various use of control groups, wide age ranges within samples (30s to 70s), small sample sizes, different measurements of head-injury exposure, and the lack of any longitudinal studies of neuropsychological performance among NFL retirees.

Study Aims

In the present investigation, we sought to fill gaps and limitations in the literature by comparing the neuropsychological performance of an exclusively older group of NFL retirees cross-sectionally and longitudinally to matched controls, and asses if potential differences in neuropsychological functioning correlate to head-injury exposure. This study has several advantages over the existing literature. First, only older retirees (50+) were included because increasing age is a the most significant known risk factor for cognitive impairment, MCI, and dementia. Most literature to date has included small samples of NFL retirees that have spanned many years in age, and their inclusion of young, healthy, and recently retired players may encumber findings in elderly NFL retirees. Second, this was the first study to examine the longitudinal changes in neuropsychological performance among elderly NFL retirees. Serial evaluations of neurocognitive change will identify if NFL retirees have faster rates of cognitive decline than their non-NFL peers and may also help answer if players with more head-injury exposure or longer NFL careers may be more at risk for cognitive decline over time. Third, only one study to date has compared the neuropsychological performance of NFL players with

cognitive impairment to a clinical sample of elderly patients with cognitive impairment (Randolph et al., 2013). Because a proportion of NFL players in this study were cognitively impaired (i.e., meeting criteria for MCI or dementia), we matched these players as closely as possible to a clinical sample of older individuals with MCI or dementia. This allowed us to evaluate if NFL players with cognitive impairment (MCI or dementia) display different neuropsychological patterns than a sample of clinical patients without cumulative head-injury exposure. Finally, the current study was able to assess if differences in neuropsychological performances were related to a wider array of head-injury exposure variables, including the number of reported concussions, reported concussions with loss of consciousness (LOC), games played, games started, years played in the NFL, and age starting to play tackle football.

Hypotheses

Based on the existing literature, we hypothesized that if an NFL career and cumulative head-injury exposure results in long-term neuropsychological impairment, then NFL players will display significantly worse baseline and longitudinal neuropsychological performance compared to healthy controls and a clinical sample in the areas of verbal memory, confrontation naming, and executive functioning. In addition, we hypothesized that neuropsychological performance in these domains would also negatively correlate to head-injury exposure variables, demonstrating a dose-response relationship between head injury exposure and cognitive impairment.

Method

Participants

Data were collected via an ongoing prospective longitudinal clinical-research investigation of aging and cognition among NFL retirees at the University of Texas Southwestern Medical Center (UTSW). Because this particular cohort of former NFL players included participants who had normal cognition, MCI, and dementia, two different control groups were used. Cognitively normal former players were compared to a cognitively normal control group that were recruited simultaneously with former NFL players, and matched as closely as possible by age, education, and estimated IQ. In order to evaluate if players with cognitive impairment (MCI or dementia) display different neuropsychological patterns than non-NFL players with MCI and dementia, we matched former players with MCI and dementia as closely as possible by age, education, and diagnosis to a clinical sample of patients derived from archived neuropsychological data within the UTSW neuropsychological clinic. Additional details for each group are reported below. Demographics of each participant group are found in Table 1.

Table 1

Demographics of Former NFL Players, Cognitively Normal Controls, and a Clinical Sample of Patients with MCI and Dementia

	Former NFL Players (n = 53)	**Cognitively Normal Controls (n = 26)**	**Clinical Sample (n = 22)**
Age, *M* (SD)	65.4 (7.8)	64.9 (7.4)	70.8 (8.4)
Years of Education, *M* (SD)	16.3 (0.9)	16.2 (2)	17.3 (1.6)
Caucasian, N (%)	42 (79)	24 (92)	21 (95)
African American, N (%)	11 (21)	2 (8)	1 (5)

NFL Players

All NFL retirees included were at least 50 years of age (range 50 to 79) and recruited through presentations at local NFL retiree gatherings, meetings of local NFL Players Association Chapter, local advertising, and/or word of mouth among retired NFL players. In this sample, 53 former NFL players underwent a clinical interview, comprehensive neuropsychological testing, neuroimaging, and a neurological exam. Players were 22 to 50 years retired from the league (*M* = 35.1, *SD* = 7.67), and had 15 to 19 years of education (*M* = 16.3, *SD* = 0.94). Forty-two were Caucasian and 11 were African American. At the baseline visit, 27 were employed full-time, 8 part-time, 11 were retired, and 1 was unemployed (missing data on 6). Twenty-eight players from the initial 52 returned for follow-up 13 to 59 months later (*M* = 26.1, *SD* = 12.76). Detailed concussion histories were collected via self and informant report, and defined using American Academy of Neurology (1997) criteria. Medical conditions and surgical history were also collected through completed questionnaires and self-and/or informant report during a semi-structured clinical interview by either a neuropsychologist or behavioral neurologist. Games played, years played in the NFL, and games started were collected through a website of archived statistics (www.pro-football-reference.com). Playing career statistics on two NFL players were

unable to be located. Playing career statistics and concussion history for NFL retirees are presented in Table 2. Retirees averaged 5.63 concussions, 2.22 concussions with LOC, 8.89 years in the NFL, 115.12 games played, and 48.66 games started. Former players, on average, started 36% of their career games, and 30% of former players in the current sample started at least 50% of their career games. Primary positions of the players were lineman (n = 22, 42%), running back (n = 8, 15%), linebacker (n = 7, 13%), safety (n = 7, 13%), cornerback (n = 4, 8%), quarterback (n = 2, 4%), and wide receiver (n = 2, 4%). Although the age at which NFL players began playing tackle football was not collected during the initial phases of the study, we attempted to collect this information retrospectively via telephone, obtaining an approximately 30% response rate. NFL retirees began playing tackle football between 5 and 14 years old (M = 11, SD = 2.33).

Table 2

Playing Career Statistics and Concussion History for NFL Players

	N	**Range**	***M***	***SD***
No. of Concussions	48	0-18	5.63	4.50
No. of Grade 3 Concussions	50	0-13	2.22	2.41
Years Playing Pro	53	1-15	8.89	3.49
Games Played	51	15-224	115.12	5.10
Games Started	50	0-203	48.66	52.76
Age Started Playing	19	5-14	10.99	2.33

Healthy Controls

A cognitively normal, healthy control group was assembled that was matched as closely as possible to the retired NFL players by age, education, and estimated IQ. These 26 controls

were aged 52 to 77 (*M* = 64.88, *SD* = 7.36), and obtained 12 to 20 years of education (*M* = 16.23, *SD* = 2.03; see table 1). Twenty-four were Caucasian and 2 were African American. were recruited simultaneously with NFL players and from healthy aging studies at The Center for BrainHealth at the University of Texas Dallas (UTD), and underwent neuropsychological testing and neuroimaging. Fifteen healthy controls returned for a follow-up visit from 8 to 38 months later (*M* = 18.73, *SD* = 7.43). Medical conditions and surgical history were collected through self-report questionnaires. None of the control participants reported any history of neurological disease or concussion, and did not participate in college or professional football.

Clinical Sample of Patients with MCI and Dementia

In order to compare the neuropsychological performance of former NFL players with MCI or dementia, a second control group was retrospectively obtained from archived data within the UTSW Neuropsychology Clinic. This clinical sample was referred for clinical neuropsychological evaluation as part of routine clinical care, with diagnoses made by the evaluating neuropsychologist. We matched former NFL players as closely as possible to patients seen within the neuropsychology clinic based on age, education, and diagnosis (i.e., MCI or dementia). Clinical patients ranged in age from 57 to 86 (*M* = 70.82, *SD* = 8.44) and obtained 14 to 20 years of education (*M* = 17.27, *SD* = 1.64). One was African American and the rest Caucasian. Data on demographic, neuropsychological results, medical histories, medications, and diagnosis was collected via each clinical participant's neuropsychological report. Participants from this clinical sample were excluded if it was noted within the neuropsychological report that they were undergoing litigation, showed evidence of malingering, or had a noted history of concussion, moderate-severe TBI, or a confirmed major territory stroke. Clinical patients who

reported suspected transient ischemic attacks (n = 3) were included. All clinical controls were 50 years and older, and diagnosed with MCI (N=17), probable Alzheimer's disease (N=4), or Lewy body dementia (N=1) by the evaluating neuropsychologist. Archived neuropsychological evaluations took place between 2008 and 2019. Thirteen clinical patients had available follow-up neuropsychological evaluation ranging from 11 to 38 months later (M = 19.31, SD = 9.04).

Consent and IRB Approval

The Longitudinal Study of Aging NFL Players study was approved by the UTSW IRB. The clinical sample of participants all consented for their archived neuropsychological data and medical history to be used for research purposes at the time of neuropsychological assessment.

Measures

All participants underwent a comprehensive neuropsychological battery that included measures of attention, processing speed, executive functioning, language, visuospatial abilities, verbal and nonverbal memory, and depression. These measures were specifically chosen by two neuropsychologists and a behavioral neurologist in order to provide a comprehensive assessment of former players. Measures from two consecutive visits (i.e., noted as baseline and follow-up) were included in this study. Each neuropsychological measure was scored according to manual specifications and converted to normative T-scores, with the exception of the depression questionnaire. Primary measures of comparison included 11 primary tests: Trail Making A (TMTA) and B (TMTB), Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding, WAIS-IV Digit Span, Controlled Word Association Test (COWAT), Animal Fluency,, Boston Naming Test-2nd edition (BNT-2), Rey Complex Figure (RCFT) copy and delayed recall, California

Verbal Learning Test-2nd edition (CVLT-II) total learning and delayed recall. Test batteries differed slightly between NFL players and the clinical sample (i.e., data from the UTSW neuropsychology clinic) due to different clinical practice procedures. Due to these differences, two measures were available to compare between former NFL players and healthy controls that were not available in a large enough sample to compare in the clinical sample, The Texas Card Sorting Test (TCST; Kaltreider et al., 1999), and the Beck Depression Inventory-2nd edition (BDI-II; Beck, Steer, & Brown, 1996). All measures for all groups were administered in standard fashion by a neuropsychologist, trained interns/post-doctoral fellows, or trained psychometrists. For our specific hypotheses, we used the CVLT-II total learning and delayed recall as the measure of verbal memory, BNT-2 as the measure of confrontation naming, and the TCST and TMTB as measures of executive functioning.

Diagnoses of MCI and Dementia

In order to maintain consistency in diagnosis of MCI between our formal NFL players and clinical sample, MCI diagnoses were determined using adapted Jak and Bondi (2009) actuarial MCI criteria. This method has been utilized before in aging NFL retiree research (Baker et al., 2018). Jak and Bondi's actuarial method differs from conventional clinical criteria in that MCI diagnosis is made solely based on objective neuropsychological data. An MCI diagnosis was met when participants either a) displayed impairment (i.e., < 16th percentile) in 2 or more scores of neuropsychological impairment within one domain (i.e., attention/processing speed/dysexecutive, language, or memory), or b) showed impairment on one or more neuropsychological score in all 3 domains (see Table 3). Dementia diagnoses for the retired athletes were determined by consensus with a cognitive neurologist (J.H.) and two

neuropsychologists (N.D. and M.C.) using neuropsychological data, neurologic exam results, clinical interview information, and neuroimaging using DSM-IV criteria (American Psychiatric Association, 2000). Overall, 26 players were cognitively normal, 22 were diagnosed with MCI, and 5 with dementia (4 presumed to be due to AD, and 1 presumed to be Lewy body dementia).

Table 3

Neuropsychological Measures within Domains

Domain	Measure
Attention/Processing Speed/Executive	Trail Making Test A
	Trail Making Test B
	Rey-Osterrieth Complex Figure Copy
	WAIS-IV Digit Span
	WAIS-IV Coding
Language	Boston Naming Test-2
	Animal Fluency
	Controlled Word-Association Test
Memory	California Verbal Learning Test-II Total Learning
	California Verbal Learning Test-II Long Delay Recall
	Rey-Osterrieth Complex Figure Delayed Recall

Abbreviations: WAIS-IV = Weschler Adult Intelligence Scale Fourth Edition

Data analyses

Neuropsychological Functioning Between Groups of Retired NFL Players and Controls

To compare neuropsychological performance between groups of retired NFL players and their respective controls. Normative neuropsychological T-scores were entered as dependent variables into separate independent sample *t*-tests, with the exception of the BDI-II, which were entered as a raw score. Mean comparisons were first conducted between all former players and

their respective controls. Additional *t*-tests were conducted on subgroups based on impairment level (i.e., cognitively normal NFL controls were compared to healthy controls, and cognitively impaired NFL players were compared to clinical controls). Two measures, the TCST and BDI-II, were available to compare between the normal controls and cognitively normal players only. To asses longitudinal performance, repeated measure ANCOVAs controlling for months between visits were used to examine mean differences between visits 1 and 2 in neuropsychological performance via a time by group interaction. Similar secondary analyses were conducted based on impairment level (e.g., cognitively normal NFL controls were compared to healthy controls, and cognitively impaired NFL players were compared to clinical controls). Homogeneity of variance was assessed using Levene's test of equality of variance. When violated, the Welch-Satterthwaite method was used to assess if results remained stable. Outliers were identified for each group (i.e., normal controls, cognitively normal players, clinical controls, and impaired players) and calculated by multiplying the interquartile range between each variable by 1.5, and removed if they exceeded this distance from the mean (Hoaglin Iglewicz, & Tukey, 1986; Hoaglin & Iglewicz, 1987). In total, a very small number of outliers (i.e., 9 outliers or < .1% of available datapoints) within neuropsychological measures were detected and removed over the two time points. We corrected for type-1 error and false-discovery rate using the Holms-Step Down procedure. Analyses were defined as "approaching" or "trending" toward significance if they were $p < .05$ but did not reach significance after multiple comparisons.

Correlation of Neuropsychological Functioning with Head-injury Exposure

Pearson correlations were used to examine the relationship between head-injury exposure and measures of neuropsychological functioning. To assess whether head-injury exposure was significantly associated with neuropsychological changes over time, mean differences of

neuropsychological measures between visits one and two were computed, and then examined in partial correlations controlling for time between visits in relation to head-injury exposure. Head-injury exposure variables included years played in the NFL, number of concussions, number of concussions with LOC, games played, games started, and age started playing tackle football. One outlier was removed for number of concussions (one player reported sustaining 50 concussions). Individual quadratic regressions were used explore for potential non-linear relationships between neuropsychological performances between head-injury exposure and neuropsychological performance at baseline and over time. We corrected for type-1 error and false-discovery rate using the Holms-Step Down procedure. Analyses were defined as "approaching" or "trending" toward significance if they were $p < .05$ but did not reach significance after multiple comparisons.

Results

Descriptive Statistics

Despite efforts to match groups as closely as possible, the clinical sample had on average 1.28 more years of education than the former NFL players with cognitive impairment ($p = .003$). Eight healthy controls and 2 impaired players were missing data on medical and surgical history. To impute missing data on the total number of risk factors, we used regression imputation predicted by age and race ($F = 9.006$, $p < .001$, $R^2 = .195$), which was accurate within +/- 1 vascular risk factor for 71 of 89 participants, or 80% of the sample. For the 10 cases with imputed values, vascular factors ranged from 0 to 2. Welch ANOVA revealed that no differences were observed between groups in the total number of vascular risk factors (Table 5). From

baseline to follow-up, 5 cognitively normal players and 2 healthy controls converted from normal cognition to MCI.

Table 4

Age and Education Differences Between Groups

Group	Age, M (SD)	*t*	*p*	Education, M (SD)	*t*	*p*
Controls (n=48)	67.60 (8.34)	1.375	.172	16.71 (1.92)	1.312	.192
Former NFL Players (n=53)	65.40 (7.79)			16.32 (0.94)		
CN Controls (n=26)	64.88 (7.36)	1.848	.071	16.23 (2.03)	-.510	.612
CN Players (n=26)	61.57 (6.25)			16.61 (1.03)		
Clinical Sample (n=22)	70.82 (8.44)	.680	.500	17.27 (1.64)	3.093	.003
Impaired Players (n=27)	69.33 (6.84)			16.19 (0.74)		

Note: CN = Cognitively Normal

Table 5

Total Number of Vascular Risk Factors of Cognitively Normal and Cognitively Impaired NFL Retirees, Normal Controls, and Clinical Controls

Group	**N**	***M***	***SD***	**Range**	***F***	***p***
CN Controls	26	1.27	0.78	0-3	.557	.646
CN Players	26	1.54	1.77	0-8		
Clinical Sample	22	1.73	1.70	0-5		
Impaired Players	27	1.30	1.40	0-4		

Note: CN = Cognitively Normal. *F*-value and *p*-values are ANOVA values. No post-hoc comparisons were made due to non-significant *F*-value.

Neuropsychological Functioning Between All Retired NFL players and All Controls

Although several violations of homogeneity of variance occurred throughout the analyses, all *p*-values remained the same (i.e., stayed significant or stayed non-significant) when

using the Welch- Satterthwaite method. As such, original means and significance values are reported throughout the results.

Baseline Performance

We hypothesized that if an NFL career and cumulative head-injury exposure results in long-term neuropsychological impairment, then NFL players would show worse baseline neuropsychological performance in verbal memory, confrontation naming, and executive functioning than controls. T-tests comparing the entire sample of NFL players to all controls revealed that NFL players performed similarly on all measures, with the exception of the BNT-2. Players performed significantly worse on the BNT-2 ($t = 6.48$, $p < .001$) by a mean normative T-difference of 12.41 points. NFL players also performed slightly worse (i.e., mean difference T-score of 3.59 to 6.23) on WAIS-IV Digit Span ($p = .035$) and Coding ($p = .016$), but these differences were not statistically significant after Holm's correction for multiple comparisons (see Table 6).

Table 6

Neuropsychological Comparison of Means Between All Former NFL Players and All Controls

NP Measure	Group	N	*M*	*SD*	*M*-difference	*t*	*p*
TMT A	Control	48	46.90	11.32	1.35	0.689	.492
	Player	52	48.25	8.20			
TMT B	Control	48	47.42	11.06	0.32	0.141	.888
	Player	53	47.74	11.51			
Coding	Control	43	52.67	8.77	-4.39	2.431	.017
	Player	50	48.28	8.62			
Digit Span	Control	43	52.74	9.26	-3.81	2.143	.035
	Player	48	48.94	7.67			
FAS	Control	45	48.00	9.90	-0.19	0.095	.926
	Player	53	47.81	9.96			
Animals	Control	46	46.72	12.84	-0.81	0.321	.749

	Player	53	45.91	12.25			
BNT	Control	43	53.86	12.21	-12.41	6.512	<.001*
	Player	49	41.45	8.58			
CVLT Total	Control	48	52.02	13.97	-5.08	1.958	.053
	Player	52	46.94	11.95			
CVLT DR	Control	48	48.44	15.30	-2.96	1.067	.288
	Player	52	45.48	12.34			
RCFT Copy	Control	43	45.70	14.36	0.03	0.032	.992
	Player	51	45.73	12.60			
RCFT DR	Control	43	47.72	18.68	-2.08	0.587	.558
	Player	53	45.64	16.02			

Note: All scores are T-scores. *Abbreviations:* TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, Total = Total Words Learned, DR = Delayed Recall

Longitudinal Performance

It was hypothesized that if an NFL career and cumulative head-injury exposure results in long-term neuropsychological impairment, then NFL players would show worse longitudinal neuropsychological performance in verbal memory, confrontation naming, and executive functioning than controls. NFL players had an average of 26.1 months between visits (SD = 12.76), whereas healthy controls had 19.01 months between visits (SD = 8.07), which was statistically significant (t = -2.502, p = .015). ANCOVAs, controlling for time between visits, compared the changes in baseline and follow-up performance of all retired NFL players to all controls. NFL players performed similarly over time with no significant differences observed between groups (as measured by the interaction effect between time and group) following Holms correction. Only performance on the RCFT delayed recall approached significance (p = .018), which occurred due to a slight improvement in the performance of the controls over time, while retired NFL players performed similarly over time (see Table 7).

Table 7

Longitudinal Neuropsychological Performance of All NFL Players Versus All Controls

NP Measure	Group	N	Time	EMM	*SE*	95% CI LB	95% CI UB	Change (T)	*F*	*p*
TMT A	Control	28	1	48.34	1.86	44.60	52.07	2.41	0.312	.579
			2	50.75	2.18	46.37	55.13			
	NFL	28	1	47.63	1.86	43.90	51.36	0.70		
			2	48.32	2.18	43.95	52.70			
TMT B	Control	28	1	51.22	1.77	47.66	54.78	-1.18	0.277	.601
			2	50.04	2.23	45.56	54.52			
	NFL	27	1	46.22	1.81	42.59	49.85	0.30		
			2	46.52	2.28	41.95	51.08			
Coding	Control	27	1	53.84	1.58	50.67	57.00	-0.69	0.001	.984
			2	53.15	1.62	49.90	56.39			
	NFL	26	1	49.13	1.61	45.91	52.36	-0.71		
			2	48.42	1.65	45.11	51.73			
Digit Span	Control	27	1	52.84	1.80	49.23	56.45	-1.69	0.117	.733
			2	51.15	1.86	47.43	54.88			
	NFL	26	1	48.40	1.83	44.72	52.08	-1.10		
			2	47.31	1.89	43.51	51.11			
COWAT	Control	28	1	46.83	1.56	43.70	49.97	0.41	2.223	.112
			2	47.24	1.69	43.85	50.64			
	NFL	27	1	44.95	1.59	41.76	48.14	-2.65		
			2	42.30	1.73	38.84	45.77			
Animals	Control	28	1	50.01	2.23	45.53	54.48	0.11	0.024	.877
			2	50.11	1.87	46.37	53.85			
	NFL	28	1	45.50	2.23	41.02	49.97	0.50		
			2	45.99	1.87	42.25	49.74			
BNT	Control	27	1	54.57	1.85	50.86	58.28	-0.60	0.173	.679
			2	53.97	1.82	50.32	57.62			
	NFL	27	1	42.17	1.85	38.46	45.88	-1.51		
			2	40.66	1.82	37.02	44.31			

CVLT Total	Control	28	1	53.95	2.15	49.64	58.26	-0.96	0.001	.979
			2	52.98	2.58	47.80	58.16			
	NFL	27	1	44.87	2.19	40.48	49.26	-1.04		
			2	43.83	2.63	38.55	49.12			
CVLT DR.	Control	27	1	48.03	2.80	42.41	53.66	-1.37	0.334	.556
			2	46.67	2.74	41.18	52.16			
	NFL	27	1	43.26	2.80	37.64	48.89	-3.45		
			2	39.82	2.74	34.32	45.31			
RCFT Copy	Control	27	1	44.98	2.57	39.82	50.14	-1.24	0.404	.528
			2	43.74	2.98	37.77	49.72			
	NFL	26	1	48.10	2.62	42.84	53.36	-4.02		
			2	44.08	3.04	37.98	50.17			
RCFT DR	Control	27	1	47.61	3.42	40.75	54.47	5.01	5.96	.018
			2	52.62	3.38	45.83	59.41			
	NFL	28	1	47.38	3.35	40.65	54.11	-1.69		
			2	45.69	3.32	39.03	52.35			

Note: ANCOVAS controlling for age, education, race, and month's between visit. Average months between visit was "Change" denotes Time 2 performance subtracted by Time 1 performance. F-statistic and p-values are denoting the interaction effect between time and group. All scores are T-scores. *Abbreviations:* EMM = estimated marginal mean, *SE* = standard error, CI = confidence interval, LB = lower bound, UB = upper bound, M-diff. = mean difference, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, Total = Total Words Learned, DR = Delayed Recall

Cognitively Normal NFL Players Versus Normal Controls

Baseline Performance

It was hypothesized that if an NFL career and cumulative head-injury exposure results in long-term neuropsychological impairment, then NFL players would show worse baseline neuropsychological performance in verbal memory, confrontation naming, and executive functioning than controls. T-tests comparing cognitively normal NFL players to cognitively normal controls revealed that NFL players performed similarly on most measures. NFL players performed worse on the BNT-2 ($t = 4.113$, $p < .001$) and CVLT-II total words learned ($t = 3.253$,

p = .002), while endorsing significantly more depressive symptoms on the BDI-II (t = 3.698 p = .001). Differences that trended toward significance included the CVLT delayed recall (t = 2.597 p = .012) and WAIS-IV Coding (t = 2.271, p = .028), though these were not significant after correcting for multiple comparisons and false discovery rate (Table 8).

Table 8

Neuropsychological Comparison of Cognitively Normal NFL Players and Normal Controls

NP Measure	Group	n	*M*	*SD*	*M*-difference	*t*	*p*
TMT A	CN Control	26	49.62	8.41	0.14	0.071	.933
	CN Player	25	49.76	6.48			
TMT B	CN Control	26	52.92	7.06	1.35	0.688	.494
	CN Player	26	54.27	7.04			
Coding	CN Control	21	56.29	6.92	-5.04	2.271	.028
	CN Player	24	51.25	7.83			
Digit Span	CN Control	21	53.67	9.93	-3.21	1.271	.211
	CN Player	22	50.45	6.33			
FAS	CN Control	23	50.83	9.74	0.25	0.100	.92
	CN Player	26	51.08	7.72			
Animals	CN Control	24	51.67	10.00	0.33	0.118	.908
	CN Player	26	52.00	10.24			
BNT	CN Control	21	56.62	11.66	-12.07	4.113	<.001*
	CN Player	22	44.55	7.17			
CVLT Total	CN Control	26	61.65	8.29	-8.85	3.253	.002*
	CN Player	25	52.80	11.00			
CVLT DR	CN Control	26	59.62	8.82	-6.82	2.597	.012
	CN Player	25	52.80	9.90			
RCFT Copy	CN Control	21	48.90	12.11	-2.55	0.767	.447
	CN Player	26	46.35	10.75			
RCFT DR	CN Control	21	60.05	13.64	-5.51	1.495	.142
	CN Player	26	54.54	11.63			
TCST	CN Control	20	57.63	13.44	-7.36	1.983	.054
	CN Player	24	50.28	11.17			
BDI-II	CN Control	26	2.92	3.62	7.28	3.698	.001*
	CN Player	25	10.20	9.33			

Note: All scores are T-scores except for BDI-II. *Abbreviations:* CN = Cognitively Normal, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, TCST = Texas Card Sorting Test, BDI-II = Beck Depression Inventory - 2nd edition.

Longitudinal Performance

It was hypothesized that if an NFL career and cumulative head-injury exposure results in long-term neuropsychological impairment, then NFL players would show worse longitudinal neuropsychological performance in verbal memory, confrontation naming, and executive functioning than controls. ANCOVAs controlling for time between visits did not reveal any significant differences in neuropsychological performance from baseline and follow-up (as measured by time x group interaction) between cognitively normal retired NFL players and cognitively normal controls (see Table 9).

Table 9

Longitudinal Neuropsychological Performance of Cognitively Normal NFL Players Versus Cognitively Normal Controls

NP Measure	Group	n	Time	EMM	*SE*	95% CI LB	95% CI UB	Change (T)	*F*	*p*
TMT A	CN Control	15	1	51.77	1.94	47.78	55.76	1.43	1.472	.236
			2	53.20	2.76	47.51	58.90			
	CN NFL	13	1	48.49	2.10	44.18	52.81	6.66		
			2	55.15	2.99	48.99	61.31			
TMT B	CN Control	15	1	56.25	1.82	52.50	60.00	-3.46	0.377	.545
			2	52.79	2.83	46.96	58.61			
	CN NFL	13	1	51.33	1.97	47.27	55.38	-0.77		
			2	50.56	3.06	44.26	56.85			
Coding	CN Control	14	1	56.12	2.11	51.76	60.48	-0.54	0.253	.62
			2	55.58	2.40	50.62	60.53			

	CN NFL	12	1	51.11	2.29	46.37	55.85	0.13		
			2	51.24	2.60	45.86	56.63			
Digit Span	CN Control	14	1	54.86	2.48	49.72	59.99	-1.85	0.027	.82
			2	53.01	3.01	46.79	59.23			
	CN NFL	12	1	49.00	2.70	43.42	54.58	-1.42		
			2	47.58	3.27	40.82	54.34			
COWAT	CN Control	15	1	49.37	2.10	45.05	53.69	-0.30	0.048	.828
			2	49.07	2.56	43.80	54.34			
	CN NFL	13	1	45.50	2.27	40.83	50.17	-0.88		
			2	44.62	2.77	38.92	50.32			
Animals	CN Control	15	1	53.20	2.81	47.41	59.00	0.04	0.376	.545
			2	53.24	2.25	48.60	57.88			
	CN NFL	13	1	51.31	3.04	45.04	57.57	-2.20		
			2	49.11	2.44	44.09	54.13			
BNT	CN Control	14	1	55.26	2.59	49.90	60.63	-0.07	0.6	.446
			2	55.19	2.53	49.96	60.42			
	CN NFL	12	1	45.78	2.82	39.94	51.61	-2.58		
			2	43.20	2.75	37.51	48.88			
CVLT Total	CN Control	15	1	62.42	1.70	58.91	65.93	-3.35	1.064	.312
			2	59.07	2.70	53.50	64.64			
	CN NFL	12	1	49.23	1.92	45.27	53.19	0.18		
			2	49.41	3.04	43.13	55.69			
CVLT DR.	CN Control	15	1	59.84	2.56	54.55	65.13	-6.91	2.005	.170
			2	52.93	3.26	46.20	59.65			
	CN NFL	12	1	50.20	2.89	44.24	56.17	-0.94		
			2	49.26	3.68	41.68	56.85			
RCFT Copy	CN Control	14	1	49.52	3.20	42.92	56.12	-5.16	0.983	.331
			2	44.36	4.25	35.59	53.13			
	CN NFL	13	1	43.98	3.33	37.11	50.86	0.63		
			2	44.62	4.43	35.48	53.75			
RCFT DR	CN Control	14	1	57.60	3.35	50.70	64.50	3.17	0.511	.482
			2	60.76	3.31	53.93	67.60			
	CN NFL	13	1	55.90	3.48	48.71	63.09	0.05		
			2	55.95	3.45	48.83	63.06			
TCST	CN Control	13	1	56.25	4.20	47.55	64.96	7.35	1.356	.256
			2	63.61	3.68	55.98	71.23			
	CN NFL	12	1	49.84	4.38	40.75	58.92	2.15		

			2	51.98	3.84	44.02	59.95			
BDI-II (raw)	CN Control	15	1	3.16	1.54	-0.02	6.33	0.44	0.057	.853
			2	3.59	1.91	-0.34	7.53			
	CN NFL	13	1	8.20	1.67	4.77	11.64	0.11		
			2	8.32	2.07	4.06	12.57			

Note: ANCOVAs controlling for time between visits. All scores are T-scores except for BDI-II.
Abbreviations: CN = Cognitively Normal, EMM = estimated marginal mean, SE = standard error, CI = confidence interval, LB = lower bound, UB = upper bound, M-diff. = mean difference, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, TCST = Texas Card Sorting Test, BDI-II = Beck Depression Inventory - 2nd edition.

Cognitively Impaired Former Players Versus Clinical Controls

Baseline Performance

It was hypothesized that if an NFL career and cumulative head-injury exposure results in long-term neuropsychological impairment, then NFL players would show worse baseline neuropsychological performance in verbal memory, confrontation naming, and executive functioning than controls. In independent samples *t*-tests comparing cognitively impaired retired NFL players to clinical controls, NFL players performed similarly on all measures with the exception of the BNT-2, where they performed worse ($t = 4.030$, $p < .001$; Table 10).

Table 10

Neuropsychological Comparison of Cognitively Impaired Retired NFL Players and Clinical Controls

NP Measure	Group	n	*M*	*SD*	*M*-difference	*t*	*p*
TMT A	CI Control	22	43.68	13.52	3.17	0.965	.339
	CI Player	27	46.85	9.43			
TMT B	CI Control	22	40.91	11.52	0.53	0.161	.872
	CI Player	27	41.44	11.56			
Coding	CI Control	22	49.23	9.10	-3.69	1.447	.155
	CI Player	26	45.54	8.55			
Digit Span	CI Control	22	51.86	8.72	-4.21	1.684	.099
	CI Player	26	47.65	8.55			
FAS	CI Control	22	45.05	9.38	-0.38	0.126	.899
	CI Player	27	44.67	10.96			
Animals	CI Control	22	41.32	13.61	-1.28	0.361	.720
	CI Player	27	40.04	11.25			
BNT	CI Control	22	51.23	12.41	-12.30	4.030	<.001*
	CI Player	27	38.93	8.93			
CVLT Total	CI Control	22	40.64	10.22	0.88	0.300	.765
	CI Player	27	41.52	10.23			
CVLT DR	CI Control	22	35.23	9.70	3.48	1.197	.237
	CI Player	27	38.70	10.43			
RCFT Copy	CI Control	22	42.64	15.89	2.44	0.551	.584
	CI Player	25	45.08	14.47			
RCFT DR	CI Control	22	35.95	14.95	1.12	0.259	.796
	CI Player	27	37.07	15.09			

Note: All scores are T-scores. CI = Cognitively Impaired, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test.

Longitudinal Performance

It was hypothesized that if an NFL career and cumulative head-injury exposure results in long-term neuropsychological impairment, then NFL players would show worse baseline neuropsychological performance in verbal memory, confrontation naming, and executive functioning than controls. Retired NFL players performed similarly over time with no significant

differences observed between groups (as measured by the interaction effect between time and group) following Holms correction. Only performance on the RCFT delayed recall approached significance ($F = 6.932$, $p = .014$), which occurred due to a slight improvement in the performance of the clinical controls over time, while retired NFL players performed similarly over time.

Table 11

Longitudinal Neuropsychological Performance of Cognitively Impaired NFL Players Versus Cognitively Impaired Controls

NP Measure	Group	n	Time	EMM	*SE*	95% CI LB	95% CI UB	Change (T)	*F*	*p*
TMT A	CI Control	13	1	44.26	3.16	37.74	50.78	2.85	2.533	.124
			2	47.11	3.06	40.81	53.40			
	CI NFL	15	1	46.97	2.94	40.91	53.03	-3.87		
			2	43.11	2.84	37.25	48.96			
TMT B	CI Control	13	1	45.05	2.59	39.71	50.39	1.28	0.0023	.963
			2	46.33	3.41	39.30	53.37			
	CI NFL	14	1	41.81	2.49	36.67	46.95	1.45		
			2	43.26	3.28	36.49	50.04			
Coding	CI Control	13	1	51.23	2.31	46.46	56.00	-0.86	0.088	.769
			2	50.37	2.08	46.07	54.66			
	CI NFL	14	1	47.57	2.23	42.98	52.17	-1.41		
			2	46.16	2.00	42.03	50.30			
Digit Span	CI Control	13	1	50.72	2.69	45.17	56.27	-1.43	0.051	.823
			2	49.29	2.31	44.52	54.05			
	CI NFL	14	1	47.83	2.59	42.49	53.17	-0.88		
			2	46.95	2.22	42.36	51.54			
COWAT	CI Control	13	1	44.02	2.34	39.18	48.86	1.08	2.703	.113
			2	45.10	2.13	40.70	49.50			
	CI NFL	14	1	44.34	2.26	39.68	49.00	-4.14		
			2	40.20	2.05	35.96	44.43			
Animals	CI Control	13	1	45.57	3.15	39.09	52.06	0.77	0.20	.659

			2	46.34	2.83	40.52	52.17			
	CI NFL	15	1	41.11	2.93	35.08	47.14	2.33		
			2	43.44	2.63	38.02	48.85			
BNT	CI Control	13	1	53.35	2.58	48.04	58.66	-0.91	0.001	.998
			2	52.45	2.66	46.98	57.91			
	CI NFL	15	1	39.70	2.40	34.76	44.64	-0.88		
			2	38.82	2.47	33.73	43.90			
CVLT Total	CI Control	13	1	43.90	2.89	37.95	49.85	1.58	0.666	.422
			2	45.48	3.90	37.46	53.51			
	CI NFL	15	1	41.62	2.69	36.08	47.15	-1.84		
			2	39.78	3.62	32.32	47.25			
CVLT DR.	CI Control	12	1	32.96	2.78	27.22	38.69	5.02	3.268	.083
			2	37.98	3.22	31.32	44.63			
	CI NFL	15	1	37.97	2.48	32.84	43.09	-5.01		
			2	32.95	2.88	27.01	38.90			
RCFT Copy	CI Control	13	1	40.67	3.92	32.57	48.78	2.56	2.891	.103
			2	43.23	4.38	34.17	52.29			
	CI NFL	13	1	51.64	3.92	43.53	59.74	-8.25		
			2	43.39	4.38	34.33	52.44			
RCFT DR	CI Control	13	1	36.10	4.69	26.44	45.76	6.47	6.932	.014
			2	42.57	4.67	32.95	52.19			
	CI NFL	15	1	40.65	4.36	31.66	49.63	-2.74		
			2	37.91	4.34	28.96	46.85			

Note: ANCOVAs controlling for time between visits. All scores are T-scores. *Abbreviations:* CN = Cognitively Normal, EMM = estimated marginal mean, SE = standard error, CI = confidence interval, LB = lower bound, UB = upper bound, M-diff. = mean difference, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, TCST = Texas Card Sorting Test, BDI-II = Beck Depression Inventory - 2nd edition, Total = Total Words Learned, DR = Delayed Recall

Correlations with Head-injury Exposure

Head-injury exposure and baseline neuropsychological performance

It was hypothesized that if an NFL career and cumulative head-injury exposure results in long-term neuropsychological impairment, then retired NFL player's performance on

neuropsychological measures would negatively correlate to degree of head-injury exposure. Pearson correlations were conducted between neuropsychological measures and number of concussions, number of concussions with LOC, years playing professional football, games played, games started, and age started playing tackle football. Additional quadratic regressions were also conducted to evaluate the potential for non-linear relationships. No neuropsychological measures were significantly correlated with any head-injury exposure variable after correcting for multiple comparisons. Eight correlations approached statistical significance (after Holms correction), and were weakly to moderately correlated to head-injury exposure variables (see Table 12). These included: total concussions with RCFT copy (R = .394, p = .006) [though this was in the opposite direction than hypothesized]; years playing professionally with COWAT (R = -.326, p = .017); NFL games played with CVLT-II total words learned (R = -.351, p = .013), CVLT-II delayed recall (R = -.282, p = .047), and RCFT delayed recall (R = -.307 p = .028); NFL games started with WAIS-IV Coding (R = -.317, p = .030); and age started playing football with RCFT delayed recall (R = -.543 p = .016) and TCST (R = -.572 p = .021). None of these relationships appeared to be better fit by a quadratic non-linear relationship as measured by change in F and R-squared, and significance and non-significance values were retained. Only the BNT-2 performance with years played in the NFL approached significance in a curvilinear trend (p = .01), but upon visual inspection this appeared to be due to one participant and was not considered reliable.

Table 12

Pearson Correlations Between Baseline Neuropsychological Performance and Head-injury Exposure in All NFL Players

NP measure		Total Concussions	Concussions w/LOC	Years Playing Pro	NFL Games Played	NFL Games Started	Age Started Playing
TMT A	*R*	-.139	-.143	-.017	-.032	-.208	-.29
	p	*.350*	*.326*	*.905*	*.826*	*.152*	*.228*
	N	47	49	52	50	49	19
TMT B	*R*	.025	.022	.093	.035	-.026	.012
	p	*.864*	*.878*	*.508*	*.807*	*.857*	*.960*
	N	48	50	53	51	50	19
Coding	*R*	.012	-.029	-.196	-.248	-.317	-.074
	p	*.935*	*.846*	*.172*	*.089*	*.030*	*.769*
	N	45	47	50	48	47	18
Digit Span	*R*	-.12	-.131	.034	-.012	.038	.309
	p	*.445*	*.391*	*.818*	*.937*	*.803*	*.228*
	N	43	45	48	46	45	17
COWAT	*R*	-.038	.006	-.326	-.271	-.109	.026
	p	*.799*	*.969*	*.017*	*.054*	*.452*	*.917*
	N	48	50	53	51	50	19
Animals	*R*	.001	-.006	-.135	-.195	-.084	.05
	p	*.995*	*.967*	*.335*	*.169*	*.562*	*.840*
	N	48	50	53	51	50	19
BNT	*R*	.121	-.046	-.174	-.213	-.112	-.096
	p	*.423*	*.756*	*.223*	*.141*	*.449*	*.696*
	N	46	48	51	49	48	19
CVLT Total	*R*	-.099	-.21	-.263	-.351	-.068	-.198
	p	*.508*	*.148*	*.059*	*.013*	*.643*	*.417*
	N	47	49	52	50	49	19
CVLT DR	*R*	.079	-.044	-.272	-.282	-.012	-.203
	p	*.597*	*.766*	*.051*	*.047*	*.934*	*.405*
	N	47	49	52	50	49	19
RCFT Copy	*R*	.394	.227	-.163	-.178	-.308	-.083
	p	.006	.122	.252	.216	.032	.743
	N	47	48	51	50	49	18

RCFT DR	*R*	.021	-.123	-.225	-.307	-.136	-.543
	p	*.886*	*.394*	*.105*	*.028*	*.346*	*.016*
	N	48	50	53	51	50	19
TCST	*R*	-.005	-.032	-.043	-.202	-.188	-.572
	p	*.973*	*.837*	*.772*	*.178*	*.216*	*.021*
	N	43	45	48	46	45	16
BDI-II	*R*	.251	.142	-.100	-.098	-.113	.150
	p	*.089*	*.332*	*.482*	*.501*	*.438*	*.54*
	N	47	49	52	50	49	19

Abbreviations: R = Pearson Correlation, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, TCST = Texas Card Sorting Test, BDI-II = Beck Depression Inventory-2nd edition, Total = Total Words Learned, DR = Delayed Recall

Pearson correlations evaluating neuropsychological performance and head-injury exposure variables were also were conducted on cognitively normal and cognitively impaired NFL retirees (see Table 13 and Table 14). In cognitively normal retired players, results showed games played was moderately negatively correlated with performance on the CVLT-II total words learned (R = -.639, p = .001) and CVLT-II delayed recall (R = -.611 p = .002). Five other associations approached statistical significance after correcting for multiple comparisons, including: years playing professional football with CVLT-II delayed recall (R = -.505 p = .01), NFL games played with RCFT delayed recall (R = -.421, p = .031), NFL games started with CVLT-II total words learned (R = -.483, p = .017) and delayed recall (R = -.408, p = .048). Age started playing tackle football also correlated with RCFT delayed recall approaching significance (R = -.725 p = .042), but had a very small sample size (n = 8). In cognitively impaired NFL retirees, there were no significant associations between neuropsychological performance and head-injury exposure variables after correcting for multiple comparisons (Table 14), including CVLT-II performance and games played. A scatter plot depicting the relationship between NFL games played and CVLT-II performance (total words learned and delayed recall) for cognitively

normal and impaired players can be found in Figure 1 Five associations approach statistical significance, which included: total concussions with RCFT copy (R = .496 p = .019), COWAT with years playing professionally (R = -.432 p = .024), NFL games played with WAIS-IV Coding (R = -.403 p = .046), NFL games started with WAIS-IV Coding (R = -.418 p = .042), and age started playing tackle football with RCFT delayed recall (R = -.609 p = .047). None of these relationships appeared to be better fit by a quadratic non-linear relationship as measured by change in F and R-squared, and significance and non-significance values were retained.

Table 13

Pearson Correlations Between Baseline Neuropsychological Performance and Head-injury Exposure in Cognitively Normal Retired Players

NP measure		Total Concussions	Concussions w/LOC	Years Playing Pro	NFL Games Played	NFL Games Started	Age Started Playing
TMT A	*R*	-.308	-.237	-.029	.048	-.265	-.359
	p	*.143*	*.266*	*.892*	*.822*	*.211*	*.383*
	n	24	24	25	24	24	8
TMT B	*R*	-.062	-.096	.287	.360	-.015	-.015
	p	*.770*	*.647*	*.154*	*.077*	*.942*	*.971*
	n	25	25	26	25	25	8
Coding	*R*	.02	-.113	-.039	.022	-.234	.253
	p	*.929*	*.608*	*.855*	*.921*	*.282*	*.545*
	n	23	23	24	23	23	8
Digit Span	*R*	.097	.166	.319	.277	.175	.512
	p	*.675*	*.471*	*.148*	*.224*	*.448*	*.240*
	n	21	21	22	21	21	7
COWAT	*R*	-.221	-.144	-.133	-.14	-.172	-.206
	p	*.289*	*.493*	*.518*	*.505*	*.412*	*.624*
	n	25	25	26	25	25	8
Animals	*R*	-.192	-.135	-.149	-.225	-.354	-.006
	p	*.358*	*.521*	*.468*	*.280*	*.083*	*.988*
	n	25	25	26	25	25	8

BNT	*R*	-.057	-.295	-.301	-.322	-.29	-.07
	p	*.795*	*.172*	*.154*	*.133*	*.18*	*.869*
	n	23	23	24	23	23	8
CVLT Total	*R*	-.307	-.226	-.403	-.639*	-.483	-.482
	p	*.144*	*.287*	*.046*	*.001*	*.017*	*.226*
	n	24	24	25	24	24	8
CVLT DR	*R*	-.114	-.157	-.505	-.611*	-.408	-.707
	p	*.596*	*.465*	*.010*	*.002*	*.048*	*.050*
	n	24	24	25	24	24	8
RCFT Copy	*R*	.272	.182	-.142	-.171	-.24	-.059
	p	*.188*	*.384*	*.488*	*.414*	*.247*	*.890*
	n	25	25	26	25	25	8
RCFT DR	*R*	-.073	.007	-.365	-.431	-.371	-.725
	p	*.728*	*.974*	*.067*	*.031*	*.068*	*.042*
	n	25	25	26	25	25	8
TCST	*R*	-.019	-.073	-.113	-.176	-.289	-.692
	p	*.931*	*.742*	*.600*	*.423*	*.181*	*.057*
	n	23	23	24	23	23	8
BDI-II	*R*	.212	-.012	-.077	-.026	-.113	-.546
	p	*.320*	*.957*	*.713*	*.904*	*.600*	*.161*
	n	24	24	25	24	24	8

Abbreviations: R = Pearson Correlation, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, TCST = Texas Card Sorting Test, BDI-II = Beck Depression Inventory-2nd edition, Total = Total Words Learned, DR = Delayed Recall

Table 14

Pearson Correlations Between Baseline Neuropsychological Performance and Head-injury Exposure in Cognitively Impaired Retired Players

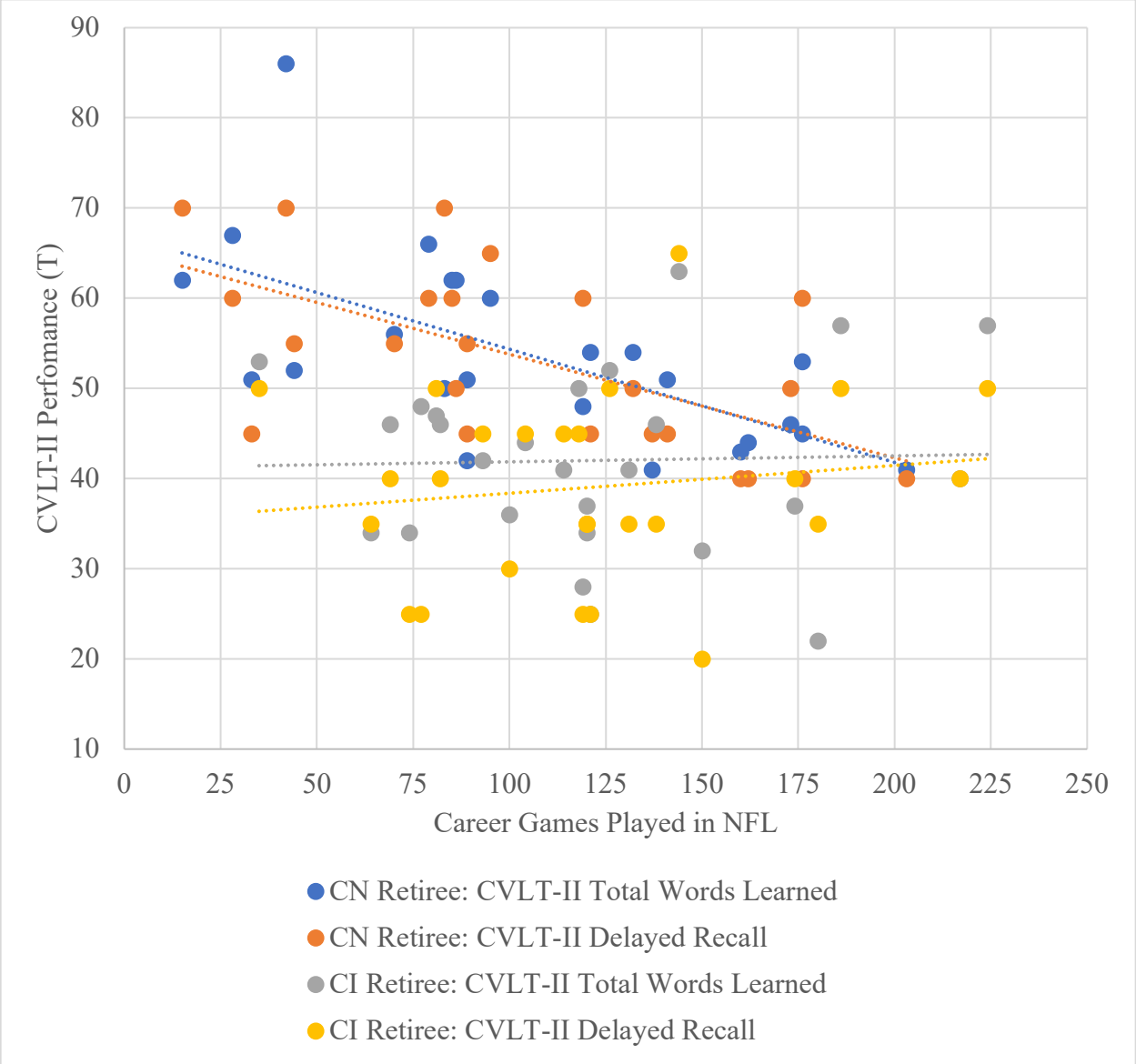
NP measure		Total Concussions	Concussions w/LOC	Years Playing Pro	NFL Games Played	NFL Games Started	Age Started Playing
TMT A	*R*	-.043	-.091	.040	-.044	-.199	-.285
	p	*.847*	*.666*	*.845*	*.832*	*.340*	*.396*
	n	23	25	27	26	25	11
TMT B	*R*	-.033	.121	.177	-.019	-.133	.029
	p	*.880*	*.563*	*.377*	*.928*	*.525*	*.934*

	n	23	25	27	26	25	11
	R	-.051	.041	-.239	-.403	-.418	-.088
Coding	*p*	*.822*	*.847*	*.240*	*.046*	*.042*	*.810*
	n	22	24	26	25	24	10
	R	-.296	-.246	-.105	-.155	-.067	.342
Digit Span	*p*	*.182*	*.246*	*.611*	*.459*	*.756*	*.333*
	n	22	24	26	25	24	10
	R	.009	.092	-.432	-.334	-.141	.144
COWAT	*p*	*.968*	*.662*	*.024*	*.095*	*.501*	*.673*
	n	23	25	27	26	25	11
	R	.051	.113	-.006	-.075	.034	.087
Animals	*p*	*.817*	*.590*	*.974*	*.714*	*.872*	*.800*
	n	23	25	27	26	25	11
	R	.171	.070	-.004	-.06	-.078	-.14
BNT	*p*	*.435*	*.739*	*.985*	*.771*	*.711*	*.682*
	n	23	25	27	26	25	11
	R	-.054	-.246	-.007	.03	.201	-.077
CVLT Total	*p*	*.806*	*.236*	*.973*	*.883*	*.336*	*.821*
	n	23	25	27	26	25	11
	R	.117	.040	.053	.137	.225	.001
CVLT DR	*p*	*.593*	*.848*	*.794*	*.505*	*.279*	*.999*
	n	23	25	27	26	25	11
	R	.496	.250	-.179	-.184	-.367	-.090
RCFT Copy	*p*	*.019*	*.249*	*.392*	*.378*	*.078*	*.805*
	n	22	23	25	25	24	10
	R	-.028	-.184	-.032	-.162	-.101	-.609
RCFT DR	*p*	*.900*	*.379*	*.872*	*.430*	*.632*	*.047*
	n	23	25	27	26	25	11
	R	-.034	.034	.197	-.101	-.121	-.428
TCST	*p*	*.887*	*.879*	*.356*	*.646*	*.592*	*.290*
	n	20	22	24	23	22	8
	R	.291	.301	-.084	-.144	-.14	.474
BDI-II	*p*	*.178*	*.144*	*.676*	*.483*	*.503*	*.141*
	n	23	25	27	26	25	11

Abbreviations: R = Pearson Correlation, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, TCST = Texas Card Sorting Test, BDI-II = Beck Depression Inventory-2nd edition, Total = Total Words Learned, DR = Delayed Recall

Figure 1

NFL Games Played and Baseline CVLT-II Performance for Cognitively Normal and Cognitively Impaired NFL Players



Note: Playing career statistics missing on two players (one cognitively normal and one cognitively impaired).

Head-injury exposure and neuropsychological change over time

We hypothesized that if an NFL career and cumulative head-injury exposure has an impact on long-term neuropsychological functioning, then retired NFL player's performance on neuropsychological measures over time would negatively correlate to degree of head-injury exposure. Neuropsychological change scores were computed from baseline to follow-up (negative values represent a decline). Partial correlations, controlling for time between visits, were conducted between neuropsychological change scores and number of concussions, number of concussions with LOC, years playing professional football, games played, games started, and age started playing tackle football. No neuropsychological change scores were significantly correlated with any head-injury exposure variable (see Table 15).

Sample sizes were small when evaluating cognitively normal retired players (Table 16) and cognitively impaired retired players (Table 17) separately. Only 8 cognitively impaired retirees and 4 healthy retiree had available data on age of playing tackle football in longitudinal analysis, and because effects of these associations would likely be unstable, they were not reported. Partial correlations between longitudinal neuropsychological performance and head-injury exposure in cognitively normal retired players were not significant, though WAIS-IV Coding approached significance (R = -.697, p = .025). Partial correlations between longitudinal neuropsychological performance and head-injury exposure in cognitively impaired retired NFL players were also not significant, although the associations between the TCST and number of concussions (R = .703, p = .023) and number of concussions with LOC (R = .746, p = .013) approached significance in the opposite direction than hypothesized (i.e., greater number of concussions were approached significant correlation with better performance). None of these

relationships appeared to be better fit by a quadratic non-linear relationship as measured by change in F and R-squared, and non-significance values were retained.

Table 15

Partial Correlations Between Longitudinal Neuropsychological Performance and Head-injury Exposure in All NFL Players

NP measure		Total Concussions	Concussions w/LOC	Years Playing Pro	NFL Games Played	NFL Games Started	Age Started Playing
TMT A	*R*	.170	.026	-.172	-.253	.083	.279
	p	*.407*	*.897*	*.391*	*.213*	*.693*	*.406*
	n	27	28	28	27	26	12
TMT B	*R*	.214	.222	-.055	-.137	-.098	.278
	p	*.305*	*.275*	*.790*	*.514*	*.648*	*.437*
	n	23	24	24	23	22	8
Coding	*R*	-.177	-.382	.035	.013	-.114	-.294
	p	*.443*	*.079*	*.878*	*.956*	*.632*	*.410*
	n	22	23	23	22	21	11
Digit Span	*R*	-.171	.145	-.087	.089	.125	.107
	p	*.448*	*.510*	*.694*	*.694*	*.590*	*.769*
	n	23	24	24	23	22	11
COWAT	*R*	.220	.103	-.132	-.135	-.209	-.060
	p	*.291*	*.617*	*.520*	*.521*	*.327*	*.861*
	n	26	27	27	26	25	12
Animals	*R*	.095	.052	-.269	-.055	.382	.137
	p	*.652*	*.800*	*.183*	*.792*	*.066*	*.706*
	n	26	27	27	26	25	11
BNT	*R*	-.074	-.155	-.309	-.174	-.376	.212
	p	*.724*	*.450*	*.125*	*.405*	*.070*	*.531*
	n	26	27	27	26	25	12
CVLT Total	*R*	.264	.247	-.182	-.112	.15	-.139
	p	*.203*	*.224*	*.373*	*.596*	*.484*	*.684*
	n	26	27	27	26	25	12
CVLT DR	*R*	-.001	-.103	-.127	-.030	.120	.144

	p	*.996*	*.618*	*.535*	*.887*	*.576*	*.673*
	n	26	27	27	26	25	12
RCFT Copy	*R*	-.283	-.273	.192	.161	.116	-.231
	p	*.171*	*.187*	*.357*	*.441*	*.590*	*.521*
	n	26	26	26	26	25	11
RCFT DR	*R*	-.054	.162	-.176	-.113	-.039	.328
	p	*.794*	*.418*	*.381*	*.582*	*.854*	*.324*
	n	27	28	28	27	26	12
TCST	*R*	.233	.215	.12	.072	.294	.609
	p	*.296*	*.337*	*.594*	*.749*	*.195*	*.109*
	n	23	23	23	23	22	9
BDI-II	*R*	-.001	-.066	.446	.200	.236	-.072
	p	*.994*	*.745*	*.020*	*.328*	*.256*	*.834*
	n	27	28	28	27	26	12

Note: Partial correlations controlled for time between visits. All scores entered were T-scores except for the BDI-II. *Abbreviations: R* = Pearson Correlation, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, TCST = Texas Card Sorting Test, BDI-II = Beck Depression Inventory-2nd edition, Total = Total Words Learned, DR = Delayed Recall

Table 16

Partial Correlations Between Longitudinal Neuropsychological Performance and Head-injury Exposure in Cognitively Normal Retired Players

NP measure		Total Concussions	Concussions w/LOC	Years Playing Pro	NFL Games Played	NFL Games Started
TMT A	*R*	.477	.117	-.178	-.230	.003
	p	*.117*	*.718*	*.581*	*.472*	*.994*
	n	13	13	13	13	13
TMT B	*R*	.123	-.057	-.155	-.239	-.100
	p	*.702*	*.861*	*.631*	*.455*	*.757*
	n	13	13	13	13	13
Coding	*R*	-.489	-.697	-.151	-.171	-.291
	p	*.152*	*.025*	*.677*	*.636*	*.415*

	n	11	11	11	11	11
Digit Span	*R*	-.268	-.492	.218	.194	-.060
	p	*.486*	*.179*	*.573*	*.617*	*.879*
	n	10	10	10	10	10
COWAT	*R*	.144	.293	-.288	-.259	-.426
	p	*.655*	*.355*	*.363*	*.416*	*.168*
	n	13	13	13	13	13
Animals	*R*	.337	.424	-.054	-.049	.471
	p	*.284*	*.170*	*.866*	*.879*	*.122*
	n	13	13	13	13	13
BNT	*R*	-.275	-.561	-.404	-.456	-.403
	p	*.413*	*.072*	*.218*	*.159*	*.219*
	n	12	12	12	12	12
CVLT Total	*R*	.54	.136	-.052	-.099	.173
	p	*.086*	*.691*	*.878*	*.771*	*.611*
	n	12	12	12	12	12
CVLT DR	*R*	.152	-.161	.173	.072	.009
	p	*.655*	*.636*	*.611*	*.832*	*.979*
	n	12	12	12	12	12
RCFT Copy	*R*	-.063	-.132	.115	.052	-.038
	p	*.845*	*.682*	*.722*	*.872*	*.906*
	n	13	13	13	13	13
RCFT DR	*R*	-.134	-.364	-.140	-.193	-.232
	p	*.677*	*.245*	*.663*	*.547*	*.468*
	n	13	13	13	13	13
TCST	*R*	-.383	-.401	.103	.127	.289
	p	*.245*	*.222*	*.762*	*.710*	*.389*
	n	12	12	12	12	12
BDI-II	*R*	-.067	-.209	.406	.332	.478
	p	*.835*	*.514*	*.190*	*.291*	*.116*
	n	13	13	13	13	13

Note: Partial correlations controlled for time between visits. All scores entered were T-scores except for the BDI-II. *Abbreviations: R* = Pearson Correlation, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, TCST = Texas Card Sorting Test, BDI-II = Beck Depression Inventory-2nd edition, Total = Total Words Learned, DR = Delayed Recall

Table 17

Partial Correlations Between Longitudinal Neuropsychological Performance and Head-injury Exposure in Cognitively Impaired Retired Players

NP measure		Total Concussions	Concussions w/LOC	Years Playing Pro	NFL Games Played	NFL Games Started
TMT A	*R*	-.159	-.062	-.352	-.384	-.419
	p	*.605*	*.834*	*.218*	*.195*	*.175*
	n	14	15	15	14	13
TMT B	*R*	.340	.399	.032	-.008	-.085
	p	*.280*	*.188*	*.918*	*.980*	*.805*
	n	13	14	14	13	12
Coding	*R*	.227	.022	.271	.275	-.065
	p	*.528*	*.950*	*.420*	*.441*	*.869*
	n	11	12	12	11	10
Digit Span	*R*	-.289	.135	-.199	.127	.115
	p	*.362*	*.660*	*.515*	*.694*	*.736*
	n	13	14	14	13	12
COWAT	*R*	.396	.358	-.023	-.030	-.402
	p	*.202*	*.230*	*.940*	*.927*	*.220*
	n	13	14	14	13	12
Animals	*R*	-.181	.123	-.505	-.173	.248
	p	.573	.690	.078	.592	.462
	n	13	14	14	13	12
BNT	*R*	.211	.324	-.166	.124	-.427
	p	*.489*	*.259*	*.571*	*.688*	*.166*
	n	14	15	15	14	13
CVLT Total	*R*	.058	.374	-.296	-.142	-.010
	p	*.850*	*.187*	*.305*	*.643*	*.975*
	n	14	15	15	14	13
CVLT DR	*R*	-.076	.049	-.312	-.134	-.191
	p	*.806*	*.867*	*.278*	*.662*	*.551*
	n	14	15	15	14	13
RCFT Copy	*R*	-.439	-.098	.357	.309	.103
	p	*.153*	*.763*	*.255*	*.329*	*.763*
	n	13	13	13	13	12
RCFT DR	*R*	-.114	.234	-.334	-.039	.097
	p	*.711*	*.422*	*.243*	*.898*	*.764*

	n	14	15	15	14	13
	R	.703	.746	.226	.086	-.047
TCST	*p*	*.023*	*.013*	*.531*	*.813*	*.905*
	n	11	11	11	11	10
	R	.034	-.087	.482	.160	.182
BDI-II	*p*	*.912*	*.768*	*.081*	*.602*	*.572*
	n	14	15	15	14	13

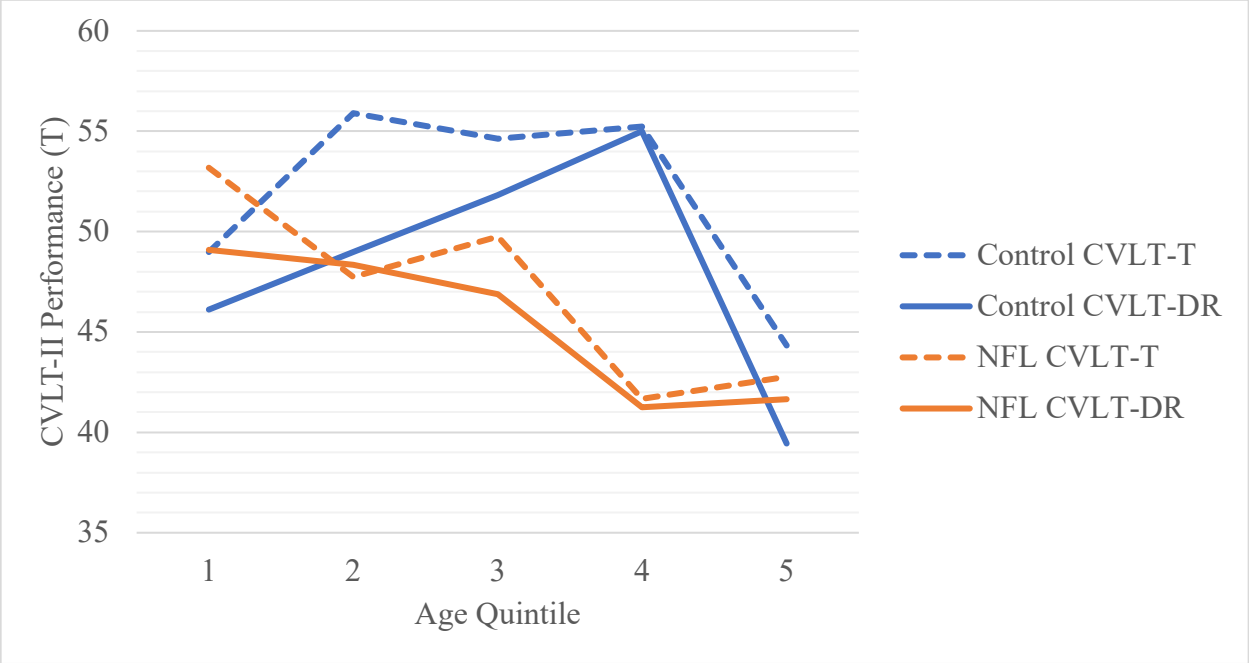
Note: Partial correlations controlled for time between visits. All scores entered were T-scores except for the BDI-II. *Abbreviations: R* = Pearson Correlation, TMT = Trail Making Test, COWAT = Controlled Word Association Test, BNT = Boston Naming Test – 2nd edition, CVLT= California Verbal Learning Test – 2nd edition, RCFT = Rey Complex Figure Test, TCST = Texas Card Sorting Test, BDI-II = Beck Depression Inventory-2nd edition, Total = Total Words Learned, DR = Delayed Recall

Verbal Memory Performance Between Former NFL Players and Controls in Age-Quintiles

In order to further explore CVLT-II performance in this sample, post-hoc correlational analyses were conducted that evaluated the impact of age on CVLT-II performance. In correlational analyses between age, CVLT-total words learned, and CVLT-II delayed recall, increasing age was significantly correlated with lower CVLT total words learned (R = -.368, p = .007) and CVLT-II delayed recall (R = .290, p = .037) for former NFL players. Age was not significantly correlated with CVLT-II total words (R = -.130, p = .380) or delayed recall (R = -.107, p = .467). CVLT-II performance was stratified into age-quintiles for former players and controls to visualize this effect, which can be found in Figure 2. Visual inspection suggested CVLT-II performance among former NFL players declines at a linear rate with increasing age, but is variable until after the age of 75 for controls, where it is appears to decline.

Figure 2

Verbal Memory Performance by Age Quintiles for Former NFL Players and Controls



Note: Quintile 1 = 52 to 60 for Controls and 50 to 58 for Players; Quintile 2 = 61 to 64 for Controls and 59 to 62 for Players; Quintile 3 = 65 to 71 for Controls and 63 to 67 for Players; Quintile 4 = 72 to 75 for Controls and 68 to 74 for Players; Quintile 5 = 76 and up for Controls and 75 and up for Players.

Confrontation Naming Performance: Post-Hoc Analyses

In order to further explore confrontation naming performance in this sample, post-hoc *t*-tests and correlational analyses were conducted that evaluated the impact of IQ, demographic, vascular, and depression factors on BNT-2 performance. To assess if norms had an effect on our findings, correlational analyses were conducted between raw BNT-2 scores head-injury exposure variables.

No mean differences in estimated IQ were found between cognitively normal players (M = 113.78) and controls (M = 114; p = .999), or between impaired former players (M = 104.96)

and the clinical sample (M = 107.37; p = .831). No significant correlation was observed between age and BNT-2 performance in former players (R = -.231, p = .110) or their respective controls (R = .075, p = .632), or between total number of vascular risk factors in former players (R = -.218, p = .125) or their respective controls (R = .186, p = .233). BNT-2 performance was not significantly correlated to BDI-II scores in former NFL players (R = .127, p = .374) or controls (R = -.209, p = .338). BNT-2 normative performance did not significantly differ (t = -0.254, p = .801) between African Americans (M = 42.11, n = 10) and Caucasians (M = 41.30, n = 40). BNT-2 raw score performance did not significantly differ (t = 0.976, p = 334) between African Americans (M = 49.20, n = 10) and Caucasians (M = 51.54, n = 41). Raw BNT-2 performance did not correlate to number of concussions (R = .121, p = .423), concussions with LOC (R = -.046, p = .756), years playing professionally (R = -.174, p = .223), NFL games played (R = -.213, p = .141), NFL games started (R = -.112, p = .449), or age started playing tackle football (R = -.096, p = .696).

Discussion

This study compared the neuropsychological functioning of cognitively normal and cognitively impaired former NFL players at baseline and over time compared to matched healthy controls and a clinical sample of patients with MCI and dementia. The relationship between career head-injury exposure and neuropsychological test scores at baseline and over time in these former players was also evaluated. This is the first study to investigate the neuropsychological functioning of retired NFL athletes longitudinally, and only the second study to compare retired NFL athletes with MCI and dementia to a clinical sample, matched by diagnosis. Between-group comparisons revealed that NFL retirees performed similarly to controls at baseline and over time

in virtually all areas of functioning, including processing speed, attention, executive functioning, language fluency, visuospatial functioning, and visual memory. Only baseline performance on a measure of confrontation naming (i.e., BNT-2) differed from controls in both cognitively normal and cognitively impaired former NFL athletes. Verbal memory scores (i.e., CVLT-II) among cognitively normal retirees were significantly lower than cognitively normal controls. However, it should be noted that the normal control sample performed in the above average range (M = 61.65), which was above the 84th percentile, and cognitively normal players' verbal memory performance still fell solidly within the average range (M = 52.8), suggesting that this finding may be driven by an above average healthy control group. Cognitively normal players also endorsed more depressive symptoms on the BDI-II than controls. Dose-response relationships between neuropsychological performance and number of concussions, concussions with loss of consciousness, years playing professionally, NFL games played, NFL games started, and age started playing tackle football were mostly non-significant after correcting for multiple comparisons in this cohort of retired NFL players. Only performance on the CVLT-II (i.e., total words learned and delayed recall) was moderately negatively correlated with NFL games played in cognitively normal NFL retirees. This relationship was not observed in cognitively impaired retirees, and no significant linear or non-linear relationships were observed between any neuropsychological measure over time and head-injury exposure.

Differences in verbal memory among retired NFL players have been reported in prior literature (Wright et al., 2016; Alosco et al., 2017; Baker et al., 2018), and in previous publications using a smaller sample of the UTSW cohort of former NFL players (Hart et al., 2013; Strain et al., 2015). In the current study, only cognitively normal NFL retirees showed significantly lower verbal memory functioning compared to controls. We also found that scores

on the CVLT-II (total words learned and delayed recall) in cognitive normal retirees were significantly ($p < .001$ and $p = .002$) negatively correlated with games played in the NFL, and trended toward significance for years played ($p = .01$) and games started in the NFL ($p = .048$) after adjusting for multiple comparisons. Previous research using this cohort found that hippocampal volume, a region intimately tied to verbal memory functioning, to be reduced in players with NFL careers of over 120 games and with a greater frequency of concussions with LOC (Strain et al., 2015). Interestingly we did not find CVLT-II performance to be correlated with number of concussions with LOC, but only games played, suggesting that a longer NFL career rather than concussion frequency, may be associated with lower verbal memory functioning in former NFL players. Importantly however, these associations only appeared in cognitively normal players and only in their baseline visit, and no differences were observed in verbal memory performance between former players and controls over time. This may suggest that a longer career in the NFL may be associated with lower verbal memory functioning in former players without MCI or dementia, and this association may dissipate in the presence of MCI or dementia. Although our data and design cannot offer mechanistic explanations, others have previously posited that cumulative sub concussive head impacts over a long NFL career may reduce cerebral reserve and lead to an earlier expression of cognitive impairment later in life (Randolph & Kirkwood, 2009). When we evaluated normative CVLT-II performance over age-quintiles, we found that CVLT-II performance diminishes as NFL player's age in a more linear fashion, whereas in our control groups, CVLT-II performance stays relatively constant with increasing age, supporting the possibility that NFL players may have reduced cerebral reserve that leads to earlier expression of verbal memory impairment. In addition to reduced cerebral reserve, it is possible that cumulative TBI or subconcussive impacts may predispose former NFL

players to temporal lobe dysfunction, leading to verbal memory difficulties. A review of the pertinent neuroradiological literature suggests that TBI may result in medial temporal lobe dysfunction, hippocampal atrophy, white matter tract injury (i.e., corpus callosum), and subsequent network disruption following injury, though the strongest evidence to date of long-term neuroanatomical changes is in moderate to severe TBI, and it remains unknown if a single or cumulative mild TBI or repetitive "subconcussive" hit to the head can result in similar neuroradiological changes (Bigler, 2013). Unfortunately, games played is only a proxy measure for "subconcussive" impacts, which by definition are vague and include any blow to the head that does not result in concussion, no matter how mild. In order to more fully evaluate the potential relationship between sub concussive impacts and long-term neurocognitive performance, prospective longitudinal designs are needed. Ideally, biomechanical forces to the head measured over an NFL career using helmet accelerometers paired with routine longitudinal neuropsychological follow-up could answer this question, but no NFL accelerometer data has been published as of yet. Thus, although the mechanisms are not fully understood, it is possible that cumulative mild head impacts sustained over a long NFL career could lead to lower verbal memory performance compared to those without the same head-injury exposure through white matter injury/network disruption, temporal lobe dysfunction, and/or lowered cerebral reserve. However, direct evidence of this mechanism is lacking, and additional prospective longitudinal studies of neuropsychological functioning are needed. Specifically, studies that enroll NFL players early following their NFL careers may help elucidate the impact an NFL career has on verbal memory performance in these aging athletes.

Differences in confrontation naming (as measured by the BNT-2) were the most consistent finding in the between-group analyses, occurring in both cognitively normal and

cognitively impaired retirees compared to their respective control groups. In the former players with MCI and dementia, 12 of 27 (44%) scored in the impaired range, compared to 3 of 22 (14%) of the clinical patients with MCI and dementia. Even among the NFL retirees that did not meet criteria for MCI and dementia, 12 out of 22 players scored below the average range (<25th percentile) and 6 of 22 (27%) scored in the impaired range (<16th percentile), compared to only 2 of the 21 of cognitively normal controls. Lower confrontation naming performance has been found in subsamples of this retired NFL cohort in previous publications (Hart et al., 2013; Strain et al., 2017). A recent 2018 study investigating a combined sample of NFL and National Hockey League (NHL) players (n=21), found that NFL and NHL players had lower performance on the Neuropsychological Assessment Battery (NAB) Naming test, compared to an age-matched former elite athlete control group. However, mean differences were small (less than 0.5 SD) and did not survive correction after adjusting for premorbid IQ. A 2017 publication using a subset of the UTSW cohort of retired players found that performance on the BNT-2 was related to reduced white matter integrity in NFL retirees, particularly along the forceps major and minor tracts, which could reduce naming abilities (Strain et al., 2017), and it was posited that cumulative head-injuries may disrupt naming performance through this mechanism. However, the current investigation did not find a significant relationship between confrontation naming performance and number of concussions, number of concussions with LOC, years playing in the NFL, NFL games played, NFL games started, or age at which players started tackle football. Thus, reduced BNT-2 performance in this cohort was not significantly related to cumulative head-injury exposure, suggesting that impairments in naming performance in former NFL retirees may be due to other factors. Although BNT-2 is a very commonly used clinical neuropsychological measure, it is not without psychometric concerns. The BNT-2 has been criticized for high ceiling

effects (Harry & Crowe, 2014), and the potential impact that age, IQ, cultural, linguistic, and ethnic background can have on performance (Strauss et al., 2006). In order to examine the potential impact of some of these factors, we ran post-hoc analyses on BNT-2 performance within our NFL players and controls. We found that estimated IQ was not significantly different between former NFL players and their control groups (*p's* < .05). Race/ethnicity did not appear to be a factor in performance either, as African Americans did not differ in normative or raw score performance compared to Caucasians among former NFL players (*p's* < .05). Normative BNT-2 performance also did not significantly correlate with age, vascular risk factors, BDI-II scores in former NFL players (*p's* < .05). Lastly, in order to more thoroughly examine BNT-2 performance, we ran correlations between raw BNT-2 performance, head-injury exposure factors, BDI-II score, and vascular risk factors and found no significant associations (*p's* < .05). In sum, although a high percentage of former NFL players in this sample showed impaired BNT-2 performance, we did not find any association between head-injury exposure and BNT-2 performance at baseline or over time. These differences also did not appear to be driven by demographic, mood, or vascular factors. Clearly, more research is needed to discern the etiology of these observed differences among cognitively normal former NFL players and former NFL players with MCI and dementia.

This is one of the first investigations evaluating the neurocognitive performance of cognitively impaired former NFL players compared to clinical patients, and only one previous study to date has shared a similar design. In 2013, Randolph et al. compared performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) between retired NFL players with amnestic MCI and clinical controls with amnestic MCI recruited from academic medical centers. No significant differences were seen between NFL retirees and the

clinical sample in RBANS Index scores measuring episodic memory, visuospatial abilities, language, or attention. The authors also did not find a significant association between years of professional play and scores on the RBANS Total Score Index (Randolph et al., 2013). Results from the current investigation echoed these findings, as we did not find significant differences in neuropsychological functioning between NFL retirees with cognitive impairment and our clinical sample with MCI and dementia, apart from the aforementioned baseline BNT-2 scores. In addition, we did not identify any neuropsychological change scores that differed from controls over time, and found no significant dose-response relationships between head-injury exposure and neuropsychological performance at baseline or over time in our impaired former athletes. Taken in totality, our findings from a small convenience sample of former NFL players with MCI and dementia did not support the hypothesis that cumulative head-injury exposure sustained over an NFL career relates to later-in-life differences in neurocognitive performance compared to age- and diagnosis- matched clinical patients with MCI and dementia.

The current investigation yielded a very low number of significant dose-response relationships between head-injury exposure and neuropsychological functioning. Although several associations approached significance, a total of 456 correlational comparisons were made, and only two were significant after correcting for multiple comparisons (i.e., CVLT-II total words learned/delayed recall and NFL games played in cognitively normal NFL retirees). There were also no significant non-linear relationships between neuropsychological performance and head-injury exposure. We expanded upon a previous publication using this cohort, that found no linear association between number of concussions and years played in the NFL with neuropsychological composites of attention/processing speed, language, and memory (Fields et al., 2019). More specifically, in the present investigation, we evaluated performances of 13

individual neuropsychological measures within the battery, compared these performances against three additional head-injury exposure variables (games played, games started, and age started playing tackle football), evaluated performances over two consecutive time points, and evaluated for non-linear relationships. Apart from the aforementioned CVLT-II findings in cognitively normal retirees, we found no significant linear or non-linear association between neuropsychological performances at baseline or over time with number of concussions, number of concussions with LOC, years played in the NFL, NFL games played, NFL games started, or age started playing tackle football. Although our sample size was limited for data pertaining to age in which NFL players started playing tackle football (n = 16 to 19 for baseline correlational analyses), our sample size is comparable to the well-cited Stamm et al. (2015) study, which reported that 21 players who started playing tackle football prior to age 12 exhibited worse performance on the Wisconsin Card Sorting Test (WCST) and the Neuropsychological Assessment Battery (NAB) list-learning test than 21 players who began playing after age 12. Unlike our investigation, however, Stamm and colleagues selected only these measures from a larger neuropsychological battery and did not report on additional available measures out of the DETECT cohort. This is problematic for at least two reasons. First, clinical neuropsychological measures are not routinely given in isolation, and interpretation is reliant upon evaluating patterns within and across domains of functioning. Second, reporting only significant findings may appear to overestimate the risk for cognitive decline later in-life among former NFL players. For example, if the current study only reported CVLT-II performances in cognitively normal retirees, the findings may appear to be more impactful in this isolated context and the larger context of null-findings would be missed. Additionally, Stamm et al. arbitrarily decided to use 12 as the determining age split and did not report on any potential linear relationship. Although the

authors argued that critical neurodevelopmental milestones are occurring between age 10 and 12, and exposure to repetitive head injury could alter long-term projections of hippocampal volume, there was no literature cited to support this hypothesis. Lastly, there were significant group differences on a measure of sight-word pronunciation (Wide Range Achievement Test-4th edition), which is more commonly thought of as a measure of premorbid intellectual functioning, rather than a test of reading skills in adults (Mullen & Fouty, 2014). Thus, it is possible that the two groups differed in premorbid intellectual abilities, and differences may have been attributed to these premorbid differences, rather than age of first exposure to tackle football. These criticisms were also outlined in a 2016 study by Solomon et al., who tried to replicate Stamm et al's. results. In a cohort of 45 former NFL players aged 30 to 60, Solomon and colleagues found no significant association between neuropsychological performances on a comprehensive clinical neuropsychological battery (9 tests measuring verbal and visual memory, processing speed, attention, language, and executive functioning) and years of pre-high school football (Solomon et al., 2016). As such, when evaluating neuropsychological functioning using a comprehensive battery, there appears to be very limited evidence that head-injury exposure during an NFL career is associated with worse neurocognitive performance later in life. Apart from a moderate linear relationship between games played and CVLT-II performance in our sample of cognitively normal retirees, our current results suggest that cumulative concussions and/or head-injury exposure sustained over an NFL career does not relate to lower neurocognitive performance later in life.

Our findings also suggested that cognitively normal NFL players endorse more depressive symptoms than cognitively normal controls as measured by the BDI-II (M = 10.20 vs. M = 2.92), though we were not able to compare BDI-II scores between impaired former players

and clinical patients, as different depression measures were routinely used in the UTSW neuropsychology clinic. However, despite the observed difference between groups, we did not find a significant linear or non-linear relationship between BDI-II scores and head-injury exposure variables in cognitively normal or impaired retirees, nor did we find that head-injury exposure variables were associated with depression symptoms over time. Previous literature has suggested a higher prevalence of depression among former NFL players, especially among those with more extensive concussion histories (Guskiewicz et al., 2007; Kerr, Marshall, Harding, & Guskiewicz, 2012). A 2007 investigation sent a general health survey to all members of the NFL Retired Player's Association (n = 3,729). They received a total of 2552 returned surveys, and found that 269 players (11.1%) reported a previous or current diagnosis of depression. Approximately 60% of the respondents reported sustaining at least one concussion (n= 1513), and of those, 595 reported sustaining 3 or more. When comparing the association between concussion and depression, retired NFL players reporting three or more previous concussions were three times more likely to report a diagnosis of depression, and those with a history of one or two previous concussions were 1.5 times more likely to report a diagnosis of depression compared to retired NFL players with no reported history of concussion. The author's resent the survey 9 years later and received 1044 responses (Kerr et al., 2012). From 2001 to 2010, greater frequency of self-reported concussions significantly increased the odds (up to ~27% more likely) of player's reporting a diagnosis of clinical depression (Kerr et al., 2012), further suggesting that recurrent concussion was associated with clinical depression later in life. As a result of this research, others have attempted to evaluate the head-injury exposure and depressive symptoms using objective depression screeners, such as the BDI-II. In 2018, Clark et al. examined the relationship between retired NFL players (n = 30) with and without history of 3+ concussions,

and found that concussion history was not associated with greater endorsement of symptoms on the BDI-II, and both groups endorsed minimal depression symptoms (Clark et al., 2018). Similarly, the aforementioned Solomon et al. (2016) study examined the impact of years of pre-high school football on neuropsychological and mood measures, and found that BDI-II scores were not significantly related to years of pre-high school among NFL retirees (n = 45). These seemingly conflicting findings between reported diagnoses of clinical depression and objectively measured depressive symptoms may be due to methodological differences, as survey data are prone to recall bias and depression diagnoses may not have been accurately reported in the survey studies. Another possibility is the significantly smaller sample sizes in the Clark et al., Solomon et al., and current study compared to the thousands of responses received in the survey data. Thus, it is possible that a much larger sample size would be needed to detect the association between concussion and depressive symptoms. It remains unclear why NFL players may report more depressive symptoms in the current study. Depression is influenced by a number of factors, including numerous psychosocial stressors. Former NFL players may be at higher risk of depression due to unique psychosocial factors within the NFL population, such as higher levels of chronic pain due to arthritis/orthopedic injury, difficulty transitioning to employment following retirement from the NFL, and/or substance use (Guskiewicz et al., 2007). Other stressors, such as financial stressors, may also play a role in the development of depression symptoms. A 2015 study of over 2,000 former NFL players revealed that 15.7% filed for bankruptcy 12 years following retirement (Carlson, Kim, Lusardi, & Camerer, 2015). As such, the relationship between depression symptoms and an NFL career could be multifactorial in nature, rather than due to head-injury exposure alone, and more research evaluating the

relationship between head-injury exposure, psychosocial factors post-retirement, and late-life depression is needed in these former athletes.

Limitations

Although the current study has several methodological strengths, and is the first prospective longitudinal evaluation of neuropsychological performance in retired NFL players, it does have several limitations. First, sample sizes were small when stratifying cognitively normal versus cognitively impaired retirees over time. Nonetheless, our findings were consistent when evaluating a larger combined group of retired NFL players, providing more confidence in our results. Future prospective studies should aim to replicate our findings with larger samples. Second, our clinical sample of patients with MCI and dementia were not recruited prospectively alongside our retired NFL players. Although an attempt was made to match this sample by demographics and diagnosis, other group differences could exist because we were limited to collecting medical and background information contained in the neuropsychological reports. Information contained in neuropsychological reports can differ between clinicians, and not all clinicians capture the same types of information in their reports, and thus it is possible that some background and medical information was omitted in a clinical setting for the sake of brevity. Third, diagnoses of MCI and dementia could have also varied by clinician, as individual clinicians may use different diagnostic criteria that could have also changed over time. Although we made sure that all participants with MCI met the same Jak and Bondi actuarial criteria, clinical patients were initially screened and collected based on individual diagnoses among various physicians, possibly introducing some sampling noise. This study also lacked ratings of everyday functional abilities to differentiate MCI and or dementia, thus it is possible that the

threshold between MCI and dementia may have changed for some participants if these measures were included. Fourth, our cognitively normal group, although recruited alongside our NFL sample, exhibited above average verbal memory performance and may not represent the general population of cognitive normal aging individuals given their above average performance. Fifth, we collected concussion and medical data via self and/or informant report, and, as with much concussion research, corroboration with medical records was not feasible, and thus some of these data may be prone to recall bias. However, each player was carefully interviewed and asked to describe their concussion history in detail using a semi-structured interview pertaining to concussion history throughout athlete's playing career, post-traumatic amnesia, lingering symptoms, and recovery timelines, giving us more confidence in the validity head-injury exposure levels within our sample. Sixth, we had a limited data regarding when former players began playing tackle football, and because of these smaller sample sizes, some comparisons lacked power to compare in correlational analyses. Finally, although we adjusted for multiple comparisons, we ran an abundance of statistical analyses which could inflate the chances for type-1 error.

General Conclusions and Future Directions

We hypothesized that former NFL players would show significantly worse baseline and longitudinal neurocognitive performance compared to controls in areas of confrontation naming, executive functioning, and verbal memory, and that differences found in these measures would negatively correlate to head-injury exposure variables. Hypotheses were only partially supported, as NFL retirees displayed worse confrontation naming, but only at baseline, and there was no association between confrontation naming and head-injury exposure variables. In regard to

verbal memory, cognitively impaired NFL players showed no difference from clinical controls, but baseline performance on the CVLT-II differed between cognitively normal NFL retirees and cognitively normal controls. In addition, baseline performance on the CVLT-II in cognitively normal retirees was significantly correlated with games played in the NFL, and only approached a significant relationship ($p < .05$) with games started and years playing professionally after correcting for multiple comparisons. CVLT-II baseline performance also showed no association with total concussions, concussions with LOC, or age starting tackle football. There was no association between change in verbal memory over time and any measures of head-injury exposure. Cognitively normal retired players reported more depressive symptoms than cognitively normal controls at baseline, but depressive symptoms were not correlated with head-injury exposure at baseline and did not differ from controls over time. No other neuropsychological performances, including executive functioning measures (i.e., TMT B and TCST) were significantly different between former players and their respective control groups at baseline or change over time, and no performances at baseline or over time related significantly to head-injury exposure variables. In sum, the current findings suggest that NFL retirees generally do not have lower cognitive functioning compared to non-athlete controls later in life, and furthermore suggests head-injury exposure obtained over an NFL career is not strongly related to cognitive functioning later-in-life.

Future, larger prospective longitudinal studies examining the neurocognitive performance of NFL athletes over time are greatly needed to help clarify risk of long-term cognitive impairment. In this study, the correlations between CVLT-II and BNT-2 performance and number of NFL games played requires further exploration to determine possible mechanisms. Future studies evaluating biomarkers and neuroimaging findings over time may help determine if

the relationship between these aspects of cognitive functioning and head-injury exposure are static vs. progressive, and if there are potential mediators (i.e., white matter damage or presence of neuropathology) to these relationships. Overall, the literature evaluating the impact of sports-related concussion on cognitive functioning later in life is significantly lacking in prospective longitudinal research. Although it would require considerable coordination, time, and expense, beginning baseline examinations shortly after an NFL career is finished, and matching NFL players to both healthy non-athlete peers and non-contact elite athletes (e.g., professional baseball or basketball players) may further elucidate differences in neurocognitive functioning over time, and risk of neurodegenerative disease in former NFL players.

Appendix A

Additional Analyses and Results

Additional exploratory analyses were conducted to further evaluate the neuropsychological performance of former NFL players. P-values were set at < .05 due to their exploratory nature.

As mentioned earlier, TCST and BDI-II data were not available in large enough numbers to run meaningful analyses in the clinical sample of patients derived from the UTSW neuropsychology clinic due to infrequency of use. However, the Wisconsin Card Sorting Test (WCST) and Geriatric Depression Scale (GDS) was readily available for exploratory analyses. In order to compare the performances of the former NFL players on a measure of concept formation, the number of sorts on the WCST was converted to a T-score using available metanorms (Rhodes, 2004) and compared to TCST T-scores. The BDI-II and GDS were compared on percent of depressive symptoms endorsed. For example, if 10 of 30 items were endorsed on the GDS or 7 of 21 items were endorsed on the BDI-II, then these would be considered levels of depressive symptoms (30% endorsement). When comparing former NFL players to their respective controls using independent samples T-tests, controls performed slightly better on their card sorting tasks compared to former NFL players (p = .015), though performance was still in the average range (Mean T = 47.03; see Table X). When evaluating only cognitively impaired players compared to the clinical sample, this difference approached significance but was not statistically significant (p =. 087). Depression results were similar to the primary analyses in that former NFL players endorsed greater depressive symptoms than controls (35% vs. 15%, p < .001). No statistically significant difference in percentage of depressive

symptoms endorsed was observed between cognitively impaired players (30%) and the clinical sample (24%, see Table X).

Additional exploratory independent samples T-tests breaking down neuropsychological performances by age brackets (50 to 64 and 65 and older) and primary position played (speed vs. non-speed position) were also conducted (see Tables X through X). Correlations between head-injury exposure and neuropsychological functioning were also conducted for speed and non-speed former players. Longitudinal changes are not reported due to very small cell sizes in some groups ($n < 10$). Results were very similar to the primary analysis, in that former players routinely performed lower on the BNT and endorsed more depression symptoms than controls for all age-brackets and primary positions (*p's* < .05). Former players who were 65 and older performed worse on a card sorting task (either TCST or WCST) than their respective control groups ($p = .006$). In non-speed players, number of concussions was positively correlated with RCFT copy performance ($R = .522$, $p = .006$), years playing professionally was negatively correlated to COWAT performance ($R = -.422$, $p = .016$), games played was negatively correlated to WAIS-IV Coding ($R = -.467$, $p = .018$), COWAT ($R = -.386$, $p = .047$), and Animal fluency ($R = -.484$, $p = .01$). In speed players, only age started playing was significantly negatively correlated with RCFT delayed recall performance ($R = -.970$, $p = .001$), but sample size was so low this is likely an unstable result ($n = 6$). Of note, while these correlations were significant at the $p < .05$ level, they would not survive Holmes correction for multiple comparison and false discovery rate.

Lastly, two logistic regression models were conducted to evaluate if neuropsychological measures could differentiate group membership between former NFL players and their respective controls. The first model evaluated the baseline performance of the 11 primary

neuropsychological measures (Table X). The overall model was able to significantly differentiate between groups and demonstrated adequate fit ($\chi^2 = 43.061$, $p < .001$; Nagelkerke $R^2 = .525$; Hosmer and Lemeshow Test: $\chi^2 = 15.040$, $p = .058$). Worse performance on WAIS-IV coding and the BNT predicted NFL group membership (*p's* < .05), with BNT showing the larger effect (Exp(b) = .875). Accuracy of classification improved from 51.2% for the null model to 84.9% after neuropsychological measures were added. The second model evaluated if neuropsychological change scores on the 11 primary measures between visits 1 and 2 could predict group membership. This model was not significant ($\chi^2 = 13.941$, $p = .235$, Nagelkerke $R^2 = .394$), suggesting that changes in neuropsychological functioning over time did not significantly predict group membership.

Appendix B

Additional Tables

Table 18

Mean Comparisons of Card Sorting Tasks and Percentage of Depressive Symptoms

	Group	*M*	SD	*t*	*p*
Card Sort (T)[a]	Control (N=42)	53.27	13.05	2.471	.015
	NFL (N=48)	47.03	10.94		
	Clinical Sample (n=22)	49.31	11.60	1.748	.087
	Impaired Player (n=24)	43.77	9.87		
Depression Sx (%)[b]	Control (N=41)	15	16	4.127	<.001
	NFL (N=52)	35	26		
	Clinical Control (n=17)	24	18	1.001	.323
	Impaired Player (n=27)	30	23		

[a] Card Sort T scores were derived from the Texas Card Sorting Test for former NFL players and healthy controls, and the Wisconsin Card Sorting Test for the clinical sample
[b] Depression symptom percentage ratios were derived from the Beck Depression Inventory-II for former NFL players and healthy controls, and the Geriatric Depression Scale for the clinical sample

Table 19

Baseline Neuropsychological Comparison of All Former NFL Players vs. All Controls by Age Brackets

Age		Group	n	*M*	*SD*	*t*	*p*
50 to 64	TMT A	Control	19	48.68	11.56	-.272	.787
		NFL	24	49.46	7.00		
	TMT B	Control	19	47.79	12.57	-.774	.443
		NFL	25	50.52	10.80		
	Coding	Control	16	52.88	10.06	1.185	.243
		NFL	24	49.50	7.91		
	Digit Span	Control	16	51.00	8.99	-.053	.958
		NFL	22	51.14	6.78		
	COWAT	Control	18	49.89	8.30	.186	.853
		NFL	25	49.40	8.63		

	Animal Fluency	Control	18	44.56	12.99	-1.061	.295
		NFL	25	48.52	11.39		
	BNT	Control	16	53.06	12.18	2.750	.009
		NFL	23	43.70	9.11		
	CVLT Total	Control	19	52.63	13.53	.561	.578
		NFL	25	50.48	11.86		
	CVLT DR	Control	19	47.63	14.28	-.234	.816
		NFL	25	48.60	13.11		
	CVLT Recognition	Control	19	51.32	14.32	.833	.409
		NFL	25	48.20	10.50		
	RCFT Copy	Control	16	42.81	18.93	-.525	.603
		NFL	23	45.70	15.31		
	RCFT IR	Control	16	50.25	18.91	.377	.708
		NFL	25	48.28	14.44		
	RCFT DR	Control	16	47.88	20.07	-.114	.910
		NFL	25	48.52	15.93		
	Card Sort[a]	Control	16	52.36	14.30	.787	.436
		NFL	24	48.94	12.89		
	Depression Sx. (%)[b]	Control	15	15.62	11.15	-3.004	.005
		NFL	24	40.08	30.15		
65+	TMT A	Control	29	45.72	11.21	-.550	.585
		NFL	28	47.21	9.10		
	TMT B	Control	29	47.17	10.19	.661	.512
		NFL	28	45.25	11.75		
	Coding	Control	27	52.56	8.12	2.263	.028
		NFL	26	47.15	9.24		
	Digit Span	Control	27	53.78	9.44	2.784	.008
		NFL	26	47.08	8.00		
	COWAT	Control	27	46.74	10.80	.118	.906
		NFL	28	46.39	10.97		
	Animal Fluency	Control	28	48.11	12.78	1.331	.189
		NFL	28	43.57	12.72		
	BNT	Control	27	54.33	12.44	5.205	.000
		NFL	26	39.46	7.72		
	CVLT Total	Control	29	51.62	14.48	2.283	.026
		NFL	27	43.67	11.27		
	CVLT DR	Control	29	48.97	16.17	1.710	.093
		NFL	27	42.59	11.04		

CVLT Recognition	Control	29	47.76	15.84	.949	.347
	NFL	27	44.26	11.15		
RCFT Copy	Control	27	47.41	10.87	.585	.561
	NFL	28	45.75	10.14		
RCFT IR	Control	27	51.48	15.23	1.294	.201
	NFL	28	46.39	13.91		
RCFT DR	Control	27	47.63	18.19	.989	.327
	NFL	28	43.07	15.93		
Card Sort[a]	Control	26	53.83	12.47	2.876	.006
	NFL	24	45.11	8.40		
Depression Sx. (%)[b]	Control	26	15.48	18.15	-2.665	.010
	NFL	28	30.10	21.84		

[a] Card Sort T scores were derived from the Texas Card Sorting Test for former NFL players and healthy controls, and the Wisconsin Card Sorting Test for the clinical sample
[b] Depression symptom percentage ratios were derived from the Beck Depression Inventory-II for former NFL players and healthy controls, and the Geriatric Depression Scale for the clinical sample

Table 20

Baseline Neuropsychological Comparison of Non-speed NFL Players vs. Controls

	Group	n	*M*	*SD*	*t*	*p*
TMT A	Control	48	46.90	11.32	-.124	.901
	NFL	29	47.21	9.38		
TMT B	Control	48	47.42	11.06	.202	.840
	NFL	29	46.86	12.57		
Coding	Control	43	52.67	8.77	2.193	.032
	NFL	27	47.89	9.07		
Digit Span	Control	43	52.74	9.26	1.986	.051
	NFL	25	48.48	7.09		
COWAT	Control	45	48.00	9.90	.693	.491
	NFL	29	46.31	10.75		
Animal Fluency	Control	46	46.72	12.84	.069	.945
	NFL	29	46.52	11.05		
BNT	Control	43	53.86	12.21	4.191	.000
	NFL	28	42.36	9.72		

CVLT Total	Control	48	52.02	13.97	1.634	.106
	NFL	28	46.61	13.86		
CVLT DR	Control	48	48.44	15.30	.844	.401
	NFL	28	45.54	12.86		
RCFT Copy	Control	43	45.70	14.36	-.156	.876
	NFL	28	46.25	14.85		
RCFT DR	Control	43	47.72	18.68	.595	.553
	NFL	29	45.07	18.32		
Card Sort[a]	Control	42	53.27	13.05	2.494	.015
	NFL	25	45.43	11.33		
Depression Sx. (%)[b]	Control	41	15.53	15.79	-3.516	.001
	NFL	25	31.86	23.09		

[a] Card Sort T scores were derived from the Texas Card Sorting Test for former NFL players and healthy controls, and the Wisconsin Card Sorting Test for the clinical sample
[b] Depression symptom percentage ratios were derived from the Beck Depression Inventory-II for former NFL players and healthy controls, and the Geriatric Depression Scale for the clinical sample

Table 21

Baseline Neuropsychological Comparison of Speed NFL Players vs. Controls

	Group	n	*M*	*SD*	*t*	*p*
TMT A	Control	48	46.90	11.32	-1.185	.240
	NFL	22	49.95	6.23		
TMT B	Control	48	47.42	11.06	-0.657	.514
	NFL	23	49.22	10.26		
Coding	Control	43	52.67	8.77	1.759	.084
	NFL	22	48.68	8.44		
Digit Span	Control	43	52.74	9.26	1.617	.111
	NFL	22	48.95	8.25		
COWAT	Control	45	48.00	9.90	-0.762	.449
	NFL	23	49.87	8.89		
Animal Fluency	Control	46	46.72	12.84	0.469	.641
	NFL	23	45.13	14.09		
BNT	Control	43	53.86	12.21	4.702	<.001
	NFL	20	40.05	6.95		
CVLT Total	Control	48	52.02	13.97	1.364	.177
	NFL	23	47.61	9.64		

CVLT DR	Control	48	48.44	15.30	0.822	.414
	NFL	23	45.43	12.24		
RCFT Copy	Control	43	45.70	14.36	-0.022	.982
	NFL	22	45.77	9.07		
RCFT DR	Control	43	47.72	18.68	0.243	.809
	NFL	23	46.65	13.24		
Card Sort[a]	Control	42	53.27	13.05	1.269	.209
	NFL	22	49.19	10.49		
Depression Sx. (%)[b]	Control	41	15.53	15.79	-4.325	<.001
	NFL	22	40.04	29.34		

[a] Card Sort T scores were derived from the Texas Card Sorting Test for former NFL players and healthy controls, and the Wisconsin Card Sorting Test for the clinical sample
[b] Depression symptom percentage ratios were derived from the Beck Depression Inventory-II for former NFL players and healthy controls, and the Geriatric Depression Scale for the clinical sample

Table 22

Correlations Between Head-injury Exposure and Neuropsychological Functioning by Primary Position

Speed v. Non-speed			Concussions	Concussions w/LOC	Years playing pro	Games Played	Games started	Age started tackle football
Nonspeed	TMT A	*R*	-.195	-.273	-.108	-.099	-.195	-.293
		p	.340	.151	.576	.624	.339	.331
		n	26	29	29	27	26	13
	TMT B	*R*	-.058	-.234	.005	-.126	-.092	-.037
		p	.779	.221	.978	.530	.656	.904
		n	26	29	29	27	26	13
	Coding	*R*	.037	-.215	-.365	-.467	-.324	-.189
		p	.863	.280	.061	.018*	.122	.556
		n	24	27	27	25	24	12
	Digit Span	*R*	-.283	-.189	.105	.082	.117	.468
		p	.202	.365	.616	.709	.604	.146
		n	22	25	25	23	22	11
	COWAT	*R*	-.003	-.034	-.442	-.386	-.126	-.081
		p	.989	.862	.016*	.047*	.540	.792

		n	26	29	29	27	26	13
	Animal Fluency	*R*	.084	-.058	-.267	-.484	-.164	.037
		p	.684	.765	.161	.010*	.425	.905
		n	26	29	29	27	26	13
	BNT	*R*	.124	-.021	-.045	-.154	-.214	-.292
		p	.553	.914	.820	.453	.304	.332
		n	25	28	28	26	25	13
	CVLT Total	*R*	-.165	-.277	-.203	-.374	-.108	-.093
		p	.430	.154	.300	.060	.607	.764
		n	25	28	28	26	25	13
	CVLT DR	*R*	.043	-.140	-.256	-.352	-.090	-.065
		p	.839	.478	.189	.078	.670	.834
		n	25	28	28	26	25	13
	RCFT Copy	*R*	.522	.338	-.225	-.237	-.324	-.111
		p	.006*	.079	.250	.233	.106	.732
		n	26	28	28	27	26	12
	RCFT DR	*R*	.136	-.082	-.189	-.301	-.120	-.422
		p	.508	.671	.326	.127	.559	.151
		n	26	29	29	27	26	13
	Card Sort	*R*	-.091	-.262	-.038	-.328	-.211	-.592
		p	.689	.205	.856	.127	.346	.071
		n	22	25	25	23	22	10
	Depression Sx	*R*	.296	.233	-.161	-.057	.018	-.019
	(%)	*p*	.143	.223	.405	.778	.929	.950
		n	26	29	29	27	26	13
Speed	TMTA	*R*	-.083	-.003	.219	.195	-.065	-.169
		p	.722	.991	.327	.383	.772	.749
		n	21	21	22	22	22	6
	TMTB	*R*	.131	.252	.270	.332	.181	.405
		p	.562	.258	.213	.121	.409	.426
		n	22	22	23	23	23	6
	Coding	*R*	-.021	.120	.087	.086	-.331	.790
		p	.926	.603	.700	.704	.133	.062
		n	21	21	22	22	22	6
	Digit Span	*R*	.070	-.097	-.051	-.103	-.083	.347
		p	.764	.677	.823	.649	.713	.500
		n	21	21	22	22	22	6
	COWAT	*R*	-.152	.044	-.119	-.040	.023	.696

	p	.499	.847	.588	.856	.919	.125
	n	22	22	23	23	23	6
Animal Fluency	*R*	-.055	.039	.025	.076	-.026	.296
	p	.810	.863	.912	.730	.907	.569
	n	22	22	23	23	23	6
BNT	*R*	.328	.253	-.099	-.165	.228	.675
	p	.170	.296	.677	.487	.333	.211
	n	19	19	20	20	20	5
CVLT Total	*R*	.010	-.132	-.405	-.317	.033	-.720
	p	.964	.560	.055	.140	.882	.106
	n	22	22	23	23	23	6
CVLT DR	*R*	.140	.066	-.302	-.189	.093	-.452
	p	.533	.769	.161	.388	.675	.368
	n	22	22	23	23	23	6
RCFT Copy	*R*	.173	.112	-.029	-.059	-.224	.015
	p	.452	.627	.899	.795	.316	.977
	n	21	21	22	22	22	6
RCFT DR	*R*	-.175	-.195	-.310	-.318	-.156	-.970
	p	.435	.386	.149	.140	.478	.001*
	n	22	22	23	23	23	6
Card Sort	*R*	.091	.192	-.047	-.014	-.062	-.544
	p	.694	.405	.834	.950	.785	.264
	n	21	21	22	22	22	6
Depression Sx (%)	*R*	.312	.094	-.038	-.043	-.166	.341
	p	.169	.685	.865	.850	.460	.508
	n	21	21	22	22	22	6

*Note: * $p < .05$*

Table 23

Logistic Regression: Baseline Neuropsychological Predictors of Group Membership

	B	*SE*	Wald	*p*	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
TMT A	.028	.038	.536	.464	1.028	.955	1.107
TMT B	.046	.038	1.486	.223	1.047	.973	1.127
Coding	-.092	.041	4.921	.027	0.912	.841	0.989
Digit Span	-.077	.040	3.674	.055	0.926	.856	1.002
COWAT	.020	.034	0.341	.559	1.020	.955	1.089
Animal Fluency	.057	.032	3.112	.078	1.058	.994	1.127
BNT	-.133	.035	14.571	.000	0.875	.818	0.937
CVLT Total	-.060	.043	1.961	.161	0.942	.866	1.024
CVLT DR	.002	.044	0.002	.962	1.002	.920	1.092
RCFT Copy	-.003	.024	0.017	.895	0.997	.950	1.046
RCFT DR	.034	.029	1.403	.236	1.035	.978	1.096

Controls were reference group (N=42) and NFL Players were predicted group (N=44). Omnibus test was significant ($\chi^2 = 43.061$, $p < .001$, Nagelkerke $R^2 = .525$). Hosmer and Lemeshow Test approached significance ($\chi^2 = 15.040$, $p = .058$) and classification accuracy improved from 51.2% for the null model to 84.9% after neuropsychological measures were added.

Table 24

Logistic Regression: Longitudinal Neuropsychological Predictors of Group Membership

	B	*SE*	Wald	*p*	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
TMT A	.009	.042	0.051	.822	1.009	.930	1.095
TMT B	-.005	.053	0.008	.928	0.995	.898	1.104
Coding	.223	.147	2.309	.129	1.250	.937	1.666
Digit Span	.217	.121	3.208	.073	1.242	.980	1.574
COWAT	-.129	.065	3.967	.046	0.879	.774	0.998
Animal Fluency	-.068	.055	1.531	.216	0.934	.838	1.041
BNT	-.038	.056	0.460	.498	0.963	.864	1.074
CVLT Total	-.047	.056	0.721	.396	0.954	.855	1.064
CVLT DR	.045	.054	0.673	.412	1.046	.940	1.163
RCFT Copy	.040	.037	1.180	.277	1.041	.968	1.120
RCFT DR	-.101	.054	3.561	.059	0.904	.814	1.004

Controls were reference group (N=42) and NFL Players were predicted group (N=44). Omnibus test was not significant ($\chi^2 = 13.941$, $p = .235$, Nagelkerke $R^2 = .394$). Hosmer and Lemeshow

Test was not significant ($\chi^2 = 10.898$, $p = .208$) and classification accuracy improved from 55% for the null model to 72.5% after neuropsychological measures were added.

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