**Boston University**

**OpenBU** **http://open.bu.edu**

Boston University Theses & Dissertations Boston University Theses & Dissertations

2021

# The effect of repetitive head impact exposure on white matter lesion volume

https://hdl.handle.net/2144/43494

*"Downloaded from OpenBU. Boston University's institutional repository."*

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

# THE EFFECT OF REPETITIVE HEAD IMPACT EXPOSURE ON WHITE MATTER LESION VOLUME

by

**CHRISTINA MARIE NOWAK**

B.A., Middlebury College, 2017

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2021

© 2021 by
CHRISTINA MARIE NOWAK
All rights reserved

Approved by

First Reader _____

Michael L. Alosco, Ph.D.
Associate Professor of Neurology

Second Reader _____

Ronald Killiany, Ph.D.
Professor of Anatomy & Neurobiology

## DEDICATION

Dedicated to my noble, loyal Labrador, Sandy.

## ACKNOWLEDGEMENTS

Throughout the writing of this thesis I have received a great deal of support and assistance.

I would like to thank my advisor Dr. Mike Alosco for all he has taught me in the past year and his guidance as I continue my education and career in research. I would also like to thank my second reader, Dr. Ron Killiany, for his help and support in data analysis and furthering my understanding of FLAIR MRI. I would like to additionally thank the research team for their data collection, and the many faculty and staff who encouraged me and pushed me to sharpen my thinking at a higher level over the past two years (Dr. Doug Rosene, Dr. Linda Afifi, and others).

Additionally, I want to thank my family, loved ones, and friends. I am grateful for your unwavering love, encouragement, and support through all of my academic, athletic, professional, and personal endeavors. I am thankful to my Dad for inspiring me to pursue further education and his military service which has inspired my research pursuits. To my Mum and sister, Teresa: I am blessed to have such brilliant scientific role models in my life, and am grateful for the supportive texts and phone calls that have helped me overcome any task. Lastly, but certainly not least, to my amazing friends, from the Golden Gate Bridge to the snowy shores of Lake Champlain, and my classmates who have become close friends: thank you for your love, support, and all of the shared laughter; I am truly lucky to have so many wonderful people in my life.

**THE EFFECT OF REPETITIVE HEAD IMPACT EXPOSURE ON WHITE MATTER LESION VOLUME**

**CHRISTINA MARIE NOWAK**

## ABSTRACT

Contact and collision sports (CCS) expose athletes to countless repetitive head impacts (RHI) across a single season, potentially leading to increased risk of long-term difficulties in cognition and the development of neurodegenerative disease. There is mixed literature on whether RHI from CCS result in changes to white matter and long-term neurobehavioral outcomes, therefore this research project seeks to provide supporting evidence by comparing the total volume of fluid-attenuated inversion recovery (FLAIR) white matter lesions in individuals with a history of RHI from CCS to those without a history of RHI from the Boston University Alzheimer's Disease Research Center (BU ADRC). The RHI participants were matched to a group of non-RHI participants based on age (+/- 5 years). Effects of RHI on white matter hyperintensities (WMHs) are evaluated, while considering hippocampal volume across RHI and non-RHI groups.

When controlling for age, sex, education, and total hippocampal volume, those with a history of football were found to have a significantly greater WMH volume (p=.02) compared to those without a history of football play. Compared to the non-RHI group, the RHI group including all athletes (n=42) had a greater WMH volume, although it did not reach a level of significance (p=.91).

This investigation provided preliminary evidence for a link between high RHI exposure and WMHs in football players, and a non-significant relationship between RHI and increased WMHs in those with a history of CCS compared to individuals in the non-RHI group. Future research should expand upon this investigation, by examining RHI exposure and WMH consequences in a diverse assortment of sports, follow athletes longitudinally for repeated in vivo MRIs and post-mortem neuropathological confirmation, and include more female athletes.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AD | Alzheimer's Disease |
| ADRC | Alzheimer's Disease Research Center |
| ANCOVA | Univariate analysis of covariance |
| APOE | Apolipoprotein E |
| BMI | Body mass index |
| BU | Boston University |
| CCS | Contact and collision sports |
| CERAD | Consortium to Establish a Registry for Alzheimer's Disease |
| CTE | Chronic traumatic encephalopathy |
| CVD | Cardiovascular disease |
| DAI | Diffuse axonal injury |
| DTI | Diffuse tensor imaging |
| eTIV | Estimated total intracranial volume |
| FA | Fractional anisotropy |
| FEM | Finite element models |
| FLAIR | Fluid-attenuated inversion recovery |
| LST | Lesion Segmentation Tool |
| MCI | Mild cognitive impairment |
| MINT | Multilingual Naming Test |
| MMSE | Mini-Mental State Examination |
| MoCA | Montreal Cognitive Assessment |
| MRI | Magnetic resonance imaging |
| mTBI | Mild traumatic brain injury |
| NACC | National Alzheimer's Coordinating Center |
| NFL | National Football League |

| | |
|---|---|
| NFTs | Neurofibrillary tangles |
| NINCDS-ADRDA | National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association |
| NP | Neuropsychological |
| p-tau | Phosphorylated tau |
| RHI | Repetitive head impacts |
| ROIs | Regions of interest |
| SPM | Statistical Parametric Mapping |
| UDS | Uniform Data Set |
| WM | White matter |
| WMHs | White matter hyperintensities |
| WML | White matter lesion |

# INTRODUCTION

There is increasing evidence that repetitive head impact (RHI) exposure from contact and collision sports (CCS) is associated with increased risk of long-term problems with cognition and mood, including those from the neurodegenerative disease chronic traumatic encephalopathy (CTE) [1]. RHI includes the exposure to cumulative, recurrent concussive and subconcussive events [2,3,4,5]. A concussion is a direct or indirect head impact that results in shearing of or tensile forces to axons as result of acceleration, deceleration, and/or rotational forces of the brain produced by the impact. A concussion includes a constellation of clinical symptoms that generally resolve within days or weeks [4], although they can persist for months [6] or longer than a year [7]. In contrast, a subconcussive event entails transferring mechanical energy to the brain with sufficient force to compromise axonal integrity [2,4,5,8,9], without overt clinical symptoms. In a 2015 review, 16% of published CTE subjects with pathologically confirmed cases, their next-of-kin reported no history of concussion [10], suggesting that subconcussive head impact can reach the threshold for development of the disease in the absence of overt concussion. This emphasizes the need to prospectively assess the prospective risks and consequences of exposure to RHI, particularly subconcussive impacts. It remains unknown what the threshold of impact intensity required to induce this neuronal damage is, and whether there is a minimal threshold impact level that is not damaging to neuronal function is also uncertain. In particular, repetitive subconcussive blows to the head have been shown to play a prominent role in cognitive disorders later in life [11,12].

### *CCS and RHI Exposure*

Investigations of RHI have primarily been conducted in the setting of CCS, such as American football, boxing, soccer, and ice hockey. With over 4.5 million amateur athletes playing tackle football annually [13], it has one of the largest concussion rates [14,15]. Studies utilizing helmet-based accelerometer have estimated that collegiate-level amateur football players average over 1,000 subconcussive impacts per season, and high school players averaging 600 subconcussive impacts per season [16]. In addition to these registered subconcussive blows, surveys of high school and college football players reported approximately 1 out of 2 players are concussed each year, and about 1 in 3 sustain more than one concussion in a year [17,18]. Concussive and subconcussive blows to the head in amateur high school and college athletes is particularly concerning as they can result in both acute and chronic changes in neurological function [19-24]. Cumulative effects of RHI from a single high school football season can yield changes in the brain that are measurable on magnetic resonance imaging (MRI), as well as a decline in neuropsychological (NP) testing performance despite a lack of concussion diagnosis [25].

### *Neurobehavioral Outcomes*

RHI can result in mild traumatic brain injury (mTBI) or concussion and there is mixed literature on whether fewer, more severe head impacts or a greater number of less severe RHIs result in long-term neurobehavioral outcomes [11]. Indirect measures of RHI, such as age of first exposure to CCS and/or years of CCS participation have been correlated with differences in brain structure in retired athletes as compared to those without RHI exposure [26,27]. There is growing evidence that cumulative RHI can be accompanied by

persistent post-concussive symptoms, long-term difficulties with cognition, as well as the potential development of CTE [1,28]. CTE can result in long-term behavior, cognitive, mood, and motor symptoms. From these, a list of clinical symptoms has been established for CTE, with clinical variants presenting first in a behavior/mood variant, a cognitive variant, or a combination of the two [29]. Initial behavioral symptoms include verbal and physical violence, explosivity, and impulsivity [29,30] and mood symptoms include depression and hopelessness [29]. Changes in cognitive functioning have been noted in episodic memory impairment and executive dysfunction [29]. Similarly, RHIs in amateur football are linked to acute [19,20,31] and chronic [21-24] neurological consequences, and depression is common after TBI of all severities [32,33]. Exposure to RHI can also result in numerous other types of pathologies that may contribute to cognitive, behavior, and mood symptoms [29,34,35].

### *Neuropathology of CTE*

CTE can only be diagnosed by autopsy examination and is included in a group of neurodegenerative disorders called tauopathies which are characterized based on the abnormal accumulation of hyperphosphorylated tau protein [36,37]. Tau protein is one of the major components of neurofibrillary tangles (NFTs) and in normal brains, phosphorylated tau (p-tau) epitopes are typically rapidly dephosphorylated [37]. Pathologies of disorders such as CTE are associated with tau proteins that have become hyperphosphorylated insoluble aggregates, or NFTs. In CTE, there is a distinct pattern of p-tau that distinguishes it from other tauopathies like Alzheimer's Disease (AD). In 2015, a panel of neuropathologists established the diagnostic criteria for CTE, and determined a

pathognomonic lesion of CTE to be “an accumulation of abnormal hyperphosphorylated tau (p-tau) in neurons and astroglia distributed around small blood vessels at the depths of cortical sulci and in an irregular pattern” (McKee et al., 2016; Figure 1) [39]. These pathognomonic lesions suggest cerebral microvasculature could be disrupted during head impact and result in formation of NFTs [40]. The pattern of NFTs in the cortical laminae differs, as NFTs are mostly found more superficially (Layers II and III) in CTE, as opposed to Layers III and IV in AD [28]. Additionally, the tau pathology of CTE is a less uniform cortical NFT distribution than AD, with NFTs, neuropil threads, and glial tangles confined to the frontal, temporal, and insular cortices; they are especially prominent in the medial temporal lobe and lead to neuronal death [28]. The causes of symptoms of CTE and RHI has been of focus, as the p-tau lesions of CTE have been associated with memory loss, mood and behavioral changes [41], and impaired cognitive functioning [42,43]. It has been posited that head trauma triggers a release of tau from its normal location in the axonal cytoskeleton, leads to it amassing in somatodendritic compartments, and ultimately results in NFT formation [43]. However, the precise mechanisms that drives the accumulation of tau and disease progression following RHI in CTE are still unknown. Moreover, exposure to RHI can lead to other types of pathologies that may contribute to the cognitive and mood symptoms, including white matter (WM) degeneration or injury [44,45].

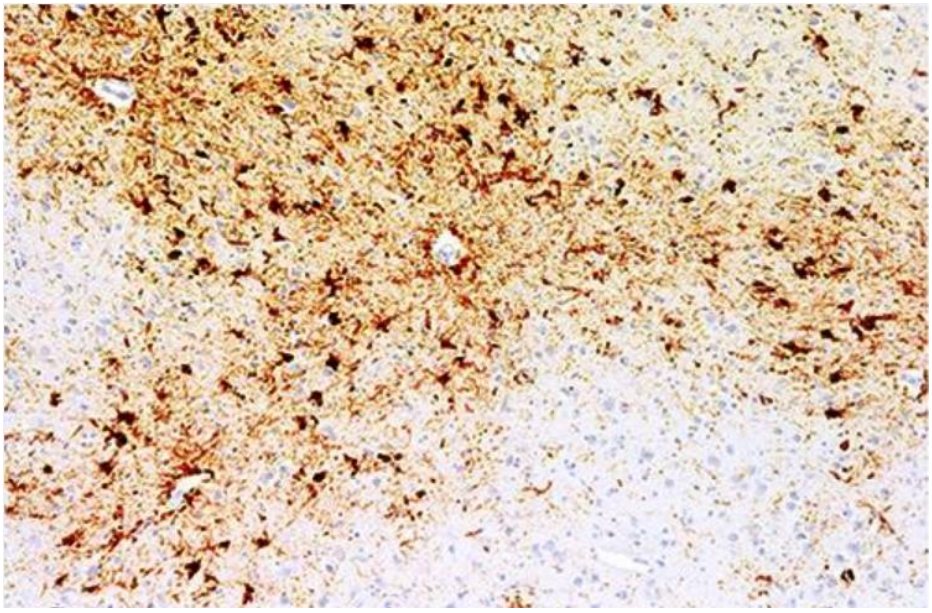

**Figure 1.** *Pathognomonic CTE Lesion.* A microscopic image depicting the histopathological hallmark of CTE including a perivascular p-tau lesion in the sulcal depths. (Adapted from McKee et al., 2016) [39].

### *WM Changes Following RHI*

RHI and CTE result in a wide array of changes in the brain. Finite element models (FEM) have attempted to identify specific peak brain location "strain and stress" [46] responses to concussion and subconcussive head impacts, utilizing recorded impact kinematics to simulate the biomechanical event (i.e., the head trauma) [47-50]. Diffuse tensor imaging (DTI) of concussion patients demonstrates that fractional anisotropy (FA) is reduced in several WM locations, particularly in cerebellar WM, the cingulum, and corpus callosum [45]. Axonal damage can continue weeks after an acute concussion [51], demonstrating a more chronic effect of head impacts on WM changes.

Moreover, a 2017 study [52] integrated WM anisotropy from DTI scans into FEM, enabling enhanced observation of connectivity. An assortment of studies [47,48,50]

demonstrated that regardless of the location of the head impact itself, the regions near the brainstem in central brain regions, such as the corpus callosum, fornix, thalamus, and midbrain absorb the peak stresses and strains of concussive injury. Given the direct effect on the corpus callosum, as well as the connection of the fornix to the anterior thalamus and hippocampus, these studies suggest that these WM tracts are particularly susceptible to injury during a blow to the head. WM tracts are composed of mostly myelinated axons and glia distributed in bundles or tracts also known as fascicles WM, and connect distinct areas of the cortex. As two major WM tracts, these are susceptible to RHI effects given their vulnerability to damage during head impact, the cell types that compose them making them susceptible to the tauopathies present in CTE, and their location in the brain and the regions they connect, whose functions are relevant to the clinical symptoms of CTE.

McKee et al. (2009) establish thinning of the corpus callosum, primarily its anterior and mid-portions, as one of the most common gross pathology features of CTE [28]. They also found neuropil neurites and fibrillary astrocytic tangles within the corpus callosum and subcortical WM structures. Furthermore, Alosco et al. (2019) [54] examined the relationship of white matter hyperintensities (WMHs) and cerebrovascular disease with dementia in 180 deceased men over the age of 40 who had CTE and had played football. They found [54] that a longer history of football play (utilized to measure RHI exposure) was associated with more WMHs and a greater distribution of NFTs in the greater dorsolateral frontal cortex. In CTE, the neuropathologic consequences of RHI can lead to dementia; these changes include p-tau and WMHs, in addition to non-RHI related

pathologic changes such as arteriolosclerosis [54]. Arteriolosclerosis, while not related to the RHI proxy (years of play), was individually found to contribute to dementia [54]. Therefore, the route of progressing to dementia in CTE remains uncertain, but likely involves both tau and non-tau pathologic conditions such as cerebro- and cardiovascular disease. Cerebrovascular disease frequently coincides with neurodegenerative disease, such as AD, and contributes to cognitive decline [54-56]. In individuals with CTE, cerebrovascular disease can also include WM degeneration as a result of RHI. Additionally, arteriolosclerosis is common with aging and cardiovascular disease (CVD) [54]. Rates of cardiovascular disease CVD mortality have been shown to be higher in retired National Football League (NFL) players compared to men in the general United States public [57,58]. Other factors that influence CVD mortality risk in former NFL players include race, position played, and body mass index (BMI) [57].

In both experimental models of and clinically documented TBI, the hippocampus has also been identified as a region highly vulnerable to brain injury [59]. Hippocampal atrophy can occur within weeks to months following a TBI. Hippocampal atrophy results in deficits in long-term potentiation – the long-lasting surge in synaptic strength which facilitates learning and memory [59]. The primary output tract of the hippocampus is the fornix, and given the high interconnectivity of the region, in addition to the established atrophy in the fornix following blows to the head [37], the fornix and hippocampus are major regions of interest (ROIs) for CTE, especially given the decreased FA demonstrated in DTI studies.

As WM tracts are especially vulnerable to the shearing forces that often result from TBI, diffuse damage can result in WM injury following a head impact [60]. Diffuse axonal injury (DAI) can result in widespread cognitive function by disruption of cortical-subcortical pathways [61]. The trauma or secondary ischemia are potential direct and indirect causes of DAI. Specifically, brain shifting and edema can impair cerebral blood supply, cause secondary infarction within the corpus callosum, and result in the anatomy of the corpus callosum becoming even more susceptible to further injury from future head impacts [60]. While DAI can only be confidently diagnosed ex vivo through microscopic examination, neuroimaging findings, such as hemorrhages in the corpus callosum may allow for high accuracy conclusion *in vivo* [62]. Therefore, given the association of TBIs and RHI to documented damage to the corpus callosum, the fornix, and structures connected by the fornix, WM structures are major ROIs in examining anatomical changes resulting from RHI. Neuroinflammation and gliosis are long-term associations of RHI [1,63] and CTE [1,39], and can result in WMHs [64,65]. On T2-weighted MRI scans of the brain, white matter lesions (WMLs) appear as WMHs, but appear hypointense on T1-weighted images. WMHs could reflect DAI associated with RHI. While DTI can detect the more subtle WM microstructural changes, and is ideal for detecting early WM injury from RHI exposure or CTE, this analysis on DTI is not clinically routine [12]. In contrast, evaluating WMHs on fluid-attenuated inversion recovery (FLAIR) sequence is clinically routine as it has increased sensitivity to WMHs [12,66].

***FLAIR WMHs***

MRI studies of individuals who have suffered an mTBI, including a sports-related concussion, have demonstrated WMHs on FLAIR sequence [67], which is set to null fluids and highlight hyperintense lesions. Currently, there are a number of variables that are correlated with WMH burden. One of the greatest predictors of WMH severity is age, as most older adults demonstrate a degree of WMH burden, even in non-demented adults [68]. As the brain ages, WMHs proliferate [69,70], are typical by age 45, with age-related WMHs commonly positioned around the lateral ventricles, particularly around the anterior and posterior horns [71]. In cognitively normal samples, WMHs are more common in women compared to men – though causation varies and remains unexplained [72] – and women have significantly higher ratio of WMH volume to WM volume as compared to men [73]. Additionally, WMH burden can be affected by race. Independent of age, sex, and hypertension, Blacks have a higher prevalence of WMHs on MRI than European Americans [74]. In several studies, severe WMH are significantly associated with lower cognitive performance in individuals with lower levels of education, but this association of severity of WMH and lower cognitive functions is not present in those with high levels of education [75,76]; therefore, it is purported that education can modulate the effects of WMH on cognition by establishing a greater cognitive reserve.

Increased CVD risk factors and type 2 diabetes have also been linked to increased WMH burden. WMH are most commonly associated with aging and CVD, and generally reflect microvascular cerebral hypoperfusion resulting in small-vessel ischemic disease [12,77-79]. Diabetes increases the risk for vascular dementia and cerebromicrovascular disease,

manifesting as WMHs on MRI [80,81]. Studies have demonstrated [80] that one potential mechanism by which diabetes increases microvascular disease may be through its effect on blood flow regulation – as measured by decreased blood flow velocities in the middle cerebral arteries with increased WMHs. However, results have also suggested [82] that WMH burden is associated with poorer cognitive performance independent of diabetes-related factors.

***WMH Burden & Cognitive Associations***

Periventricular and deep WMHs are related to an accelerated cognitive decline [77,79]. An *ex vivo* MRI study found an association between increased WMH burden with vascular and Alzheimer's pathologies, and increased WMH burden was associated with faster decline in perceptual speed, suggesting that WMH burden may even reflect additional injury to the tissue [83]. Regardless of cognitive status, ischemic injury has been considered the main cause of WMHs, but a 2017 *ex vivo* study [84] of AD patients linked parietal WMHs with axonal loss and demyelination independent of ischemic injury; as WMH severity was positively correlated with p-tau pathology, these results potentially suggest Wallerian degeneration resulting from cortical AD pathology [84].

Additionally, WML pathology has been found to negatively influence progression from mild cognitive impairment (MCI) to AD [85], as well as having been linked to inferior performance on a variety of cognitive tests include the Mini-Mental State Examination (MMSE), word list learning and recall, and visual memory as compared to MCI patients who did not convert to AD [86]. While age-related WMHs are common near the lateral ventricles, declining performance on the Consortium to Establish a Registry for AD

(CERAD) NP battery has been significantly associated with increased lesion loads in the fornices and WM tracts of the limbic system [87].

Cerebral hypoperfusion has also been shown to be associated with a higher risk of dementia in the general population and quicker cognitive decline [79], and WMHs have been linked to poorer performance on cognitive testing. In studies of former NFL players, more years of football play (greater exposure to RHIs) have been associated with increased WMHs and WML burden, dementia [54], poorer executive function performance [12], and greater deficits in NP measures of "naming, word finding, and visual/verbal episodic memory" [88]. Additionally, in one study, veterans with mTBI *and* WMH performed worse on cognitive tests of working memory compared to veterans with mTBI *without* WMH on FLAIR imaging [89,90]. Additionally, a threshold dose-dependent relationship has been demonstrated between estimated RHI and future risk for cognitive and neurobehavioral impairment in football [11], soccer [91], and boxing [92]. RHIs sustained playing football do not have an established baseline risk or threshold, but likely involve a multitude of individual-specific factors such as cognitive reserve or body mass index [93]. Furthermore, significantly poorer performance on memory tasks in soccer players are associated with lower levels of FA [91], demonstrating an association of RHI from ball heading with abnormal WM microstructure; concussion history did not have a significant effect on FA or cognitive performance [91].

***WMHs and RHI***

FLAIR WMHs are less common in mTBI as compared to moderate and severe TBI, and typically following concussion, signs of acute injury are not visible on conventional MRI

[94,95]. Despite modern MRI advancements and higher field strengths, hemorrhages in concussed patients may not be detected on conventional images [96], yet a decrease in brain volume between acute TBI and follow-up months after the injury has been reported [97]. More advanced imaging, namely observation of FLAIR imaging, have demonstrated an increase in WMHs in athletes compared to controls over the course of a single season of ice hockey [94]. One study demonstrated a significantly greater number of cerebral FLAIR lesions in those with a history of TBI (83% mild-TBI) than age-matched controls (42% vs 22% after controlling for age-related causes), with more subcortical than deeper lesions in the TBI groups [98]. The link between RHIs and WMHs on MRI may be best explained by fluctuations in perfusion levels given that a single mTBI can acutely decrease cerebral perfusion [67,99]; therefore, RHIs may result in enduring changes in cerebral perfusion [12]. As aforementioned, CTE has been well-documented in former NFL players [1], and studies in former NFL players [88,100] have reported reductions in cerebral perfusion. Furthermore, neuropathological evidence in former boxers links tau and microvascular pathology [101] and a study of 201 patients [102] correlated CTE pathology with microvascular disease-induced blood-brain barrier leakage. It has been hypothesized that microvascular injury resulting from RHIs, quantified on MRI as WMHs, contributes to the pathogenesis of the hallmark CTE-related perivascular p-tau deposits at the base of sulci [28,43,101].

Additionally, FLAIR lesions have been linked with decreased verbal memory scores in veterans with mTBI [90]. In former NFL players, WM alterations are notable on MRI [12,88], associated with RHI [12], and affect executive function [12]. Imaging studies

[88,100,103,104] of living, former American football players have demonstrated disruption of the blood-brain barrier and alterations in cerebral blood flow, which may be related to or cause chronic WM degeneration and alter cognitive outcomes [105]. Utilizing MRI, FreeSurfer-calculated WMHs, and NP testing, Alosco et al. (2017) [12] studied 86 former NFL players and 23 age-matched controls without RHI exposure. RHIs were quantified via a cumulative head impact index score, based on self-report, position played, and "impact exposure frequencies from published helmet accelerometer studies in former amateur football players" [12]; therefore, a higher cumulative head impact index score represents a greater exposure to RHIs. They found that an increased volume of WMHs were associated with greater cumulative RHI exposure, as well as worse executive function [12]. Consequently, in former NFL players, RHI exposure may result in long-term microvascular and non-microvascular pathologies which are reflected in increased WMHs and negatively impact cognition.

As a noninvasive neuroimaging technique, MRI has enabled a greater understanding of WM injury in mTBI and RHI, enhancing our ability to track pathophysiological changes following RHI. WM injury measures derived from MRI correlate with cognitive and neurobehavioral deficits, suggesting a prognostic role of MRI following RHI.

### *Study Objectives*

The primary aim of this investigation is to determine if RHIs sustained through CCS are associated with WMH volume on FLAIR MRI. Further evidence linking RHIs to WMHs is required in order to inform appropriate patient management in clinical practice. The literature demonstrates support for cumulative subconcussive blows from American

football [106], but support for high RHI-exposure in other sports is still under preliminary examination; while these sports may result in high amounts of RHI, they have yet to demonstrate the level of thousands of subconcussive impacts in an individual during a single season of play like football [9,107]. Previous studies have focused on former NFL players, but our sample includes amateur athletes of various sports, including football. Given the existing literature, it is hypothesized that the RHI group, particularly American football players, will have a greater WMH volume than the age-matched controls without a history of RHI.

## MATERIALS AND METHODS

### *Study Sample and Design*

The sample included 84 participants (37 with normal cognition, 29 with probable or possible mild cognitive impairment, 14 with probable, possible, or confirmed dementia diagnosis, and 4 unknown; Table 1) retrospectively analyzed from the existing database of the Boston University (BU) Alzheimer's Disease Research Center (ADRC) Clinical Core Registry. The National Institute on Aging funds approximately 31 ADRC's nationwide and contributes data to the National Alzheimer's Coordinating Center (NACC). The BU ADRC follows community dwelling older adults with and without cognitive impairment age 50 years and older [108]. In 2018, the BU ADRC also began to recruit and enroll participants with exposure to RHI. These include male and female participants with a history of playing CCS, military service, physical violence, and other

sources. All participants have a study partner (family member or other) who provides additional information on daily functioning. All participants are English-speaking older adults with adequate visual acuity and hearing. Participants are excluded for a history of a serious mental illness (e.g., bipolar disorder, schizophrenia), non-AD and non-AD-Related-Dementias, neurological disorders (e.g., brain tumor, multiple sclerosis), or medical conditions that preclude study participation [108]. BU ADRC recruitment and additional registry data has been described elsewhere [108-111].

Each year, participants are administered neurological examinations, NP testing, and measures of functional independence. Participants also have a baseline MRI. With consent and in order to corroborate self-reported medical histories, participants' medical records are acquired from their health care providers. Procedures were approved by the BU Medical Center Institutional Review Board. Participants (or their Legally Authorized Representatives) provided written informed consent prior to participation in the BU ADRC protocol.

The current sample included participants with and without a history of exposure to RHI from the BU ADRC who had an MRI. The RHI and non-RHI groups were age-matched +/- 5 years, resulting in 42 with a history of RHI and 42 without (non-RHI control).

***MRI Data Acquisition***

Starting in 2013, ADRCs began to submit structural MRI sequences on patients enrolled in the study. The specifications have been described elsewhere [112,113]. MRI data was acquired through the BU ADRC data set and analyses were conducted at BU, with

participants selected from those who have quantitated volume of WMHs from ante-mortem FLAIR MRI data available.

***MRI Data Processing & FLAIR WMHs***

The software package Statistical Parametric Mapping (SPM) was used to analyze the brain imaging data sequences. Lesions were segmented by the lesion growth algorithm (Schmidt et al., 2012) as implemented in the Lesion Segmentation Tool (LST) toolbox version 2.0.1 (https://www.statistical-modelling.de/lst.html) for SPM [114]. The FLAIR MRI sequence utilizes inversion recovery fixed to nullify fluids. For example, this can suppress cerebrospinal fluid, enabling enhancement of periventricular hyperintense lesions. The open source toolbox for LST was used in FLAIR images to segment T2 hyperintense lesions. It enables segmentation of brain lesions, by segmenting T2-hyperintense lesions from T1 and FLAIR images, first segmenting the T1 images into three main tissue classes: cerebrospinal fluid, gray matter, and WM. Then, together with the co-registered FLAIR intensities, lesion belief maps are calculated. Through the use of a prechosen initial threshold ($\kappa$=0.5), a threshold is created for these maps, and an initial binary lesion map is attained. This map is subsequently grown along voxels that appear hyperintense in the FLAIR image, resulting in a lesion probability map. These methods have been evaluated for good reliability, accuracy, and reproducibility of WMH segmentation [115,116]. Figure 3A and Figure 3B demonstrate examples of FLAIR images with WM signal abnormalities highlighted.

FreeSurfer 6.0 software was used to calculate estimated total intracranial volume (eTIV) and right and left hippocampal volumes for each participant from their T1 weighted MRI

scans. Through a blend of segmentation and an atlas, FreeSurfer software performs an automated segmentation process of brain tissue on MRIs, sectioning the brain into regions of gray and white matter, and hypointense regions in the WM [117,118]. FreeSurfer v6.0 has improved upon its atlas compared to previous versions, as it automatically segments the hippocampal regions into a smaller number of subfields than previously possible [119]. Studies have demonstrated [117,118] that the FreeSurfer technique is comparable to the accuracy level and precision of manual labeling.

### *Diagnostic Procedures*

Diagnoses are determined at a multidisciplinary BU ADRC consensus panels, which include neurologists, neuropsychologists, geriatricians, and geriatric psychiatrists. The participants' medical and psychosocial history, NP testing results, and neuroimaging are presented and discussed prior to a diagnosis being made. A diagnosis of cognitively normal is determined from NP test scores that are within normal age- and education-determined normal ranges (i.e., >-1.5 SD above the normative mean) [120] and the consensus panel determining that the individual is cognitively normal upon discussion of the presented materials. Per Peterson (2004), a diagnosis of MCI is used to denote an irregular state of cognitive impairment which manifests early such as prodromal forms of dementia [121]. Through the use of criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984) [122], subjects were diagnosed with "Possible AD" or "Probable AD." For analyses purposes, these subjects were combined into a single dementia group. Four subjects were missing a BU ADRC

consensus diagnosis, while twenty-five subjects were missing a NACC diagnosis within the dataset; of those, only three were lacking a diagnosis across both categories.

### *NP Assessment*

Participants' global cognitive status, executive function, language, attention, visuospatial, and episodic memory skills were evaluated through the administration of a comprehensive NP test battery (Table 2 outlines some test results across groups). This includes the tests which make up the Uniform Data Set (UDS) of the NACC, including the MMSE, Montreal Cognitive Assessment (MoCA), Logical Memory Immediate and Delayed Recall, Craft Story Immediate and Delayed Recall, Trail Making Tests A and B, Digit Span and Number Span Forward and Backward, Phonemic (Letters F and L) and Semantic (Animal and Vegetable) Verbal Fluency, 30-item Boston Naming Test, and Benson Complex Figure Copy and Recall. During a single session, a trained psychometrist administers this NP assessment.

### *Statistical Methods*

All analyses were performed using IBM SPSS v26 computer software. Between group differences (RHI vs non-RHI) were evaluated using chi-square (sex and race) and independent-samples t-tests (age and education; significance level 5%). In the literature, severe WMHs have been shown to be significantly associated with lower cognitive performance in those with lower levels of education, but not in those with high levels of education [75, 76]. However, in the present study, education did not differ significantly across the two groups ($p=.22$; Table 1). Race was homogenous between the two groups ($p=.97$). While there were statistical differences in certain characteristics at baseline,

many of these statistical differences were not clinically meaningful as they were consistent across the RHI and non-RHI groups; for example, race, as the majority of the sample were white. Independent samples two-sided t-tests were used to determine differences between the RHI and non-RHI groups' NP outcome measures (Table 2). Given these established relationships of age, sex, and years of education with WMHs, our primary model was examining the effect of RHI through CCS exposure on WMHs.

Between group differences of the effect of RHI on the outcome variable of WMH volume were evaluated using a univariate analysis of covariance (ANCOVA). When looking at the association of RHI and WMH volume, our primary model accounted for age, sex, and years of education. The ANCOVA was repeated with hippocampal volume included, given its association with AD [123,124]. Then, a sensitivity analysis was conducted in the RHI individuals with a history of football, with the covariates of age, sex, and years of education, and again with hippocampal volume.

Through a means tables and independent-samples t-test, it was demonstrated that our sample's eTIV and sex are highly correlated values ($p<.001$), with men having greater intracranial volume on average (male mean eTIV = 1613081.12 ± 155385.82; female mean eTIV = 1405441.45 ± 151948.71). Given that there are generally sex differences in WMH burden and the high correlation of sex with eTIV in our sample, the binary variable of sex was utilized to account for sex differences in the sample to maintain consistency across analyses. There was a significant difference in sex across the groups, as the RHI group was predominantly (78.6%) male as compared to the non-RHI group (31% male) ($p<.001$; Table 1).

Additionally, the hippocampal region is highly vulnerable to brain injury, and studies have demonstrated a strong association with AD progression – that hippocampal volume and ratio are reduced in those with Alzheimer's Disease [123,124] and MCI [125] compared to controls. In our sample, the RHI group had a significantly greater left ($p=.05$) hippocampal volume and a non-significant greater right hippocampal volume ($p=.14$). Hippocampal volume was negatively correlated with WMH burden across the sample ($r(81)=-.464$; $p<.001$). Therefore, a secondary model examined the effect of RHI through CCS exposure on WMH burden while accounting for age, sex, years of education, and hippocampal volume.

The sample (N=84) was reduced to 83 for the ANCOVA analyses given one outlier. In the non-RHI group, one outlier was removed from ANCOVA analysis, as their WMH burden was more than seven standard deviations above the mean (Figure 2). WMHs are more prevalent and severe in individuals with AD, preclinical AD, and in older adults [68,126], and there is a positive linear relationship between odds and severity of WMHs and hypertension [127,128]. Given the age of the participant (age = 73 years; mean age of total sample = 64.01 ± 9.4; mean age of non-RHI group = 65.38 ± 8.7), lack of CCS-related RHI-history, diagnosis of probable Alzheimer's Disease, and hypertension, it suggests that the individual's WMHs are a result of medical history, and *not* an error in the data pipeline when calculating WMH burden. It is possible that the individual has a large number of WMHs, but regardless, they are not representative of our sample.

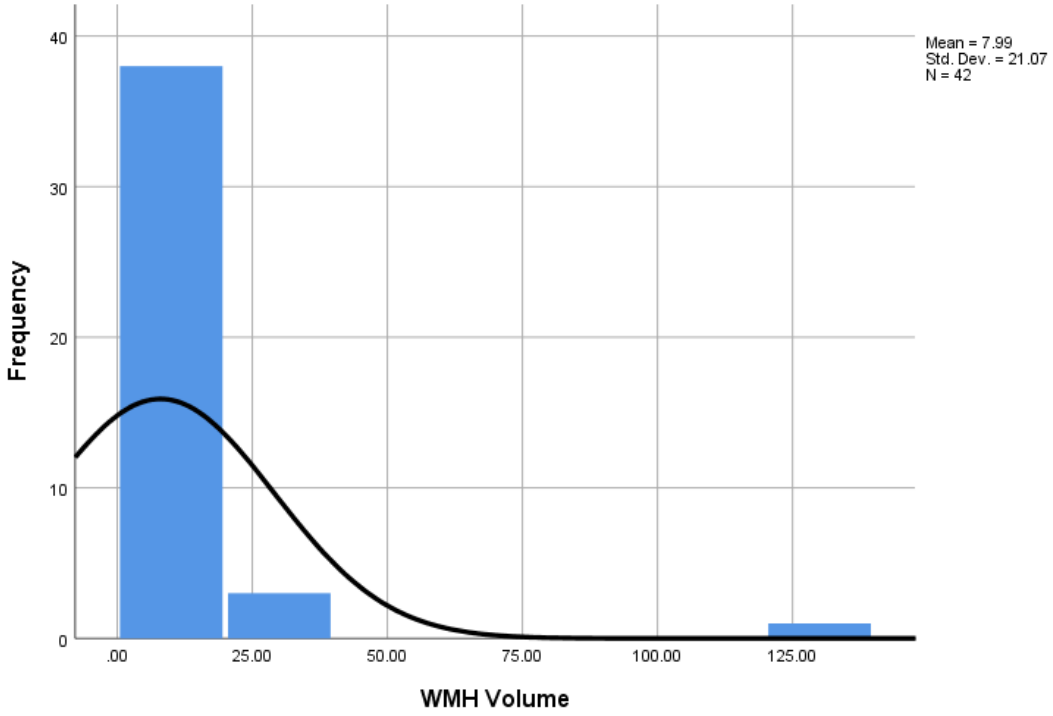


Figure 2. *WMH Volume for Non-RHI Subjects*. The outlier (WMH volume =132.681) was more than 7 SDs above the mean WMH volume for the non-RHI group (mean = 7.99; SD = 21.07).

# RESULTS

## *Demographic Data*

Table 1 shows the demographic data of the entire sample and divided into the two groups. Age ranged from 47 to 83 years old, with the mean age of the sample being 64.01 ± 9.4 years (N=84). The mean education level of the sample was 16.92 ± 2.2 years (Table 1). Using an independent-sample two-tailed t-tests, there was no significant difference in age (p=.18) or education (p=.22) between the groups. There was no significant difference in race across the two groups when comparing for white vs other (p=1.0), nor was there a significant difference in diagnosis across the groups (p=.21). Of the MCI subjects included, 6 were determined to have probable MCI and 2 had possible MCI. Through independent-samples two-tailed t-tests, there was no significant difference in NP test performance across the two groups except for Trails A (p=.03) and Trails B (p=.001), with the non-RHI group completing the two tests faster than the RHI group on average (higher scores denoting a greater impairment). Three individuals had a documented history of diabetes. Within the sample, 16.9% of cases had hypertension history values missing, primarily in the RHI group (n=29 available, 13 unavailable), so this variable was not included in analyses.

The majority of patients included in the analysis were white (88.1%), black (7.1%), Asian (3.6%), and American Indian or Alaska Native (1.2%); therefore, for analyses, race was classified as either white (88.1%) or other (11.9%). There was little variation in baseline education across the RHI groups (p=.44). Additionally, more women (69%) than men

comprised the non-RHI study population, but more men (78.6%) were included in the RHI group.

Sport history is not mutually exclusive; it accounts for the number of subjects who answered “yes” to a history of each sport across the 42 RHI participants, meaning that someone could have a history of >1 sport. The RHI group included athletes from a variety of sports, some of whom played more than one sport: football (23), soccer (19), hockey (10), boxing (6), lacrosse (5), wrestling (3), diving (3), martial arts (2), and rugby (2). Twenty-three participants only had a history of one sport; 12 played 2 sports; 7 had a history of 3+ sports**.**

**Table 1.** *Demographic Descriptive Statistics of RHI and Non-RHI Groups*

| ***Demographic*** | **Total Sample** | **RHI** | **Non-RHI** | **p-value** |
|---|---|---|---|---|
| ***N*** | 84 | 42 | 42 | -- |
| **Age at Visit**: Mean ± SD years | 64.01 ± 9.4 | 62.64 ± 9.8 | 65.38 ± 8.7 | .18 |
| **Sex**: n(%) | 46 Males (54.8%)<br>38 Females (45.2%) | 33 Males (78.6%)<br>9 Females (21.4%) | 13 Males (31%)<br>29 Females (69%) | .001***** |
| **Education**: Mean ± SD years | 16.92 ± 2.2 | 17.21 ± 2.0 | 16.62 ± 2.3 | .22 |
| **Race** (%) | | | | 1.00 |
| White | 88.1% | 88.1% | 88.1% | -- |
| Other | 11.9% | 11.9% | 11.9% | -- |
| **BU Consensus Diagnosis** | | | | .21 |
| n | 80 | 39 | 41 | |
| Normal Cognition | 37 (46.25%) | 14 (35.90%) | 23 (56.10%) | -- |
| MCI | 29 (36.25%) | 18 (46.15%) | 11 (26.83%) | -- |
| Dementia | 14 (17.5%) | 7 (17.95%) | 7 (17.07%) | -- |
| *Diagnosis Unavailable* | *4* | *3* | *1* | -- |

***** = statistically significant difference between RHI and non-RHI groups ($p<.05$)

Table 2. *NP Test Performance of RHI and Non-RHI Groups* Independent-Samples 2-tailed T-Tests performed on the sample. A higher score on the MoCA, Craft Story Recall: Verbatim, Craft Story Recall: Delayed, Digit Span Backward, Verbal Fluency (FAS), and Multilingual Naming Test (MINT) represented a better testing performance. A lower score for Trails A and Trails B demonstrates performing the task faster, and, thus, better.

| **Cognitive Test Scores** Mean ± SD | Total | RHI | Non-RHI | p-value |
|---|---|---|---|---|
| *MoCA* Raw Score | N=56 | 23.54 ± 6.5 n=26 | 24.33 ± 6.4 n=30 | .65 |
| *Craft Story Recall: Verbatim* Raw Score | N=56 | 14.15 ± 7.6 n=26 | 15.40 ± 8.7 n=30 | .57 |
| *Craft Story Recall: Delayed* Raw Score | N=56 | 12.42 ± 5.6 n=26 | 12.60 ± 6.4 n=30 | .91 |
| *Trails A* Total Seconds | N=56 | 38.03 ± 27.2 n=29 | 27.66 ± 7.0 n=38 | .03* |
| *Trails B* Total Seconds | N=65 | 119.63 ± 88.2 n=27 | 67.13 ± 20.3 n=38 | .001* |
| *Digit Span Backward* Raw Score | N=56 | 6.81 ± 2.6 n=26 | 7.40 ± 2.9 n=30 | .42 |
| *Verbal Fluency* Raw Score | N=70 | 24.31 ± 8.9 n=29 | 28.17 ± 10.9 n=41 | .12 |
| *MINT* Raw Score | N=56 | 29.19 ± 5.5 n=26 | 28.63 ± 4.2 n=30 | .67 |
| ***** = statistically significant difference between RHI and non-RHI groups ($p<.05$) | | | | |

***WMH Volume***

As previously discussed, WMHs are more common in individuals with a history of TBI [129,130] or higher cumulative head impact index scores in CCS athletes [12] than healthy controls, and WMH burden increases with TBI severity [129,130]. Our RHI group had a greater WMH volume as compared to the non-RHI group, although it did not reach a level of significance ($p=.91$). As consistent with past studies [68,126], WMHs were positively correlated with age in our sample ($r(81)=.526$; $p<.001$). Furthermore, women have an increased number of WMHs and greater WMH volume relative to their WM volume as compared to men [72,73], and head and size differs across the sexes [131,132], with men generally having larger heads and thus intracranial volume. In this study, men and women did not have a significantly different volume of WMHs ($p=.379$). Race did not differ across the two RHI groups, nor did it have a significant effect on WMH volume ($p=.86$).

There was no significant effect of RHI history on WMH volume after controlling for age, sex, and education, $F(1,78) = 1.261$, $p=.27$. When hippocampal volume was factored in as an additional covariate, there was still no significant effect of RHI on WMHs; $F(1,78) = 1.827$, $p=.18$. Figures 3A and 3B are examples of WMH segmentation on axial FLAIR slices at the level of the ventricles for a non-RHI (Figure 3A) and an RHI subject with a history of football and hockey play (Figure 3B). Table 3 demonstrates the mean WMH volume, as well as FreeSurfer-calculated left, right, and total hippocampus volumes.

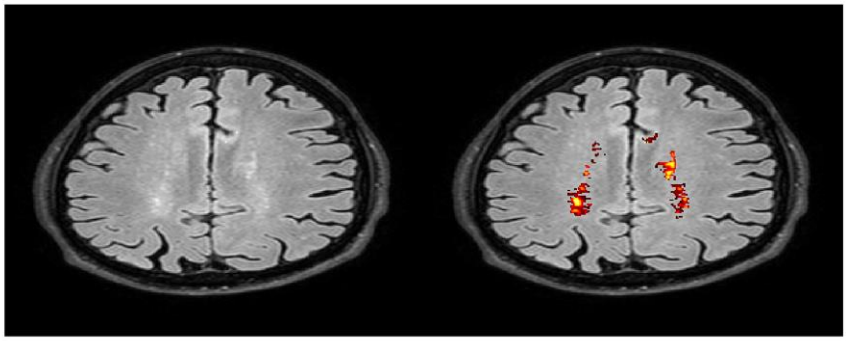

**Figure 3A.** *LST-produced FLAIR Image for non-RHI subject.* Axial slice at the level above the ventricles for a non-RHI subject. The subject has no history of CCS. The left image represents the FLAIR image and the right is the overlay of the segmentation of the FLAIR image with WMHs in red and yellow. Most of the WMHs are found periventricularly in this individual. The individual's WMH volume = 4 across 14 total lesions.

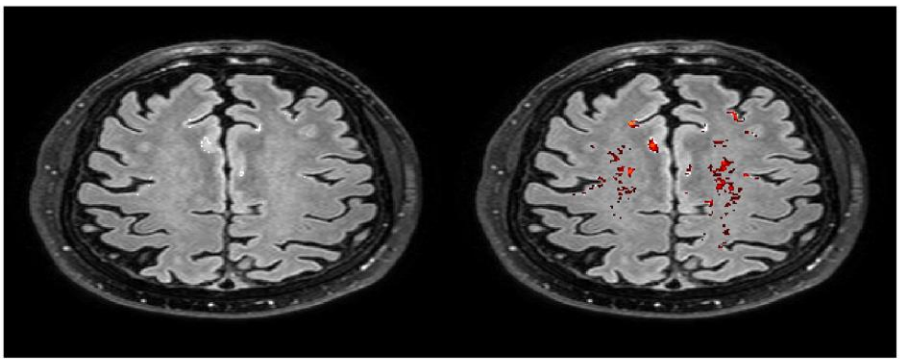

**Figure 3B.** *LST-produced FLAIR Image for RHI subject.* Axial slice at the level above the ventricles for an RHI subject. The subject has a history of CCS, including American football and ice hockey. The left image represents the FLAIR image and the right is the overlay of the segmentation of the FLAIR image with WMHs in red and yellow. The individual's WMH volume = 6 across 20 total lesions.

**Table 3:** ***Brain Volumetrics across RHI and Non-RHI Groups*** Including p-values calculated through 2-tailed independent-samples t-tests; * = *statistically significant value (p<.05).* Includes Cohen's d-value to calculate effect size.

| **Location** (Mean ± SD) | **Total** (N=83) | **RHI** (n=42) | **Non-RHI** (n=41) | **p-value** | **Cohen's d-value** |
|---|---|---|---|---|---|
| WMH Volume | 5.05±7.70 | 5.41±7.94 | 4.95±7.54 | .91 | 0.06 |
| Left Hippocampus | 3718.25±52.81 | 3820.47±71.27 | 3613.54±75.51 | .05* | 2.82 |
| Right Hippocampus | 3782.11±53.82 | 3860.57±76.85 | 3701.73±74.15 | .14 | 2.10 |
| Total Hippocampus Volume | 7500.36±934.42 | 7681.04±910.94 | 7315.27±932.74 | .07 | 0.40 |

***WMH Volume in Football Players***

A sequence of ANCOVA tests were utilized. The goal was to investigate the effect of RHI on WMH volume, while controlling for age, sex, and education in the primary model. Additionally, the RHI group included athletes from a variety of backgrounds. Given the diverse background of sports in our RHI group, an ANCOVA was conducted to compare RHI participants with a history of football play to non-football players (including all non-RHI and non-football RHI individuals).

When the sample was refined to examine the effects of RHI from a history of football play to those with no history of football play (non-football playing RHI and non-RHI individuals), while still examining the covariates of age, sex, and education, the model demonstrated that there was a statistical trend on WMH volume; $F(1,78) = 3.147$, $p=.08$. However, when total hippocampal volume was included as a covariate with age, sex, and

education, those with a history of football compared to those without have a significantly greater WMH volume; $F(1,78) = 5.784$, $p=.02$.

## DISCUSSION

The existing literature examining WMHs in athletes with a history of concussions and CCS exposure is mixed. The existing literature is focused on acute and chronic outcomes of football, a male-dominated sport; this study extends what is currently known about the relationship between RHIs and WMHs by examining the effects of RHI in diverse background of CCS, and across females and males with a history of RHI. In this investigation we observed that when accounting for age, sex, and education, RHI did not have a significant effect on WMHs. When hippocampal volume was included as a covariate, there was still no significant effect of RHI on WMHs, but the model improved (from p=.27 to p=.18). Indeed, there was a statistically significant negative correlation between WMH volume and hippocampal volume.

When the model was reduced to compare just football players to those with no history of football (meaning non-RHI and RHI with no history of football), the model improved and there was a statistical trend, suggesting that other sports may have less RHI exposure than football or that the relationship between RHI and WMHs may differ in non-football players. When hippocampal volume was included as a covariate, the model became significant (p=.02), demonstrating a significant relationship between RHI from football and increased WMHs. Given the diverse sports included in our RHI group, there was a concern that the other sports may suppress the effects of RHI in football players; for that reason, an ANCOVA was run to compare football players with the non-football players (all non-football RHI and non-RHI individuals). Furthermore, given that reduced hippocampal volume and ratio in those with Alzheimer's Disease [123,124] and MCI

[125] compared to controls is highly documented in the literature, the intention was to include a sub-analysis which accounted for hippocampal volume to be sensitive to potential AD effects on WMH volume.

***Diverse CCS History***

Not all football players or individuals with a large RHI exposure will develop long-term neurological consequences. Additional risk factors, such as CVD, diabetes, or genetic factors (e.g. apolipoprotein E (APOE)), may interact with RHIs and increase one's vulnerability to the long-term effects of RHIs on the brain. Previous studies have been focused on WMHs in former NFL players compared to controls [12,88]. The findings in this investigation are consistent with and relate to those of American football players that found an increased RHI exposure was associated with increased WM abnormalities [12,88] and WM rarefaction [54]. The results of this study suggest that playing football at the professional level is not necessary for WM changes to occur, but that RHIs even at the amateur level of football play can cause greater WMH burden as compared to controls with no history of RHI and even athletes of other CCS. A 2016 pilot study [94] of 45 collegiate level hockey players matched 3:1 with controls found no significant change in number of WMHs on MRI across one season of play, though a reduction in brain volume was noted. This could suggest that football has a greater exposure to RHIs or that the increased WMHs could potentially be a result of the more severe head impacts in football as compared to other sports.

Additionally, as our sample included those who wrestled, dived, played lacrosse, and more, it is difficult to estimate the number of RHIs an individual may have sustained over

a single season. There is variability in RHI exposure in this study given the diverse sport history, and even RHI exposure variability within the football players, since position is highly associated with RHI exposure [54]. In football, and increasingly in ice hockey and soccer, the documentation of this exposure is increasing from accelerometer studies as well as MRI studies across single seasons of play. This single season exposure to RHI would be valuable to look at, in addition to the association between the number of years of play with WMHs, as this study had the limitation of not having exact number of years of play.

The literature on football-induced RHIs, WMHs, and other long-term outcomes in former football players is well-documented [12,40,88,133,134], while the research in other CCS is more limited and other sports may not demonstrate as uniform RHI exposure as football. Lipton et al. (2013) [91] conducted a DTI study which demonstrated a reduced FA in amateur soccer players associated with RHI as measured by self-reported heading for the 12 months prior. Their results demonstrated a potential for a generally "safe" threshold of headings, and exposure below said threshold may not result in lower FA [91]. However, they also noted [91] that heading technique and impact location is not uniform, which may result in varying location of brain abnormalities and potentially undetectable, subtle WM changes in other locations. Furthermore, a 2018 DTI study [135] in male and female soccer players demonstrated that even with a comparable RHI exposure (measured through self-reported exposure to headings over the prior 12 months), women had lower FA and broader evidence of WM alteration than men. These results demonstrate initial evidence for divergent brain responses to RHI across the sexes,

at least in soccer players. This potential for WMH sex-differences in response to RHI will likely need to involve sports like soccer and ice hockey, as there is more female involvement and there are even professional women's leagues for these sports; football is an almost exclusively male sport with few exceptions [136]. Similarly, a 2017 study of ice hockey players reported a decreased FA in female hockey players over the course of a season, while FA in males did not change significantly [137], demonstrating alteration of WM microstructure over a single season. Additionally, football and ice hockey are helmet-wearing sports, whereas soccer heading is a direct contact with the ball. There is also the need for more late-outcome studies for non-football CCS, rather than just across single seasons.

This study documents the long-term effects of RHIs from football on aging athletes as compared to athletes of other CCSs and those without a CCS history. Given the age of the sample, it would be valuable to prospectively follow young football players and track their WMH burden over time to determine whether WMHs continue to multiply with age even years after play has ceased. As axonal damage can continue weeks after an acute concussion [51], the mechanism of *how* RHIs affect WM remains unclear. As arteriolosclerosis is common with aging and CVD, which is common in individuals who previously played American football [57,58], CVD history would be valuable in determining the cause of greater WMHs. Likely the WMHs in this study are a result of a combination of CVD and axonal injury as a result of RHI. Therefore, this study lends support to the notion that CTE results from both tau and non-tau pathologic conditions.

***Hippocampal Volume***

Hippocampal volume was included as a covariate in analyses to account for the correlation of reduced hippocampal volume with AD progression, RHIs, the normal aging process [138], or other factors such as hippocampal sclerosis [139]. When hippocampal volume was included as a covariate, subjects who had played football had a significantly higher WMH volume than those who had no history of football (p=.02). In our sample, the non-RHI had a decreased hippocampal volume in comparison to the RHI group, though not statistically significant, which is expected given the timing of hippocampal atrophy during CTE and AD presentation. Studies have noted that NFTs typically do not emerge in the hippocampus until the later stages of CTE [36], while hippocampal atrophy is a hallmark of AD [140,141], can present prior to clinical symptoms of AD [142], and is even a predictor of progressing from MCI to AD [125]. Our models improved with HV, suggesting that either it mediates the association between RHH and WMHs, or that the model was accounting for the rates of AD among the two groups. In the non-RHI group, 26.83% of individuals had MCI and 17.07% had dementia; the rate of MCI is greater than reported rates in population-based studies of those 70-89 [143] or 75 and older [144], and the rate of AD is greater than the Alzheimer's Association-reported [145] 11.3% in Americans 65 and older. One explanation for this is our sample: ADRC samples often include people who are at risk for AD or have a family history of AD, with genetic components increasing for AD [146], and even those who present as clinically normal could have early hippocampal atrophy indicative of later cognitive decline [142]. A greater loss of hippocampal volume

is also associated with increased WMHs in AD [146,148], with one study reporting [149] a linear relationship between WMHs and hippocampal atrophy, suggesting a relationship between AD-related hippocampal atrophy and vascular pathology (WMHs). While the RHI group is 36% MCI, this could represent cognitive impairment as a result of the RHIs sustained through CCS as it is much higher than the reported incidence rate of MCI among the population [143,144]. The greater hippocampal volume in the RHI group could be further supported by the greater ratio of men to women in the RHI group, as men tend to have greater hippocampal volumes. Therefore, given the relationship of hippocampal volume with AD and WMHs, as well as our sample's demographics, the inclusion of hippocampal volume improving our model suggests that it is removing noise or confounding factors by accounting for AD etiology in the non-RHI group. However, this study did not look at the spatial distributions of WMHs, which may differ across various neurodegenerative diseases [66] and could reflect the cognitive domains that are influenced by the WMH and potentially the differing NP test performances seen across our RHI and non-RHI groups (Table 2).

***Limitations***

This investigation has several limitations. Its sample size was relatively small, though it included MRI LST data, cognitive testing, and an age-matched group of non-RHI controls to provide an effective comparison group. With a larger sample size, greater evaluation across sport populations would also be possible, rather than just football. Additionally, this study was not able to control for vascular factors, such as hypercholesterolemia or arteriolosclerosis, which can contribute to increased WMH

volume [150]. History of diabetes was not incorporated in our model because very few individuals in the sample (n=3 of 70 available variables) had diabetes, but future studies should look into the relationship of increased WMHs in those with diabetes with a history of RHI. Our sample was 88.1% white, therefore, other races were underrepresented in the sample, and given the increased CVD mortality rate [57] and higher prevalence of WMHs in black individuals, a more diverse sample would be beneficial for examining effects of RHI on WMHs across the population. Longitudinal evaluations of both subject groups would provide meaningful evidence regarding the reversibility of findings of the greater number and volume of WMHs in those with a history of football.

***Conclusion***

This investigation provided preliminary evidence for a link between high RHI exposure and WM lesions in football players only. When controlling for age, sex, education, and total hippocampal volume, those with a history of football compared to those without have a significantly greater WMH volume (p=.02). Compared to the non-RHI group, our RHI group including all athletes (n=42) had a greater WMH volume, although it did not reach a level of significance (p=.91). Football players have the best documented exposure to RHI, but the existing literature varies, and often utilizes either current athletes or head impact by measure of concussion history, rather than RHI which includes subconcussive blows to the head that are sustained over even a single season of CCS play. These RHIs can lead to neuropathological changes over time, therefore, future studies should continue to evaluate the repercussions of RHI exposure through CCS play beyond merely measuring concussions. Future research should expand upon this investigation, by

looking at RHI exposure and WMH consequences in a diverse assortment of sports, following athletes longitudinally for repeated in vivo MRIs and post-mortem neuropathological confirmation, and include female athletes, especially given the emerging evidence for decreased FA in female athletes.

## REFERENCES

[1] McKee, A. C., Stern, R. A., Nowinski, C. J., Stein, T. D., Alvarez, V. E., Daneshvar, D. H., Lee, H. S., Wojtowicz, S. M., Hall, G., Baugh, C. M., Riley, D. O., Kubilus, C. A., Cormier, K. A., Jacobs, M. A., Martin, B. R., Abraham, C. R., Ikezu, T., Reichard, R. R., Wolozin, B. L., Budson, A. E., … Cantu, R. C. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain: A Journal of Neurology*, *136*(Pt 1), 43–64. https://doi.org/10.1093/brain/aws307

[2] Erlanger D. M. (2015). Exposure to sub-concussive head injury in boxing and other sports. *Brain Injury*, *29*(2), 171–174. https://doi.org/10.3109/02699052.2014.965211

[3] Carman, A. J., Ferguson, R., Cantu, R., Comstock, R. D., Dacks, P. A., DeKosky, S. T., Gandy, S., Gilbert, J., Gilliland, C., Gioia, G., Giza, C., Greicius, M., Hainline, B., Hayes, R. L., Hendrix, J., Jordan, B., Kovach, J., Lane, R. F., Mannix, R., Murray, T., … Fillit, H. M. (2015). Expert consensus document: Mind the gaps—advancing research into short-term and long-term neuropsychological outcomes of youth sports-related concussions. *Nature Reviews. Neurology*, *11*(4), 230–244. https://doi.org/10.1038/nrneurol.2015.30

[4] Belanger, H. G., & Vanderploeg, R. D. (2005). The neuropsychological impact of sports-related concussion: a meta-analysis. *Journal of the International Neuropsychological Society: JINS*, *11*(4), 345–357. https://doi.org/10.1017/s1355617705050411

[5] Dashnaw, M. L., Petraglia, A. L., & Bailes, J. E. (2012). An overview of the basic science of concussion and subconcussion: where we are and where we are going. *Neurosurgical Focus*, *33*(6), 1–9. https://doi.org/10.3171/2012.10.FOCUS12284

[6] Ponsford, J., Willmott, C., Rothwell, A., Cameron, P., Kelly, A. M., Nelms, R., Curran, C., & Ng, K. (2000). Factors influencing outcome following mild traumatic brain injury in adults. *Journal of the International Neuropsychological Society: JINS*, 6(5), 568–579. https://doi.org/10.1017/s1355617700655066

[7] Bigler E. D. (2008). Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *Journal of the International Neuropsychological Society: JINS*, 14(1), 1–22. https://doi.org/10.1017/S135561770808017X

[8] Montenigro, P. H., Bernick, C., & Cantu, R. C. (2015). Clinical features of repetitive traumatic brain injury and chronic traumatic encephalopathy. *Brain Pathology* (Zurich, Switzerland), 25(3), 304–317. https://doi.org/10.1111/bpa.12250

[9] Talavage, T. M., Nauman, E. A., Breedlove, E. L., Yoruk, U., Dye, A. E., Morigaki, K. E., Feuer, H., & Leverenz, L. J. (2014). Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. *Journal of Neurotrauma*, *31*(4), 327–338. https://doi.org/10.1089/neu.2010.1512

[10] Stein, T. D., Alvarez, V. E., & McKee, A. C. (2015). Concussion in Chronic Traumatic Encephalopathy. *Current Pain and Headache Reports*, *19*(10), 47. https://doi.org/10.1007/s11916-015-0522-z

[11] Montenigro, P. H., Alosco, M. L., Martin, B. M., Daneshvar, D. H., Mez, J., Chaisson, C. E., Nowinski, C. J., Au, R., McKee, A. C., Cantu, R. C., McClean, M. D., Stern, R. A., & Tripodis, Y. (2017). Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players. *Journal of Neurotrauma*, *34*(2), 328–340. https://doi.org/10.1089/neu.2016.4413

[12] Alosco, M. L., Koerte, I. K., Tripodis, Y., Mariani, M., Chua, A. S., Jarnagin, J., Rahimpour, Y., Puzo, C., Healy, R. C., Martin, B., Chaisson, C. E., Cantu, R. C., Au, R., McClean, M., McKee, A. C., Lin, A. P., Shenton, M. E., Killiany, R. J., & Stern, R. A. (2017). White matter signal abnormalities in former National Football League players. *Alzheimer's & Dementia (Amsterdam, Netherlands)*, *10*, 56–65. https://doi.org/10.1016/j.dadm.2017.10.003

[13] Guskiewicz, K. M., Weaver, N. L., Padua, D. A., & Garrett, W. E., Jr (2000). Epidemiology of concussion in collegiate and high school football players. *The American Journal of Sports Medicine*, *28*(5), 643–650. https://doi.org/10.1177/03635465000280050401

[14] Guthrie R. M. (2015). Emerging data on the incidence of concussion in football practice at all levels of amateur play. *The Physician and Sports Medicine*, *43*(4), 333–335. https://doi.org/10.1080/00913847.2015.1081552

[15] Daneshvar, D. H., Nowinski, C. J., McKee, A. C., & Cantu, R. C. (2011). The epidemiology of sport-related concussion. *Clinics in Sports Medicine*, *30*(1), 1–vii. https://doi.org/10.1016/j.csm.2010.08.006

[16] Bailes, J. E., Petraglia, A. L., Omalu, B. I., Nauman, E., & Talavage, T. (2013). Role of subconcussion in repetitive mild traumatic brain injury. *Journal of Neurosurgery*, *119*(5), 1235–1245. https://doi.org/10.3171/2013.7.JNS121822

[17] Llewellyn, T., Burdette, G. T., Joyner, A. B., & Buckley, T. A. (2014). Concussion reporting rates at the conclusion of an intercollegiate athletic career. *Clinical Journal of Sport Medicine: Official Journal of the Canadian Academy of Sport Medicine*, *24*(1), 76–79. https://doi.org/10.1097/01.jsm.0000432853.77520.3d

[18] Langburt, W., Cohen, B., Akhthar, N., O'Neill, K., & Lee, J. C. (2001). Incidence of concussion in high school football players of Ohio and Pennsylvania. *Journal of Child Neurology*, *16*(2), 83–85. https://doi.org/10.1177/088307380101600203

[19] Collins, M. W., Lovell, M. R., Iverson, G. L., Cantu, R. C., Maroon, J. C., & Field, M. (2002). Cumulative effects of concussion in high school athletes. *Neurosurgery*, *51*(5), 1175–1181. https://doi.org/10.1097/00006123-200211000-00011

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

[21] Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Harding, H. P., Jr, Matthews, A., Mihalik, J. R., & Cantu, R. C. (2007). Recurrent concussion and risk of depression in retired professional football players. *Medicine and Science in Sports and Exercise*, *39*(6), 903–909. https://doi.org/10.1249/mss.0b013e3180383da5\

[22] Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Cantu, R. C., Randolph, C., & Jordan, B. D. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery*, *57*(4), 719–726. https://doi.org/10.1093/neurosurgery/57.4.719

[23] Singh, R., Meier, T. B., Kuplicki, R., Savitz, J., Mukai, I., Cavanagh, L., Allen, T., Teague, T. K., Nerio, C., Polanski, D., & Bellgowan, P. S. (2014). Relationship of collegiate football experience and concussion with hippocampal volume and cognitive outcomes. *JAMA*, *311*(18), 1883–1888. https://doi.org/10.1001/jama.2014.3313

[24] Seichepine, D. R., Stamm, J. M., Daneshvar, D. H., Riley, D. O., Baugh, C. M., Gavett, B. E., Tripodis, Y., Martin, B., Chaisson, C., McKee, A. C., Cantu, R. C., Nowinski, C. J., & Stern, R. A. (2013). Profile of self-reported problems with executive functioning in college and professional football players. *Journal of Neurotrauma*, *30*(14), 1299–1304. https://doi.org/10.1089/neu.2012.2690

[25] Davenport, E. M., Whitlow, C. T., Urban, J. E., Espeland, M. A., Jung, Y., Rosenbaum, D. A., Gioia, G. A., Powers, A. K., Stitzel, J. D., & Maldjian, J. A. (2014). Abnormal white matter integrity related to head impact exposure in a season of high school varsity football. *Journal of Neurotrauma*, *31*(19), 1617–1624. https://doi.org/10.1089/neu.2013.3233

[26] Stamm, J. M., Koerte, I. K., Muehlmann, M., Pasternak, O., Bourlas, A. P., Baugh, C. M., Giwerc, M. Y., Zhu, A., Coleman, M. J., Bouix, S., Fritts, N. G., Martin, B. M., Chaisson, C., McClean, M. D., Lin, A. P., Cantu, R. C., Tripodis, Y., Stern, R. A., & Shenton, M. E. (2015). Age at First Exposure to Football Is Associated with Altered Corpus Callosum White Matter Microstructure in Former Professional Football Players. *Journal of Neurotrauma*, *32*(22), 1768–1776. https://doi.org/10.1089/neu.2014.3822

[27] Stamm, J. M., Bourlas, A. P., Baugh, C. M., Fritts, N. G., Daneshvar, D. H., Martin, B. M., McClean, M. D., Tripodis, Y., & Stern, R. A. (2015). Age of first exposure to football and later-life cognitive impairment in former NFL players. *Neurology*, *84*(11), 1114–1120. https://doi.org/10.1212/WNL.0000000000001358

[28] McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., Santini, V. E., Lee, H. S., Kubilus, C. A., & Stern, R. A. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *Journal of Neuropathology and Experimental Neurology*, *68*(7), 709–735. https://doi.org/10.1097/NEN.0b013e3181a9d503

[29] Stern, R. A., Daneshvar, D. H., Baugh, C. M., Seichepine, D. R., Montenigro, P. H., Riley, D. O., Fritts, N. G., Stamm, J. M., Robbins, C. A., McHale, L., Simkin, I., Stein, T. D., Alvarez, V. E., Goldstein, L. E., Budson, A. E., Kowall, N. W., Nowinski, C. J., Cantu, R. C., & McKee, A. C. (2013). Clinical presentation of chronic traumatic encephalopathy. *Neurology*, *81*(13), 1122–1129. https://doi.org/10.1212/WNL.0b013e3182a55f7f

[30] Mez, J., Solomon, T. M., Daneshvar, D. H., Stein, T. D., & McKee, A. C. (2016). Pathologically Confirmed Chronic Traumatic Encephalopathy in a 25-Year-Old

Former College Football Player. *JAMA Neurology*, *73*(3), 353–355. https://doi.org/10.1001/jamaneurol.2015.3998

[31] Iverson, G. L., Gaetz, M., Lovell, M. R., & Collins, M. W. (2004). Cumulative effects of concussion in amateur athletes. *Brain Injury*, *18*(5), 433–443. https://doi.org/10.1080/02699050310001617352

[32] Kreutzer, J. S., Seel, R. T., & Gourley, E. (2001). The prevalence and symptom rates of depression after traumatic brain injury: a comprehensive examination. *Brain Injury*, *15*(7), 563–576. https://doi.org/10.1080/02699050010009108

[33] Seel, R. T., Kreutzer, J. S., Rosenthal, M., Hammond, F. M., Corrigan, J. D., & Black, K. (2003). Depression after traumatic brain injury: a National Institute on Disability and Rehabilitation Research Model Systems multicenter investigation. *Archives of Physical Medicine and Rehabilitation*, *84*(2), 177–184. https://doi.org/10.1053/apmr.2003.50106

[34] Mez, J., Daneshvar, D. H., Kiernan, P. T., Abdolmohammadi, B., Alvarez, V. E., Huber, B. R., Alosco, M. L., Solomon, T. M., Nowinski, C. J., McHale, L., Cormier, K. A., Kubilus, C. A., Martin, B. M., Murphy, L., Baugh, C. M., Montenigro, P. H., Chaisson, C. E., Tripodis, Y., Kowall, N. W., Weuve, J., … McKee, A. C. (2017). Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football. *JAMA*, *318*(4), 360–370. https://doi.org/10.1001/jama.2017.8334

[35] Montenigro, P. H., Baugh, C. M., Daneshvar, D. H., Mez, J., Budson, A. E., Au, R., Katz, D. I., Cantu, R. C., & Stern, R. A. (2014). Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimer's Research & Therapy*, *6*(5), 68. https://doi.org/10.1186/s13195-014-0068-z

[36] McKee, A. C., Stein, T. D., Kiernan, P. T., & Alvarez, V. E. (2015). The neuropathology of chronic traumatic encephalopathy. *Brain Pathology (Zurich, Switzerland)*, *25*(3), 350–364. https://doi.org/10.1111/bpa.12248

[37] Stein, T. D., Alvarez, V. E., & McKee, A. C. (2014). Chronic traumatic encephalopathy: a spectrum of neuropathological changes following repetitive brain trauma in athletes and military personnel. *Alzheimer's Research & Therapy*, *6*(1), 4. https://doi.org/10.1186/alzrt234

[38] Stein, T. D., Alvarez, V. E., & McKee, A. C. (2014). Chronic traumatic encephalopathy: a spectrum of neuropathological changes following repetitive

brain trauma in athletes and military personnel. *Alzheimer's Research & Therapy*, *6*(1), 4. https://doi.org/10.1186/alzrt234

[39] McKee, A. C., Cairns, N. J., Dickson, D. W., Folkerth, R. D., Keene, C. D., Litvan, I., Perl, D. P., Stein, T. D., Vonsattel, J. P., Stewart, W., Tripodis, Y., Crary, J. F., Bieniek, K. F., Dams-O'Connor, K., Alvarez, V. E., Gordon, W. A., & TBI/CTE group (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathologica*, *131*(1), 75–86. https://doi.org/10.1007/s00401-015-1515-z

[40] Gavett, B. E., Stern, R. A., & McKee, A. C. (2011). Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clinics in Sports Medicine*, *30*(1), 179–xi. https://doi.org/10.1016/j.csm.2010.09.007

[41] McKee AC, Gavett BE, Stern RA, Nowinski CJ, Cantu RC, Kowall NW, Perl DP, Hedley-Whyte ET, Price B, Sullivan C, Morin P, Lee HS, Kubilus CA, Daneshvar DH, Wulff M, Budson AE. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *Journal of Neuropathology Experimental Neurology*, 2010 Sep;69(9):918-29. doi: 10.1097/NEN.0b013e3181ee7d85. PMID: 20720505; PMCID: PMC2951281

[42] Albayram, O., Kondo, A., Mannix, R., Smith, C., Tsai, C., Li, C., . . . Zhou, X. Z. (2017). Cis P-tau is induced in clinical and preclinical brain injury and contributes to post-injury sequelae. *Nature Communications*, *8*(1). doi:10.1038/s41467-017-01068-4

[43] Geddes, J. F., Vowles, G. H., Nicoll, J. A., & Révész, T. (1999). Neuronal cytoskeletal changes are an early consequence of repetitive head injury. *Acta Neuropathologica*, *98*(2), 171–178. https://doi.org/10.1007/s004010051066

[44] Dallmeier, J. D., Meysami, S., Merrill, D. A., & Raji, C. A. (2019). Emerging advances of in vivo detection of chronic traumatic encephalopathy and traumatic brain injury. *The British Journal of Radiology*, *92*(1101), 20180925. https://doi.org/10.1259/bjr.20180925

[45] Rutgers, D. R., Toulgoat, F., Cazejust, J., Fillard, P., Lasjaunias, P., & Ducreux, D. (2008). White matter abnormalities in mild traumatic brain injury: a diffusion tensor imaging study. *AJNR. American Journal of Neuroradiology*, *29*(3), 514–519. https://doi.org/10.3174/ajnr.A0856

[46] Cubon, V. A., Murugavel, M., Holmes, K. W., & Dettwiler, A. (2018). Preliminary evidence from a prospective DTI study suggests a posterior-to-anterior pattern of recovery in college athletes with sports-related concussion. *Brain and Behavior*, *8*(12), e01165. https://doi.org/10.1002/brb3.1165

[47] McAllister, T., Ford, J., Ji, S., Beckwith, J., Flashman, L., Paulsen, K., & Greenwald, R. (2012). Maximum principal strain and strain rate associated with concussion diagnosis correlates with changes in corpus callosum white matter indices. *Annals of Biomedical Engineering*, 40(1), 127–140.

[48] Patton, D. A., McIntosh, A. S., & Kleiven, S. (2015). The biomechanical determinants of concussion: Finite element simulations to investigate tissue-level predictors of injury during sporting impacts to the unprotected head. *Journal of Applied Biomechanics*, 31(4), 264–268.

[49] Viano, D. C., Casson, I. R., Pellman, E. J., Zhang, L., King, A. I., & Yang, K. H. (2005). Concussion in Professional Football: Brain Responses by Finite Element Analysis: Part 9. *Neurosurgery*, *57*(5), 891–916. doi: 10.1227/01.neu.0000186950.54075.3b

[50] Zhang, L., Yang, K. H., & King, A. I. (2004). A Proposed Injury Threshold for Mild Traumatic Brain Injury. *Journal of Biomechanical Engineering*, *126*(2), 226–236. doi: 10.1115/1.1691446

[51] Blumbergs, P. C., Scott, G., Manavis, J., Wainwright, H., Simpson, D. A., & McLean, A. J. (1994). Staining of amyloid precursor protein to study axonal damage in mild head injury. *Lancet (London, England)*, *344*(8929), 1055–1056. https://doi.org/10.1016/s0140-6736(94)91712-4

[52] Giordano, C., Zappalà, S., & Kleiven, S. (2017). Anisotropic finite element models for brain injury prediction: the sensitivity of axonal strain to white matter tract inter-subject variability. *Biomechanics and Modeling in Mechanobiology*, *16*(4), 1269–1293. https://doi.org/10.1007/s10237-017-0887-5

[53] Patton, D. A., McIntosh, A. S., & Kleiven, S. (2013). The biomechanical determinants of concussion: finite element simulations to investigate brain tissue deformations during sporting impacts to the unprotected head. *Journal of Applied Biomechanics*, *29*(6), 721–730. https://doi.org/10.1123/jab.29.6.721

[54] Alosco, M. L., Stein, T. D., Tripodis, Y., Chua, A. S., Kowall, N. W., Huber, B. R., Goldstein, L. E., Cantu, R. C., Katz, D. I., Palmisano, J. N., Martin, B., Cherry, J. D., Mahar, I., Killiany, R. J., McClean, M. D., Au, R., Alvarez, V., Stern, R. A.,

Mez, J., & McKee, A. C. (2019). Association of White Matter Rarefaction, Arteriolosclerosis, and Tau with Dementia in Chronic Traumatic Encephalopathy. *JAMA Neurology*, *76*(11), 1298–1308. Advance online publication. https://doi.org/10.1001/jamaneurol.2019.2244

[55] Alosco, M. L., Duskin, J., Besser, L. M., Martin, B., Chaisson, C. E., Gunstad, J., Kowall, N. W., McKee, A. C., Stern, R. A., & Tripodis, Y. (2017). Modeling the Relationships Among Late-Life Body Mass Index, Cerebrovascular Disease, and Alzheimer's Disease Neuropathology in an Autopsy Sample of 1,421 Subjects from the National Alzheimer's Coordinating Center Data Set. *Journal of Alzheimer's Disease: JAD*, *57*(3), 953–968. https://doi.org/10.3233/JAD-161205

[56] Deramecourt, V., Slade, J. Y., Oakley, A. E., Perry, R. H., Ince, P. G., Maurage, C. A., & Kalaria, R. N. (2012). Staging and natural history of cerebrovascular pathology in dementia. *Neurology*, *78*(14), 1043–1050. https://doi.org/10.1212/WNL.0b013e31824e8e7f

[57] Baron, S. L., Hein, M. J., Lehman, E., & Gersic, C. M. (2012). Body mass index, playing position, race, and the cardiovascular mortality of retired professional football players. *The American Journal of Cardiology*, *109*(6), 889–896. https://doi.org/10.1016/j.amjcard.2011.10.050

[58] Tucker, A. M., Vogel, R. A., Lincoln, A. E., Dunn, R. E., Ahrensfield, D. C., Allen, T. W., Castle, L. W., Heyer, R. A., Pellman, E. J., Strollo, P. J., Jr, Wilson, P. W., & Yates, A. P. (2009). Prevalence of cardiovascular disease risk factors among National Football League players. *JAMA*, *301*(20), 2111–2119. https://doi.org/10.1001/jama.2009.716

[59] Atkins C. M. (2011). Decoding hippocampal signaling deficits after traumatic brain injury. *Translational Stroke Research*, *2*(4), 546–555. https://doi.org/10.1007/s12975-011-0123-z

[60] Graham D, Gennarelli T, McIntosh T. Trauma. In: Graham D, Lantos P, editors (2002) *Greenfield's Neuropathology*. Vol. 1. London: Arnold, Hodder Headline Group. pp. 823–898.

[61] Gennarelli, T. A., Thibault, L. E., Adams, J. H., Graham, D. I., Thompson, C. J., & Marcincin, R. P. (1982). Diffuse axonal injury and traumatic coma in the primate. *Annals of Neurology*, *12*(6), 564–574. doi: 10.1002/ana.410120611

[62] Vieira, R. C., Paiva, W. S., de Oliveira, D. V., Teixeira, M. J., de Andrade, A. F., & de Sousa, R. M. (2016). Diffuse Axonal Injury: Epidemiology, Outcome and

Associated Risk Factors. *Frontiers in Neurology*, *7*, 178. https://doi.org/10.3389/fneur.2016.00178

[63] Lin, A. P., Ramadan, S., Stern, R. A., Box, H. C., Nowinski, C. J., Ross, B. D., & Mountford, C. E. (2015). Changes in the neurochemistry of athletes with repetitive brain trauma: preliminary results using localized correlated spectroscopy. *Alzheimer's Research & Therapy*, *7*(1), 13. https://doi.org/10.1186/s13195-015-0094-5

[64] Fazekas, F., Kleinert, R., Offenbacher, H., Schmidt, R., Kleinert, G., Payer, F., Radner, H., & Lechner, H. (1993). Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*, *43*(9), 1683–1689. https://doi.org/10.1212/wnl.43.9.1683

[65] Wardlaw, J. M., Valdés Hernández, M. C., & Muñoz-Maniega, S. (2015). What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *Journal of the American Heart Association*, *4*(6), 001140. https://doi.org/10.1161/JAHA.114.001140

[66] Lindemer, E. R., Greve, D. N., Fischl, B., Augustinack, J. C., Salat, D. H., & Alzheimer's Disease Neuroimaging Initiative (2017). Differential Regional Distribution of Juxtacortical White Matter Signal Abnormalities in Aging and Alzheimer's Disease. *Journal of Alzheimer's Disease: JAD*, *57*(1), 293–303. https://doi.org/10.3233/JAD-161057

[67] Bigler, E. D., Abildskov, T. J., Goodrich-Hunsaker, N. J., Black, G., Christensen, Z. P., Huff, T., Wood, D. M., Hesselink, J. R., Wilde, E. A., & Max, J. E. (2016). Structural Neuroimaging Findings in Mild Traumatic Brain Injury. *Sports Medicine and Arthroscopy Review*, *24*(3), e42–e52. https://doi.org/10.1097/JSA.0000000000000119

[68] Brickman, A. M., Muraskin, J., & Zimmerman, M. E. (2009). Structural neuroimaging in Altheimer's disease: do white matter hyperintensities matter?. *Dialogues in Clinical Neuroscience*, *11*(2), 181–190. https://doi.org/10.31887/DCNS.2009.11.2/ambrickman

[69] Guo, H., Siu, W., D'Arcy, R. C., Black, S. E., Grajauskas, L. A., Singh, S., Zhang, Y., Rockwood, K., & Song, X. (2017). MRI assessment of whole-brain structural changes in aging. *Clinical Interventions in Aging*, *12*, 1251–1270. https://doi.org/10.2147/CIA.S139515

[70] Boutet, C., Rouffiange-Leclair, L., Schneider, F., Camdessanché, J. P., Antoine, J. C., & Barral, F. G. (2016). Visual Assessment of Age-Related White Matter Hyperintensities Using FLAIR Images at 3 T: Inter- and Intra-Rater Agreement. *Neuro-Degenerative Diseases*, *16*(3-4), 279–283. https://doi.org/10.1159/000441420

[71] d'Arbeloff, T., Elliott, M. L., Knodt, A. R., Melzer, T. R., Keenan, R., Ireland, D., Ramrakha, S., Poulton, R., Anderson, T., Caspi, A., Moffitt, T. E., & Hariri, A. R. (2019). White matter hyperintensities are common in midlife and already associated with cognitive decline. *Brain Communications*, *1*(1), fcz041. https://doi.org/10.1093/braincomms/fcz041

[72] Sachdev, P. S., Parslow, R., Wen, W., Anstey, K. J., & Easteal, S. (2009). Sex differences in the causes and consequences of white matter hyperintensities. *Neurobiology of Aging*, *30*(6), 946–956. https://doi.org/10.1016/j.neurobiolaging.2007.08.023

[73] Fatemi, F., Kantarci, K., Graff-Radford, J., Preboske, G. M., Weigand, S. D., Przybelski, S. A., Knopman, D. S., Machulda, M. M., Roberts, R. O., Mielke, M. M., Petersen, R. C., Jack, C. R., Jr, & Vemuri, P. (2018). Sex differences in cerebrovascular pathologies on FLAIR in cognitively unimpaired elderly. *Neurology*, *90*(6), e466–e473. https://doi.org/10.1212/WNL.0000000000004913

[74] Nyquist, P. A., Bilgel, M. S., Gottesman, R., Yanek, L. R., Moy, T. F., Becker, L. C., Cuzzocreo, J., Prince, J., Yousem, D. M., Becker, D. M., Kral, B. G., & Vaidya, D. (2014). Extreme deep white matter hyperintensity volumes are associated with African American race. *Cerebrovascular Diseases (Basel, Switzerland)*, *37*(4), 244–250. https://doi.org/10.1159/000358117

[75] Dufouil, C., Alpérovitch, A., & Tzourio, C. (2003). Influence of education on the relationship between white matter lesions and cognition. *Neurology*, *60*(5), 831–836. https://doi.org/10.1212/01.wnl.0000049456.33231.96

[76] Fernández-Cabello, S., Valls-Pedret, C., Schurz, M., Vidal-Piñeiro, D., Sala-Llonch, R., Bargallo, N., Ros, E., & Bartrés-Faz, D. (2016). White matter hyperintensities and cognitive reserve during a working memory task: a functional magnetic resonance imaging study in cognitively normal older adults. *Neurobiology of Aging*, *48*, 23–33. https://doi.org/10.1016/j.neurobiolaging.2016.08.008

[77] Garde, E., Mortensen, E. L., Krabbe, K., Rostrup, E., & Larsson, H. B. (2000). Relation between age-related decline in intelligence and cerebral white-matter

hyperintensities in healthy octogenarians: a longitudinal study. *Lancet (London, England)*, *356*(9230), 628–634. https://doi.org/10.1016/S0140-6736(00)02604-0

[78] Brickman, A. M., Guzman, V. A., Gonzalez-Castellon, M., Razlighi, Q., Gu, Y., Narkhede, A., Janicki, S., Ichise, M., Stern, Y., Manly, J. J., Schupf, N., & Marshall, R. S. (2015). Cerebral autoregulation, beta amyloid, and white matter hyperintensities are interrelated. *Neuroscience Letters*, *592*, 54–58. https://doi.org/10.1016/j.neulet.2015.03.005

[79] Wolters, F. J., Zonneveld, H. I., Hofman, A., van der Lugt, A., Koudstaal, P. J., Vernooij, M. W., Ikram, M. A., & Heart-Brain Connection Collaborative Research Group (2017). Cerebral Perfusion and the Risk of Dementia: A Population-Based Study. *Circulation*, *136*(8), 719–728. https://doi.org/10.1161/CIRCULATIONAHA.117.027448

[80] Novak, V., Last, D., Alsop, D. C., Abduljalil, A. M., Hu, K., Lepicovsky, L., Cavallerano, J., & Lipsitz, L. A. (2006). Cerebral blood flow velocity and periventricular white matter hyperintensities in type 2 diabetes. *Diabetes Care*, *29*(7), 1529–1534. https://doi.org/10.2337/dc06-0261

[81] Wang, D. Q., Wang, L., Wei, M. M., Xia, X. S., Tian, X. L., Cui, X. H., & Li, X. (2020). Relationship Between Type 2 Diabetes and White Matter Hyperintensity: A Systematic Review. *Frontiers in Endocrinology*, *11*, 595962. https://doi.org/10.3389/fendo.2020.595962

[82] Hughes, T. M., Sink, K. M., Williamson, J. D., Hugenschmidt, C. E., Wagner, B. C., Whitlow, C. T., Xu, J., Smith, S. C., Launer, L. J., Barzilay, J. I., Ismail-Beigi, F., Bryan, R. N., Hsu, F. C., Bowden, D. W., Maldjian, J. A., Divers, J., Freedman, B. I., & AA-DHS MIND and ACCORD MIND Investigators (2018). Relationships between cerebral structure and cognitive function in African Americans with type 2 diabetes. *Journal of Diabetes and its Complications*, *32*(10), 916–921. https://doi.org/10.1016/j.jdiacomp.2018.05.017

[83] Arfanakis, K., Evia, A. M., Leurgans, S. E., Cardoso, L., Kulkarni, A., Alqam, N., Lopes, L. F., Vieira, D., Bennett, D. A., & Schneider, J. A. (2020). Neuropathologic Correlates of White Matter Hyperintensities in a Community-Based Cohort of Older Adults. *Journal of Alzheimer's Disease: JAD*, *73*(1), 333–345. https://doi.org/10.3233/JAD-190687

[84] McAleese, K. E., Walker, L., Graham, S., Moya, E., Johnson, M., Erskine, D., Colloby, S. J., Dey, M., Martin-Ruiz, C., Taylor, J. P., Thomas, A. J., McKeith, I. G., De Carli, C., & Attems, J. (2017). Parietal white matter lesions in Alzheimer's

disease are associated with cortical neurodegenerative pathology, but not with small vessel disease. *Acta Neuropathologica*, *134*(3), 459–473. https://doi.org/10.1007/s00401-017-1738-2

[85] Prasad, K., Wiryasaputra, L., Ng, A., & Kandiah, N. (2011). White matter disease independently predicts progression from mild cognitive impairment to Alzheimer's disease in a clinic cohort. *Dementia and Geriatric Cognitive Disorders*, *31*(6), 431–434. https://doi.org/10.1159/000330019

[86] Defrancesco, M., Marksteiner, J., Deisenhammer, E., Kemmler, G., Djurdjevic, T., & Schocke, M. (2013). Impact of white matter lesions and cognitive deficits on conversion from mild cognitive impairment to Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *34*(3), 665–672. https://doi.org/10.3233/JAD-122095

[87] Bilello, M., Doshi, J., Nabavizadeh, S. A., Toledo, J. B., Erus, G., Xie, S. X., Trojanowski, J. Q., Han, X., & Davatzikos, C. (2015). Correlating Cognitive Decline with White Matter Lesion and Brain Atrophy Magnetic Resonance Imaging Measurements in Alzheimer's Disease. *Journal of Alzheimer's Disease: JAD*, *48*(4), 987–994. https://doi.org/10.3233/JAD-150400

[88] Hart, J., Jr, Kraut, M. A., Womack, K. B., Strain, J., Didehbani, N., Bartz, E., Conover, H., Mansinghani, S., Lu, H., & Cullum, C. M. (2013). Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: a cross-sectional study. *JAMA neurology*, *70*(3), 326–335. https://doi.org/10.1001/2013.jamaneurol.340

[89] Tate, D. F., Gusman, M., Kini, J., Reid, M., Velez, C. S., Drennon, A. M., Cooper, D. B., Kennedy, J. E., Bowles, A. O., Bigler, E. D., Lewis, J. D., Ritter, J., & York, G. E. (2017). Susceptibility Weighted Imaging and White Matter Abnormality Findings in Service Members with Persistent Cognitive Symptoms Following Mild Traumatic Brain Injury. *Military Medicine*, *182*(3), e1651–e1658. https://doi.org/10.7205/MILMED-D-16-00132

[90] Clark, A. L., Sorg, S. F., Schiehser, D. M., Luc, N., Bondi, M. W., Sanderson, M., Werhane, M. L., & Delano-Wood, L. (2016). Deep white matter hyperintensities affect verbal memory independent of PTSD symptoms in veterans with mild traumatic brain injury. *Brain Injury*, *30*(7), 864–871. https://doi.org/10.3109/02699052.2016.1144894

[91] Lipton, M. L., Kim, N., Zimmerman, M. E., Kim, M., Stewart, W. F., Branch, C. A., & Lipton, R. B. (2013). Soccer heading is associated with white matter

microstructural and cognitive abnormalities. *Radiology*, *268*(3), 850–857. https://doi.org/10.1148/radiol.13130545

[92] Bernick, C., & Banks, S. (2013). What boxing tells us about repetitive head trauma and the brain. *Alzheimer's Research & Therapy*, *5*(3), 23. https://doi.org/10.1186/alzrt177

[93] Stern, R. A., Riley, D. O., Daneshvar, D. H., Nowinski, C. J., Cantu, R. C., & McKee, A. C. (2011). Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *3*(10 Suppl 2), S460–S467. https://doi.org/10.1016/j.pmrj.2011.08.008

[94] Jarrett, M., Tam, R., Hernández-Torres, E., Martin, N., Perera, W., Zhao, Y., Shahinfard, E., Dadachanji, S., Taunton, J., Li, D. K., & Rauscher, A. (2016). A Prospective Pilot Investigation of Brain Volume, White Matter Hyperintensities, and Hemorrhagic Lesions after Mild Traumatic Brain Injury. *Frontiers in Neurology*, *7*, 11. https://doi.org/10.3389/fneur.2016.00011

[95] McCrory, P., Meeuwisse, W. H., Aubry, M., Cantu, B., Dvorák, J., Echemendia, R. J., Engebretsen, L., Johnston, K., Kutcher, J. S., Raftery, M., Sills, A., Benson, B. W., Davis, G. A., Ellenbogen, R. G., Guskiewicz, K., Herring, S. A., Iverson, G. L., Jordan, B. D., Kissick, J., McCrea, M., … Turner, M. (2013). Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *British Journal of Sports Medicine*, *47*(5), 250–258. https://doi.org/10.1136/bjsports-2013-092313

[96] Wilson, D., Charidimou, A., & Werring, D. J. (2014). Advances in understanding spontaneous intracerebral hemorrhage: insights from neuroimaging. *Expert Review of Neurotherapeutics*, *14*(6), 661–678. https://doi.org/10.1586/14737175.2014.918506

[97] Zhou, Y., Kierans, A., Kenul, D., Ge, Y., Rath, J., Reaume, J., Grossman, R. I., & Lui, Y. W. (2013). Mild traumatic brain injury: longitudinal regional brain volume changes. *Radiology*, *267*(3), 880–890. https://doi.org/10.1148/radiol.13122542

[98] Trifan, G., Gattu, R., Haacke, E. M., Kou, Z., & Benson, R. R. (2017). MR imaging findings in mild traumatic brain injury with persistent neurological impairment. *Magnetic Resonance Imaging*, *37*, 243–251. https://doi.org/10.1016/j.mri.2016.12.009

[99] Wang, Y., Nelson, L. D., LaRoche, A. A., Pfaller, A. Y., Nencka, A. S., Koch, K. M., & McCrea, M. A. (2016). Cerebral Blood Flow Alterations in Acute Sport-Related Concussion. *Journal of Neurotrauma*, *33*(13), 1227–1236. https://doi.org/10.1089/neu.2015.4072

[100] Amen, D. G., Willeumier, K., Omalu, B., Newberg, A., Raghavendra, C., & Raji, C. A. (2016). Perfusion Neuroimaging Abnormalities Alone Distinguish National Football League Players from a Healthy Population. *Journal of Alzheimer's Disease: JAD*, *53*(1), 237–241. https://doi.org/10.3233/JAD-160207

[101] Buée, L., Hof, P. R., Bouras, C., Delacourte, A., Perl, D. P., Morrison, J. H., & Fillit, H. M. (1994). Pathological alterations of the cerebral microvasculature in Alzheimer's disease and related dementing disorders. *Acta Neuropathologica*, *87*(5), 469–480. https://doi.org/10.1007/BF00294173

[102] Wardlaw, J. M., Makin, S. J., Valdés Hernández, M. C., Armitage, P. A., Heye, A. K., Chappell, F. M., Muñoz-Maniega, S., Sakka, E., Shuler, K., Dennis, M. S., & Thrippleton, M. J. (2017). Blood-brain barrier failure as a core mechanism in cerebral small vessel disease and dementia: evidence from a cohort study. *Alzheimer's & Dementia*, *13*(6), 634–643. https://doi.org/10.1016/j.jalz.2016.09.006

[103] Marchi, N., Bazarian, J. J., Puvenna, V., Janigro, M., Ghosh, C., Zhong, J., Zhu, T., Blackman, E., Stewart, D., Ellis, J., Butler, R., & Janigro, D. (2013). Consequences of repeated blood-brain barrier disruption in football players. *PloS one*, *8*(3), e56805. https://doi.org/10.1371/journal.pone.0056805

[104] Weissberg, I., Veksler, R., Kamintsky, L., Saar-Ashkenazy, R., Milikovsky, D. Z., Shelef, I., & Friedman, A. (2014). Imaging blood-brain barrier dysfunction in football players. *JAMA Neurology*, *71*(11), 1453–1455. https://doi.org/10.1001/jamaneurol.2014.2682

[105] Filley, C. M., & Kelly, J. P. (2018). White Matter and Cognition in Traumatic Brain Injury. *Journal of Alzheimer's Disease: JAD*, *65*(2), 345–362. https://doi.org/10.3233/JAD-180287

[106] Slobounov, S. M., Walter, A., Breiter, H. C., Zhu, D. C., Bai, X., Bream, T., Seidenberg, P., Mao, X., Johnson, B., & Talavage, T. M. (2017). The effect of repetitive subconcussive collisions on brain integrity in collegiate football players over a single football season: A multi-modal neuroimaging study. *NeuroImage. Clinical*, *14*, 708–718. https://doi.org/10.1016/j.nicl.2017.03.006

[107] Merchant-Borna, K., Asselin, P., Narayan, D., Abar, B., Jones, C. M., & Bazarian, J. J. (2016). Novel Method of Weighting Cumulative Helmet Impacts Improves Correlation with Brain White Matter Changes After One Football Season of Sub-Concussive Head Blows. *Annals of Biomedical Engineering*, *44*(12), 3679–3692. https://doi.org/10.1007/s10439-016-1680-9

[108] Jefferson, A. L., Wong, S., Gracer, T. S., Ozonoff, A., Green, R. C., & Stern, R. A. (2007). Geriatric performance on an abbreviated version of the Boston naming test. *Applied Neuropsychology*, *14*(3), 215–223. https://doi.org/10.1080/09084280701509166

[109] Ashendorf, L., Jefferson, A. L., O'Connor, M. K., Chaisson, C., Green, R. C., & Stern, R. A. (2008). Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *23*(2), 129–137. https://doi.org/10.1016/j.acn.2007.11.005

[110] Galetta, K. M., Chapman, K. R., Essis, M. D., Alosco, M. L., Gillard, D., Steinberg, E., Dixon, D., Martin, B., Chaisson, C. E., Kowall, N. W., Tripodis, Y., Balcer, L. J., & Stern, R. A. (2017). Screening Utility of the King-Devick Test in Mild Cognitive Impairment and Alzheimer Disease Dementia. *Alzheimer Disease and Associated Disorders*, *31*(2), 152–158. https://doi.org/10.1097/WAD.0000000000000157

[111] Gavett, B. E., Lou, K. R., Daneshvar, D. H., Green, R. C., Jefferson, A. L., & Stern, R. A. (2012). Diagnostic accuracy statistics for seven Neuropsychological Assessment Battery (NAB) test variables in the diagnosis of Alzheimer's disease. *Applied Neuropsychology. Adult*, *19*(2), 108–115. https://doi.org/10.1080/09084282.2011.643947

[112] Alosco, M. L., Sugarman, M. A., Besser, L. M., Tripodis, Y., Martin, B., Palmisano, J. N., Kowall, N. W., Au, R., Mez, J., DeCarli, C., Stein, T. D., McKee, A. C., Killiany, R. J., & Stern, R. A. (2018). A Clinicopathological Investigation of White Matter Hyperintensities and Alzheimer's Disease Neuropathology. *Journal of Alzheimer's Disease: JAD*, *63*(4), 1347–1360. https://doi.org/10.3233/JAD-180017

[113] Pelcher, I., Puzo, C., Tripodis, Y., Aparicio, H. J., Steinberg, E. G., Phelps, A., Martin, B., Palmisano, J. N., Vassey, E., Lindbergh, C., McKee, A. C., Stein, T. D., Killiany, R. J., Au, R., Kowall, N. W., Stern, R. A., Mez, J., & Alosco, M. L. (2020). Revised Framingham Stroke Risk Profile: Association with Cognitive

Status and MRI-Derived Volumetric Measures. *Journal of Alzheimer's disease : JAD*, *78*(4), 1393–1408. https://doi.org/10.3233/JAD-200803

[114] Schmidt, P., Gaser, C., Arsic, M., Buck, D., Förschler, A., Berthele, A., Hoshi, M., Ilg, R., Schmid, V. J., Zimmer, C., Hemmer, B., & Mühlau, M. (2012). An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *NeuroImage*, *59*(4), 3774–3783. https://doi.org/10.1016/j.neuroimage.2011.11.032

[115] Ribaldi, F., Altomare, D., Jovicich, J., Ferrari, C., Picco, A., Pizzini, F. B., Soricelli, A., Mega, A., Ferretti, A., Drevelegas, A., Bosch, B., Müller, B. W., Marra, C., Cavaliere, C., Bartrés-Faz, D., Nobili, F., Alessandrini, F., Barkhof, F., Gros-Dagnac, H., Ranjeva, J. P., … Marizzoni, M. (2021). Accuracy and reproducibility of automated white matter hyperintensities segmentation with lesion segmentation tool: A European multi-site 3T study. *Magnetic Resonance Imaging*, *76*, 108–115. https://doi.org/10.1016/j.mri.2020.11.008

[116] Rachmadi, M. F., Valdés-Hernández, M., Agan, M., Di Perri, C., Komura, T., & Alzheimer's Disease Neuroimaging Initiative (2018). Segmentation of white matter hyperintensities using convolutional neural networks with global spatial information in routine clinical brain MRI with none or mild vascular pathology. *Computerized Medical Imaging and Graphics: The Official Journal of the Computerized Medical Imaging Society*, *66*, 28–43. https://doi.org/10.1016/j.compmedimag.2018.02.002

[117] Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(20), 11050–11055. https://doi.org/10.1073/pnas.200033797

[118] Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/s0896-6273(02)00569-x

[119] Iglesias, J. E., Augustinack, J. C., Nguyen, K., Player, C. M., Player, A., Wright, M., Roy, N., Frosch, M. P., McKee, A. C., Wald, L. L., Fischl, B., Van Leemput, K., & Alzheimer's Disease Neuroimaging Initiative (2015). A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. *NeuroImage*, *115*, 117–137. https://doi.org/10.1016/j.neuroimage.2015.04.042

[120] Gavett, B. E., Poon, S. J., Ozonoff, A., Jefferson, A. L., Nair, A. K., Green, R. C., & Stern, R. A. (2009). Diagnostic utility of the NAB List Learning test in Alzheimer's disease and amnestic mild cognitive impairment. *Journal of the International Neuropsychological Society: JINS*, *15*(1), 121–129. https://doi.org/10.1017/S1355617708090176

[121] Petersen R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, *256*(3), 183–194. https://doi.org/10.1111/j.1365-2796.2004.01388.x

[122] McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939–944. https://doi.org/10.1212/wnl.34.7.939

[123] Vijayakumar, A., & Vijayakumar, A. (2012). Comparison of hippocampal volume in dementia subtypes. *ISRN Radiology*, *2013*, 174524. https://doi.org/10.5402/2013/174524

[124] Schuff, N., Woerner, N., Boreta, L., Kornfield, T., Shaw, L. M., Trojanowski, J. Q., Thompson, P. M., Jack, C. R., Jr, Weiner, M. W., & Alzheimer's Disease Neuroimaging Initiative (2009). MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain: A Journal of Neurology*, *132*(Pt 4), 1067–1077. https://doi.org/10.1093/brain/awp007

[125] Henneman, W. J., Sluimer, J. D., Barnes, J., van der Flier, W. M., Sluimer, I. C., Fox, N. C., Scheltens, P., Vrenken, H., & Barkhof, F. (2009). Hippocampal atrophy rates in Alzheimer disease: added value over whole brain volume measures. *Neurology*, *72*(11), 999–1007. https://doi.org/10.1212/01.wnl.0000344568.09360.31

[126] Kandel, B. M., Avants, B. B., Gee, J. C., McMillan, C. T., Erus, G., Doshi, J., Davatzikos, C., & Wolk, D. A. (2016). White matter hyperintensities are more highly associated with preclinical Alzheimer's disease than imaging and cognitive markers of neurodegeneration. *Alzheimer's & Dementia (Amsterdam, Netherlands)*, *4*, 18–27. https://doi.org/10.1016/j.dadm.2016.03.001

[127] Liao, D., Cooper, L., Cai, J., Toole, J. F., Bryan, N. R., Hutchinson, R. G., & Tyroler, H. A. (1996). Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control. The ARIC Study. Atherosclerosis Risk

in Communities Study. *Stroke*, *27*(12), 2262–2270. https://doi.org/10.1161/01.str.27.12.2262

[128] Dufouil, C., de Kersaint-Gilly, A., Besançon, V., Levy, C., Auffray, E., Brunnereau, L., Alpérovitch, A., & Tzourio, C. (2001). Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. *Neurology*, *56*(7), 921–926. https://doi.org/10.1212/wnl.56.7.921

[129] Berginström, N., Nordström, P., Nyberg, L., & Nordström, A. (2020). White matter hyperintensities increases with traumatic brain injury severity: associations to neuropsychological performance and fatigue. *Brain Injury*, *34*(3), 415–420. https://doi.org/10.1080/02699052.2020.1725124

[130] Narayana P. A. (2017). White matter changes in patients with mild traumatic brain injury: MRI perspective. *Concussion (London, England)*, *2*(2), CNC35. https://doi.org/10.2217/cnc-2016-0028

[131] Luders, E., Toga, A. W., & Thompson, P. M. (2014). Why size matters: differences in brain volume account for apparent sex differences in callosal anatomy: the sexual dimorphism of the corpus callosum. *NeuroImage*, *84*, 820–824. https://doi.org/10.1016/j.neuroimage.2013.09.040

[132] Ruigrok, A. N., Salimi-Khorshidi, G., Lai, M. C., Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure. *Neuroscience and Biobehavioral Reviews*, *39*(100), 34–50. https://doi.org/10.1016/j.neubiorev.2013.12.004

[133] Omalu, B. I., DeKosky, S. T., Minster, R. L., Kamboh, M. I., Hamilton, R. L., & Wecht, C. H. (2005). Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery*, *57*(1), 128–134. https://doi.org/10.1227/01.neu.0000163407.92769.ed

[134] Omalu, B. I., DeKosky, S. T., Hamilton, R. L., Minster, R. L., Kamboh, M. I., Shakir, A. M., & Wecht, C. H. (2006). Chronic traumatic encephalopathy in a national football league player: part II. *Neurosurgery*, *59*(5), 1086–1093. https://doi.org/10.1227/01.NEU.0000245601.69451.27

[135] Rubin, T. G., Catenaccio, E., Fleysher, R., Hunter, L. E., Lubin, N., Stewart, W. F., Kim, M., Lipton, R. B., & Lipton, M. L. (2018). MRI-defined White Matter Microstructural Alteration Associated with Soccer Heading Is More Extensive in Women than Men. *Radiology*, *289*(2), 478–486. https://doi.org/10.1148/radiol.2018180217

[136] Lipton M. L. (2019). Rethinking Youth Sports. *Cerebrum: The Dana Forum on Brain Science, 2019*, cer-09-19.

[137] Sollmann, N., Echlin, P. S., Schultz, V., Viher, P. V., Lyall, A. E., Tripodis, Y., Kaufmann, D., Hartl, E., Kinzel, P., Forwell, L. A., Johnson, A. M., Skopelja, E. N., Lepage, C., Bouix, S., Pasternak, O., Lin, A. P., Shenton, M. E., & Koerte, I. K. (2017). Sex differences in white matter alterations following repetitive subconcussive head impacts in collegiate ice hockey players. *NeuroImage. Clinical*, *17*, 642–649. https://doi.org/10.1016/j.nicl.2017.11.020

[138] Schuff, N., Amend, D. L., Knowlton, R., Norman, D., Fein, G., & Weiner, M. W. (1999). Age-related metabolite changes and volume loss in the hippocampus by magnetic resonance spectroscopy and imaging. *Neurobiology of Aging*, *20*(3), 279–285. https://doi.org/10.1016/s0197-4580(99)00022-6

[139] Tsai, M. H., Pardoe, H. R., Perchyonok, Y., Fitt, G. J., Scheffer, I. E., Jackson, G. D., & Berkovic, S. F. (2013). Etiology of hippocampal sclerosis: evidence for a predisposing familial morphologic anomaly. *Neurology*, *81*(2), 144–149. https://doi.org/10.1212/WNL.0b013e31829a33ac

[140] Chow, N., Aarsland, D., Honarpisheh, H., Beyer, M. K., Somme, J. H., Elashoff, D., Rongve, A., Tysnes, O. B., Thompson, P. M., & Apostolova, L. G. (2012). Comparing hippocampal atrophy in Alzheimer's dementia and dementia with lewy bodies. *Dementia and Geriatric Cognitive Disorders*, *34*(1), 44–50. https://doi.org/10.1159/000339727

[141] van de Pol, L., Gertz, H. J., Scheltens, P., & Wolf, H. (2011). Hippocampal atrophy in subcortical vascular dementia. *Neuro-Degenerative Diseases*, *8*(6), 465–469. https://doi.org/10.1159/000326695

[142] Goukasian, N., Porat, S., Blanken, A., Avila, D., Zlatev, D., Hurtz, S., Hwang, K. S., Pierce, J., Joshi, S. H., Woo, E., & Apostolova, L. G. (2019). Cognitive Correlates of Hippocampal Atrophy and Ventricular Enlargement in Adults with or without Mild Cognitive Impairment. *Dementia and Geriatric Cognitive Disorders Extra*, *9*(2), 281–293. https://doi.org/10.1159/000490044

[143] Roberts, R. O., Geda, Y. E., Knopman, D. S., Cha, R. H., Pankratz, V. S., Boeve, B. F., Tangalos, E. G., Ivnik, R. J., Rocca, W. A., & Petersen, R. C. (2012). The incidence of MCI differs by subtype and is higher in men: The Mayo Clinic Study of Aging. *Neurology*, *78*(5), 342–351. https://doi.org/10.1212/WNL.0b013e3182452862

[144] Caracciolo, B., Palmer, K., Monastero, R., Winblad, B., Bäckman, L., & Fratiglioni, L. (2008). Occurrence of cognitive impairment and dementia in the community: a 9-year-long prospective study. *Neurology*, *70*(19 Pt 2), 1778–1785. https://doi.org/10.1212/01.wnl.0000288180.21984.cb

[145] Facts and figures. (n.d.). Retrieved March 25, 2021, from https://www.alz.org/alzheimers-dementia/facts-figures

[146] Sims, R., Hill, M., & Williams, J. (2020). The multiplex model of the genetics of Alzheimer's disease. *Nature Neuroscience*, *23*(3), 311–322. https://doi.org/10.1038/s41593-020-0599-5

[147] Fiford, C. M., Manning, E. N., Bartlett, J. W., Cash, D. M., Malone, I. B., Ridgway, G. R., Lehmann, M., Leung, K. K., Sudre, C. H., Ourselin, S., Biessels, G. J., Carmichael, O. T., Fox, N. C., Cardoso, M. J., Barnes, J., & Alzheimer's Disease Neuroimaging Initiative (2017). White matter hyperintensities are associated with disproportionate progressive hippocampal atrophy. *Hippocampus*, *27*(3), 249–262. https://doi.org/10.1002/hipo.22690

[148] Legdeur, N., Visser, P. J., Woodworth, D. C., Muller, M., Fletcher, E., Maillard, P., Scheltens, P., DeCarli, C., Kawas, C. H., & Corrada, M. M. (2019). White Matter Hyperintensities and Hippocampal Atrophy in Relation to Cognition: The 90+ Study. *Journal of the American Geriatrics Society*, *67*(9), 1827–1834. https://doi.org/10.1111/jgs.15990

[149] de Leeuw, F. E., Barkhof, F., & Scheltens, P. (2004). White matter lesions and hippocampal atrophy in Alzheimer's disease. *Neurology*, *62*(2), 310–312. https://doi.org/10.1212/01.wnl.0000103289.03648.ad

[150] van Dijk, E. J., Breteler, M. M., Schmidt, R., Berger, K., Nilsson, L. G., Oudkerk, M., Pajak, A., Sans, S., de Ridder, M., Dufouil, C., Fuhrer, R., Giampaoli, S., Launer, L. J., Hofman, A., & CASCADE Consortium (2004). The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension (Dallas, Tex.: 1979)*, *44*(5), 625–630. https://doi.org/10.1161/01.HYP.0000145857.98904.20

# CURRICULUM VITAE