Influence of Lifetime Mild Traumatic Brain Injury and Repetitive Head Impact Exposure on the Aging Brain

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A dissertation submitted to
the Faculty of Graduate Studies
in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy

Graduate Program in Clinical Developmental Psychology
York University
Toronto, Ontario

June 2023

Abstract

This dissertation aims to examine associations between remote mild traumatic brain injury (mTBI), and cortical thickness, subcortical volumes, and cognitive functioning via a systematic literature review and retrospective data analyses. Study 1 consisted of a systematic review of the literature investigating long-term brain impacts, assessed *in vivo* using neuroimaging methods, of exposure to mTBI and repetitive head impacts (RHIs) during adulthood. Findings from the systematic review showed that remote mTBI/RHI exposure was associated with neurological abnormalities revealed by neuroimaging across several modalities (i.e., diffusion tensor imaging, magnetoencephalography, magnetic resonance spectroscopy, positron emission tomography, spectral domain optical coherence tomography, and several magnetic resonance imaging techniques), though conclusions are limited due to methodological constraints in the studies examined. Given the gaps in the literature identified in Study 1 (i.e., a lack of research on long-term mTBI exposures in veteran samples), Study 2 consisted of analyses to examine associations between mTBI exposure and cortical thickness across the brains of Vietnam War Veterans. Data from this sample of service members was obtained from the Alzheimer's Disease Neuroimaging Initiative - Department of Defense (ADNI-DOD). Participants included 47 male veterans with mTBI exposures (mean age = 69.43, SD = 5.02) and 82 controls (veterans without mTBIs; mean age = 68.51, SD = 4.69). Associations between mTBI, age, education, cognitive status, PTSD symptoms, and cortical thickness were examined. Three regions, i.e., the left caudal middle frontal and bilateral superior frontal cortices, showed greater cortical thickness for the mTBI group. These findings indicate potential regions for future analyses examining long-term mTBI sequelae. Finally, given the close association between TBI and Alzheimer's disease pathology, study 3 examined the impact of mTBI on cortical thickness and subcortical volumes in AD-vulnerable regions, as well as memory functioning in this cohort. Narrowing ROIs to those implicated in AD revealed several regions that were associated with mTBI exposures (i.e., left lateral temporal cortex, right posterior cingulate cortex, right amygdala, and right inferior frontal cortex). These studies show that mTBI can have long-term but circumscribed effects on the brain.

Keywords: brain injury, aging, neurodegeneration, cortical thickness, subcortical volumes

Acknowledgments

There are many people who I would like to acknowledge and thank for supporting me through this PhD and the completion of this dissertation. It would not be possible to mention everyone here, but I hold each person who has shown kindness and care to me during this process, very dear to me. I would like to thank my supervisor Dr. Magdalena Wojtowicz for taking me into her lab (as her very first PhD student!) and for supporting me throughout all of my projects and endeavors. Thank you to my lovely labmates as well for making the work atmosphere a fun and encouraging one. I would also like to thank my committee members Dale Stevens and Gary Turner for their commitment, guidance, and fine-tuning of my work along the way. I am grateful to each of the professors and supervisors who have deeply impacted me and my outlook on providing psychological care throughout my training, with special thanks to Drs. Nalini Iype and Jennifer Stanga for their invaluable impact on my life.

I would like to thank my family including my late grandmother (Jean Echlin), as well as my aunt (Donna Echlin), uncle (Ken Echlin), and my aunt and uncle (Suzanne and Bob Echlin). It is thanks to each of you that I had a desire to pursue higher education, and you have each been an incredible inspiration for all aspects of my academic pursuits. Thank you for your encouragement and support of me throughout my life. Thank you to my brothers (Dale, Tom, and Kevin) for giving me some inspiration to do this type of research and for helping me create the brain images for this dissertation. I must also thank my little nieces (Anayis, Aislynn, Evynhe, Eden, and Hazel) who motivate me to push onward and lead by the best example I am capable of in the hopes that you will each go on to live beautiful lives by just being the incredible people you are.

Thank you to all of my friends who saw me through to this point and kept me going when I needed it. To name a few, Alethea Baptista, David Miranda, Sam Feldman, Melissa Ferland, Volodymyr Slyvka, Alica Rogojin, Alanna Pierias, and Jennifer Wong. The shared laughter and tears with each of you grounded me and fueled me to carry on with my work, even when I wanted nothing more but to be spending that time with each of you! I am also very grateful for the incredible cohort of women I joined this program with including Marette Abdelmaseh, Kathryn Pierce, Oana Bucea, Annie Mills, and Samantha Buckley. I cannot imagine a better group of friends to go through this program with, you are each wonderful and inspiring!

Finally, I would like to thank my boyfriend Alex Porthukaran, who was incredibly

supportive with helping me achieve these milestones. You have shown me more kindness, patience, and care during this process than I ever thought possible. I am so grateful that I have you and I look forward to what the future brings. Thank you to Alex's family (who have become family to me as well), including his sister, Annie Porthukaran, and parents, Sheela and John Porthukaran (and of course their puppy, Daisy). You have each brought so much happiness and love into my life that I have been forever changed by knowing you.

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Glossary of Abbreviations

Aβ – Beta Amyloid
AD – Alzheimer's disease
ApoE ε4 – Apolipoprotein Epsilon 4
DTI – Diffusion Tensor Imaging
FA – Fractional Anisotropy
MCI – Mild Cognitive Impairment
MD – Mean Diffusivity
fMRI – Functional Magnetic Resonance Imaging
MRI – Magnetic Resonance Imaging
mTBI – Mild Traumatic Brain Injury
RD – Radial Diffusivity
RHI – Repetitive Head Impacts
SCI – Subconcussive Impacts
TBI – Traumatic Brain Injury
WMH – White Matter Hyperintensities
WMHV – White Matter Hyperintensity Volumes

Chapter 1: General Introduction

1.1 Overview of the Healthy Aging Trajectory

Healthy aging is a gradual process that eventually leads to a reduction in gray and white matter and an expansion of the ventricular system, accompanied by subtle cognitive changes (Gunning-Dixon & Raz, 2003). Without any major disruptions, the progression of cognitive development follows an inverted U-shape pattern in which peak performance and a plateau are reached in adulthood followed by decline with advancing age that occurs at various rates depending on brain health and brain reserve factors (Fjell & Walhovd, 2010; Lindenberger, 2008). However, ubiquitous risk factors, such as head trauma, may alter the trajectory of this healthy aging process at any point throughout the lifespan. Investigating how healthy aging transitions to pathological aging has become a major public health priority.

1.2 Mild TBI, Subconcussive Impacts, Repetitive Head Impacts, and Aging

Mild traumatic brain injury (mTBI) is a common injury encountered across the lifespan, with a variety of biopsychosocial consequences. In Canada, incidence rates of TBIs have reportedly increased between 2005 and 2014 (Rao, McFaull, Thompson, & Jayaraman, 2017), with falls being the most common cause of injury. Mild TBIs or concussions account for 70-90% of all treated TBI cases and occur most commonly in males and teenagers/young adults (Cassidy et al., 2004). Despite their prevalence, many questions remain about the potential long-term consequences of mTBI. With greater severity, TBIs are the leading cause of death and disability across the lifespan (Faul & Coronado, 2015; Keenan & Bratton, 2006), but in milder forms more incipient processes may produce changes in brain health and cognitive ability that fluctuate in an unknown or variable way with age (e.g., adverse psychiatric, cognitive, psychosocial and neurological morbidities; Ponsford, Cameron, Fitzgerald, Grant, & Mikocka-Walus, 2011; Vanderploeg, Curtiss, Luis, & Salazar, 2007). Evidence suggests that atrophy of the brain typically seen with aging may be exacerbated TBI (Cole, Leech, & Sharp, 2015), yet it is unclear whether this is due to an interaction with aging or an ongoing neurodegenerative process, or the initiation of a neurodegenerative disease. Given overlap in neuropathological processes, Alzheimer's disease (AD) is often studied as an outcome or used as a proxy for studying neurodegeneration following TBI in the literature (Uryu et al., 2007; Rothermundt, Peters, Prehn, & Arolt, 2003). However, in

terms of the aging or recovery trajectory, some amount of recovery or compensation is possible following TBI depending on the nature of the injury and its severity, while neurodegenerative diseases promote a steady decline in brain health with age (Jicha & Carr, 2010; Schneider et al., 2014). In addition, the literature regarding associations between mTBI and the development of AD is mixed, with some indicating an increased risk (Bigler, 2013; Fann et al., 2018; Gan et al., 2021; Gardner et al., 2014; Lee et al., 2013) and others indicating no increased risk (Crane et al., 2016; Dams-O'Connor et al., 2013; Julien et al., 2017). In light of these insights, research has shifted focus toward understanding the heterogeneous impact of mild head injuries and how they may contribute to neuropathological changes in the aging brain.

In addition, there is growing concern about the potential short- and long-term consequences of exposure to repetitive head impacts (RHI) which may include mild TBIs (see section 2.6.2 for a definition) or subconcussive injuries (SCI). The usual symptoms of a concussion include noise sensitivity, fatigue, visual disturbances, irritability, decreased memory and concentration, headaches, dizziness, judgement problems, depression and anxiety (Ryan & Warden, 2003). Alternatively, an SCI refers to a hit to the head or body that involves forces that are insufficient to produce symptoms associated with a concussion (i.e., minimal short-term effects) and, therefore, are typically undiagnosed and/or mismanaged (Shuttleworth-Edwards, Smith, & Radloff, 2008; Slobounov et al., 2017). Researchers have shown that such injuries may cause cumulative damage to the brain and changes to cognitive status over time (Bazarian et al., 2014). This form of injury is typically studied in professional or elite athlete populations, and these samples are unique and disparate from the general population (Baugh et al., 2012); therefore, the literature about SCI/RHIs in non-athlete adults is lacking. Further, little is currently known about the potential influence of exposure to mTBI and RHIs on the brain with age and how this may relate to the development of neurodegenerative diseases.

In individuals with a history of mTBI, it is expected that depending on the injury (e.g., complicated or uncomplicated), structural imaging findings may or may not be present, but findings in months or years following the injury are less clear (Clark et al., 2021; Wang et al., 2015). However, studies using other imaging modalities like DTI or fMRI typically report some evidence of alteration in this timeframe, and findings suggest that differences can be found in those with complicated or uncomplicated mTBIs (Eierud et al., 2014; Palacios et al., 2017; Panenka et al., 2015). Less is known overall about how the brain changes one or more decades

after mTBI exposure (Sundman, Hall, & Chen, 2014). MacKenzie and colleagues (2002), observed that cascading pathological events occur in the brain well after the initial injury, including whole brain atrophy at 11 months post-injury. Thus, it appears that head injuries could have lasting effects on the brain that may worsen over time (particularly for injuries with loss of consciousness). Generally, the literature suggests that variability in outcomes in those who sustain an mTBI are common (Borgaro, Prigatano, Kwasnica, & Rexer, 2003; Pertab, James, & Bigler, 2009). Further research is needed to fill this gap regarding the long-term outcomes of mTBI (and RHIs) in older adulthood, using advanced neuroimaging techniques (McCrea et al., 2009).

1.3 The Aging Brain and Neurodegeneration

Of all neurodegenerative diseases, AD is the most commonly occurring (Jorm & Jolley, 1998; Selkoe & Lansbury, 1999), accounting for 60 to 80 percent of all dementia diagnoses (Garre-Olmo, 2018). It is characterized by pathological changes in the brain (e.g., atrophy and an accumulation of proteins like tau and amyloid plaques) that are influenced by cumulative environmental influences encountered with age (Bufill et al., 2009). Of note, previous research has suggested that changes in the brain associated with healthy aging and with AD both independently impact distinct areas of the brain, but have joint impacts on the hippocampi and entorhinal cortices (Raji, Lopez, Kuller, Carmichael, & Becker, 2009). Eventually, these pathological changes result in a range of clinical symptoms (e.g., progressively declining cognitive, affective, and motor symptoms), that are usually first detected as memory impairments, which lead to the eventual loss of independent functioning. The presence of these clinical symptoms is recognized as the overarching syndrome, dementia. For preventative reasons, it is critical to identify potentially modifiable risk factors that appear early-on in the disease process which may contribute to pathological aging and the potential development or progression of this disease.

Despite growing awareness of the contributing factors that lead to AD diagnoses, it is exceptionally difficult to detect early signs of AD (i.e., preclinical stages) because behavioural symptoms are mostly absent (Morris, 2005; Sperling et al., 2011; Zetterberg & Bendlin, 2020). A probable diagnosis of AD is made after clinical symptoms appear and significant damage to the brain has already occurred (Ewers, Sperling, Klunk, Weiner, & Hampel, 2011). Of the available resources, neuropsychological tests are the best predictors of current and future levels of

impairment (Millis et al., 2001; Tierney, Yao, Kiss, & McDowell, 2005). The literature has consistently indicated that the most saliently affected domains in both AD and TBI is memory impairment (Breed et al., 2008; Christodoulou et al., 2001; Jahn, 2013; McDowell, Whyte, & D'Esposito, 1997). Memory processes normally rely on brain regions that are often selectively impaired by both TBI and AD (Dickerson & Sperling, 2008; Umile, Sandel, Alavi, Terry, & Plotkin, 2002a). This impairment may be transient following an mTBI, but prolonged impairment may be indicative of more significant neuropathological changes that may accelerate the brain aging process (Draper & Ponsford, 1973; McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017; Yang et al., 2015).

1.4 Overlap between Aging, TBI, Mild Cognitive Impairments and AD

There appears to be some overlap between brain regions that are vulnerable to the aging process in the absence of disease, regions that are vulnerable to certain neurodegenerative diseases, and those susceptible to changes following TBI. In healthy older adults, the aging process is slower and steadier overall compared to individuals with brain injuries or neurodegenerative diseases (Hedden & Gabrieli, 2005). Notably, gray matter tends to shrink while cerebral spinal fluid filled spaces expand with age (Raz, 2004). The reason for this decline is unclear, but some suggest that this is a natural by-product of neuronal cell death. Others suggest that it relates to declines in white matter integrity, indicating that white matter disruption shows a curvilinear pattern of decline with aging that may be related to subsequent gray matter loss (Bartzokis et al., 2010; Walhovd et al., 2005). The frontal lobes, hippocampi (to a lesser extent), and cerebral white matter seem to show the earliest decline in thickness/volume with age (Jernigan et al., 2001; Raz et al., 2005). Specifically, the greatest effects of age have been observed in the inferior/superior frontal gyri and superior temporal lobe, while the anterior cingulate cortices and inferior temporal lobes were relatively spared (Fjell et al., 2009). While decline is a normative experience that comes with living a long life, healthy aging is a gradual process that is not usually accompanied by abrupt alterations in behaviour and functional ability.

The thinning of several cortical (Sabuncu & Desikan, 2011; Dickerson et al., 2009) and subcortical (Poulin, Dautoff, Morris, Barrett, & Dickerson, 2011) regions have been identified in early-AD (eAD) with some consistency. Additionally, there is strong evidence that different brain structures are impacted at different stages of the disease (Dickerson et al., 2001; Sabuncu et al.,

2011). The more recently published exploratory analyses from the 2011 study (Sabuncu et al., 2011) will be used as the theoretical backbone for a subset of the analyses in this dissertation given that previous work in other samples (including veterans with mTBIs) have replicated these findings (Hayes et al., 2017; Sabuncu et al., 2012). The areas of interest examined in these studies include the entorhinal cortex, temporopolar cortex, lateral temporal cortex, inferior parietal cortex, inferior parietal sulcus, posterior cingulate cortex, and inferior frontal cortex.

Changes across the brain associated with mild cognitive impairment (MCI) can be challenging to discern without longitudinal data to highlight conversion to AD or other sequelae (i.e., given that MCI can be due to AD or other pathology). Generally, similar observations have been noted in those with MCI (though to a lesser extent), compared to adults with early AD, and adults in the preclinical disease stages with indicators suggestive of AD (e.g., amyloid-positive individuals; Dickerson et al., 2009; Sabuncu & Desikan, 2011; Sabuncu et al., 2012). This research demonstrated that cortical thickness in those with pre-symptomatic MCI is generally not distinguishable from controls without MCI or AD until cognitive scores have declined over time (i.e., to an MMSE score of 21; Sabuncu & Desikan, 2011). Additionally, previous research has suggested that healthy aging may predominantly affect a frontal-striatal system that supports the executive control of cognitive processes, while only minimally affecting medial temporal lobe structures (Hedden & Gabrieli, 2005). This study also indicated that MCI primarily affects the entorhinal cortex, whereas reductions in hippocampal volumes are more indicative of AD. Essentially, these findings are supported with evidence for a double dissociation in frontal and hippocampal regions whereby those with early AD show early decline in integrity of hippocampal and posterior regions, while healthy aging is associated with initial decline in more anterior regions (Head, Snyder, Girton, Morris, & Buckner, 2005).

The link between TBI and AD has primarily been reported in moderate-to-severe TBIs (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003; Johnson, Stewart, & Smith, 2012; Mortimer et al., 1991), and in those with multiple TBI exposures (Fann et al., 2018). There is some evidence, though still preliminary, that mTBI may be associated with increased risk for dementia in older adults (Bigler, 2013; Fann et al., 2018; Gardner et al., 2014). The literature regarding associations between TBI exposure (including mTBI) and an earlier onset of AD have generally been mixed (Crane et al., 2016; Fleminger et al., 2003; Julien et al., 2017; Mehta et al., 1999; Nemetz et al., 1999; Nordstrom, Michaëlsson, Gustafson, & Nordström, 2014; Van Duijn et al.,

1992). Importantly, an mTBI can result in altered metabolic processes and pathological structural and functional brain changes with additional biomarkers that are remarkably similar to those found in AD (Uryu et al., 2007; Rothermundt, Peters, Prehn, & Arolt, 2003). With TBIs, cerebral blood flow, glucose metabolism, and cellular signaling pathways in the brain all may become altered in such a way that appears to be akin to the cascade of events that occurs with AD onset (Giza & Hovda, 2014). Further, both TBI and AD are associated with inflammatory and apoptotic processes that result in an accumulation of proteins such as Aβ, α-synuclein, and tau (Bigler, 2013; Uryu et al., 2002, 2007). The degree of overlap in the effects on both micro- and macro-level structures and pathophysiology is highly suggestive of a potentially common immune or repair response that is implicated in both TBI and AD (Kempuraj et al., 2020).

1.5 Summary and Aims

A deeper understanding of how mTBI or RHI history impacts brain health with age is needed, particularly given that 33.2% percent of people aged 85 and older were diagnosed with Alzheimer's dementia in 2020 (Rajan et al., 2021). For those who are at-risk for developing AD, it is presently unclear whether mTBI confers this risk in those who were not otherwise at-risk or worsens the trajectory in those who were already at-risk. Further, some studies that have examined cortical and subcortical differences in mTBI report an age by concussion exposure interaction, suggesting the possibility of accelerated aging in those with a history of injury (Fann et al., 2018). Much of the literature related to this topic has focused on athletes (professional and collegiate) and less research has been devoted to examining veterans or other populations (Cassidy et al., 2004). The first study aimed to address this gap by synthesizing findings from studies that include all populations (e.g., athletes, veterans, the general population). The second study characterizes the relationship between mTBI exposure and cortical thickness via both hypothesis-driven and exploratory analyses across the whole brain while also examining the relationship between mTBI exposure and white matter hyperintensity volumes (WMHV) in order to address gaps in the literature identified in study 1. The third study examines cognitive functioning, cortical thickness, and subcortical volumes in AD-vulnerable regions (Sabuncu et al., 2011) in a sample of older adult Vietnam War veterans with and without mTBI histories. Additional factors such as age at first injury and the number of mTBI exposures are also examined.

Chapter 2: Systematic Review of the Long-Term Neuroimaging Correlates of Mild Traumatic Brain Injury and Repetitive Head Injuries

2.1 Overview

The aim of this chapter was to synthesize relevant information from published literature regarding associations between mTBI exposure and neurological outcomes later in life in order to inform the subsequent chapters of this dissertation.

2.2 Publication Status and Author Contributions

The following chapter is based on the manuscript: Echlin, H. V., Rahimi, A., & Wojtowicz, M. (2021). Systematic review of the long-term neuroimaging correlates of mild traumatic brain injury and repetitive head injuries. Frontiers in Neurology, 12, 726425. doi: https://doi.org/10.3389/fneur.2021.726425

The content of this chapter does not exactly replicate the published article in Frontiers in Neurology. Thus, it is not a copy of the original published article and is not suitable for citation. Holly Echlin (i.e., the first author) developed the conceptual rationale for the study, searched the literature, and synthesized and interpreted the data. She was also the primary contributing author of the manuscript and produced the initial draft and completed all major revisions.

2.3 Abstract

Objective: To systematically review the literature on the long-term neuroimaging findings (⩾10 years from exposure) for exposure in adulthood to mild traumatic brain injury (mTBI) and repetitive head impacts (RHIs) using neuroimaging across all available populations.
Data sources: Four electronic databases: MEDLINE, SPORTDiscus, PsycINFO, and EMBASE.
Study selection: All articles were original research and published in English. Studies examined adults with remote exposure to mTBI and/or RHIs from ten or more years prior in addition to any associated neuroimaging findings.
Data extraction: Parameters mainly included participants' population, age, years since head injury, race, sex, education level, and any neuroimaging findings. Scores for the level of evidence and risk of bias were calculated independently by two authors.
Results: 5,521 studies were reviewed, of which 34 met inclusion criteria and were included in

this study. The majority of adults in these studies showed positive neuroimaging findings one or more decades following mTBI/RHI exposure. This was consistent across study populations (i.e., veterans, athletes, and the general population). There was evidence for altered protein deposition patterns, micro- and macro-structural, functional, neurochemical, and blood flow-related differences in the brain for those with remote mTBI/RHI exposure.
Conclusion: Findings from these studies suggest that past mTBI/RHI exposure may be associated with neuroimaging findings. However, given the methodological constraints related to relatively small sample sizes and the heterogeneity in injury types/exposure and imaging techniques used, conclusions drawn from this review are limited. Well-designed longitudinal studies with multimodal imaging and in-depth health and demographic information will be required to better understand the potential for having positive neuroimaging findings following remote mTBI/RHI.
Keywords: neuroimaging, neurodegeneration, systematic review, mTBI, repetitive head impacts

2.4 Introduction

Traumatic brain injuries (TBIs) are estimated to affect sixty-nine million individuals around the world each year (Dewan et al., 2019) and according to the World Health Organization, mild traumatic brain injuries (mTBIs) account for approximately 70-90% of all treated TBI cases (Cassidy et al., 2004). MTBIs, some of which are termed concussions, refer to an alteration in brain function induced by biomechanical forces, such as an impact to the head or body, which results in a range of clinical signs and symptoms (i.e., physical, psychological, cognitive; McCrory et al., 2017). More recently, research has also been devoted to better understanding the long-term effects of repetitive head impacts (RHIs) which refers to milder impacts to the head or body which are associated with subthreshold or no clinical signs or symptoms upon impact (Belanger, Vanderploeg, & McAllister, 2016). Given the prevalence of these injuries, there has been a growing interest in the potential long-term consequences of mTBI and cumulative effects of exposure to RHIs.

Some research suggests that having multiple TBIs can alter long-term recovery trajectories in the brain such that neuropathology may be perpetuated throughout the chronic stages post-injury (Bigler, 2013). It is not yet fully known how this cascade may affect brain health and quality of life with advancing age, but this literature suggests that repetitive head

injuries lead to cerebral atrophy, which potentially increases degenerative effects on the brain over time (Bigler, 2013). In addition, exposure to repetitive head impacts (i.e., mTBI and SCIs during the lifetime) has also been linked to late-life depression and cognitive impairment (Montenigro et al., 2017), and these are often associated with structural changes in the brain (Fjell & Walhovd, 2010). Research has begun to shift focus towards understanding the long-term effects of such injuries and whether they may also be linked to neurodegeneration, given that this link has been established for moderate/severe head injuries. Some preliminary research is beginning to show that this may be the case (Baugh et al., 2012), but more evidence, including from well-designed longitudinal studies is still needed.

Prior to 2010, research was limited on this topic and generally focused on retired boxers (e.g., Roberts, 1969) or specific case study investigations (Geddes, Vowles, Robinson, & Sutcliffe, 1996; Handratta, Hsu, Vento, Yang, & Tanev, 2010; Omalu et al., 2005; Parker, 1934). Longitudinal data investigating the long-term sequelae of mTBI and systematic reviews of the literature have focusing on synthesizing information beyond a decade from injury exposure have been limited (Asken, DeKosky, Clugston, Jaffee, & Bauer, 2018; Ayubcha et al., 2020; Koerte, Lin, Willems, et al., 2015; Lee et al., 2018; Lin, Charney, Shenton, & Koerte, 2018; Manley et al., 2017; Sparks, Lawrence, & Hinze, 2020; Sundman, Hall, & Chen, 2014). That is, these systematic reviews covered specific areas which either involved examining athletes, veterans, and the general population using one neuroimaging modality (i.e., diffusion tensor imaging; DTI) or using several neuroimaging modalities to examine only one population (e.g., athletes). Professional and collegiate athletes are unique populations with greater exposure to head injuries, increased severity of head injuries, other physical injuries, and additional confounds such as increased rates of mental health and/or substance use histories (Wojtowicz et al., 2018, 2017). This limits the generalizability of findings to non-athlete adults and points to a gap in the literature about the study of other populations.

However, multimodal neuroimaging is critical for a comprehensive understanding of the potential long-term sequelae of mTBI/RHIs. Some studies using structural MRI have noted volume and thickness difference in individuals with a history of mTBI (Gardner & Yaffe, 2015; Hayes et al., 2017). Studies using DTI to investigate white matter integrity have noted evidence of diffuse axonal injury following injury (Povlishock & Christman, 1995; Smith, Meaney, & Shull, 2003) which may contribute to the disconnection and/or dysfunction of large-scale

functional networks (Tang et al., 2012). In fact, altered functional connectivity has also been observed in asymptomatic individuals with a history of mTBI/concussion (e.g., Churchill, Hutchison, Di Battista, Graham, & Schweizer, 2017; Orr et al., 2016). This highlights the importance of fMRI studies in understanding potential neural re-organization post-injury (Sharp, Scott, & Leech, 2014).

Additionally, assessing protein accumulation using positron emission tomography (PET) can provide useful information regarding the neuropathological sequelae of exposure to mTBI/RHIs in the long term. That is, if an accelerated aging or neurodegenerative process is suspected, understanding protein deposition patterns can assist with disentangling various neuropathological processes and enabling identification of outcomes. Studies have also highlighted the utility of proton magnetic resonance spectroscopy (MRS) for its predictive value in quantifying metabolites (i.e., potential indicators of a persistent neuroinflammatory process) that may relate to post-injury recovery (Shutter, Tong, & Holshouser, 2004). These biomarkers may facilitate identifying injury or disease pathology (Ruprecht, Scheurer, & Lenz, 2019; Tsitsopoulos & Marklund, 2013).

To date, a comprehensive systemic review of the neuroimaging literature across all populations with exposure to remote mTBI/RHIs has not been conducted. While prior systematic review articles have compared studies examining outcomes for long-term mTBIs, many of these focused on a single population (Manley et al., 2017; Sparks et al., 2020), or one particular method (e.g., only PET or DTI; Asken et al., 2018; Ayubcha et al., 2020; Lee et al., 2018). In addition, others examined evidence across the spectrum of traumatic brain injury severities (Koerte, Lin, Willems, et al., 2015; Lin et al., 2018; Sundman et al., 2014), while the present study focuses on mTBIs. Furthermore, regular updates are required in a field that is burgeoning and quickly evolving in terms of scope and findings, particularly given the identified gap in the literature regarding the effects of mTBI beyond ten years post-injury (Sundman et al., 2014). Therefore, with the aim of synthesizing findings about the long-term effects (i.e., ten or more years post-injury/exposure) of mTBI and RHIs on the brain, this systematic review will examine evidence from a broad range of neuroimaging modalities to provide a comprehensive, and in-depth discussion of the current state of the literature.

2.5 Method

2.5.1 | Search Strategy

This study was developed in accordance with PRISMA guidelines. Initial keywords were selected based on a previous relevant review (Manley et al., 2017) and from scans of the relevant literature (i.e., snowball searching). These keywords were then submitted to a librarian with expertise in health studies and systematic reviews in order to collaboratively draft a MEDLINE search strategy. The draft search strategy was adapted in accordance with the CADTH Peer Review Checklist for Search Strategies according to the Press 2015 Guideline Statement. Afterwards, this draft was tested to ensure that known relevant studies were included. The resulting MEDLINE search was translated to conform to each of the other databases used (see supplementary Table 1 for the search strategy for MEDLINE). The following databases were comprehensively searched by investigator HE: MEDLINE, SPORTDiscus, PsycINFO, and EMBASE. Grey literature searches were also performed (e.g., snowball searches, google searches, and ProQuest Dissertations and Theses search). The search was conducted on January 12, 2021 and was limited to peer-reviewed articles that were published in English, with no date restrictions.

2.5.2 | Selection Criteria

The selection criteria for inclusion included: 1) the samples included at least one group of adults who had a history of RHIs or at least one mTBI (complicated or uncomplicated), 2) a follow-up period of at least ten years post-injury, 3) neuroimaging acquired >10 years after exposure to mTBI/RHI, 4) a minimum average age of 28 (i.e., studies were searched to ascertain that the average age for the reported injuries was 18 years or older, to identify injuries that occurred in adulthood), 5) discussion of outcomes and sequelae due to head injury (e.g., seizures, smaller brain volumes, etc.), 6) the availability of the full text in a journal or database, and 7) the use original research that has been published in English. Studies were excluded from the review if 1) they were animal studies, review articles, case reports, book chapters, conference abstracts, editorials/commentaries/expert opinion, theses, or dissertations or 2) individuals were diagnosed with neurological conditions other than TBI (e.g., stroke or epilepsy) Studies with clinical

populations could only be included if the clinical population was compared separately or used as a control group for comparison with an mTBI/RHI-exposed sample that met inclusion criteria. Studies were also included if rationale could be provided to account for the ten years between injury and neuroimaging (e.g., professional athletic career ended more than ten years ago, according to age at neuroimaging acquisition) even when participants' time since last injury was not explicitly reported.

Two of the authors (HE and AR) discerned the studies' eligibility for inclusion by first independently reviewing titles and abstracts. Studies that did not meet the exclusion criteria at this step were further evaluated in the full text review stage. Article inclusion was decided upon via discussion between both authors.

2.5.3 | Risk of Bias and Level of Evidence

The level of evidence and risk of bias of the included studies were rated by two authors, and disagreements in ratings were settled by discussion between the two. The Downs and Black checklist was used to assess the risk of bias (Downs & Black, 1998), while the level of evidence was assessed using the Oxford 11 Level of Evidence (OCEBM Levels of Evidence Working Group, 2011). While the provided cut-offs for scores embedded in the Downs and Black checklist indicate that scores lower than 14 suggest poor methodological quality (Hooper, Jutai, Strong, & Russell-Minda, 2008), applying this criterion to observational studies that do not include randomization, blinding, and/or reporting of adverse events, etc., results in lower scores. However, given that others have used this measure in this field (Manley et al., 2017) and have reported similar ratings, the broad utility of this measure for the current review is to provide a way to compare the relative risk of bias between studies within this paper. Similarly for the Oxford 11 Level of Evidence rating, to understand the integrity of the design of one paper, one might check the level of evidence score in order to compare it with a similar study or against the average provided.

2.5.4 | Data Extraction

After the abstracts and titles were screened and the full texts were reviewed by authors HE and AR, a standardized method in Covidence was used to extract the data from the included

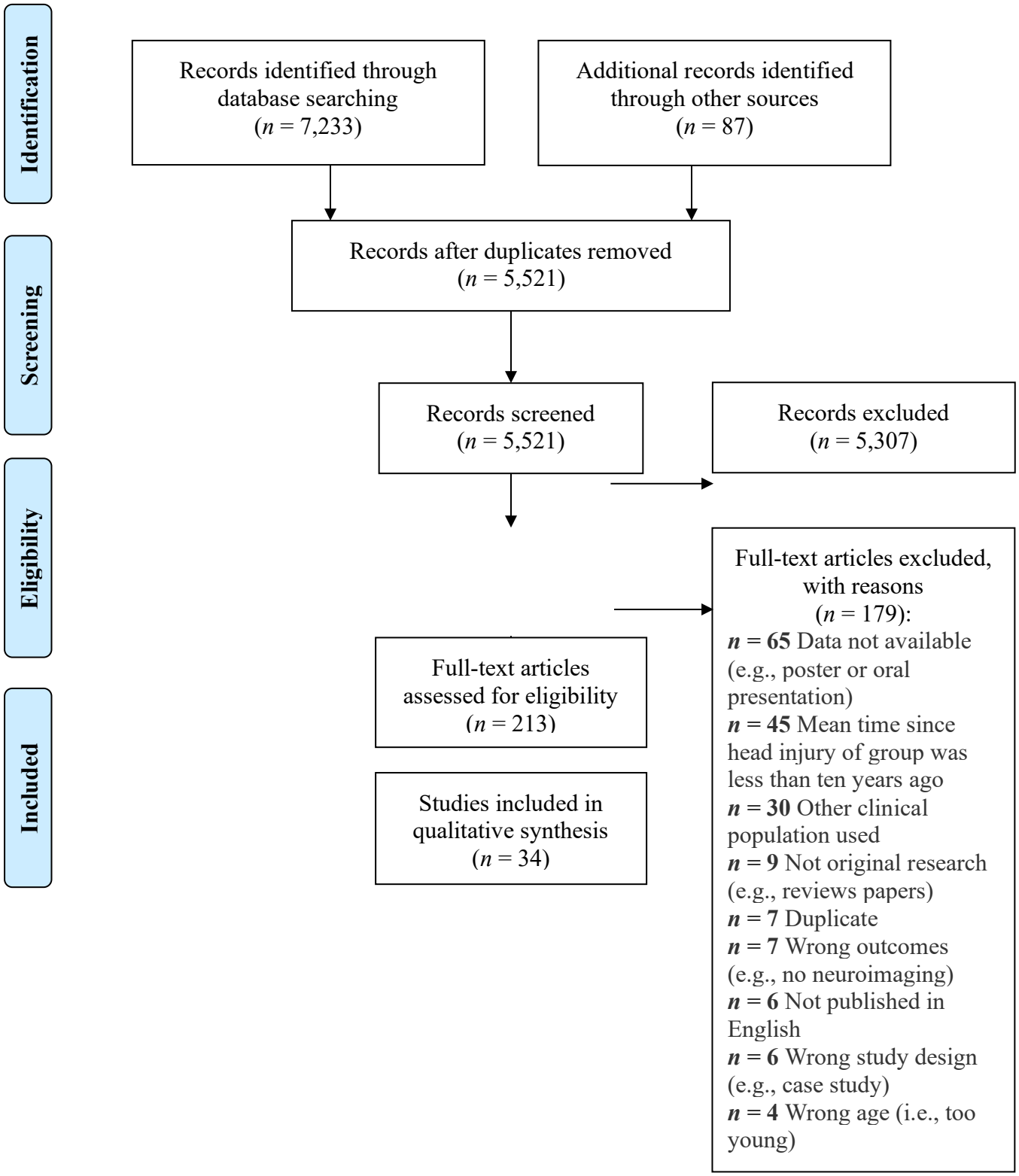
articles. One author extracted the data and a second author reviewed it for accuracy and to confirm that it was comprehensive. Once the data were extracted, all three authors reviewed the finalized tables. The information extracted from the included studies mainly consisted of study design, demographic information about the sample, the type of head injury exposure and the context within which it occurred, the type of neuroimaging modality used for assessment, any reports of potential diagnoses, and time since the injury. This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020178475) and has been published (Echlin, Rahimi, & Wojtowicz, 2021).

2.6 Results

In total, the database searches and the grey literature searches resulted in 7,233 articles being identified (see Figure 1). Covidence identified and removed 1,712 duplicates. In the first stage of screening, 5,521 articles were reviewed. After exclusion of ineligible articles, 214 articles were screened in the full-text review stage and 34 were deemed eligible for inclusion in this review. Appendix D contains relevant information from each of the studies included in this review. Appendix B includes a summary of the risk of bias ratings and ratings of the methodological quality of included studies. According to the Downs and Black criteria for rating methodological quality, the average score for the included studies was 9.8. Given the context of the studies that were included as well as the guidelines for their assessment, the methodological quality of the studies in this review overall is considered to be poor. However, it is important to note that ideal control groups are difficult to establish for this population and that certain methodological procedures (e.g., blinding) are not possible for observational studies, which lowered the scores. Two studies in this review were rated as a level 3 (i.e., cohort study) for their level of evidence. The remaining 32 studies were rated as a level 4 (i.e., case-series).

Figure 1

PRISMA Flow Diagram



2.6.1 | Description of Studies

There were 34 articles identified that characterized the brain and the potential long-term associations of mTBIs and/or RHIs using neuroimaging. The imaging techniques used in these papers included DTI (*n* = 12 studies), measures of functional connectivity (i.e., functional MRI or magnetoencephalography; *n* = 9 studies), MRS (*n* = 5 studies), optical coherence tomography (OCT; *n* = 2 studies), perfusion weighted imaging (PWI; *n* = 1), arterial spin labelling (ASL; *n* = 1), PET (*n* = 4 studies), structural neuroimaging measures (e.g., MRI scans; n = 18 studies), and susceptibility weighted imaging (SWI; *n* = 3 studies). The populations examined included veterans, athletes, and individuals from the general population who had sustained a mTBI or were exposed to RHIs. The majority of studies examined professional or university-level athletes (*n* = 26; American football was the most common sport) and four of these articles included professional fighters. Only two studies used a veteran population, five included the general population, and one study had a mix of athletes and the general population. In total, two of the included studies were longitudinal and the rest were cross-sectional. Almost all of the included studies reported significant differences between groups with regard to brain structure, function, and pathology.

2.6.2 | Definition of mTBIs/Concussion and Repetitive Head Injuries

MTBI/concussion were typically defined using recommended guidelines that were relevant when the paper was published. In several studies, participants were asked to self-report prior diagnoses of mTBIs, though the description of how a mTBI/concussion was defined was often not fully transparent (Clark et al., 2018; Ford, Giovanello, & Guskiewicz, 2013; Haglund & Bergstrand, 1990; June et al., 2020; Small et al., 2013; Wang, Wei, Yu, Li, & Li, 2017). In several studies, participants were asked to self-report their concussion history after being provided with a standard definition (Malec et al., 2007; McCrory et al., 2009; Paul McCrory et al., 2017, 2013; Meeuwisse et al., 2017; Menon, Schwab, Wright, & Maas, 2010; Robbins et al., 2014) according to guidelines that were most up-to-date at the time of study publication (Casson, Viano, Haacke, Kou, & LeStrange, 2014; Goswami et al., 2016; Hart et al., 2013; Kelman, Hodge, Stanwell, Mustafic, & Fraser, 2020; Koerte, Hufschmidt, et al., 2016; Kuhn, Zuckerman,

Solomon, Casson, & Viano, 2017; Lepage et al., 2019; Misquitta et al., 2018; Monti et al., 2013; Multani et al., 2016; Rajesh et al., 2017; Rowland et al., 2018; Tremblay et al., 2013, 2019; Vasilevskaya et al., 2020). Other studies used medical chart reviews (Gardner et al., 2016) or questionnaires (Corrigan & Bogner, 2007) and/or interviews to attain these data, with some studies also using certified neuropsychologists or physicians to collect such information (Chong, Peplinski, Ross, & Berisha, 2018; De Beaumont et al., 2013; Gilmore et al., 2020; Tremblay et al., 2013, 2019). For participants who were medically diagnosed with mTBI, the Glascow Coma Scale was often used to ascertain that participants' scores fell between 13 to 15. Of the studies that reported participants' experience of loss of consciousness (LOC) or post-traumatic amnesia (PTA), injury severity was based on participants experiencing LOC for 30 minutes or less, and/or having less that 24 hours of PTA, according to criteria from the Mild Traumatic Brain Inury Committee (Mild Traumatic Brain Injury Committee, 1993).

Definitions and operationalization of RHIs were variable. Studies opted to define RHIs in multiple ways, typically using estimation methods. For instance, some studies used exposure to contact sports as a proxy for repetitive head impact exposure (Bryant et al., 2020; Haglund & Bergstrand, 1990; Koerte, Lin, Willems, et al., 2015; Lin et al., 2015; Ware et al., 2020; Wilde et al., 2016; Zivadinov et al., 2018) which sometimes included participants' estimates of ball headings per session/week (Koerte, Mayinger, et al., 2016; Lipton et al., 2013) and/or the number of times players recalled being taken out of play due to head impact (Hampshire, MacDonald, & Owen, 2013).

2.6.3 | Diffusion Tensor Imaging

Several studies captured in this review examined white matter pathology in retired professional athletes (n = 8). Some studies reported differences in fractional anisotropy (FA) between retired professional players and controls. For instance, Hart et al. (2013) observed that retired players with cognitive or mood-related symptoms had lower FA in the corpus callosum, bilateral frontal and parietal regions, and the left temporal lobe than matched controls. However, athletes without mood or cognitive symptoms in this study were not significantly different from controls in terms of white matter FA. In addition, Zivadinov et al. (2018) reported no observable differences between retired professional athletes (NFL and NHL) and controls, and no associations between lifetime concussion history and white matter disruption. In former college-

level football athletes associations were observed between white matter disruption (i.e., lower FA) in the corpus callosum and superior longitudinal fasciculus, and greater number of concussions as well as longer career duration (Clark et al., 2018). In contrast, greater FA was observed in the retired NFL players in this study. It was also observed that retired NFL and college players in non-speeded positions (i.e., offensive or defensive linemen) with a higher number of concussions had lower FA in the forceps minor compared to those with zero or one reported concussion.

Two studies examined retired CFL players for associations between RHIs or mTBI exposure and indicators of white matter pathology. Multani and colleagues (2016) found higher axial diffusivity (but not FA, MD, or RD) in the right hemispheres of the retired CFL players, specifically in the superior longitudinal fasciculus, corticospinal tract, and anterior thalamic radiations. Using machine learning, Goswami et al. (2016) found that MD and RD (but not FA) in the uncinate fasciculus (particularly at the orbitofrontal and temoporal ends) differentiated controls and athletes with 79-84% sensitivity and specificity. In retired soccer players, a higher reported frequency of heading the ball (more than 885 per year) was associated with lower FA at three locations in the temporo-occipital white matter in a group of amateur soccer players (Lipton et al., 2013). In addition, this study did not find observable differences between professional athletes and controls or associations with lifetime concussion history when looking at white matter disruption.

For boxers, one study found no group differences in FA or the apparent diffusion coefficient (ADC; Wilde et al., 2016) while another study using the same sample did, but in different regions (Ware et al., 2020). Lower FA in the splenium and higher MD in the genu of the corpus callosum was found for boxers (Ware et al., 2020). Additionally, years of boxing was associated with lower FA in the right ventral striatum, right uncinate fasciculus, and right cerebral peduncle and with the ADC in the left inferior longitudinal fasciculus and left uncinate fasciculus (Wilde et al., 2016).

Studies that examined adults in the general population who were exposed to remote mTBI typically found higher AD, RD, and MD (but not FA) in areas that included the fornix/stria terminalis, anterior corona radiata, superior longitudinal fascilus, cingulum angular bundle, the anterior aspect of the corpus callosum, and frontal white matter (Chong et al., 2018; June et al., 2020; Tremblay et al., 2019). These studies demonstrated white matter differences in adults with

remote mTBI compared to healthy controls who were either the same age or younger. In contrast, Rajesh et al. (2017) found no differences in FA between adults with remote mTBI exposure and controls. See Table 1 for a summary of the DTI findings.

Table 1

Aggregated Results for All DTI Studies

Lead Author	FA	MD/ADC	RD	AD
Hart et al., 2013	Corpus callosum (↓) Bilateral frontal regions (↓) Bilateral parietal regions (↓) Left temporal lobe (↓)	N/R	N/R	N/R
Zivadinov et al., 2020	*Null findings for group differences	*Null findings for group differences	N/R	N/R
Clark et al., 2018	Corpus callosum (↓ for college players but ↑ for retired players) Superior longitudinal fasciculus (↓ for college players but ↑ for retired players)	N/R	N/R	N/R
Multani et al., 2016	*Null findings for group differences	*Null findings for group differences	*Null findings for group differences	Superior longitudinal fasciculus (↑) Corticospinal tract (↑) Anterior thalamic radiations (↑)
Goswami et al., 2016	N/R	Able to differentiate between controls and athletes (79-84% sensitivity and specificity)	Able to differentiate between controls and athletes (79-84% sensitivity and specificity)	N/R
Lipton et al., 2013	Temporo-occipital white matter (↓)	N/R	N/R	N/R
Wilde et al., 2016	*Null findings for group differences Right ventral striatum (↓; with years of boxing) Right uncinate	*Null findings for group differences Left inferior longitudinal fasciculus (↑;	N/R	N/R

	fasciculus (↓; with years of boxing) Right cerebral peduncle (↓; with years of boxing)	with years of boxing) Left uncinate fasciculus (↑; with years of boxing)		
Ware et al., 2020	Splenium of the corpus callosum (↓)	Genu of the corpus callosum (↑)	*Null findings for group differences	N/R
June et al., 2020	N/R	N/R	Fornix/stria terminalis (↑)	Anterior corona radiata (↑) Superior longitudinal fasciculus (↑)
Tremblay et al., 2019	N/R	Anterior corpus callosum (↑) Frontal white matter (↑)	N/R	N/R
Chong et al., 2018	N/R	Left cingulum angular bundle (↓) Right cingulum angular bundle (↑) Left corticospinal tract (↑) Right inferior longitudinal fasciculus (↓) Uncinate fasciculi (↓) Forceps major (↑) Forceps minor (↓)	Anterior thalamic radiations (↓) Left and right cingulum angular bundle (↑) Left and right cingulum cingulate gyrus (↑) Left and right corticospinal tract (↑) Left uncinate fasciculus (↓) Right uncinate fasciculus (↓) Forceps minor (↓)	N/R
Rajesh et al., 2017	*Null findings for group differences	N/R	N/R	N/R

Note. Directionality, depicted using arrows, is reported for the experimental group in reference to control groups unless otherwise specified. N/R = not reported.

2.6.4 | Functional Connectivity Using MRI or MEG

2.6.4.1 | Task-Based fMRI

Several studies used event-related fMRI to examine blood oxygen level dependent (BOLD) signal changes while participants performed cognitive tasks (n = 4). Two studies used item/relational memory tasks (Ford et al., 2013; Monti et al., 2013). When comparing middle-aged adults with remote mTBIs versus younger adults with recent mTBIs, Monti et al. (2013) found that the younger adults showed more activity in the prefrontal cortex and parietal regions than the middle-aged adults overall. Also, the middle-aged adults with remote mTBI had less neural activity compared to matched controls in several regions in the right medial prefrontal cortex, bilateral frontopolar cortex, and middle and superior frontal gyri during memory performance (i.e., areas that may be associated with better performance). Investigating retired NFL players with low versus high frequency concussion exposure (three or more concussions), Ford and colleagues (2013) found that both concussion groups recruited similar regions for item memory retrieval, but differences in neural recruitment were notable during relational memory retrieval. Specifically, the high frequency concussion group showed less efficiency in neural recruitment and tended to recruit medial PFC regions more than the low frequency concussion group.

Two studies examined aspects of executive functioning and working memory (Clark et al., 2018; Hampshire et al., 2013). Retired NFL players who were given the executive functioning task showed hyperactivation and hypoconnectivity of the dorsolateral frontal and frontopolar cortices and tended to recruit frontopolar regions when task difficulty increased, while controls did not (Hampshire et al., 2013). For retired NFL players who were given the working memory task, no association between concussion history or career duration were found with BOLD signal. However, players in non-speeded positions (offensive or defensive linemen) with three or more concussions had lower BOLD signal changes during a working memory task than the low frequency concussion group. The opposite pattern was found for speed position athletes, such that lower BOLD signals were found in the low frequency concussion group (Clark et al., 2018).

2.6.4.2 | Resting-State fMRI

Two studies used resting-state functional MRI (rs-fMRI) to examine group differences between adults with mTBI history and controls. Goswami and colleagues (2016) found higher rs-fMRI connectivity between the anterior temporal lobe and orbitofrontal cortex in retired CFL players compared to controls. In another study, decreased functional connectivity between a key node of the default mode network (i.e., the posterior cingulate cortex) and the right frontal pole/anterior prefrontal cortex was observed in only the younger adults with recent mTBIs compared to controls but not in the older adults with remote mTBIs and controls (Rajesh et al., 2017).

One study used resting-state magnetoencephalography to examine small-worldness, clustering coefficient and modularity in veterans who sustained a mTBI during their deployment approximately ten years prior (Rowland et al., 2018). They found that those who had developed PTSD showed higher levels of small-worldness and clustering coefficient than the group who did not develop PTSD. There were no controls included in this study.

2.6.5 | Magnetic Resonance Spectroscopy

De Beaumont and colleagues (2013), reported glutamate/H_2O ratios in the M1 region negatively correlated with the number of reported concussions in retired former athletes. An age by group interaction was observed for M1 glutamate concentrations indicating further decreases in M1 glutamate with age for those with a head injury history. Another study quantified metabolites in 15 retired athletes (who sustained head injuries several decades prior) in the medial temporal lobes and the prefrontal cortices including: N-acetylaspartate (NAA), myo-inositol (mI), choline-containing compounds (Cho), as well as H_2O for an internal reference (Tremblay et al., 2013). They found significantly increased ratios of mI/H_2O and abnormal reductions in Cho in the left medial temporal lobes and increased Cho when referenced to H_2O, in the right prefrontal cortex of retired athletes.

In a sample of retired professional soccer players with no history of TBI but exposure to RHIs from ball headings, notable differences in neurochemistry were identified in comparison with non-contact sport athlete controls (Koerte, Lin, Muehlmann, et al., 2015). Cho and mI were significantly elevated in the soccer group and mI and glutothione were significantly related to lifetime estimates of RHIs in the soccer group. In contrast, Zivadinov et al. (2018) reported that they found no long-term differences in relative concentrations of NAA, glutamine (Glu), and

glutamate (Gln), relative to the concentration of creatine (Cr) and phosphocreatine (PCr) in the corpus callosum and fornix between retired NHL/NFL players and non-contact sport controls.

Finally, using an in vivo method of visualizing atomic structures/concentrations in 2D for differentiating checmicals called Localized COrrelated SpectroscopY (L-COSY), Lin and colleagues (2015) examined five retired professional athletes (football, wrestling, and baseball) and five matched athlete controls and found significantly higher levels of Gln/Glu (31%), choline (65%), fucosylated molecules (60%) and phenylalanine (46%) in the former athlete group.

2.6.6 | Cerebral Blood Flow and Volume

Using perfusion weighted imaging (PWI), Zivadinov and colleagues (2018) reported no significant differences in cerebral blood volume (CBV), perfusion cerebral blood flow (CBF), and mean transit time (MTT) in white matter-signal abnormalities, global and regional gray matter, and white matter brain structures between retired NHL/NFL players and non-contact sport controls. In contrast, Hart et al. (2013) used arterial spin labelling (ASL) to compare retired NFL players with cognitive impairments and/or depression to retired NFL players without such impairments and matched controls. Retired NFL players with cognitive/mood impairments had decreased bloodflow to the left temporal pole and increased bloodflow to the superior temporal gyrus and inferior parietal lobule than both control groups. Altered bloodflow to these areas was associated with neurocognitive performance (e.g., poorer naming, verbal memory, and word finding ability).

2.6.7 | Positron Emission Tomography

Small et al. examined PET scans after intravenous injections of 2-(1-{6-[(2-[F-18]fluoro-ethyl)(methyl) amino]−2 naphthyl}ethylidene)malononitrile (FDDNP) to measure tau and amyloid in a small sample of retired NFL players with mood and cognitive symptoms (n = 5) compared to matched controls (Small et al., 2013). They found that FDDNP binding signals were higher in the retired NFL group than controls in the caudate, putamen, thalamus, subthalamus, midbrain, cerebellar white matter, and the amygdala. A recent PET tau imaging study used 5mCi of [F-18]AV-1451 tracer in a group of retired professional and semi-professional contact sport athletes who were split into groups depending on whether they were carriers of one/two copies of

an APOE4 allele (Vasilevskaya et al., 2020). They found that APOE4 carriers had significantly higher cortical gray matter PET tau SUVR values, suggesting higher susceptiblity to increased cortical protein deposition for this group.

In a non-athlete study, subjects who were involved in the Alzheimer's Disease Neuroimaging Initiative (ADNI) were split into groups based on whether they had been diagnosed with AD, had mild cognitive impairments (MCI) due to AD, had preclinical AD, or were healthy controls (Wang et al., 2017). In those with preclinical AD and self-reported mTBI exposure, average cortical thickness was smaller when collapsing across the AD-vulnerable regions and this difference was specifically observed in the precuneus and superior and inferior parietal cortices, compared to non-mTBI controls. The average cortical thickness of these eight regions was also correlated with CSF T- Tau in the preclinical mTBI group. In addition, a longitudinal study that used 15O-water PET, found higher resting cerebral blood flow in the orbitofrontal and lateral temporal regions in adults from the general population with exposure to mTBI (June et al., 2020). Both increases and decreases were seen in prefrontal, cingulate, insular, hippocampal, and ventral temporal regions with longitudinal follow-up.

2.6.8 | Spectral Domain Optical Coherence Tomography

Kelman and colleagues (2020) used optical coherence tomography (OCT; i.e., a potential indicator of white matter atrophy) to measure thinning of the retinal nerve fibre layer (RNFL) in a sample of 13 retired rugby league players in comparison with normative data. The RNFL was four micrometres thinner in the athlete group than the comparison sample. The specific areas that were significantly different between the retired athletes and normative data were the left inferonasal and left nasal sectors. This technique was also used in a longitudinal study that examined these outcomes in a veteran population (Gilmore et al., 2020). They reported that veterans with a history of mTBI had greater RNFL thinning compared to controls and that greater tissue loss was associated with higher ratings of mTBI severity (i.e., using Minnesota Blast Exposure Screening Tool severity scores).

2.6.9 | Structural Imaging

2.6.9.1 | Cavum Septum Pellucidum (CSP)

Several studies examined the occurrence and characteristics of a cavum septum pellucidum. Using a sample of 50 amateur boxers with high match (i.e., higher number of matches; average of 54 fights in their career) versus 25 low match exposure (i.e., average of 6 fights in their career) to examine whether morphological changes could be found when compared to track and field/soccer player controls (Haglund & Bergstrand, 1990). Using a 0.5T MRI, they reported no differences between these groups in the width of the ventricular system, anterior horn index, width of cortical sulci, signs of vermian atrophy, or the occurrence of a CSP. However, they observed that a CSP was found more often in track and field athlete controls than the boxers. Using a 1.5T MRI, Casson et al. (2014) found that 7% of their sample of retired NFL players had evidence of brain atrophy (i.e., enlarged ventricles and thinned corpus callosums) and large CSP, while 69% had a small cavum septum pellucidum.

More recently, 3T MRI was used to examine the occurrence and length of CSP, as well as its ratio to septum length in 72 former NFL players (presenting with cognitive, mood, and behavioural symptoms) and 14 former non-contact sport athlete controls (Koerte, Hufschmidt, et al., 2016). The authors found that former symptomatic NFL players had a higher rate of CSP as well as greater length of CSP (including its ratio to septum length). The presence of a CSP was also more common in a group of retired NFL players with cognitive and mental health symptoms (94%) than matched controls (18%; Gardner et al., 2016) and the length of the CSP in retired NFL players was significantly longer as well. Similar to these findings, another sample of 45 retired NFL players found that 7% had a CSP, 71% had a small one, and 22% did not have one (Kuhn, Zuckerman, & Solomon, 2016).

2.6.9.2 | Subcortical Structures

Studies that focused on examining differences between groups in subcortical volumes typically examined the hippocampus, amygdala, corpus callosum, and cingulate gyrus in retired professional athletes. Most recently, Bryant et al. examined structural MRI scans in a sample of older retired professional fighters and younger active professional fighters to compare brain volumes and correlations with age at first exposure (AFE) to fighting (Bryant et al., 2020). Earlier AFE was associated with smaller volumes in the posterior corpus callosum and bilateral hippocampi and amygdalae in both groups. In the active fighters' group, there was also an association between AFE and smaller left amygdala volume while smaller right amygdala

volume was associated with earlier AFE in the retired fighters group.

Studies consistently identified atrophy in the hippocampus (June et al., 2020; Misquitta et al., 2018; Monti et al., 2013) and less consistently in other structures like the amygdala or cingulate gyrus in those with remote mTBI exposure (Lepage et al., 2019). For instance, in a comprehensive longitudinal study (June et al., 2020), adults with mTBI history had smaller volumes than controls in white matter in the temporal lobe and the hippocampus at baseline, but volumes remained stable across subsequent visits. In retired CFL players, the number of years in the CFL was also significantly related to smaller volumes in the bilateral hippocampus and amygdala (Misquitta et al., 2018).

2.6.9.3 | Cortical Thickness

For studies that examined cortical thickness in adults with exposure to remote mTBI, some consistent patterns of reduced thickness have been observed. Thinner temporal lobes (Goswami et al., 2016; Koerte, Mayinger, et al., 2016; Tremblay et al., 2013; Wang et al., 2017), frontal lobes (Koerte, Mayinger, et al., 2016; Tremblay et al., 2013), and areas of the parietal lobes (Koerte, Mayinger, et al., 2016; Tremblay et al., 2013; Wang et al., 2017) have been noted in retired CFL players, former professional soccer players, adults with mTBI history and preclincal AD, and former college/university-level athletes who played ice hockey or football.

Tremblay and colleagues found that for former university/college athletes, increased age and having a mTBI history was associated with greater lateral ventricular volume expansion and thinner cortices (i.e., frontal, temporal, and parietal regions) compared to age matched controls (Tremblay et al., 2013). Additionally, former professional soccer players who had long-term exposure to heading the ball (i.e., played the sport for an average of 22.4 years) were found to have more cortical thinning with age in the occipital cortex (i.e., in addition to the temporal, posterior parietal, and left frontal cortices; Koerte, Mayinger, et al., 2016).

Finally, adults from the general population with mTBI exposure and preclinical AD (described in section 2.6.6) had reduced cortical thickness than controls when averaged across eight AD-vulnerable regions (i.e., superior and inferior parietal cortex, middle and inferior temporal gyrus, precuneus, posterior cingulate cortex, entorhinal cortex, and temporal pole), and in three of these regions specifically, including the precuneus and superior and inferior parietal cortex (Wang et al., 2017). Of note, no group differences were found in any of these regions

between controls and adults with mTBI and normal cognition. Similarly, a recent study examining cortical thickness in a sample of older adults with remote mTBIs compared to controls found no significant differences between groups as well (Rajesh et al., 2017). See Table 2 for a summary of the structural imaging findings.

Table 2

Aggregated Results for All Structural Imaging Studies

Lead Author	Cavum Septum Pellucidum (CSP)	Subcortical	Cortical
Haglund et al., 1990	*Null findings for group differences	*Null findings for group differences (i.e., vermis)	*Null findings for group differences (i.e., cortical sulci)
Casson et al., 2014	CSP (↑)	Corpus callosum (↓)	N/R
Koerte, Hufschmidt, Muehlmann, et al., 2016	CSP (↑)	N/R	N/R
Gardner et al., 2016	CSP (↑)	N/R	N/R
Kuhn et al., 2016	CSP (↑)	N/R	N/R
Bryant et al., 2020	N/R	Posterior corpus callosum (↓; with years of fighting exposure) Bilateral hippocampi (↓; with years of fighting exposure) Bilateral amygdalae (↓; with years of fighting exposure)	N/R
June et al., 2020	N/R	Temporal lobe white matter (↓) Bilateral hippocampi (↓)	N/R
Misquitta et al., 2013	N/R	Bilateral hippocampi (↓)	N/R
Monti et al., 2013	N/R	Bilateral hippocampi (↓) *Null findings for group differences in the putamen, caudate, and thalamus	N/R
Lepage et al., 2019	N/R	Bilateral hippocampi (↓) Bilateral amygdalae (↓) Bilateral cingulate gyri (↓)	N/R
Wang et al., 2017	N/R	N/R	*Null findings for normal cognition group

			Inferior parietal cortex (↓) Superior parietal cortex (↓) Precuneus (↓) Mean thickness of 8 cortical regions (↓)[1]
Goswami et al., 2016	N/R	N/R	Anterior temporal lobe (↓)
Tremblay et al., 2013	N/R	N/R	Bilateral frontal cortex (↓) Right temporo-parietal cortex (↓) Right temporal cortex (↓)
Koerte, Mayinger, Muehlmann, et al., 2016	N/R	N/R	Bilateral temporal cortex (↓) Bilateral posterior parietal cortex (↓) Bilateral occipital cortex (↓) Left frontal cortex (↓)
Rajesh et al., 2017	N/R	N/R	*Null findings for group differences

Note. Directionality, depicted using arrows, is reported for the experimental group in reference to control groups unless otherwise specified. N/R = not reported.

[1] The 8 cortical regions include the entorhinal cortex, temporal pole, inferior temporal gyrus, middle temporal gyrus, inferior parietal cortex, superior parietal cortex, precuneus, and posterior cingulate cortex.

2.6.9.4 | Ventricular and Global Brain Volume

Two studies examined ventricular size, skull diameter, and global brain volume. Zivadinov and colleagues (2018) found no significant differences between retired NHL/NFL players and non-contact sport controls when examining global and regional brain volumes. Another study examining professional fighters and controls however, reported that the maximum width of the anterior horns of the lateral ventricles and the interior diameter of the skull were significantly larger in the professional fighters (Wilde et al., 2016).

2.6.10 | Susceptibility Weighted Imaging

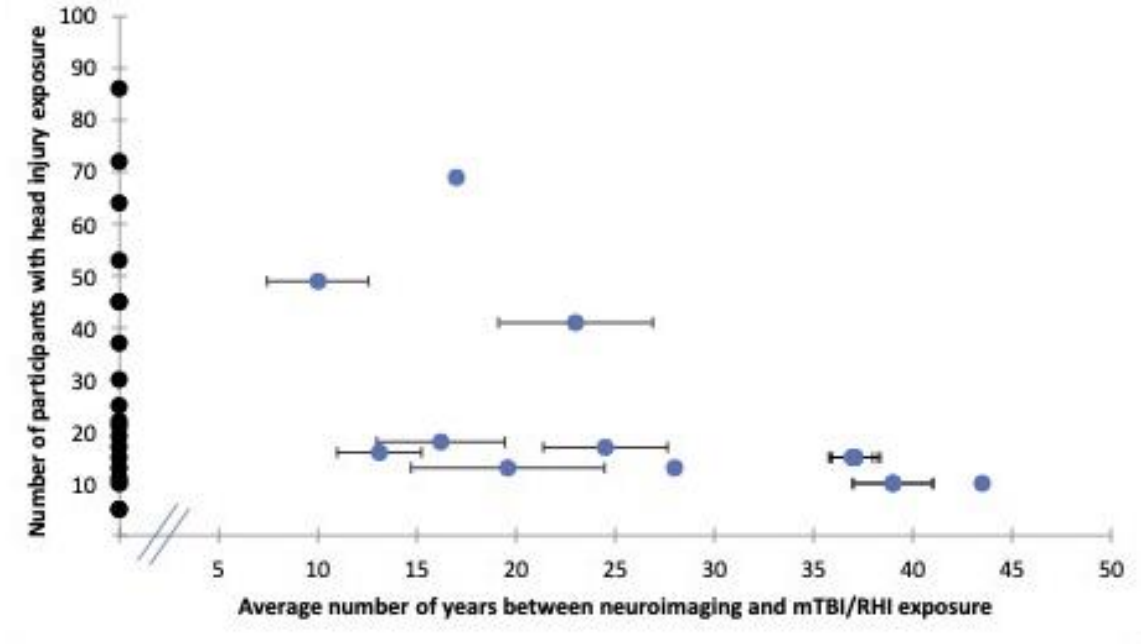
Three studies used SWI to detect hemosiderin deposition, which may be indicative of prior hemorrhages. Two studies examined the same sample of 45 retired NFL players and found that 9% of participants had microbleeds in the parenchyma of the brain (Casson et al., 2014; Kuhn et al., 2017). In contrast, no significant differences in the presence of cerebral microbleeds were observed between retired professional contact sport athletes and noncontact sport athlete controls in another study, though the control group had a higher number of participants with at least one cerebral microbleed (i.e., 33%) than the retired athletes group (i.e., 9.5%; Zivadinov et al., 2018).

2.7 Discussion

A total of 34 studies were identified that related to the long-term effects of mTBIs and RHIs on the brain (see Figure 2). The included studies used various neuroimaging techniques (i.e., PET scans, MRS, PWI, ASL, MTI, DTI, OCT, SWI, or fMRI) to examine brain health. All of the studies included in this review had a lower level of evidence (i.e., level four), with the exception of two studies that were rated a level three. In addition, risk of bias scores were below the cut-off value of 14 for most of the included studies, which indicates a threat to their internal and external validity.

Figure 2

The average years since head injury exposure and number of participants with head injury exposure per study



Note. Bars indicate the standard error and were plotted where available. Black dots represent studies that did not explicitly state years since head injury exposure but used other estimates, such as years since playing sport, or met criteria because follow-up occurred at least one decade after exposure to sport. See supplemental tables for more details.

2.7.1 | Athletes

The majority of the neuroimaging studies included in this review were conducted with retired professional athletes. Of these, the majority of the samples comprised retired NFL or CFL players (Casson et al., 2014; Clark et al., 2018; Coughlin et al., 2017; Ford et al., 2013; Gardner et al., 2016; Goswami et al., 2016; Hampshire et al., 2013; Hart et al., 2013; Koerte, Hufschmidt, et al., 2016; Kuhn et al., 2016; Lepage et al., 2019; Misquitta et al., 2018; Multani et al., 2016; Small et al., 2013; Vasilevskaya et al., 2020). The other studies included professional fighters (Bryant et al., 2020; Haglund & Bergstrand, 1990; Ware et al., 2020; Wilde et al., 2016) or athletes from other contact sports (De Beaumont et al., 2013; Kelman et al., 2020; Koerte, Lin, Muehlmann, et al., 2015; Koerte, Mayinger, et al., 2016; Lin et al., 2015; Lipton et al., 2013; Tremblay et al., 2013, 2019; Zivadinov et al., 2018). The neuroimaging research done in former NFL or CFL players has revealed differences compared to control samples in the presence and

greater length of cavum septum pellucidum and volumes in the amygdala and hippocampus using structural MRI (Gardner et al., 2016; Koerte, Hufschmidt, et al., 2016; Lepage et al., 2019; Misquitta et al., 2018). There was some evidence of differences in white matter microstructure using DTI, most consistently observed in the corpus callosum and superior longitudinal fasciculus (Clark et al., 2018; Hart et al., 2013; Multani et al., 2016), however, not all studies reported all DTI metrics (i.e., FA, RD, MD, or axial diffusivity) and/or similar regions with observed differences, if any (See Table 1). There was also some evidence of altered neural recruitment in areas supporting relational memory performance as identified by fMRI (Ford et al., 2013; Monti et al., 2013), and greater accumulations of amyloid-β and neurofibrillary tangles shown on PET scans (Small et al., 2013; Vasilevskaya et al., 2020). Though studies were cross-sectional and correlational, findings suggested a relationship between exposure to remote mTBI and/or RHIs and observable differences in brain structure and function using neuroimaging. However, it is notable that there was some variability in reported differences (e.g., observed differences in different regions and/or using different metrics, or differences between studies in the brain regions that they chose to investigate) and that there was limited replication of findings. Further, there was significant variability in the operationalization of mTBI and RHIs, making comparisons across studies difficult.

Findings from studies that examined former professional fighters were inconsistent in that some found no brain-related differences between fighters and controls (Haglund & Bergstrand, 1990; Wilde et al., 2016), while others did (Ware et al., 2020). In the earlier study, it is noteworthy that the use of a lower-strength MRI scanner (0.5 tesla) might have contributed to some variable findings, in addition to making comparisons to the more recent studies that use higher field strength MRI difficult. Overall, two studies found evidence of similar white matter disruptions in the corpus callosum associated with the duration of exposure to boxing in professional fighters (Bryant et al., 2020; Ware et al., 2020). Future studies should aim to replicate findings about the long-term effects of RHIs in this population, specifically by examining the uncinate fasciculus and inferior longitudinal fasciculus.

Other studies examined athletes who played a variety of professional contact sports including rugby (Kelman et al., 2020), soccer (Koerte, Lin, Muehlmann, et al., 2015; Koerte, Mayinger, et al., 2016; Lipton et al., 2013), a mix of several sports (Lin et al., 2015; Zivadinov et al., 2018) and/or levels of play (e.g., university level and professional; Tremblay et al., 2019), as

well as university-level hockey/football (De Beaumont et al., 2013; Tremblay et al., 2013). The imaging techniques used in these studies were also diverse. However, there was evidence of different levels of metabolites in several brain regions for athletes compared to controls which may be indicative of neuroinflammation (De Beaumont et al., 2013; Koerte, Lin, Muehlmann, et al., 2015; Lin et al., 2015; Tremblay et al., 2013) and white matter disruption in widespread areas (Kelman et al., 2020; Lipton et al., 2013; Tremblay et al., 2019). As per the above sections, methodological considerations (i.e., distinct study designs and methods for selecting brain regions and quantifying metabolites) limit the conclusions that can be drawn from these data.

2.7.2 | Veterans and Service Members

Published articles that focused on the long-term neuroimaging findings associated with RHIs/mTBI in veterans were limited. With only two studies identified in relation to this topic, the ability to make interpretations was severely limited. One study reported thinning of retinal nerve fibre layer (RNFL) thickness (Gilmore et al., 2020) and the other found that altered functional connectivity (i.e., hyperconnectivity) after mTBI was associated with post-deployment development of PTSD (Rowland et al., 2018). More research is needed to understand whether RNFL thickness is truly an indicator of white matter loss and neurodegeneration in this population. Also, given that hyperconnectivity was only seen in those who had developed PTSD, future research will be needed in order to confirm group differences and to better understand preliminary findings about functional connectivity in those who do and do not develop PTSD. Overall, a greater amount of research is needed to better understand the long-term consequences of RHIs and mTBI in veteran populations.

2.7.3 | General Population

Six of the studies that were included in this review examined participants from the general population. For two of these studies, groups were divided into younger and older adults who had recent or remote mTBIs, respectively for comparisons of brain structure and functional activation (Monti et al., 2013; Rajesh et al., 2017). Both of these studies reported hypoactivation in several brain areas along with greater white matter disruption and smaller cortical and subcortical volumes; however, their findings were not consistent (i.e., poorer outcomes in the

older adults with remote mTBIs in one study and no differences between the remote mTBI group and controls in the other study). For the remaining studies, the control groups were either another clinical population (Chong et al., 2018; Wang et al., 2017) or age matched adults without a TBI history (June et al., 2020; Tremblay et al., 2019; Wang et al., 2017). No discernable trends were identified across the studies that compared adults with mTBI to other clinical populations. For the studies that compared adults with mTBI to control participants without a mTBI history, findings were also generally disparate. Two of these studies found no group differences (Tremblay et al., 2019; Wang et al., 2017) while the other found alterations in cerebral blood flow, atrophy in subcortical structures, and other indicators of white matter disruption in several areas in the mTBI group (June et al., 2020). While the diversity of the designs used for examining the long-term neuroimaging findings associated with mTBI in the general population was a strength, the lack of replication of these studies, their correlational design, and inconsistency in findings were important factors that limited their generalizability.

2.7.4 | Repetitive Head Injuries

Some of the studies included in this review focused on examining the potential long-term effects of RHIs on the brain (Bryant et al., 2020; Haglund & Bergstrand, 1990; Hampshire et al., 2013; Koerte, Lin, Muehlmann, et al., 2015; Koerte, Mayinger, et al., 2016; Lepage et al., 2019; Lin et al., 2015; Lipton et al., 2013; Ware et al., 2020; Wilde et al., 2016; Zivadinov et al., 2018). One major challenge of this line of research is the variability in defining and capturing RHIs. All studies relied on self-reported proxies of RHIs, including self-reported estimations of years of sport play, estimates of ball-headings, and/or estimates of the number of times players recalled being taken out of play following head impact. None of the included studies used objective measures to support RHI exposure estimates (e.g., accelerometer data or systematic video review). However, one study attempted to quantify RHI exposure by collecting self-reported data about ball-heading exposure during a typical practice and competitive game and then extrapolated this data across a one-year timespan. They reported that history of a previous concussion did not explain differences between groups (i.e., high-, medium-, or low-heading exposure) in their DTI analyses, but estimated RHI exposure did (Lipton et al., 2013).

Importantly, some studies examined adults who had been exposed to both RHIs and mTBI, making it difficult to disentangle the unique outcomes associated with each injury type

(Ware et al., 2020; Zivadinov et al., 2018). For other studies, it was unclear whether data about mTBI exposure was collected or accounted for because only the exposure to contact sports, which was used as a proxy for RHI, was discussed (Bryant et al., 2020; Haglund & Bergstrand, 1990). One way to avoid this problem would be to exclude those who have reported having a previous mTBI but include those who have experienced repetitive impacts to the head (e.g., heading the ball in soccer). In doing this, one study found that retired professional athletes had greater levels of metabolites (e.g., choline and myo-inositol) many years after their potential RHI exposure compared to controls (Koerte, Lin, Muehlmann, et al., 2015). A similarly designed study (Koerte, Mayinger, et al., 2016) found greater cortical thinning (i.e., right inferolateral-parietal, temporal, and occipital cortex) with increasing age in soccer players than controls. However, given the lack of studies that fit these criteria, care must be taken in interpreting these findings. Inferences on a larger scale cannot be made without further research in this area.

2.7.5 | Early Versus Late Life Exposure to Head Injury

Studies that have examined age at first exposure to head injury have reported conflicting findings. Findings from several retrospective studies in this review suggest that sustaining injuries earlier in life (i.e., early adulthood) may be associated with the presence of neuroimaging findings (e.g., smaller regional volumes or white matter disruption) in the long-term compared to experincing a head injury at an older age (Bryant et al., 2020; Casson et al., 2014; Monti et al., 2013; Tremblay et al., 2019). With more evidence to support findings, this would have important implications for young adults who are at increased risk for sustaining a mTBI (e.g., athletes) or for older adults who were exposed to mTBIs in early adulthood. Importantly, one study identified in this review purported that neurological seqaelae may persist for several years post-injury before resolving (Rajesh et al., 2017). With the current methodological limitations to consider at present, more longitudinal research and a greater number of high-quality studies devoted to this topic will be needed to draw conclusions about this matter. Of note, this question was addressed in the general population (Monti et al., 2013; Tremblay et al., 2019) and in athletes (Bryant et al., 2020; Casson et al., 2014) but not in veteran samples.

2.7.6 | Limitations

This systematic review is one of the first to broadly examine the long-term effects of RHIs and mTBIs in several population groups. Given the heterogeneity of the studies included in this review, there are important limitations to consider. Firstly, there were generally small sample sizes (see Figure 2) and a lack of inclusion of other variables (e.g., genetics, substance use, mental health status, medical or psychiatric diagnoses, diet, exercise, sleep habits) that may influence the relationship between RHI or MTBI exposure and neuroimaging findings in the long-term (Sariaslan, Sharp, D'Onofrio, Larsson, & Fazel, 2016). The majority of studies employed a retrospective, cross-sectional design, with some variability in the average time since last injury/exposure to RHIs (see Figure 2). In addition, generalizability of findings was limited by the broad range of imaging data acquisition, preprocessing, and analysis methods used, the lack of replication studies, and the diverse control groups used. Furthermore, there was considerable heterogeneity in the definitions and identification of mTBI and RHIs across studies. Some studies opted for more rigorous methods than others and this should be considered when interpreting findings. Finally, there was a notable lack of data or findings regarding long-term outcomes for women with exposures to mTBI/RHI. This highlights an important gap in the literature and a need for more research devoted to investigating brain differences and health outcomes for women in the long-term.

Another limitation to this review was the selection bias for studies that were published in English. In addition, only one study (Zivadinov et al., 2018) reported entirely on and published null findings (though some reported partial null findings). Considering that studies with null findings are less likely to be published and would therefore be excluded from this review, there is a potential risk for publication bias. This review also included all relevant studies and did not discriminate based on the quality of evidence available. Therefore, it is possible that findings may have been overestimated due to the inclusion of studies with lower evidence. Finally, without post-mortem studies in this review, inferences about susceptibility to neurodegenerative diseases were not possible to address as most studies focussed on risk factors that may be associated with early neuropathology instead.

2.8 Conclusions and Future Directions

Overall, there appears to be some evidence to suggest an association between exposure to mTBI and neuroimaging findings in older adulthood. Though the neuroimaging studies captured

in this review were mostly cross-sectional in design, there was some evidence for differences in white matter microstructure (i.e., mainly in the corpus callosum and superior longitudinal fasciculus, though discrepancies were observed; Chong et al., 2018; Clark et al., 2018; Goswami et al., 2016; Hart et al., 2013; June et al., 2020; Lipton et al., 2013; Multani et al., 2016; Tremblay et al., 2019; Ware et al., 2020), smaller brain structures (Bryant et al., 2020; Gardner et al., 2016; Goswami et al., 2016; Haglund & Bergstrand, 1990; June et al., 2020; Koerte, Hufschmidt, et al., 2016; Kuhn et al., 2016; Lepage et al., 2019; Misquitta et al., 2018; Monti et al., 2013; Wang et al., 2017), neurochemical differences (De Beaumont et al., 2013; Koerte, Lin, Muehlmann, et al., 2015; Lin et al., 2015), functional brain differences (Clark et al., 2018; Ford et al., 2013; Goswami et al., 2016; Hampshire et al., 2013; Monti et al., 2013; Rowland et al., 2018), altered cerebral blood flow (Hart et al., 2013; Zivadinov et al., 2018), and greater proteinopathy (Small et al., 2013; Vasilevskaya et al., 2020; Wang et al., 2017) in adults who have a history of RHIs and/or one or more mTBIs beyond at least a decade. However, there are a number of limitations within the current literature (see section 2.7.6). Future research should be devoted to replicating and expanding the present research through addressing some of the methodological concerns highlighted in this systematic review. With the publication of more higher-powered longitudinal studies, it may be possible to better detect neural structures vulnerable to this injury, if any, over time. Based on this review, it is also evident that greater consistency and clarity is needed in the definition and identification of injuries retrospectively. A specific focus on improving our understanding of these associations in the general population and with veterans/service members is also necessary.

Furthermore, more recent studies often employed newer analysis techniques (e.g., region by region volumetric comparisons to more data-driven approaches to analyses; Misquitta et al., 2018; Tremblay et al., 2019; Wang et al., 2017) used newer technology (e.g., 0.5T MRI in 1990 versus 3T in 2020; Haglund & Bergstrand, 1990; June et al., 2020) or modalities (e.g., OCT; Gilmore et al., 2020; Kelman et al., 2020) which further complicates synthesis across studies. Furthermore, future studies should examine the amount of variance accounted for by mTBI/RHIs, beyond that of other factors that may contribute to positive neuroimaging findings or possible accelerated brain aging (e.g., genetics, lifestyle differences, illnesses, etc.). Finally, well-designed longitudinal studies are needed to understand the potential contribution of mTBI and RHIs to the aging process.

CHAPTER 3: Mild Traumatic Brain Injury Exposure and Associations with Structural Markers of Brain Health in Vietnam War Veterans

3.1 Overview

The purpose of this study was to address a gap in the literature identified in the previous chapter which highlighted the limited research on long-term outcomes related to neuroimaging findings and mTBI exposure in veteran or service member samples. The present study aimed to investigate whether there are relationships between mTBI exposure and cortical thickness using both hypothesis-driven and exploratory approaches. In addition, given the vulnerability of axonal white matter to both aging and TBI, this study also examined whether there are relationships between mTBI exposure and white matter damage, defined here as white matter hyperintensity volumes (WMHV).

3.2 Publication Status and Author Contributions

This retrospective study is currently in preparation to be submitted for publication. The content of this chapter does not exactly replicate the manuscript that is in preparation for publication. Thus, this chapter is not a copy of the manuscript and is not suitable for citation. Holly Echlin (i.e., the first author) developed the conceptual rationale for the study, applied for access to the data, and organized, analyzed, and interpreted the data. She was also the primary contributing author of the manuscript and produced the initial draft and completed all major revisions.

3.3 Abstract

Research regarding the long-term associations between cortical thickness and mTBI exposures is limited. Previous literature, including a meta-analysis, acute injury data, function connectivity differences, and data from veteran samples has suggested that the medial orbitofrontal, middle frontal, and superior frontal cortices may be associated with neural differences in the long-term. These regions were examined in a sample of Vietnam War veterans (whose data were obtained from the ADNI-DOD database) in addition to an exploratory analysis of all other cortical areas. METHODS: Participants were 47 veterans with mTBI exposures (M_{age} = 69.43, SD = 5.02) and 82 veterans without mTBIs (M_{age} = 68.51, SD = 4.69). Associations between mTBI, age, education, cognitive status, PTSD symptoms, white matter hyperintensity

volumes, and cortical thickness were examined in brain regions implicated in remote mTBI exposure. RESULTS: Older age was associated with lower thickness in the left ($p = 0.003$) and right ($p = 0.006$) pericalcarine, left ($p = 0.001$) and right ($p < 0.001$) fusiform, and left lingual ($p < 0.001$) cortices. Three regions, i.e., the left caudal middle frontal ($p = 0.017$) and the left ($p = 0.024$) and right ($p = 0.011$) superior frontal cortices, showed greater cortical thickness for the mTBI group. MTBI was also a predictor of greater cortical thickness in the left insula ($p = 0.040$), but this finding did not survive multiple comparison corrections ($p = 0.440$). MTBI was not associated with WMHV ($p = 0.908$), but age was ($p = 0.007$). CONCLUSIONS: These findings indicate that mTBI may have a circumscribed effect on the brain and highlights several potential regions for future analyses examining long-term mTBI sequelae.

Keywords: Vietnam War Veterans, Cortical Thickness, White Matter Hyperintensity Volumes, Long-Term, Mild Traumatic Brain Injury

3.4 Introduction

The systematic review conducted in study 1 identified that associations between brain structure and mTBI exposure in the long-term was an area of limited research. To address this gap, the aim of the current study was to examine the long-term effects of mTBI on cortical thickness in a sample of Vietnam War veterans from the ADNI-DOD database. Given that mTBIs are heterogeneous in nature and have the potential for widespread impacts (Li et al., 2020; Palacios et al., 2022), the current study will use both a hypothesis driven and an exploratory approach to examining the data in this sample. Previous research has demonstrated that a propensity for accelerating/decelerating forces acting on the brain and its collision with the skull during a TBI may produce a higher risk for potential impact with cortical areas near the injury site (i.e., along the grey matter-cerebral spinal fluid border), with less risk overall for subcortical structures or lobules of the cerebellum (Muller et al., 2021; Sussman et al., 2017). Given the potential for having no or limited macrostructural changes to the brain following an mTBI, targeted exploration of any potential cortical thickness differences in each hemisphere in the long-term is warranted to better understand the circumscribed nature of findings. Additionally, veteran populations with blast-related mTBIs may experience more dispersed effects on the brain due to kinetic forces with injury

and this may be apparent when examining other neurological pathologies (Davenport, Lim, Armstrong, & Sponheim, 2012; Riedy et al., 2016) that are important to consider given the limited amount of research using these modalities (e.g., examining white matter hyperintensities) and that they may become more prominent in an older adult sample (Erten-Lyons et al., 2013).

As evidenced in Study 1, the literature indicates that many cortical areas may be implicated depending on the nature of the injury and the location of the impact (Echlin et al., 2021; Koerte, Mayinger, et al., 2016; Tremblay et al., 2013; Wang et al., 2017). Despite the heterogeneity of the literature, we predicted that there would be differences in the long-term in cortical thickness for those with mTBI exposures in the middle frontal cortex (Clark et al., 2018; Cook et al., 2020; Eierud, Nathan, Bonavia, Ollinger, & Riedy, 2019; Muller et al., 2021), the medial orbital frontal cortex (Eierud et al., 2019; Martindale, Rostami, Shura, Taber, & Rowland, 2020) and the superior frontal cortex (Eierud et al., 2019; Lindemer, Salat, Leritz, McGlinchey, & Milberg, 2013; Sussman et al., 2017). These regions were chosen based on a meta-analytic review, findings from other veteran samples, or consistent findings about cortical thickness and remote mTBI that have been published in multiple studies (Clark et al., 2018; Cook et al., 2020; Eierud et al., 2019; Lindemer et al., 2013; Martindale et al., 2020; Muller et al., 2021; Sussman et al., 2017).

Further, some studies have suggested that white matter hyperintensities are associated with cortical thinning and that they are also related to cognitive decline in patients with MCI or dementia (Kim et al., 2020; Rizvi et al., 2021; Seo et al., 2012). There are mixed findings in the literature as to whether or not white matter hyperintensities are associated with mTBI exposure (Jarrett et al., 2016; Patel, Wilson, Oakes, Santhanam, & Weaver, 2020; Riedy et al., 2016), though relationships with moderate and severe TBI have been demonstrated (Berginström, Nordström, Nyberg, & Nordström, 2020; O'Phelan, Otoshi, Ernst, & Chang, 2018). Therefore, we aimed to investigate this relationship further and predicted there would be greater WMHVs in those with mTBI exposure.

3.5 Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI),

positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org. The larger study from which these data were derived has been approved by the Committee on Human Research at the University of California at San Francisco, the San Francisco VA Medical Center Research and Development Committee, and the Department of Defense Human Research Protection Office. All participants provided informed consent before being enrolled in the study. Permission was granted by ADNI to access the data for the current study and the procedures were approved by York University's Research Ethics Board.

3.5.1 | Participants

The sample consisted of 129 Vietnam War Veterans from the Alzheimer's Disease Neuroimaging Initiative – Department of Defense (ADNI-DOD) database. Data are from a multisite study examining the effects of non-penetrating brain injuries (i.e., mild or moderate) and/or PTSD diagnoses on the development of AD in a sample of male Vietnam War veterans with and without mild cognitive impairments (MCI). The data were collected between 2013 and 2019. Exclusion criteria for this sample at the initial telephone pre-screening included diagnoses of dementia, history of psychosis, schizophrenia, or bipolar affective disorder, recent history of substance use or dependence (in the past 5 years), or any neuroimaging contraindications. Given that the aim of the study was to examine long-term findings associated with mTBI, participants were also excluded (n = 2) if they indicated that their head injury occurred within ten years prior to their neuroimaging date.

Participants between the ages of 61 and 83 were split into two groups, (1) a group with exposure to one or more mTBIs, and (2) a control group with no reported head injuries in their lifetime. Those who reported any exposure to moderate or severe head injuries in their lifetime were excluded (n = 52, see criteria below). Additionally, adults who met screening criteria for MCI (see measures section below) were included, but those with moderate/severe cognitive impairments were excluded. Only one participant in the control group met screening criteria for moderate cognitive impairments and thus was excluded. Adults who endorsed symptoms of PTSD were also eligible for inclusion in this study. PTSD symptom endorsement and MCI status were not different between groups; however, their relative frequencies are presented in the results

section of study 3 (see section 4.6.1). Both variables were controlled for in all analyses. For participants who endorsed PTSD symptoms, a score of 40 or higher on the Clinician Administered PTSD Scale (CAPS) lifetime measure was used to indicate clinical significance (Weathers, Keane, & Davidson, 2001). In this sample, 47 participants reported exposures to at least one mTBI and 82 participants reported no mTBI exposures in their lifetime.

3.5.2 | Measures

3.5.2.1 | Demographic Information, mTBI, and Repetitive Head Impact History

Participants provided demographic information during an interview, specifically regarding their general health, age, education, sex, substance use, and any indicators of mental health issues. To screen for head injury history, participants also responded to a series of health-related interview questions, which included questions about their first exposure to a head injury, the number of head injuries they had, experiences and the nature of the symptoms and severity of reported TBIs. The 47 individuals with mTBIs reported loss of consciousness (LOC) for no more than 30 minutes, alteration of consciousness for no more than 24 hours, and post-traumatic amnesia (PTA) for no longer than 24 hours, if at all (National Academies of Sciences Engineering and Medicine, 2019; Qualifying Statements, 2009; von Holst & Cassidy, 2004). These interviews were administered to participants after their time in Vietnam. Participants' data were coded categorically so that those with mTBI exposures were coded as a 1 and those without mTBI exposures were indicated with a 0.

3.5.2.2 | Clinician Administered PTSD Scale for DSM-IV (CAPS)

The CAPS was used to examine lifetime and current PTSD while also ruling out psychosis or substance use issues (Blake et al., 1995). This scale ranges from 0 to 136, with higher scores indicating greater symptom severity. A cut-off for the presence of PTSD symptoms of 40 or higher was used (e.g., indicating minimally to severely symptomatic PTSD), while scores of 0 to 39 indicated an absence of PTSD symptoms, or minimal symptoms (Blake et al., 1995; Weathers et al., 2001). Scores of 65 or higher indicate clinically elevated symptom endorsement levels of PTSD (Weathers, Ruscio, & Keane, 1999). Each of the symptoms were assessed using an indication of the symptom intensity and frequency (i.e., both on a scale of 0-4). To meet criteria for a symptom,

intensity score must have been scored as a 2 or higher as well as a frequency score of 1 or higher. For the purposes of this study, this variable was coded categorically with a 0 indicating no PTSD and a 1 indicating symptomatic for PTSD.

3.5.2.3 | Montreal Cognitive Assessment (MoCA)

The MoCA is a cognitive screening test used for detecting MCI and AD (Nasreddine et al., 2005). This measure includes a brief assessment across the domains of executive functioning, speed of processing information, memory, visuospatial ability, attention, language skills, abstract reasoning, and orientation. The scale ranges from 0-30, with lower scores indicating greater impairment. Cut-off scores for this measure include: 26-30 indicating no impairments in cognition, 18-25 indicating mild cognitive impairments, 10-17 indicating moderate cognitive impairments and 9 or below indicating severe cognitive impairments. MoCA total scores were coded categorically with a 0 indicating no MCI and a 1 indicating meeting screening criteria for mild cognitive impairments.

3.5.2.4 | Neuroimaging

Neuroimaging data were obtained on qualified ADNI General Electric (GE) Healthcare systems (3T). The protocol consisted of a three-dimensional (3D), T1-weighted volumetric scan using the inversion recovery – spoiled gradient recalled (SAG IR-SPGR) echo sequence. This sequence was acquired with the following parameters: 196 sagittal slices were collected with a slice thickness of 1.2 mm and a matrix size of 256 x 256 with a voxel spatial resolution of 1.0 x 1.0 x 1.2 mm, repetition time (TR) = 7.65 ms, echo time (TE) = 3.10 ms, inversion time (TI) = 400 ms, and flip angle = 11°. All measurements were obtained from ADNI FreeSurfer output. T1-weighted images were processed using the FreeSurfer version 5.1 recon-all pipeline (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA), and geometric measures of cortical regions were computed (M. W. Weiner et al., 2014). Cortical thicknesses were examined in the cortical structures.

Measures of white matter hyperintensity burden were obtained from T2-weighted fluid attenuated inversion recovery (FLAIR) scans. This sequence was acquired with the following parameters: 42 axial slices were collected with a slice thickness of 5.0 mm and a matrix size of

256 x 256 with a voxel spatial resolution of 0.859 x 0.859 x 5.0 mm, TR = 11,000 ms, TE = 151.40 ms, TI = 2250.0 ms, and flip angle = 90°. The WMHV variable was created by dividing the WMHVs by the total white matter volume (both values reported in cm^3).

3.5.3 | Design and Analyses

Cortical brain areas were added to regression analyses to examine the relationships between our variables of interest. The predicter variables included past mTBI exposure compared with no previous history and the outcome variable was cortical thickness and WMHVs. The multiple regression analyses were conducted such that they controlled for relevant covariates (e.g., age, education, MCI scores, and CAPS scores), in order to examine the relationship between mTBI exposure and cortical thickness or WMHVs.

3.6 Results

3.6.1 | Descriptive Information

Demographic and descriptive variables are presented in Table 3 below. There were no differences in mean age between the 47 participants with mTBI exposures (M = 69.43, SD = 5.02) and the 82 participants without mTBIs (M = 68.51, SD = 4.69, p = 0.312) and their ages ranged between 61 and 83. Participants' average time since their first injury was 49.53 years and the average time since their most recent injury was 47.28 years. Within the mTBI group, 39 participants had one mTBI exposure, 5 had two mTBIs, and 3 had three mTBIs. The majority of participants in the sample were right-handed (n = 115), though there were 5 participants in the mTBI exposed group and 9 in the control group who were left-handed. There were no significant differences between the control group and those with mTBI exposures on most of the measures except for immediate story memory (t(104.98) = 2.364, p = 0.020; with higher performance in the control group), delayed memory (t(102.6) = 2.090, p = 0.039; with higher performance in the control group), endorsement of problematic alcohol use (t(91.213) = 2.214, p = 0.029; with more problematic alcohol consumption in the control group), and current PTSD symptoms (t(102.09) = -2.469, p = 0.015; with higher current PTSD symptom severity in the mTBI group). In addition, see section 4.6.1 for further descriptive analyses and Table 4 below for descriptive information about all cortical thicknesses analyzed as well as the WMHV sizes.

Table 3

Table of Descriptive Information for All Participants

	mTBI (n = 47)			Controls (n = 82)			
	N	Mean	SD	N	Mean	SD	p-values
Age	47	69.43	5.02	82	68.51	4.69	0.312
Years of Education	47	14.94	2.40	82	15.38	2.2	0.302
MoCA Score	46	23.43	2.24	78	24	1.9	0.155
MOCA score in MCI+[a]	38	22.76	1.79	61	21.34	1.57	0.266
CAPS Lifetime	46	46.91	30.26	80	35.86	38.5	0.077
CAPS Current	46	37.76	26.11	80	25.34	28.96	0.015*
CAPS score in those PTSD+[b]	28	67.86	14.91	33	78.55	18.55	0.021*
Geriatric Depression Scale Total	47	2.62	2.59	82	2.61	3.35	0.989
SCID-IV Years of Problematic alcohol Use	46	0.43	0.50	80	0.64	0.48	0.029*
Total number of mTBIs	47	1.3	0.91	0	0	0	N/A
Age at 1st injury	47	20.23	9.17	0	0	0	N/A
Time since 1st injury	47	49.53	9.49	0	0	0	N/A
Logical memory immediate	47	10.89	3.31	82	12.39	3.7	0.020*
Logical memory delayed	47	9.57	3.52	82	10.96	3.82	0.039*

Note. N/A = not applicable. The total number of mTBI exposures includes exposures before, during, or after the war, but not within ten years of their neuroimaging date. p-values are reported for Welch's t-tests between groups. * = $p < 0.05$. [a] Denotes scores for those who scored 25 or lower on the MoCA in the mTBI and control group. [b] Indicates the number of people in each group with scores $\geq$40 on the CAPS lifetime (i.e., PTSD) variable.

Table 4

Table of Descriptive Information for Cortical Thickness and White Matter Hyperintensity Volumes

	mTBI		Controls		
	Mean	SD	Mean	SD	*p*-values
Left Caudal Anterior Cingulate	2.65	0.36	2.53	0.38	0.079
Right Caudal Anterior Cingulate	2.51	0.32	2.49	0.29	0.818
Left Caudal Middle Frontal	**2.38**	**0.12**	**2.33**	**0.17**	**0.049***
Right Caudal Middle Frontal	2.33	0.13	2.31	0.16	0.524
Left Cuneus	1.83	0.14	1.82	0.13	0.687
Right Cuneus	1.83	0.14	1.82	0.14	0.639
Left Frontal Pole	2.63	0.25	2.56	0.29	0.178
Right Frontal Pole	2.44	0.25	2.45	0.26	0.991
Left Fusiform	2.62	0.14	2.65	0.19	0.428
Right Fusiform	2.69	0.18	2.66	0.18	0.367
Left Insula	2.98	0.19	2.93	0.16	0.102
Right Insula	2.69	0.18	2.66	0.18	0.385
Left Isthmus Cingulate	2.45	0.22	2.45	0.26	0.978
Right Isthmus Cingulate	2.94	0.20	2.92	0.15	0.567
Left Lateral Occipital	2.04	0.12	2.03	0.13	0.710
Right Lateral Occipital	2.14	0.13	2.13	0.14	0.604
Left Lateral Orbitofrontal	2.50	0.16	2.47	0.18	0.407
Right Lateral Orbitofrontal	2.43	0.16	2.43	0.16	0.970
Left Lingual	1.93	0.13	1.95	0.13	0.644
Right Lingual	1.96	0.15	1.95	0.13	0.541
Left Medial Orbitofrontal	2.40	0.17	2.41	0.16	0.805
Right Medial Orbitofrontal	2.34	0.20	2.33	0.17	0.755
Left Paracentral	2.30	0.12	2.28	0.15	0.375
Right Paracentral	2.26	0.14	2.26	0.16	0.846

Left Parahippocampal	2.77	0.36	2.73	0.33	0.536
Right Parahippocampal	2.71	0.34	2.71	0.30	0.976
Left Pericalcarine	1.60	0.15	1.59	0.13	0.507
Right Pericalcarine	1.58	0.16	1.55	0.12	0.331
Left Postcentral	1.90	0.13	1.88	0.13	0.519
Right Postcentral	1.89	0.11	1.88	0.13	0.386
Left Precentral	2.35	0.15	2.32	0.15	0.283
Right Precentral	2.32	0.15	2.30	0.14	0.386
Left Precuneus	2.25	0.12	2.24	0.14	0.694
Right Precuneus	2.25	0.12	2.25	0.15	0.796
Left Rostral Anterior Cingulate	2.85	0.27	2.81	0.26	0.396
Right Rostral Anterior Cingulate	2.84	0.22	2.85	0.23	0.878
Left Rostral Middle Frontal	2.17	0.14	2.14	0.14	0.218
Right Rostral Middle Frontal	2.12	0.11	2.10	0.12	0.398
Left Superior Frontal	2.53	0.14	2.49	0.16	0.123
Right Superior Frontal	2.50	0.13	2.45	0.15	0.063
Left Superior Parietal	2.06	0.13	2.05	0.16	0.685
Right Superior Parietal	2.07	0.12	2.07	0.15	0.989
Left Supramarginal	2.35	0.14	2.33	0.13	0.364
Right Supramarginal	2.38	0.13	2.37	0.14	0.638
White Matter Hyperintensity Volumes	0.010	0.020	0.010	0.010	0.806

Note. *p*-values are reported for Welch's t-tests between groups. * = $p < 0.05$. The values for the white matter hyperintensity volumes are reported in mm^3. There were 47 adults in the mTBI group and 82 in the control group.

3.6.2 | Effect of mTBI Exposure on White Matter Hyperintensity Volumes

To understand whether there is an effect of exposure to mTBI on WMHVs, a regression model was constructed with age, MoCA cut-off scores, CAPS Lifetime scores, and education included in the model as covariates. However, age was the only significant predictor of WMHVs ($\beta = 0.259$, $p = 0.007$). With increased age, WMHVs increased. The model accounted for 7.0% of the variance in WMHVs. MCI status was not a predictor of WMHV. Regression coefficients are provided in Table 5 below.

Table 5

Regression Results Predicting White Matter Hyperintensity Volumes

White Matter Hyperintensity Volumes	***B***	**S.E.**	**β**	***p***
mTBI	-0.000	0.003	-0.011	0.908
MCI Status	0.002	0.003	0.069	0.459
Age	0.001	0.000	0.259	0.007**
Education	-0.000	0.001	-0.057	0.554
CAPS Lifetime	0.000	0.000	0.127	0.198
R^2	0.070			

Note. B = unstandardized betas, β = standardized betas, and $p < 0.01$ = **.

3.6.3 | Hypothesis-Driven and Exploratory Analyses Examining mTBI Exposure and Cortical Thickness

To examine relationships between mTBI exposure and cortical thickness, linear regression models were constructed with age, MoCA cut-off scores, CAPS Lifetime scores, and education included as covariates. FDR corrections were applied to all exploratory analyses and were not applied to the theoretically driven hypotheses (i.e., regarding effects of mTBI on the middle or bilateral superior frontal cortices). Of the 44 areas examined in these analyses, 4 regions were associated with mTBI exposure, with 3 of these regions surviving false discovery rate (FDR) correction for multiple comparisons using the Benjamini Hochberg method (Benjamini & Hochberg, 1995); see Tables 6, 7, 8, and 9 and Figures 3, 4, 5, and 6. Having an exposure to mTBI was associated with greater thickness in the left caudal middle frontal cortex ($\beta = 0.223$ $p = 0.017$; 6.1% of the variance in left caudal middle frontal cortex thickness was accounted for by the model), and in the left ($\beta = 0.210$ $p = 0.024$; 8.2% of the variance in left superior frontal cortex thickness was accounted for by the model) and right superior frontal cortices ($\beta = 0.239$ $p = 0.011$; 8.0% of the variance in right superior frontal cortex thickness was accounted for by the model). MTBI exposure was also associated with greater thickness in the left insula ($\beta = 0.193$ $p = 0.040$; 6.9% of the variance in left insula cortical thickness was accounted for by the model), though this finding did not survive FDR correction ($p = 1.640$). Increased age was associated with lower thickness also in the left superior frontal cortex ($\beta = -0.186$ $p = 0.048$). Additionally, being in the group who positively screened for MCI on the MoCA was associated with greater thickness in the left insula ($\beta = -0.182$ $p = 0.050$), though this did not survive FDR correction ($p = 2.050$).

Table 6

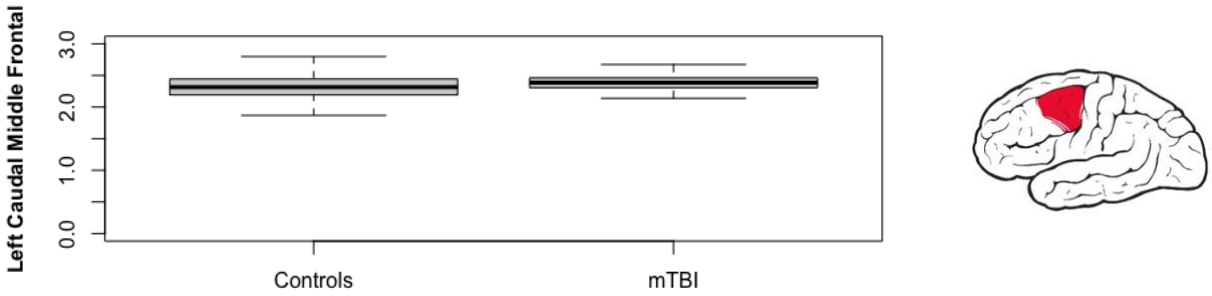
Regression Predicting Cortical Thickness in the Left Caudal Middle Frontal Cortex

	B	**S.E.**	**β**	***p***
mTBI	0.073	0.030	0.223	0.017*
MCI Status	0.006	0.036	0.014	0.874
Age	-0.004	0.003	-0.118	0.207
Education	0.008	0.007	0.116	0.222
CAPS Lifetime	-0.000	0.000	-0.044	0.649
R^2	0.061			

Note. B = unstandardized betas, β = standardized betas, and $p < 0.05$ = *.

Figure 3

mTBI Exposure and Cortical Thickness in the Left Caudal Middle Frontal Cortex (p = 0.017; β = 0.223)



Note. Units are in millimetres. The red colour within the brain image represents greater cortical thickness in the mTBI group compared to controls.

Table 7

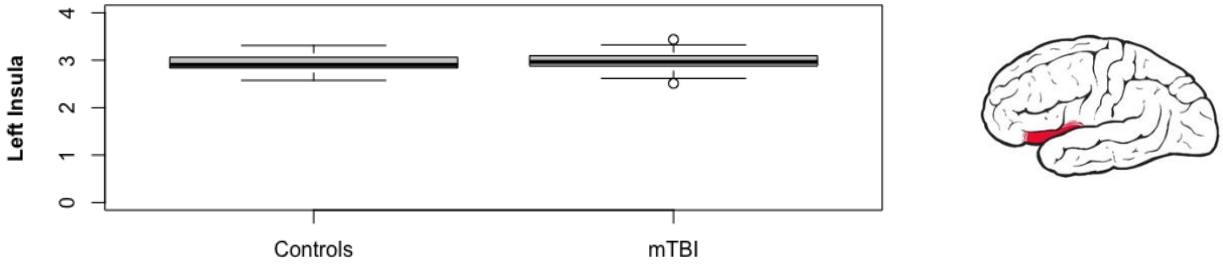
Exploratory Regression Predicting Cortical Thickness in the Left Insula

	B	**S.E.**	**β**	***p***	***Corrected p***
mTBI	0.068	0.033	0.193	0.040*	1.640[a]
MCI Status	-0.077	0.039	-0.182	0.050*	2.050[a]
Age	-0.001	0.003	-0.015	0.877	0.877
Education	-0.003	0.007	-0.045	0.638	1.046
CAPS Lifetime	-0.000	0.000	-0.013	0.894	1.047
R^2	0.069				

Note. B = unstandardized betas, β = standardized betas, and $p < 0.05$ = *. **p* = 0.040 and 0.050 before the FDR correction. [a]Did not survive the FDR correction.

Figure 4

mTBI Exposure and Cortical Thickness in the Left Insula (p = 0.040; β = 0.193)



Note. Units are in millimetres. The red colour within the brain image represents greater cortical thickness in the mTBI group compared to controls.

Table 8

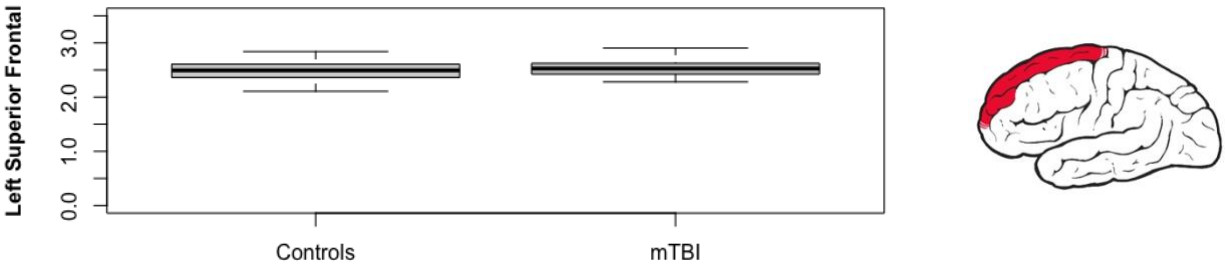
Regression Predicting Cortical Thickness in the Left Superior Frontal Cortex

	B	**S.E.**	**β**	***p***
mTBI	0.067	0.029	0.210	0.024*
MCI Status	0.024	0.035	0.061	0.500
Age	-0.006	0.003	-0.186	0.048*
Education	0.004	0.006	0.057	0.548
CAPS Lifetime	-0.001	0.000	-0.166	0.085
R^2	0.082			

Note. B = unstandardized betas, β = standardized betas, and p <0.05 = *.

Figure 5

mTBI Exposure and Cortical Thickness in the Left Superior Frontal Cortex (p = 0.024; β = 0.210)



Note. Units are in millimetres. The red colour within the brain image represents greater cortical thickness in the mTBI group compared to controls.

Table 9

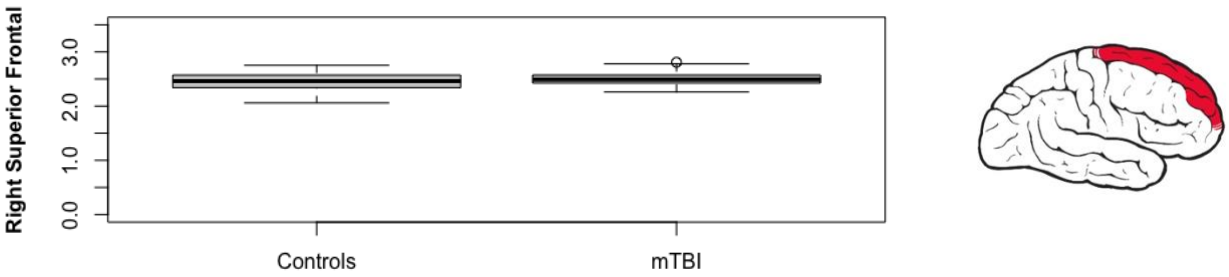
Regression Predicting Cortical Thickness in the Right Superior Frontal Cortex

	B	**S.E.**	**β**	***p***
mTBI	0.070	0.027	0.239	0.011*
MCI Status	0.016	0.032	0.046	0.619
Age	-0.004	0.003	-0.150	0.112
Education	0.006	0.006	0.104	0.272
CAPS Lifetime	-0.000	0.000	-0.125	0.195
R^2	0.080			

Note. B = unstandardized betas, β = standardized betas, and $p < 0.05$ = *.

Figure 6

mTBI Exposure and Cortical Thickness in the Right Superior Frontal Cortex ($p = 0.011$; $\beta = 0.239$)



Note. Units are in millimetres. The red colour within the brain image represents greater cortical thickness in the mTBI group compared to controls.

None of the other covariates predicted cortical thickness after FDR corrections were applied except for the age variable in the following four models (see Appendix E, Tables 15, 16, 17,18, and 19). That is, older age was associated with lower thickness in the fusiform cortex in the right (β = -0.356, $p < 0.001$, and FDR corrected $p = 0.002$; with 19.7% of the variance in right fusiform cortex thickness accounted for by the model) and left (β = -0.304, $p = 0.001$, and FDR corrected $p = 0.013$; with 9.5% of the variance in left fusiform cortex thickness accounted for by the model) hemispheres. Older age was also associated with lower thickness in the left lingual cortex (β = -0.446, $p < 0.001$, and FDR corrected $p = 0.004$) with 24.1% of the variance in left lingual cortex thickness accounted for by the model. Finally, older age was also associated with lower thickness in the pericalcarine cortex in both the left (β = -0.284, $p = 0.003$, and FDR corrected $p = 0.031$; with 12.2% of the variance in left pericalcarine cortex thickness accounted for by the model), and right pericalcarine cortex (β = -0.251, $p = 0.006$, and FDR corrected $p = 0.049$; with 10.2% of the variance in right pericalcarine cortex thickness accounted for by the model) hemispheres.

3.7 Discussion

This chapter aimed to examine brain-related differences in those with or without mTBI exposures by investigating associations with mTBI, WMHVs and cortical thickness in a Vietnam War veteran sample. Overall, exposure to mTBI was not associated with WMHVs though older age was associated with greater WMHV. Having exposures to mTBI predicted greater cortical thickness in the left caudal middle frontal cortex, and bilateral superior frontal cortices. Higher age was associated with lower thickness in the left and right fusiform, left and right pericalcarine, and left lingual cortices and these findings survived multiple comparison corrections.

3.7.1 | Exposure to mTBI and White Matter Hyperintensity Volume Findings

The WMHVs were examined between those with and without mTBI exposures in order to understand whether the presence of larger WMHV may be associated with mTBI history. Some evidence suggests that moderate and severe TBI are associated with WMH (Tong et al., 2003), and a relationship has been more consistently reported between WMHV and AD as well (Brickman, Muraskin, & Zimmerman, 2022). Previous research has also indicated that WMHV may generally be associated with macrostructural brain changes, e.g., lower cortical thickness

(Wen, Sachdev, Chen, & Anstey, 2006), though this relationship has not been thoroughly explored in the literature examining mTBI exposure and risk for AD. However, exposure to mTBI was not associated with greater WMHVs as predicted; rather a relationship was observed between WMHVs and age (such that older age was associated with greater WMHV). These findings are in alignment with the literature which has shown increases in the spread and extent of white matter hyperintensities with age (Erten-Lyons et al., 2013; Yoshita et al., 2006). Given that white matter microstructure integrity generally (and cerebral blood flow and brain iron levels, among others) is an important factor that is associated with the volume of white matter hyperintensities (Bauer, Zachariou, Seago, & Gold, 2021), it is possible that more sensitive analyses (e.g., DTI) would have provided more nuanced findings in the regions examined that could better detect group differences in cortical thickness and subcortical volumes found here (Pelletier et al., 2016). Future studies should aim to examine DTI in conjunction with the modalities used in the current study, given that DTI is able to detect early white matter changes (Wallace, Mathias, & Ward, 2018) and white matter hyperintensities may appear as a consequence of those changes. The nature of the injury exposure for participants in this study (i.e., mild, which typically results in fewer neuroimaging findings than other injury severities) may warrant more sensitive approaches to better understand the impact of mTBI exposures and associated outcomes in the long-term.

3.7.2 | Findings for Analyses of Cortical Thickness and mTBI Exposure

Overall, there were four cortical regions of the 44 examined that demonstrated greater thickness for participants with mTBI exposures compared to controls. While it is unclear based on the findings of this study why participants with mTBIs had greater cortical thickness compared to controls, others have also found enlargement of brain areas in the long-term post-injury (Ross et al., 2020). Some research suggests that issues such as chronic neuroinflammation may persist in this timeframe and could therefore contribute to the findings seen here (Simon et al., 2017). See section 5.1 for further discussion of this finding. In addition, it is notable that one of these findings did not survive the multiple comparison corrections that were applied (i.e., in the left insula) while the other three regions were predicted *a priori* and thus a multiple comparison correction was not applied. This suggests that the relationship between mTBI and macrostructural differences in the brain in the long-term may be circumscribed, with particular

susceptibility within the left caudal middle frontal and bilateral superior frontal cortices. In addition, the left insula may potentially be implicated and should be examined in future studies.

Of note, age was associated with lower thickness in five brain regions, and four of these regions may serve functions such as facial recognition (Li, Ding, & Gore, 2020; McGugin & Gauthier, 2016; Miller, Hermes, Pestilli, Wig, & Ojemann, 2017; Volfart et al., 2022). Consistent with this finding, facial recognition ability tends to decline with age (Boutet, Taler, & Collin, 2015). In addition, two of the hypothesized brain areas were associated with cortical thickness differences between groups before corrections; these were the caudal middle frontal (left) and superior frontal cortex (bilateral). These regions were identified based on findings from other veteran studies which may suggest overlap in the injury mechanism (e.g., blast injuries) that may have produced similar sequelae (Clark et al., 2018; Eierud et al., 2019; Lindemer et al., 2013). Additionally, findings about the lateralization of differences in the middle frontal cortex between groups were mixed in the literature, but were also found in the left hemisphere (Clark et al., 2018) or more rostrally (Eierud et al., 2019) in some studies. Bilateral findings for differences in the superior frontal cortex were reported in the literature as well (Lindemer et al., 2013).

The left insula also demonstrated greater thickness for those with mTBIs. Differences in this brain region have been identified in the literature, typically by studies looking at acute injury findings (Dall'Acqua et al., 2016) or those using DTI (Bendlin et al., 2008; Wada, Asano, & Shinoda, 2012) or fMRI (Lu et al., 2020; Ramage, Tate, New, Lewis, & Robin, 2019). This highlights the utility of examining areas impacted early in the injury trajectory, areas of white matter injury, or early functional connectivity alterations to understand later or developing impacts on gray matter. However, others have found this region to be sensitive to having multiple mTBIs using structural imaging as well (List, Ott, Bukowski, Lindenberg, & Floel, 2015). Alternatively, the medial orbital frontal cortex did not show differences between those with and without mTBI exposure as predicted. It is possible that this may have been due to lack of power or the heterogeneity inherent in studying mTBI (e.g., accounting for injury location or mechanism). This region has been identified as potentially vulnerable to the effects of mTBI (Eierud et al., 2019; Martindale et al., 2020) and may be worth considering in future studies, particularly if there are clinical considerations such as anosmia or hyposmia (Han et al., 2018). Overall, the findings in the four regions described above warrant further investigation in future studies.

The literature is relatively contentious and mixed about whether or not mTBIs are associated with later neurological sequelae. Though variable, the literature seems to indicate that mTBIs can produce brain changes in the long-term (Hellstrom et al., 2017; Mac Donald et al., 2019; Palacios et al., 2020; Van Der Horn et al., 2017). The research on this topic in veteran samples is more limited but is generally in alignment with the notion that mTBI is associated with differences in brain health and aging (Trotter, Robinson, Milberg, & McGlinchey, 2015; Yeh et al., 2017). Additionally, a meta-analysis by Snowden and colleagues purported that mTBI can be considered a risk factor for the development of AD and dementia, and other research has supported this finding (Gardner et al., 2014; Johnson & Stewart, 2015; Snowden, Hinde, Reid, & Christie, 2020; Van Den Heuvel, Thornton, & Vink, 2007). Thus, the literature generally supports the idea that the majority of brain regions do not show macrostructural differences in the long-term following mTBI, but rather, there may be specific long-term effects in certain regions. However, except for the theoretically identified regions of interest, given the exploratory nature of most analyses in this study, all other results must be considered with caution.

3.8 Conclusions and Future Directions

Interest has grown in addressing the broad question of how TBI, particularly mild injuries, affect brain health with age in veteran samples (McKee & Robinson, 2014; Vincent, Roebuck-Spencer, & Cernich, 2014), and this study addresses an important gap in this literature (Echlin et al., 2021). Findings from this study suggest that there are a limited number of cortical areas that may be susceptible to differences in the long-term following mTBI exposure in a sample of Vietnam War veterans. The majority of regions examined however, were not significantly different between those with and without mTBI exposures. It is therefore important to consider that sequelae due to mTBI are likely to be variable and heterogeneous depending on the context of the injury. Recovery from injury may vary and some areas may be impacted while others are spared, for example. There are also many lifestyle or other factors (e.g., sleep quality, stress, or comorbid physical or mental health issues) that may also impact the brain to a greater or similar extent which should be considered as well. Additionally, we found that WMHVs were not different between those with and without mTBI exposures which may suggest that they are not related to the cortical thickness findings reported here. Finally, the three regions identified in this study (the left caudal middle frontal cortex, bilateral superior frontal cortices) were predicted

a priori and are implicated in functions that are commonly impacted by brain injury such as visual attention, working memory, and executive functioning (Alagapan, Lustenberger, Hadar, Shin, & Fröhlich, 2019; Boisgueheneuc et al., 2006; Grambaite et al., 2011; Husa et al., 2017; Liu, Bengson, Huang, Mangun, & Ding, 2016). These regions should be examined in future research to better understand relationships between remote mTBI exposure and cortical thickness differences as well as to investigate associated behavioural sequelae. Future research should also examine whether the left insula is also implicated in remote mTBI differences. Lastly, elucidation of the findings for greater thickness in Vietnam War veterans with mTBI histories using neuroimaging modalities that examine functional connectivity and microscopic structures will also be an important future direction.

Chapter 4: Associations Between Mild Traumatic Brain Injury Exposure and Later Life Brain Structure and Cognition in Vietnam War Veterans

4.1 Overview

The aim for this chapter was to elaborate on the findings from the prior chapter by examining the influence of head injury exposure on delayed memory performance as well as cortical thickness and subcortical volumes in AD-vulnerable regions. These analyses were done in eight cortical and subcortical regions that have been identified as vulnerable to AD (Hayes et al., 2017; Sabuncu et al., 2011), as well as aging and mTBI. The relationship between performance on cognitive tasks was also examined in those with a history of mTBIs across the lifespan. This chapter used the same Vietnam War veteran data obtained from the ADNI-DOD with the aim of further characterizing brain differences following remote TBI by considering overlap with AD pathology.

4.2 Publication Status and Author Contributions

This retrospective study is currently in preparation to be submitted for publication. The content of this chapter does not exactly replicate the manuscript that is in preparation for publication. Thus, this chapter is not a copy of the manuscript and is not suitable for citation. Holly Echlin (i.e., the first author) developed the conceptual rationale for the study, applied for access to the data, and organized, analyzed, and interpreted the data. She was also the primary contributing author of the manuscript and produced the initial draft and completed all major revisions.

4.3 Abstract

Evidence suggests that past exposure to mild traumatic brain injury (mTBI) and concussion may be associated with cognitive and neurological outcomes later in life. This study examined the potential impact of mTBI history on later life memory performance and brain structure in Alzheimer's disease (AD)-vulnerable regions in a sample of Vietnam War veterans. METHODS: Participants were 47 veterans with mTBI exposures (M_{age} = 69.43, SD = 5.02) and 82 veterans without mTBIs (M_{age} = 68.51, SD = 4.69). These data were obtained from the Alzheimer's Disease Neuroimaging Initiative – Department of Defense (ADNI-DOD) database. Associations between mTBI, age, education, cognitive status, PTSD symptoms, delayed memory

performance, subcortical volumes, and cortical thickness were examined in brain regions implicated in AD and aging. RESULTS: Older age was associated with lower thickness in the left (p = 0.012) and right lateral temporal cortex (p = 0.001), left entorhinal cortex (p = 0.003), and left temporal pole (p = 0.028), while years of education was associated with greater cortical thickness in the right entorhinal cortex (p = 0.023). MTBI was a significant predictor of greater cortical thickness for the left lateral temporal cortex (p = 0.050). Additional analyses for those with a single mTBI compared to multiple mTBI exposures revealed lower cortical thickness in the right poster cingulate (p = 0.023) and larger volumes in the right amygdala (p = 0.022) for those with multiple mTBI exposures. Older age at first exposure to mTBI was associated with lower right inferior frontal thickness (p = 0.043). Screener indicated MCI status was not associated with differences in brain regions, however, there was a significant interaction between mTBI and MCI symptoms in the right posterior cingulate. MTBI exposure was not a predictor of delayed memory performance (p > 0.05). CONCLUSIONS: These findings highlight that while most brain regions were not different between those with and without mTBI exposures, there were several cortical regions that were associated with lifetime mTBI exposure in AD-vulnerable brain structures in a sample of Vietnam War veterans. MTBI is associated with differences in brain structure that are present later in life for older adult veterans, beyond the effects of PTSD symptoms, education, cognitive status, and aging.

Keywords: Vietnam War Veterans, Cortical Thickness, Subcortical Volumes, Long-Term, Mild Traumatic Brain Injury, Delayed Memory

4.4 Introduction

Those who served in the Vietnam War represent a sample of veterans with characteristics and exposures that are unique and distinct to those who served in this war. The emergence of this conflict pertained to the threat of the ongoing development of nuclear arms, conflicts between communist and capitalist ideologies, tensions between imperialist and nationalist stances within Vietnam, and the state of post-World War II and Cold War geopolitics. In this war, over 2.7 million American men and women served and over 58,000 American adults lost their lives in service (Frankum & Tucker, 2001; Thayer, 2019). About 40% of these deaths were associated with head and neck injuries (Raymont, Salazar, Krueger, & Grafman, 2011). Though there were many types

and forms of injury that servicemen encountered (e.g., environmental hazard exposures such as Agent Orange), traumatic brain injuries (TBIs) represent an area in need of further study for this population given that 14% of the returning veterans were estimated to be impacted by them (Raymont et al., 2008). Between 2000 and 2021, 453,919 service members were diagnosed with a TBI, and of all diagnosed TBIs, about 82.3% were mild. Given the potential for long-term sequelae and that the majority of TBI exposures for service members were mild TBIs (mTBI), further investigation is warranted (Cassidy et al., 2004; Terrio et al., 2009).

Though there has been growing interest in the impact of mTBIs in recent years, a better understanding of their long-term effects is still needed. Further, despite the number of Vietnam War service members who returned home with TBI exposures, there is a marked lack of research examining health-related outcomes in the long-term for these veterans (Echlin et al., 2021; Mahoney et al., 2019). While the epidemiology of mTBI in veterans is challenging to ascertain, it is estimated that approximately 17% of service members may have acquired an mTBI during their service (Wilk, Herrell, Wynn, Riviere, & Hoge, 2012). This estimate appears to be lower for Vietnam War veterans (Helmick et al., 2015), which may be due to the different mechanisms of injury (i.e., given possible differences between more severe penetrating injuries versus potentially less severe blast or blunt injuries), definitions of TBI, or injury tracking procedures. For Vietnam War veterans, about 35% of injuries were related to gunshot wounds, while 65% occurred during an explosion, compared to 19% and 81% respectively for the veterans who served in Operation Iraqi Freedom and Operation Enduring Freedom (Owens et al., 2008).

Given that there is growing interest in understanding how age at first injury impacts long-term brain health, it is noteworthy that some studies have found younger age at exposure to TBI to be detrimental to brain health or functioning in the long-term, especially in youths whose brain development is still inchoate (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005; Ewing-Cobbs, Prasad, Landry, Kramer, & DeLeon, 2004; Meehan, Taylor, & Proctor, 2011). However, older military personnel having an exposure to TBI was associated with a 60% increase in risk for developing a neurodegenerative disease (Barnes et al., 2014). Some studies also suggest that younger adults may be more resilient to the effects of a more recent mTBI than older adults (Gardner et al., 2014), but research examining age at first injury exposure in the long-term is less clear overall and further investigation is necessary (Fann et al., 2018; Marquez de la Plata et al., 2008).

It is well established that exposures to moderate and severe TBIs are strong predictors of the development of AD, which is the most common neurodegenerative disorder (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003; Johnson, Stewart, & Smith, 2012; Mortimer et al., 1991). AD represents a major public health concern that warrants further investigation given that AD accounts for 60-80% of all dementias (Alzheimer Association, 2019), and by 2060, rates of AD are projected to double from about 1.6% of the population to 3.3% (Matthews et al., 2019). In 2019, 3% of people aged 65-74, 17% of people aged 75-84, and 32% of people aged 85 or older had AD. It is not known whether these rates are similar at each age for those with mTBI histories (Alzheimer Association, 2019). Therefore, it is difficult to discern the level of risk that exposures to mTBIs confer to the development of a cascade of processes that result in the eventual diagnosis of AD, given the mixed state of the literature indicating both an increased risk (Bigler, 2013; Fann et al., 2018; Gan et al., 2021; Gardner et al., 2014; Lee et al., 2013) and no increased risk (Crane et al., 2016; Dams-O'Connor et al., 2013; Julien et al., 2017). This is because the mechanism(s) through which TBI exposure may affect an already ongoing neurodegenerative process or potentially accumulate enough risk factors to initiate one, is/are not well known.

However, there is notable overlap between processes that occur in the brain with both TBI and AD, e.g., including excitotoxicity, oxidative stress, neuroinflammation, and an accumulation of proteins that interrupt cellular functioning (Dorsett et al., 2017; Hall, Vaishnav, & Mustafa, 2010; Webers, Heneka, & Gleeson, 2020; Witcher, Eiferman, & Godbout, 2015). This research suggests that if present, these proteins (particularly amyloid-β and tau) could indicate an ongoing neuropathological process that may potentially lead to AD, but with TBI exposure, more protein accumulation can interrupt the post-injury recovery for TBI and also potentially alter the trajectory for the ongoing neuropathological process (Kokiko-Cochran & Godbout, 2018; Uryu et al., 2007). Further, given that rates of MCI also tend to be higher in veteran samples (Mohammad, Shah, & Safian, 2022; Yang, Jeng, Wu, Lin, & Chuo, 2014) than in the general population (Palmer, Backman, Winblad, & Fratiglioni, 2008), the importance of understanding brain differences in service members with mTBI exposures and MCI, who might be at risk for AD in the long-term, are underscored. Importantly, previous research has shown that cortical thinning and subcortical volume loss are most prominent in those with Mini Mental Status Exam scores of 21, which is the equivalent of a score of 15 on the Montreal Cognitive Assessment (MoCA; Sabuncu et al., 2011; van Steenoven et al., 2014). Therefore, only participants with scores above this range were

examined in the current study.

Though patterns of neurological change throughout the brain have been identified for various stages of AD (Jones et al., 2016; Sabuncu et al., 2011), more research is needed to understand this process in those who also have mTBI exposures. Some studies have undertaken this task in veteran populations, but this literature is scarce (Hayes et al., 2017; M. W. Weiner et al., 2014). One approach taken by Hayes and colleagues (2017) using a service member population was to examine the effects of mTBI in the regions identified by Sabuncu et al. (2011) as AD-vulnerable (e.g., the entorhinal cortex, temporopolar cortex, lateral temporal cortex, inferior parietal cortex, inferior parietal sulcus, posterior cingulate cortex, and inferior frontal cortex). Hayes and colleagues identified cortical thinning in these regions that was associated with mTBI exposure and reduced delayed memory performance in Iraq and Afghanistan War veterans (Hayes et al., 2017). To date, there is still a paucity of research examining the integrity of these regions or other subcortical regions like the hippocampus and amygdala (Poulin et al., 2011) in the long-term for older (e.g., Vietnam War) service members.

There were also many factors that contributed to the complexity of the mental health concerns experienced by veterans of the Vietnam War. For instance, the veterans who returned home also experienced disillusionment and stigmatization that contributed to their complex mental and physical health outcomes and general difficulty with readjustment. Between 2007 and 2009, 2,319,176 veterans who served in Vietnam received services from the Veterans Health Administration, and 15.8% of those adults had a diagnosis of PTSD (Hermes, Hoff, & Rosenheck, 2014). Though estimates vary, prevalence rates were closer to 30.9% for men and 26% for women who met criteria for PTSD at any point in their lifetime (Kulka et al., 1988; Weiss et al., 1992). General prevalence rates of PTSD in American veterans were estimated to be around 12.9% (Müller, Ganeshamoorthy, & Myers, 2017), though each war was associated with different rates of PTSD (e.g., 12.1% for Gulf War Veterans and Iraq and 13.8% Afghanistan Veterans; Holdeman, 2009; Kang, Natelson, Mahan, Lee, & Murphy, 2003). Nevertheless, rates of PTSD in these populations are higher than in the general population, as the prevalence rates in the general population are typically estimated to be between 6.1 to 9.2% (Kessler et al., 2005; Koenen et al., 2017; Van Ameringen, Mancini, Patterson, & Boyle, 2008).

Additionally, Vietnam War veterans are more likely to be diagnosed with both PTSD and substance use disorders than are veterans who served in other wars (Fontana & Rosenheck, 2008;

Kulka et al., 1990; Marmar et al., 2015). It is well known that comorbid diagnoses of PTSD and substance use disorders are associated with increased symptom severity and poorer treatment outcomes (Kessler et al., 2005; Marmar et al., 2015; Teeters, Lancaster, Brown, & Back, 2017). Importantly, TBI, substance use, and PTSD are common in veterans and are major contributors to the development of dementia (Aranda et al., 2021; Raza et al., 2021; Vasterling et al., 2018). Further, exposures to certain TBIs (e.g., blast-related) in veteran samples are associated with neural and cognitive changes that can persist for many years (Miller, Hayes, Lafleche, Salat, & Verfaellie, 2016, 2017). Cognitive changes that progress to diagnoses of mild cognitive impairments (MCI) are indicative of an ongoing neurodegenerative process (Sperling et al., 2011) wherein approximately 50-60% of adults with MCI (compared to 30% adults without MCI) may have detectable AD pathology in their brain (Kemppainen et al., 2007; Pike et al., 2007). Those who served in the Vietnam War are presently in older adulthood, and some are faced with such diagnoses in addition to the diverse sequelae described above (Weiner et al., 2014).

The objectives of this study were to examine the associations between exposures to mTBI and cortical thickness, subcortical volume, and delayed memory performance in older adulthood for a Vietnam War veteran population. We hypothesized that there would be differences in subcortical volumes and cortical thickness in disease-vulnerable regions (Sabuncu et al., 2011) for veterans with mTBI exposures compared to those without, and for veterans with multiple mTBI exposures compared to those with just one mTBI exposure. We also hypothesized that there would be an effect of the age at first mTBI exposure such that there would be lower thickness and smaller volumes for veterans whose injuries occurred at a younger age (e.g., see Campbell, Kuehn, Richards, Ventureyra, & Hutchison, 2004). It was also predicted that having mTBI exposures and poorer performance on a measure of cognitive status would be associated with lower cortical thickness and smaller amygdalar and hippocampal volumes (i.e., in AD-vulnerable regions). Finally, we hypothesized that mTBI exposure would be associated with poorer performance on a delayed memory task.

4.5 Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The

primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see www.adni-info.org. The larger study from which this data was derived has been approved by the Committee on Human Research at the University of California at San Francisco, the San Francisco VA Medical Center Research and Development Committee, and the Department of Defense Human Research Protection Office. All patients provide informed consent before being enrolled in the study. Permission was granted by ADNI to access this data for the current study and the procedures were approved by York University's Research Ethics Board.

4.5.1 | Participants

Participants were male Vietnam War Veterans (n = 129, data obtained from ADNI-DOD) with mTBI exposures or no history of TBIs. There were 47 adults (Mean age = 69.43, SD = 5.01) who reported exposures to at least one mTBI a minimum of more than ten years prior and 82 adults with no reported TBI exposures in their lifetime (mean age = 68.51, SD = 4.69). For additional details, please see section 3.3.1.

4.5.2 | Measures

All measures that were used in this study were the same as those that were used in the previous chapter because the same dataset was used for both. Information about the demographic data, Clinician Administered PTSD Scale, and Montreal Cognitive Assessment can be found in sections 3.3.2.1, 3.3.2.2, and 3.3.2.3, respectively. Additional information and measures used in the current study are described below.

4.5.2.1 | Structured Clinical Interview for SCID-I DSM-IV, Non-Patient Edition (SCID-IV, NP)

The SCID-IV, NP is a structured diagnostic interview protocol that is used to identify mood disorders, substance use disorders, and anxiety disorders (Spitzer, Williams, Gibbon, & First, 1992). The diagnostic criteria used are consistent with the DSM-IV. This protocol describes

whether certain mood or anxiety disorders occurred across an individual's lifetime, or whether diagnostic criteria were met at the approximate time of data collection. This measure queries participants' potential abuse of or dependence on alcohol, cannabis, opioids, hallucinogens/PCPS, sedatives/hypnotics/anxiolytics, stimulants, cocaine, or poly drug use. For this study, only alcohol use was examined because prior evidence indicated that there are associations between alcohol consumption and subcortical volumes (Wojtowicz et al., 2018). Scores pertaining to alcohol were coded as a 1 for those reporting experiences in their lifetime of problematic alcohol use or a 0 to indicate no lifetime experiences of problematic alcohol use.

4.5.2.2 | Wechsler Memory Scale-Revised (WMS-R): Logical Memory I and II

Memory performance was measured using the WMS-R, specifically with the Delayed Paragraph Recall subtest of the Logical Memory II subscale (Wechsler, 1987). This test assesses narrative memory ability via free recall of a verbally presented short story, followed by free recall after a 30-minute delay. This measure was selected due to it having the most complete data within this dataset and because it offered 25 bits of contextual story information that could be elicited from a participant at the short- and long-delay which is relevant for day-to-day situations.

4.5.2.3 | Geriatric Depression Scale (GDS)

The GDS is a 15-item self-report measure that is used to identify depression in older adults (Brink et al., 1983). Questions are answered in a "yes" or "no" format. Higher scores on this measure are indicative of greater endorsement of depressive symptoms. Scores ranging from 0-4 indicate a lack of depressive symptoms, scores between 5-8 are indicative of mild depression, scores between 9-11 are indicative of moderate depression, and scores between 12-15 are indicative of severe depression.

4.5.2.4 | Neuroimaging

Neuroimaging data were obtained on qualified ADNI General Electric (GE) Healthcare systems (3T) and all measurements were obtained from ADNI FreeSurfer output. See section 3.3.2.4 for additional details about the protocol and parameters. The subcortical volume measurements of anatomic brain regions were computed (M. W. Weiner et al., 2014) and the

subcortical volumes were corrected for intracranial volume (ICV) by applying the residuals method (Mathalon, Sullivan, Rawles, & Pfefferbaum, 1993). This method controls for ICV by using the mean ICV of control participants in the sample under the assumption that the experimental group (i.e., mTBI group) may have systematic differences in subcortical volumes (Sanchis-Segura, Ibañez-Gual, Aguirre, Gómez-Cruz, & Forn, 2020). Cortical thicknesses were examined in the cortical structures.

With these data, several regions of interest (ROIs) were identified for analyses including the amygdala, hippocampus, entorhinal cortex, temporopolar cortex, lateral temporal cortex, inferior parietal cortex, posterior cingulate cortex, and inferior frontal cortex (Pieper et al., 2020; Sabuncu et al., 2011). Of note, though the inferior parietal sulcus was identified in previous work, this region was encompassed within the inferior parietal cortex (IPC) and thus only the IPC was used for analyses. In addition, the lateral temporal cortex consisted of a sum of cortical thicknesses from the bank of superior temporal sulcus (STS), superior temporal, middle temporal, inferior temporal, and transverse temporal cortices (as per Hayes et al., 2017). Similarly, the inferior frontal region consisted of a sum of the pars opercularis, pars orbitalis, and pars triangularis.

4.5.3 | Design and Analyses

Several ROIs were added to regression analyses to examine the relationships between our variables of interest. The predicter variables included i) past mTBI exposure compared with no previous history ii) the number of mTBI exposures, iii) the age at first injury, and iv) PTSD scores. The primary outcome variables included i) cortical thickness from the cortical brain regions of interest (the posterior cingulate, entorhinal cortex, inferior parietal cortex, inferior frontal cortex, lateral temporal cortex, and the temporal pole), ii) the subcortical volumes of the hippocampus and amygdala, and iii) delayed memory.

To address the hypotheses of the current project, multiple regression analyses were conducted (controlling for relevant covariates: age, education, MCI scores, and CAPS scores). Specifically, a series of linear regression models were used to examine the relationship between those with or without a mTBI history and thicknesses/volumes (*hypotheses I & II*). Group differences were assessed using regression analyses to determine whether reported mTBI history is associated with cognitive status in older adulthood (*hypothesis III*). Regression analyses were

conducted to examine relationships between mTBI history, cortical thickness/subcortical volumes, and memory performance *(hypothesis IV)*. Calculations for the required sample size for statistical demonstration of effects using a multiple linear regression model indicated that with an alpha level set at 0.05, power at 0.8, and an anticipated medium effect size of f^2 at 0.15, at least 31 participants will be needed in total. The sample size available surpassed this number of required participants. Predictor and dependent variables were tested for the assumption of normality using the Shapiro-Wilk test. In all models, collinearity between predictors was explored using the variance inflation factor (VIF), with a value of 5 implemented as a threshold value (Stine, 1995).

4.6 Results

4.6.1 | Descriptive Information

See section 3.4.1 and Table 3 for an overview of the descriptive information about this sample. Chi-square analyses revealed that the *frequencies* of PTSD symptom endorsement (i.e., based on cut-off scores) within the mTBI and no-mTBI groups were very close to our statistical significance threshold ($\chi^2(1) = 3.750$, $p = 0.053$). This trend is reflected in the percentage of people with PTSD symptoms in the mTBI group (61%) compared to the percentage in the no-mTBI group (41%). In addition, CAPS lifetime *scores* among those with and without mTBI exposures were significantly different ($F(3,122) = 227$, $p < 0.001$), with greater symptom severity in controls with PTSD compared to participants with mTBI exposures ($p = 0.021$). *Frequencies* of suspected MCI (as identified by the MoCA) within the mTBI and no-mTBI groups were not significantly different ($\chi^2(1) = 0.129$, $p = 0.719$). For those with mTBI exposures, 83% also met screening criteria for MCI while 78% of controls met screening criteria for MCI.

4.6.2 | Effect of mTBI History on Cortical Thickness and Subcortical Volumes

See Table 10 for unilateral comparisons of cortical thickness values between the mTBI and control groups. Linear regression models were used to examine relationships between mTBI history and cortical thickness as well as subcortical volumes. Age, MoCA cut-off scores, CAPS Lifetime scores, and education variables were included in the regression model as covariates.

Significant findings for the mTBI variable are presented in Table 11 and Figure 7. Having an mTBI was associated with greater thickness in the left lateral temporal cortex (β = 0.184 p = 0.050), while increased age (β = -0.241 p = 0.012) was associated with lower cortical thickness in this region and 8.2% of the variance in lateral temporal thickness was accounted for by the model. No other regions were associated with mTBI exposure. There were no significant predictors of the amygdala or hippocampal volumes, or thickness in the posterior cingulate, inferior frontal, or inferior parietal cortices.

Additionally, older age was associated with smaller volume in the amygdalae (left: β = -0.207, p = 0.028, with 6.6% of the variance accounted for by the model; right: β = -0.208, p = 0.025, with 10.4% of the variance in right amygdala volume accounted for by the model) as well as the hippocampi in the left (β = -0.249, p = 0.009, with 7.8% of the variance in left hippocampal volume accounted for by the model) and right (β = -0.216, p = 0.020, with 8.0% of the variance in right hippocampal volume accounted for by the model) hemispheres. Older age was associated with lower thickness in the right lateral temporal cortex (β = -0.204, p = 0.001) and 9.3% of the variance in right lateral temporal thickness was accounted for by the model. Older age was also associated with lower cortical thickness in the left entorhinal cortex (β = -0.274, p = 0.003, with 9.6% of the variance in left entorhinal thickness accounted for by the model) and left temporal pole (β = -0.194, p = 0.028, with 5.6% of the variance in left entorhinal thickness accounted for by the model). Finally, more years of education was associated with greater cortical thickness in the right entorhinal cortex (β = 0.207 p = 0.023), and 8.9% of the variance in right entorhinal thickness was accounted for by the model.

In addition, a measure of lifetime problematic alcohol use was added to the regression models for the subcortical regions because of prior evidence suggesting associations between these variables (e.g., Wojtowicz et al., 2018), but this variable was not a predictor of subcortical volumes.

Table 10

Table of Descriptive Information for Each Unilateral Brain Region

Brain Areas	mTBI		Controls		
	Mean	SD	Mean	SD	*p*-values
Left Amygdala	1544.95	176.98	1576.34	237.70	0.396
Right Amygdala	1622.15	204.76	1659.21	263.51	0.376
Left Hippocampus	3956.85	452.04	3907.23	479.20	0.559
Right Hippocampus	3994.74	382.24	3914.97	468.05	0.296
Left Posterior Cingulate	2.5	0.17	2.48	0.19	0.504
Right Posterior Cingulate	2.48	0.22	2.44	0.16	0.239
Left Entorhinal	3.48	0.31	3.52	0.31	0.458
Right Entorhinal	3.65	0.38	3.58	0.39	0.306
Left Temporal Pole	3.54	0.30	3.59	0.34	0.436
Right Temporal Pole	3.53	0.34	3.56	0.34	0.631
Left Inferior Parietal	2.27	0.11	2.27	0.14	0.693
Right Inferior Parietal	2.34	0.13	2.33	0.14	0.679
Left Pars Opercularis	2.54	0.24	2.50	0.22	0.630
Right Pars Opercularis	2.42	0.14	2.39	0.15	0.286
Left Pars Orbitalis	2.54	0.24	2.50	0.22	0.335
Right Pars Orbitalis	2.48	0.19	2.48	0.21	0.996
Left Pars Triangularis	2.29	0.19	2.25	0.16	0.207
Right Pars Triangularis	2.26	0.14	2.25	0.15	0.739
Left Superior Temporal	2.57	0.15	2.57	0.18	0.960
Right Superior Temporal	2.56	0.13	2.57	0.17	0.731
Left Middle Temporal	2.76	0.17	2.72	0.17	0.183
Right Middle Temporal	2.75	0.13	2.77	0.16	0.471
Left Inferior	2.68	0.18	2.71	0.20	0.438

Temporal					
Right Inferior Temporal	2.74	0.17	2.73	0.21	0.755
Left Transverse Temporal	2.23	0.23	2.13	0.19	0.021*
Right Transverse Temporal	2.28	0.24	2.20	0.23	0.102
Left Bank of STS	2.29	0.18	2.25	0.20	0.211
Right Bank of STS	2.41	0.17	2.42	0.20	0.727
Left Inferior Frontal	7.25	0.46	7.14	0.44	0.205
Right Inferior Frontal	7.16	0.36	7.12	0.37	0.588
Left Lateral Temporal	12.53	0.62	12.37	0.72	0.204
Right Lateral Temporal	12.74	0.59	12.70	0.71	0.710

Note. *p*-values are reported for Welch's t-tests between groups. Subcortical volumes are reported in mm^3, and cortical thicknesses are reported in mm. There were 47 adults in the mTBI group and 82 in the control group. * $p < 0.05$.

Table 11

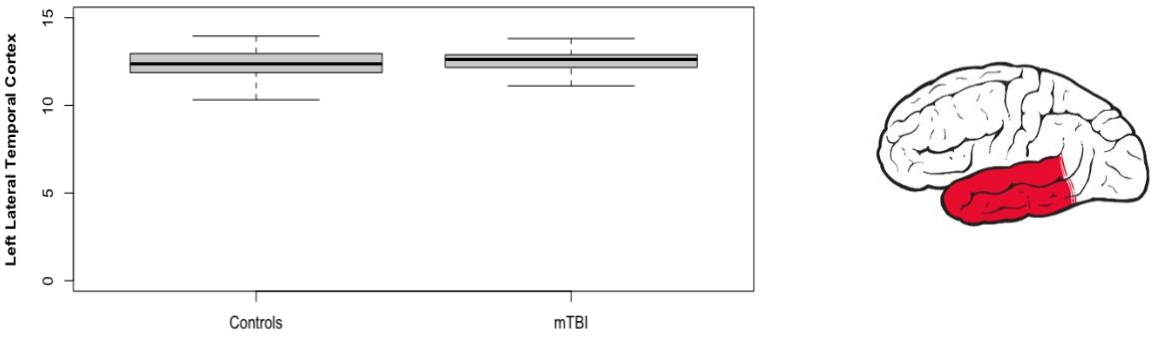
Regression Results Predicting Left Lateral Temporal Cortex

Left Lateral Temporal	***B***	**S.E.**	**β**	***p***
mTBI	0.262	0.132	0.184	0.050*
MCI Status	-0.094	0.156	-0.056	0.547
Age	-0.034	0.013	-0.241	0.012*
Education	0.036	0.029	0.120	0.210
CAPS Lifetime	-0.002	0.013	-0.102	0.292
R^2	0.082			

Note. B = unstandardized betas, β = standardized betas, and p <0.05 = *.

Figure 7

mTBI Exposure and Cortical Thickness in the Left Lateral Temporal Cortex (p = 0.050; β = 0.184)



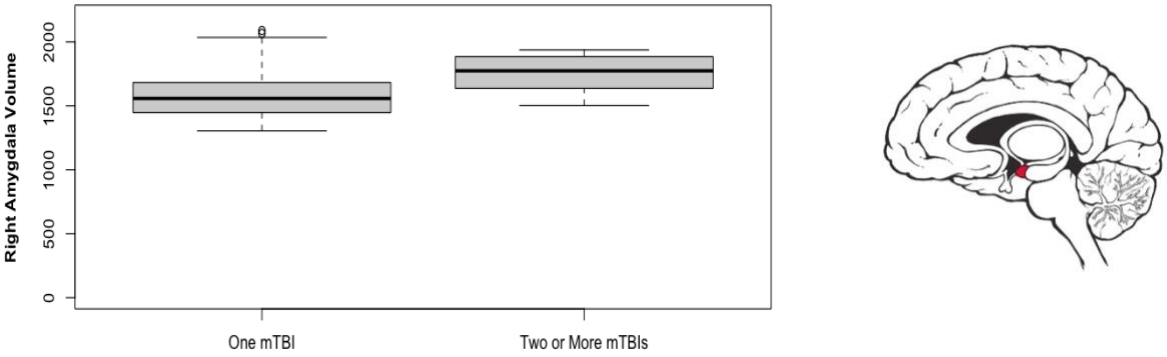
Note. Units from the summed regions of the lateral temporal cortex are in millimetres. The red colour within the brain image represents greater cortical thickness in the mTBI group compared to controls.

4.6.3 | Differential Effects of Single vs. Multiple mTBIs on Cortical Thickness and Subcortical Volumes

For the following analyses, only the mTBI group was examined since the number of mTBI exposures was the dependent variable. Wilcox rank sum tests were conducted to examine the differences in brain regions between those who had one mTBI exposure (n = 39) compared with those who had 2 or more (n = 8), due to smaller sample sizes (see Figures 8 and 9). There was a significant difference in the right posterior cingulate cortex (z = 0.510, p = 0.023) wherein those with multiple mTBI exposures (median = 2.33, n = 8, range: 2.21 to 2.48) had lower cortical thickness in the right posterior cingulate cortex than those with one mTBI (median = 2.49, n = 39, range: 1.99 to 3.09). There was also a significant difference in the right amygdala (z = 0.511, p = 0.022) wherein those with multiple mTBI exposures (median = 1774.16, n = 8, range: 1503.05 to 1937.20) had larger volume in the right amygdala than those with one mTBI (median = 1558.06, n = 39, range: 1304.54 to 2089.11). No other regions were significantly different between these groups.

Figure 8

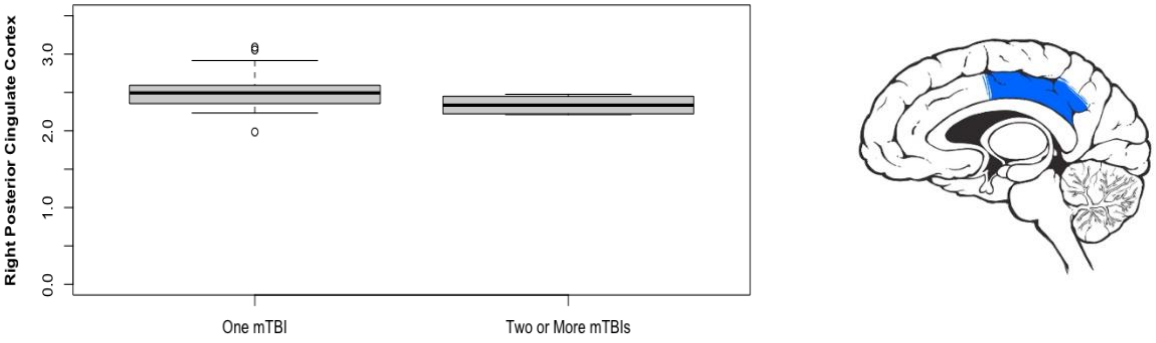
Single Versus Multiple mTBI Exposures and Volume in the Right Amygdala (p = 0.022; d = 0.804)



Note. Units are in millimetres cubed. The red colour within the brain image represents larger subcortical volume in the multiple mTBI group compared to those with one mTBI exposure.

Figure 9

Single Versus Multiple mTBI Exposures and Cortical Thickness in the Right Posterior Cingulate Cortex (p = 0.023; d = 0.803)



Note. Units are in millimetres. The blue colour within the brain image represents greater cortical thickness in the multiple mTBI group compared to those with one mTBI exposure.

4.6.4 | Effect of Age at First Injury on Cortical Thicknesses and Subcortical Volumes in the mTBI Group

To examine the potential effects of age at first injury within the mTBI group on cortical thickness/subcortical volumes, linear regression models were created (see Table 12 and Figure 10). There was an effect of age at first mTBI exposure on right inferior frontal thickness (β = -0.305, p = 0.043), wherein older age of first exposure to mTBI was associated with lower right inferior frontal thickness. The model (including age at first injury, MoCA cut-off scores, CAPS Lifetime scores, and the education variables) accounted for 12.4% of the variance in right inferior frontal thickness. This standardized beta had a medium effect size, indicating a moderate effect. The age at first injury variable was not significant for any other variables (p > 0.05).

Table 12

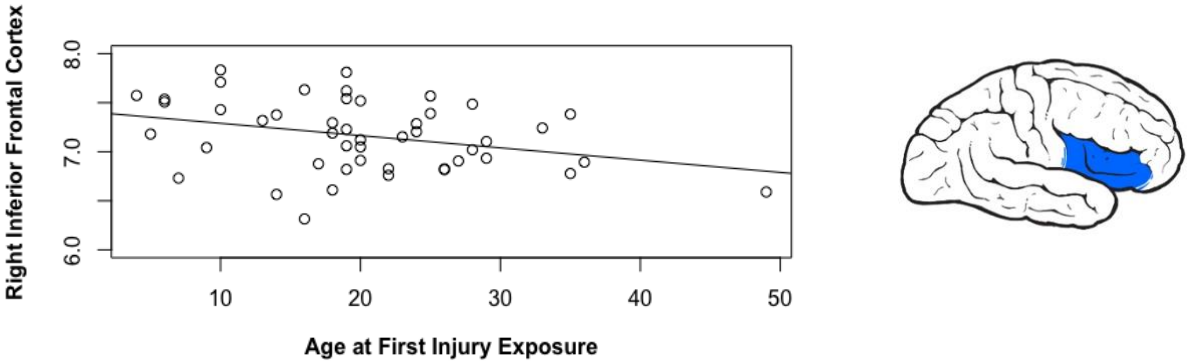
Regression Results Predicting the Right Inferior Frontal Cortex for MTBI Group Only

Right Inferior Frontal	***B***	**S.E.**	**β**	***p***
MCI Status	0.057	0.145	0.062	0.696
Age at First Injury	-0.012	0.006	-0.305	0.043*
Education	-0.012	0.023	-0.071	0.619
CAPS Lifetime	0.0009	0.002	0.091	0.614
R^2	0.124			

Note. B = unstandardized betas, β = standardized betas, and p <0.05 = *.

Figure 10

Age at First Injury Exposure and Cortical Thickness in the Right Inferior Frontal Cortex (p = 0.043; β = -0.305)



Note. Units for the summed regions of the right inferior frontal cortex are in millimetres. The blue colour within the brain image represents lower cortical thickness with age.

4.6.5 | Interaction Effects for mTBI Exposure and MoCA Status on Cortical Thicknesses and Subcortical Volumes

Further analyses were also conducted to examine potential brain differences in those with mTBI histories and who also meet screener criteria for MCI. To examine whether there is an interaction between mTBI and cognitive status, an interaction variable was entered into linear regressions with age and education as covariates. There was an effect of the interaction term (β = 0.204, p = 0.025) for the right posterior cingulate, such that those with both a history of mTBI and who positively screened for MCI on the MoCA had thicker cortices in the right posterior cingulate (see Table 13 and Figure 11). There were no other significant interactions.

Table 13

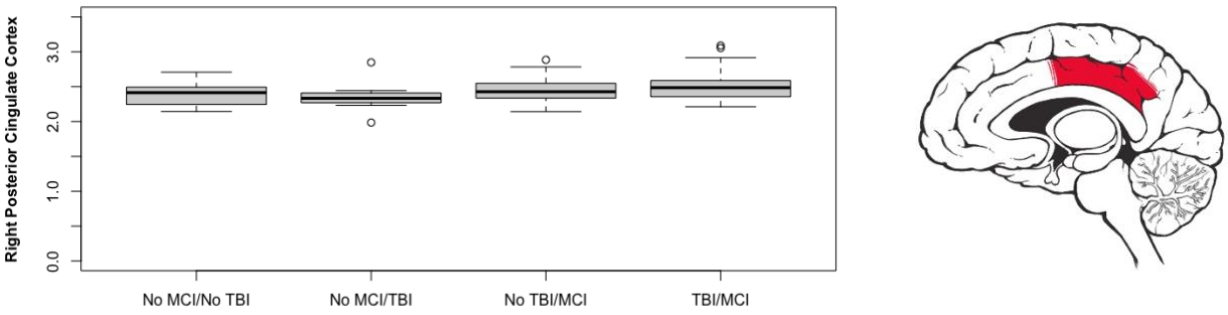
Regression Results Predicting the Right Posterior Cingulate

Right Posterior Cingulate	***B***	**S.E.**	**β**	***p***
Age	0.001	0.004	0.020	0.827
Education	0.002	0.007	0.025	0.787
MCI * mTBI	0.083	0.036	0.204	0.025*
R^2	0.042			

Note. B = unstandardized betas, β = standardized betas, and p <0.05 = *.

Figure 11

Interaction Effects for mTBI and MCI Symptoms on the Right Posterior Cingulate Cortex (p = 0.025; β = 0.204)



Note. Units are in millimetres. The red colour within the brain image represents greater cortical thickness in the mTBI group compared to controls.

4.6.6 | Effects of mTBI Exposure on Delayed Memory Performance

To examine whether there is an effect of mTBI on delayed memory performance, linear regression models were constructed (see Table 14). Exposure to mTBI was not a significant predictor of delayed memory performance (β = -0.106, p = 0.237), but the number of years of education was (β = 0.189, p = 0.040). In this case, an increase in years of education was associated with better delayed memory performance. The model accounted for 10.8% of the variance in delayed memory performance.

Table 14

Regression Results Predicting Delayed Memory Performance

Delayed Memory Performance	***B***	**S.E.**	**β**	***p***
mTBI	-0.823	0.692	-0.106	0.237
MCI Status	-1.274	0.820	-0.137	0.123
Age	-0.116	0.070	-0.148	0.103
Education	0.313	0.151	0.189	0.040*
CAPS Lifetime	-0.012	0.009	-0.118	0.205
R^2	0.108			

Note. B = unstandardized betas, β = standardized betas, and p <0.05 = *.

4.6.7 | Effects of PTSD Symptoms on Cortical Thickness and Subcortical Volumes

Two 2x2 ANOVAs were conducted to examine group differences in cortical thickness and subcortical volumes within these four groups (i.e., control with no PTSD [*n* = 47], controls with PTSD [*n* = 33], mTBI exposure and no PTSD [*n* = 18], mTBI exposure with PTSD [*n* = 28]). These analyses revealed no significant differences between the groups.

4.7 Discussion

This study examined associations between mTBI exposure, cortical thickness, subcortical volumes, white matter hyperintensity volumes, and cognitive performance in brain regions that are susceptible to AD in a Vietnam War veteran sample. It is notable, that there were many null findings when examining macro-structural brain regions that are vulnerable to AD and associations with mTBI exposure in the long-term. However, mTBI exposure was associated with greater cortical thickness in the left lateral temporal lobe and exposure to multiple mTBIs was associated with less cortical thickness in the right posterior cingulate as well as larger right amygdala volume. Furthermore, older age at first injury was associated with lower cortical thickness in the right inferior frontal cortex. When examining associations with cognitive performance, we found that poorer performance on the MoCA was not associated with differences in brain regions, however, there was a significant interaction between mTBI and MCI symptoms on the right posterior cingulate region. Exposure to mTBI was not associated with delayed memory performance in this sample (though years of education was positively associated with better performance). Finally, there were no differences in the brain regions examined for those with and without PTSD (irrespective of mTBI history). The implications of these findings are discussed in more detail below.

4.7.1 | Exposure to mTBI and Associated Cortical Thickness and Subcortical Volume Findings

Of the regions explored, mTBI history was only associated with greater cortical thickness in the left lateral temporal lobe. This was in the opposite direction to what we had hypothesized, however, recent research has found greater volumes or enlargement of certain brain regions in association with mTBI exposure after several months-to-years post-injury (Killgore et al., 2016;

Ross et al., 2020; Singh & Killgore, 2016; Sussman et al., 2017). Notably, Ross and colleagues conducted longitudinal analyses with their sample and reported increased brain volumes with greater time since the TBI exposure (Ross et al., 2020, 2021). These findings, though limited by a lack of study and replication generally, are in line with the findings of larger cortical thickness in the left lateral temporal cortex from the current study. The underlying mechanisms of this relationship are presently unknown, though it is possible that compensatory remodeling of brain structures through hyperactivity or hypertrophy, edema, and neuroinflammation may contribute to increased cortical thickness and/or volume (Ross et al., 2020). However, it may still be the case that later-stage atrophy would occur at some point following these processes and in the absence of significant facilitation of relevant functions (Abdul-Muneer et al., 2013; Carson Smith et al., 2013; Haeger, Costa, Schulz, & Reetz, 2019), though whether this is true several decades following injury is less clear. This finding also highlights that larger brain regions do not necessarily translate to better health or functioning. There is extensive complexity involved in examining the aging brain which is multifaceted and often challenging to differentiate (e.g., brain enlargement, atrophy, or no changes in size that could be the product of an ongoing healing process or problematic sequelae; Killgore et al., 2016; Lockhart & DeCarli, 2014; Ross et al., 2020, 2021; Singh & Killgore, 2016).

Of note, the majority of brain regions examined were not significantly different between those with and those without mTBI exposures. Findings from this study suggest that mTBI is not associated with many macro-level differences in the brains of this Vietnam War veteran sample beyond the effects of age, education, PTSD symptoms, and cognitive status. However, it is also possible that for less severe brain injuries, other imaging modalities that detect changes in function or white matter microstructural integrity may be more sensitive in identifying potential differences in the brain (Jantzen, 2010; Mayer, Bellgowan, & Hanlon, 2015; Palacios et al., 2020). Overall, given the unexpected finding of larger cortical thickness in the mTBI group, it is important to consider that this finding is a small difference among the many changes that are happening in the aging brain.

4.7.2 | Exposure to Multiple mTBIs and Findings for Cortical Thickness and Subcortical Volumes

The finding that multiple mTBI exposures, relative to a single mTBI, was associated with

larger right amygdala volumes is consistent with some prior research. Beauchamp and colleagues (2011) reported similar findings for those who were exposed to TBIs in childhood and followed-up ten years later. They observed enlarged volumes in the right amygdala for children with severe TBI exposures (but not mild or moderate) and the current study suggests that multiple mild TBI exposures may lead to similar outcomes. Others have also reported larger amygdala volumes for veterans with PTSD and mTBI (Bae et al., 2020; Pieper et al., 2020), which may be related to hyperactivity in the amygdala when processing threatening stimuli in the environment (Badura-Brack et al., 2018). Given that 60% of the mTBI group endorsed PTSD symptoms, it is possible that PTSD sequelae in this region may have been exacerbated by having mTBI exposures.

Notably, having exposures to more than one mTBI was associated with less cortical thickness in the right posterior cingulate. Reduction in the size of the posterior cingulate cortex has been more consistently found in those with exposure to moderate and severe TBIs (Yount et al., 2002), but some research has suggested that this area may also be vulnerable to mTBI as well (Levine et al., 2008; Zhou et al., 2013). To the author's knowledge, there are no studies identifying associations between reductions in the right posterior cingulate cortex and multiple mTBI exposures that may elucidate or address the location or lateralization of these findings. However, the chronic traumatic encephalopathy literature (where multiple TBI exposures are typically studied) has implicated the posterior cingulate cortex in a neuropathological atrophy process in the long-term (Provenzano et al., 2010; Zhou et al., 2013). Furthermore, the functional imaging research has suggested that the default mode network (DMN), of which the posterior cingulate is a hub, is susceptible to change following injury and repetitive head impact exposure (Irimia et al., 2020; Van Der Horn et al., 2017). Additional fMRI studies in this population will be an important area for further investigation to elucidate these findings.

The posterior cingulate is also a major node contained within the DMN, that appears to be involved with maintaining consciousness through cross-hemispheric connections with the temporal parietal junction (Zhang et al., 2017). Research examining the integrity of functional brain networks post-mTBI has demonstrated that the DMN is susceptible to change following injury and repetitive head impact exposure (Irimia et al., 2020; Van Der Horn et al., 2017). It is noteworthy that cortical thickness findings that were associated with multiple mTBI exposures in the current study were limited to this region given that loss of consciousness occurred for many

participants in the sample immediately following the mTBI and that researchers have shown that brain injury exposure in this region may alter networks involved in the maintenance of consciousness in the long-term (Wu et al., 2015; Zhang et al., 2017). Additional fMRI studies in this population will be important for further investigation to elucidate the sequelae following injury to this area in the short- and long-term.

4.7.3 | Age at First mTBI Exposure and Cortical Thickness and Subcortical Volume Findings

We observed that younger age at first mTBI exposure was associated with greater thickness in the right inferior frontal cortex. This finding may suggest that exposure to mTBI early in life may be associated with an alteration to structural brain development, in particular in frontal regions (De Beaumont, Tremblay, Poirier, Lassonde, & Théoret, 2012; Fiori & Guzzetta, 2015; Laube, van den Bos, & Fandakova, 2020; Pascual-Leone et al., 2011; Selemon, 2013; Spear, 2013; Zelazo & Carlson, 2012). This also means that older age at first mTBI exposure was associated with lower thickness in the right inferior frontal cortex. The literature generally suggests that evidence of neurotrauma appears to increase with older age for adults who are exposed to TBIs, and worse outcomes are often reported for older adults (Marquez de la Plata et al., 2008; Styrke, Stålnacke, Sojka, & Björnstig, 2007). Taken together, these findings may be in alignment with the accelerated aging hypothesis in that brain injury exposure at a younger age may be associated with changes to brain development while older age at injury exposure may be associated with more rapid and high yielding impact to brain health (Amgalan et al., 2022). However, to properly assess these possibilities, longitudinal study designs are necessary.

4.7.4 | Effects of Exposure to mTBI and MoCA Status on Cortical Thicknesses and Subcortical Volumes

Veterans who had a history of mTBI and screened positive for MCI were observed to have greater thickness in right posterior cingulate. Prior research has suggested that having an mTBI may be associated with a higher likelihood of future MCI (Godbolt et al., 2014; McInnes et al., 2017), and the findings from this study indicate that this effect may be multiplicative, but only in the right posterior cingulate region. Previous research has identified decreased fibre

connections and disrupted connectivity between the posterior cingulate and the hippocampus in those with MCI or early AD as early biomarkers for AD (Zhou et al., 2008). This region has also demonstrated increased susceptibility to amyloid beta burden 11 months to 17 years after moderate or severe TBIs (Scott et al., 2016). However, the degree to which having both MCI and exposure to an mTBI (as opposed to moderate or severe TBI) influence cortical thickness and subcortical volumes in age and neurodegeneration-vulnerable regions is not clearly delineated.

4.7.5 | Exposure to mTBI and Delayed Memory Performance Findings

Exposure to an mTBI was not associated with delayed memory performance in this sample. Interestingly, in a sample of Iraq and Afghanistan War veterans, mTBI and genetic risk factors for AD were moderators of the relationship between cortical thickness and episodic memory performance (Hayes et al., 2017). It is possible that the inclusion of data pertaining to genetic risk factors may be important for understanding this relationship when examining veteran samples. Alternatively, the difference in findings may also be indicative of an inherent difference between the two veteran populations themselves (e.g., the Iraq and Afghanistan War veterans were several decades younger than the Vietnam War veterans at the time of assessment) or potentially related to differences in the memory measures used. Importantly, more years of education was associated with better delayed memory performance, which is a finding with well-documented support from the cognitive reserve in aging literature (Pettigrew & Soldan, 2019; Stern, Barnes, Grady, Jones, & Raz, 2019; Tucker & Stern, 2011).

4.7.6 | Limitations and Future Directions

This study has several limitations. Firstly, mTBI exposure was self-reported and assessed several decades after the injuries. This introduces bias related to reliance on participants' memory abilities, knowledge about concussions/mTBIs, and awareness that an mTBI had occurred, among other constraints. In this study, a standard approach to defining and measuring mTBI was used in order to combat this issue, but this does not entirely eliminate these concerns. In addition, there were many factors that could contribute to changes in brain structure across the lifespan (e.g., diet, sleep, stress, physical fitness, etc.); however, this study was limited to using the measures that were collected by the larger study. Also, a large portion of the control group

met screener criteria for MCI which limits the generalizability of the findings. There may be a link between MCI and cortical thickness and subcortical volumes that obscured the effect of mTBI (Wang et al., 2009; Yi et al., 2016). Additionally, the measure of alcohol intake used here was limited in terms of quantifying alcohol intake, but it is important to note that the control group endorsed higher problematic use of alcohol in their lifetime. Despite the null findings for alcohol use in the current study, this is an important factor to consider when observing brain differences in the long-term for future research. Overall, it is important to note the complexity of the aging brain and the plethora of factors that have an influence on brain structure throughout the lifespan. It is unclear at present what level of risk is conferred by the variable findings reported (i.e., larger, smaller, or no differences in structural brain metrics). Future research using longitudinal approaches and including more sensitive neuroimaging metrics (e.g., DTI) that are paired with comprehensive health, behavioural, and cognitive data, is necessary to further elucidate these relationships.

4.8 Conclusion

These findings suggest that mTBI exposure may be associated with some, though circumscribed, structural brain differences in veterans. However, these effects must also be considered in the context of other factors including age, education, PTSD symptoms and cognitive status, in addition to other variables not examined here that may have continued to affect brain health in the decades following injury. Of note, there were many null findings in our analyses that are important to consider. This suggests that mTBI exposures generally do not disrupt the majority of AD-vulnerable brain regions. Further, it is possible that other factors alter the structure of the brain in a way that exceeds the impact of mTBI exposures (e.g., smoking, or physical activity levels; Kim et al., 2018).

Chapter 5: General Discussion

The goal with healthy aging is functional independence, such that well-being is maintained into older adulthood. For this to happen, further research is needed to understand brain changes associated with age for those with risk factors for AD, which is the most common cause of dementia. Some risk factors for AD are potentially modifiable lifestyle factors that, if altered, may aid in preserving or rehabilitating neural integrity into later life. These findings may be of particular interest for adults who are at-risk for developing a neurodegenerative disease (e.g., perhaps due to genetics or biomarkers identified through neuroimaging) and will be important for informing adults of all ages about such exposures and their possible sequelae. This dissertation aimed to address gaps in the literature by first systematically reviewing the current literature about the long-term effects of mTBI and the associated neuroimaging findings. This review identified differences compared to controls in white matter microstructure, cortical and subcortical macrostructure, neurochemistry, functional connectivity, cerebral blood flow, and proteinopathy in adults who have a history of RHIs and/or one or more mTBIs beyond at least one decade (Echlin et al., 2021). Methodological constraints limited the generalizability of findings, but the pattern of positive findings (i.e., compared to null findings) was still notable; however, these findings should be interpreted cautiously given publication biases favouring significant results.

This systematic review provided insights about neuroimaging findings and associations with mTBI in the long-term across several populations. Until now, the literature had primarily focused on specialized populations (e.g., elite athletes) who have greater exposure to head injuries, increased severity of head injuries, other physical injuries, and additional confounds such as increased rates of mental health and/or substance use histories (Manley et al., 2017; Sparks et al., 2020). Thus, a synthesis of information across populations offered more widespread and comprehensive examination, in a more generalizable manner, about mTBI and brain differences in the long-term. Previous reviews were also typically conducted with a mix of TBI severities together (Koerte, Lin, Willems, et al., 2015; Lin et al., 2018; Sundman et al., 2014; Wallace et al., 2018) which creates difficulty in discerning the unique impact of mTBI. Previous work also identified a lack of reviews focused on studying the impacts of mTBI beyond ten years post-injury (Sundman et al., 2014) and therefore, this study bolstered this literature regarding the long-term effects of mTBI and RHIs.

Furthermore, the findings from this systematic review highlighted a lack of long-term mTBI research conducted in veteran samples, which the subsequent study aimed to address. This research (i.e., study 2) was conducted using a sample of Vietnam War veterans from the ADNI-DOD database. Hypothesis-driven and exploratory analyses were conducted in 44 cortical brain regions in this sample to examine associations with mTBI exposure. Findings indicated that mTBI was associated with greater thickness in the left caudal middle frontal and bilateral superior frontal cortices, and that the left insula is an area for future study (it did not survive multiple comparison correction). This study also found no associations between mTBI exposure and WMHV. To supplement this work, further analyses were conducted in an additional 16 regions that were previously implicated in AD (Sabuncu et al., 2011) and have demonstrated a relationship with mTBI in another veteran sample (Hayes et al., 2017). There were several main findings, including 1) mTBI was associated with greater cortical thickness in the left lateral temporal cortex, 2) having multiple mTBI exposures was associated with lower cortical thickness in the right poster cingulate and larger right amygdala volume, 3) older age at first exposure to mTBI was associated with lower right inferior frontal thickness, 4) meeting screener criteria for MCI was not associated with differences in any brain regions, but there was a significant interaction between mTBI and MCI symptoms in the right posterior cingulate (i.e., such that having mTBI and MCI symptoms was associated with greater thickness in the posterior cingulate), and 5) mTBI exposure did not predict delayed memory performance in this sample.

5.1 Findings of Increased thickness and Volume

One of the most notable findings within the Vietnam War veteran sample (examined in studies 2 and 3) was an association between mTBI and greater cortical thickness or subcortical volumes. These findings are not uncommon in the literature (Dall'Acqua et al., 2017; Killgore et al., 2016; Ross et al., 2020; Singh & Killgore, 2016; Sussman et al., 2017) but are less often reported. Generally, researchers have suggested that increases in cortical thickness soon after injury may be related to factors such as swelling and inflammation, and that decreases in cortical thickness may follow after some time (Bigler, 2001; Faden, Wu, Stoica, & Loane, 2016). Therefore, one potential explanation for the findings of larger cortical thickness and subcortical volumes in this study could be related to an ongoing neuroinflammatory process (Simon et al., 2017). Of note, greater TBI severity is generally associated with greater cortical thinning or

smaller subcortical volumes (e.g., Levine et al., 2008), though findings associated with mTBI may be more variable and heterogeneous, due to the large number of possible reasons for greater thickness or thinning post-injury (i.e., unrelated to mTBI) that may become more prominently influential factors across the lifespan (e.g., severe illness).

Some other factors that may be related to the finding of greater cortical thickness and subcortical volumes following mTBI in the long-term are neuroplasticity, genetics, and physical activity. Firstly, it is possible that some individuals develop compensatory mechanisms that result in neuroplastic changes in response to TBI sequelae, which may lead to observable changes in brain structure (Kou & Iraji, 2014). Additionally, an individual's genetic makeup may also determine some amount of their susceptibility to TBI as well as their post-injury recovery (Cortes & Pera, 2021). That is, those who are genetically susceptible to TBI may be more likely to also be genetically at-risk for poorer post-injury recovery. Further, in addition to being a risk factor for AD, carrying the ε4 allele of the APOE gene has been associated with worse outcomes post-injury (Mannix & Meehan, 2015; McFadyen et al., 2021) and has been associated with lower cortical thickness in AD-vulnerable brain regions (Hayes et al., 2017). Another consideration pertaining to having greater cortical thickness is physical activity, which tends to have a positive effect on brain health and may promote neuroplasticity (Rogge, Röder, Zech, & Hötting, 2018). Some research has also indicated that physical activity might beneficially effect the timing of symptom development by delaying disease onset or progression; but there is no strong evidence that physical activity works as a permanent curative treatment (Mahalakshmi, Maurya, Lee, & Kumar, 2020; Rolland, Abellan van Kan, & Vellas, 2008). Thus, it is important to consider that these factors may have had cumulative effects on the brain across the lifespan that potentially may have differentially affected the two groups in the sample (e.g., history of exercise, as well as favourable genetics and neuroplastic response to mTBI) and were not controlled for in the current study.

In addition to generally demonstrating greater cortical thickness and subcortical volumes, the findings from this dissertation indicated no significant relationship between mTBI and WMHV, memory performance, or PTSD symptoms. Though some previous studies have indicated that moderate and severe TBI are associated with WMHV (Tong et al., 2003), others have not shown this relationship in those with mTBIs compared to controls (Jarrett et al., 2016). The findings of this dissertation are consistent with the latter, and thus offer replication of

findings to a limited area of study. It is important to note that the mixed findings may be due to differences in the number of mTBI exposures, as well as individual differences in recovery and rehabilitation (as for all of the findings reported here). Further, the lack of findings for memory performance and PTSD symptoms suggests that there may not have been sufficient changes in the brain that led to detectable outcomes due to either variable. The study authors who collected the data for ADNI (i.e., the same sample that was used in this dissertation) also did not find that PTSD symptoms increased the risk for AD as measured by amyloid PET (Weiner et al., 2017). Nor was this the case when examining AD-vulnerable regions in another sample of Vietnam War veterans (Cummins et al., 2021).

The findings observed in this dissertation are not fully in alignment with the usual outcomes that are reported in veteran populations. That is, smaller brain volumes and reduced cortical thicknesses are more often reported for veterans with mTBI exposure in the long-term (Clark et al., 2018; Hayes et al., 2017; Lindemer et al., 2013; Santhanam, Wilson, Oakes, & Weaver, 2019). However, the findings from this dissertation speak to the circumscribed impact of mTBI on the brain in relation to other factors that may be impacting the brain more substantially across the lifespan. Findings from these studies also highlight the limited areas of macrostructural differences that may be associated with mTBI exposures in the long-term. Without longitudinal methodology, causality cannot be inferred from these findings, but they provide preliminary evidence of circumscribed findings, as well as directions for future research to investigate. Findings from each of the studies contained within this dissertation contribute to the mTBI literature in a number of important ways which will be discussed below.

5.2 Relevance and Overlap Between Alzheimer's Disease and Traumatic Brain Injury Literature and Theories

Links between TBI and neurodegeneration have been substantiated most consistently in the AD literature, as it has been investigated more thoroughly and for a longer timeframe, and this literature has demonstrated that greater amyloid-beta accumulation is often found post-injury (Hong et al., 2014). Approximately one third of all AD cases can be attributed to modifiable risk factors including smoking, depression, lack of exercise, obesity, lack of mental stimulation, diet, diabetes and low levels of education, among others (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). Research has also suggested that mTBI history, another common risk factor encountered

across the lifespan, may be associated with an accelerated cortical accumulation of amyloid-beta as well (Asken et al., 2021). In another sample of Vietnam War veterans, a link has also been observed between higher cerebrospinal fluid tau and TBI. Both of these biomarkers are hallmark features of AD and have been found following mTBI and in military samples as well (Gill et al., 2018; Kenney et al., 2018). The literature has consistently reported a relationship between moderate/severe TBIs and AD, with this relationship typically extended to mTBI as well (Julien et al., 2017; Zhang, Zhang, Zou, & Cao, 2021) since AD is often used as a proxy for neurodegeneration leading to dementia, given that AD is the leading cause of dementia (Uddin et al., 2020). Overall, the evidence seems to suggest that mTBI may increase the risk for developing AD by promoting the accumulation of amyloid-beta and tau in the brain, which can lead to neurodegeneration. However, further research is needed to better understand the potential overlap in the underlying mechanisms involved in this long-term cascade for individuals with a history of mTBI, and for veterans in particular given their varied sequelae and forms of injury.

The AD literature has grown such that an understanding of the cascade of events within the neurodegenerative process itself have been more clearly elucidated in recent years. Contrary to the commonly held belief that dysfunction originates solely in the hippocampus, AD is starting to be recognized as a disconnection or 'network failure syndrome' (Agosta et al., 2012; Jones et al., 2016; Liu et al., 2014; Villain et al., 2008). This research suggests that the origins of dysfunction in the early disease stages begin with decreased white matter integrity which is associated with reduced resting-state connectivity in the posterior parietal area. This dysfunctional cascade results in a shift of processing burden and increased connectivity with adjacent nodes. Once amyloid-beta proteins accumulate in the brain and interact with pre-existing vulnerable substrates in the medial temporal area, a tau-associated whole-brain neurodegenerative process follows (Jones et al., 2016). Prior to the onset of cognitive symptoms, it is likely that changes in the brain have been ongoing for years (e.g., white matter compromise, gray matter hypometabolism and atrophy), but white matter disruptions are particularly characteristic of preclinical stages (Fischer, Wolf, Scheurich, & Fellgiebel, 2015; Honea, Swerdlow, Vidoni, & Burns, 2011; Masters et al., 2015; Mosconi et al., 2007). Given the specificity of this process, it would be challenging to ascertain whether TBI sequelae overlap with this process. The findings of study 2 provided some evidence for overlap between mTBI and AD in certain regions, but not in all of the regions that were theoretically identified. For this

reason, it is important to consider other theories of TBI and neurodegeneration that may potentially provide further characterization of post-injury sequelae.

5.3 Relationship Between Accelerated Brain Aging Hypothesis and Current Findings

Another primary way that this research is situated within the literature is with regards to the burgeoning research on the accelerated brain aging hypothesis. That is, previous research has provided support for the idea that exposure to moderate or severe TBI confers greater risk for accelerated brain aging (Belchev et al., 2022; Cole et al., 2015). This research also purports that TBI contributes to a progressive and degenerative disorder in that it may lead to cognitive decline and neurodegenerative diseases like AD (Green et al., 2014; Vasquez, Tomaszczyk, Sharma, Colella, & Green, 2018; Wood, 2017). This accelerated brain aging research underscores that the damage caused by a TBI can trigger a cascade of events, including chronic inflammation, oxidative stress, and cellular damage. These changes may lead to the accumulation of abnormal proteins, such as beta-amyloid, that are typically associated with AD (Dorsett et al., 2017; Hall et al., 2010; Webers et al., 2020; Witcher et al., 2015). However, research in this area is still ongoing and questions remain unanswered about the definitiveness of conceptualizing TBI as contributor to a progressive and neurodegenerative disorder. That is, the process through which TBI exposure may lead to higher risk for neurodegeneration due to an accelerated aging process in the brain (e.g., accelerated onset of AD or a non-AD degenerative process) as well as how this may relate to other factors acting on the brain, such as chronic inflammation or vascular damage are still unclear.

The research conducted for this dissertation has focused on mTBI in order to investigate associated long-term outcomes, because even less is known about how mTBI may fit with the proposed accelerated brain aging hypothesis. More recently, having an exposure to one or more mTBIs has begun to be considered a potential risk factor for developing AD, despite being contentiously debated in this scientific literature (Bigler, 2013; Crane et al., 2016; Dams-O'Connor et al., 2013; Fakhran & Yaeger, 2013; Fratiglioni, Ahlbom, Viitanen, & Winblad, 1993; Gan et al., 2021; Julien et al., 2017). Having a history of moderate or severe TBI is more clearly linked to higher AD or dementia risk (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003; Johnson, Stewart, & Smith, 2012; Mortimer et al., 1991) than it has been for those with a history of mTBI, though evidence from the mTBI literature has been steadily growing

(Barnes et al., 2018; Fann et al., 2018; Gan et al., 2021; Lee et al., 2013).

Despite the growing interest in understanding the long-term sequelae of mTBI, the evidence of increased risk for neurodegeneration is still less clear for those with RHIs or a single mTBI exposure (Crane et al., 2016; Dams-O'Connor et al., 2013; Julien et al., 2017) and will require further investigation. It will be important to disentangle findings from the literature, including the reason why some studies report no significant association between mTBI and neurodegenerative disorders like AD, while others have found that mTBI increases this risk (e.g., Crane et al., 2016), and to elucidate the variability in findings throughout the brain in previously published works. Thus, the evidence for the accelerated brain aging hypothesis being applicable to mTBI is still currently inconclusive and will require further investigation and sufficient replication of findings to be better understood. The research reported in these studies contributes to this field by offering insights about systematically reviewed findings to date in this field (i.e., that the majority of studies reported positive neuroimaging findings in the long-term) and about associations between mTBI and neuroimaging findings for a service member population which also indicated limited positive neuroimaging findings in the long-term.

5.4 Traumatic Brain Injury as Polypathology and Trauma-Induced Neurodegeneration

It is important to also consider that TBI has been identified as a risk factor for several neurodegenerative diseases leading to dementia, including Parkinson's disease and amyotrophic lateral sclerosis, for example (Gardner et al., 2018; Gardner & Yaffe, 2015; Liu et al., 2021). The overlap of TBI biomarkers with that of several neurodegenerative diseases suggests that it may be best understood as a polypathology that increases neurodegeneration risk less discriminately (Bagnato & Boccagni, 2020; Faden & Loane, 2015), including in veteran samples (Iacono et al., 2020). For instance, some have suggested that this overlap may come from TBI initiating the formation of misfolded oligomeric species that can then spread this pathology through a prion-like process throughout the brain (Edwards, Moreno-Gonzalez, & Soto, 2017; Goedert, 2015). Additionally, the role of neuroinflammation has been highly implicated in neurodegenerative disease processes and has three steps that could overlap with TBI: "i) an injury that initiates a disease process distinct from normal aging, ii) the establishment of a chronic inflammatory state, and iii) a cellular change that permanently alters the biology of the cells." (Herrup, 2010). Neuroinflammation may play a key role across many age-related pathologies in that it disrupts

proper cellular signaling which precludes the maintenance of toxic protein build-up in the brain (Mosher & Wyss-Coray, 2014). This model also suggests that an injury is a necessary component of this process (e.g., TBI, infection, etc.). Understanding TBI from this framework and in the context of the mTBI literature reported thus far may raise questions about whether mTBI should be considered within this spectrum of injury as another risk factor for trauma-induced neurodegeneration. The results of this dissertation in addition to the previous (though mixed) literature, may challenge commonly held perceptions that all TBIs classified as mild are transient in nature, having effects that resolve followed by a subsequent return to baseline functioning. That is, findings from the literature and from this dissertation suggest that mTBI often has circumscribed effects on brain structure in the long-term. Thus, it is important to consider that post-mTBI recovery may result in disparate post-injury recovery trajectories such as an increased time to recovery, an incomplete recovery, or that differences in brain structure may impact aging and health such that they are on an altered trajectory.

5.5 Limitations

There are several limitations that are embedded within this dissertation. The first being the use of previously collectd data which introduces room for misuse/interpretation of data since it was not collected by the author of this dissertation. That is, it is possible that the original authors and designers of the study may have had alternative rationales and considerations while creating the project. In addition, the analyses conducted were limited by low power due to relatively small samples sizes. There was also a low amount of variance accounted for in most the statistical models overall. However, this is to be expected given the complexity of predicting differences in something as complicated as the brain. In addition the study designs (i.e., systematic review and retrospectic analyses) and the nature of the phenomena being studied (TBI) limit the ability to make causal inferences about any of the findings discussed. It is also important to note that the data pertaining to participant's concussion exposure is likely to be biased by their knowledge of having an injury exposure and their memory of it. Though a standard definition was used to collect this data, it is possible that there were TBIs that went unaccounted for in both groups. Finally, there were several variables not accounted for here that may have been important contributors to brain differences across the lifespan. Many of these were not collected or available for this dataset (e.g., diet and social support).

5.6 Conclusions and Future Directions

Overall, the findings from this dissertation have highlighted some key brain areas that may be susceptible to differences following remote mTBI exposure in addition to many null findings for the effects of remote mTBI across the brain's macrostructure. Further, it is notable that the majority of studies in the review reported some significant neuroimaging differences in the long-term for those with mTBI or RHI and the retrospective studies conducted showed a limited number of brain differences for Vietnam War veterans with exposures to mTBI in the long-term. The regions affected in the brains of this Vietnam War veteran sample were congruent with those implicated in both the AD as well as the long-term mTBI literature. However, the findings from these retrospective analyses had limited overlap with AD-vulnerable regions and more consistency with some of the remote mTBI literature. Overall, brain differences between those with an without mTBI exposures in the long-term were circumscribed. This work underscores the heterogeneous nature of the potential impacts of mTBI on the brain in the long-term and underscores the importance of early detection, ongoing monitoring, clarity in how mTBI diagnoses are communicated, as well as tailored intervention to treat the ongoing sequelae that may silently occur in the long-term. Findings from this dissertation will be of particular importance for veteran and service member samples who are more likely to experience brain injuries and therefore may be faced with altered aging trajectories.

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APPENDIX A

MEDLINE search strategy.

Concussion Terms	Neuroimaging Terms	Long Term Outcome Terms
MeSH	**MeSH**	**MeSH**
Brain Concussion/ or Brain Damage, Chronic/ or Brain Injuries/ or Brain Injuries, Diffuse/ or Brain Injuries, Traumatic/ or Brain Injury, Chronic/ or Contrecoup Injury/ or Craniocerebral Trauma/ or Diffuse Axonal Injury/ or Head Injuries, Closed/	Biomarkers/ or Brain Mapping/ or Cell Tracking/ or Cerebral Angiography/ or Cerebral Ventriculography/ or Computed Tomography/ or Computed Tomography Angiography/ or Connectome/ or Diffusion Magnetic Resonance Imaging/ or Diffusion Tensor Imaging/ or Echoencephalography/ or Echo-Planar Imaging/ or Fluorine-19 Magnetic Resonance Imaging/ or Functional Neuroimaging/ or Imaging, Three-Dimensional/ or Magnetic Resonance Imaging/ or Magnetic Resonance Angiography/ or Molecular Imaging/ or Multimodal Imaging/ or Neuroimaging/ or Neuroradiography/ or Positron-Emission Tomography/ or Positron Emission Tomography Computed Single Photon Emission Computed Tomography Perfusion Imaging/ or Radionuclide Imaging/ or Spectroscopy, Near-Infrared/ or Tomography, Emission-Computed/ or Tomography, Emission-Computed, Single-Photon/ or Tomography/ or Tomography, X-Ray/ or Tomography, X-Ray Computed/ or Ultrasonography, Doppler, Transcranial/	Alzheimer Disease/ or Amyotrophic Lateral Sclerosis/ or Chronic Traumatic Encephalopathy/ or Cognition Disorders/ or Dementia/ or Endocrine System Diseases/ or Frontotemporal Dementia/ or Health Status/ or Hypopituitarism/ or Motor Neuron Disease/ or Neurodegenerative Diseases/ or Parkinson Disease, Secondary/ or Parkinson Disease/ or Septum Pellucidum/ or Tauopathies/ or TDP-43 Proteinopathies/
Keywords	**Keywords**	**Keywords**
((post* or cumulat* or mild or multiple or repetitive or subacute or sub-acute) adj3 concuss*).ti,ab,kw,kf. (((brain or crani* or head* or sport*) adj2 (accident* or damag* or impact* or injur* or trauma*)) or concussi* or postconcussi* or subconcuss* or second impact syndrome or mtbi).ti,ab,kw,kf.	(neural network or white matter or gray matter or grey matter or neural correlates or structural correlates or diffusion correlates or volumetric correlates or functional correlates or subcortical or neural or imaging or MRI or PET or magnetoencephalography or MEG or electroencephalography or EEG or functional magnetic resonance imaging or fMRI or DTI or T2* or diffusion spectrum imaging or DSI or diffusion weighted imaging or DWI or SWI or susceptibility weighted imaging or CT or FLAIR	(acquired seizure disorder or chronic traumatic encephalopath* or cte or neurodegenerative disease* or neurodegenerative disorder* or neuropathol* or neurodegenerat* or dementia* or dementia pugilistica or neurodegenerative dementia* or punch drunk or traumatic encephalopath* or alzheimer* or amyotrophic lateral sclerosis or als or motor neuron disease* or parkinson* or septum pellucidum or (cognit* adj3 impairment) or (cogniti* adj3 deficit*) or white matter tract* or tdp-43 or tauopath* or endocrine

	or diffusion* kurtosis imaging or DKI or SPECT or NIRS or fNIRS or functional near-infrared spectroscopy or resting state or functional connectivity or structural connectivity or structural covariance or functional covariance or default mode network).ti,ab,kw,kf.	dysfunction or hypopituitarism or (long term adj3 impairment) or (long term adj3 sequelae) or sequela*).ti,ab,kw,kf. (Health adj2 (outcome* or status or effect*)).ti,ab,kw,kf.

APPENDIX B

Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies.

Quality Assessment	Reporting										External Validity			Internal Validity-Bias							Internal Validity Confounding-Selection Bias						Power	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total
Bryant et al., 2020	1	1	1	0	0	1	1	0	1	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Casson et al., 2014	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	1	0	0	0	0	-	8
Chong et al., 2018	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	-	9
Clark et al., 2018	1	1	1	0	1	1	1	0	0	1	1	1	0	0	0	1	0	1	0	1	1	1	0	0	0	0	-	14
De Beaumont et al., 2013	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Ford et al., 2013	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	1	0	0	0	0	0	-	11
Gardner et al., 2016	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	1	1	0	0	1	0	-	13
Gilmore et al., 2020	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Goswami et al., 2016	1	1	1	0	1	1	0	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	9
Haglund et al., 1990	1	1	1	0	0	1	0	0	0	0	1	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	8
Hampshire et al., 2013	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	6
Hart et al., 2013	1	1	1	0	1	1	0	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	9
June et al., 2020	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	1	0	0	0	0	0	-	11
Kelman et al., 2020	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	9
Koerte et al., 2015	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Koerte et al., 2016	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	1	0	0	0	0	-	10
Koerte et al., 2016	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Kuhn et al., 2016	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Lepage et al., 2019	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Lin et al., 2015	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	-	7
Lipton et al., 2013	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Misquitta et al., 2018	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Monti et al., 2013	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Multani et al., 2016	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Rajesh et al., 2017	1	1	1	0	1	1	0	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	9
Rowland et al., 2018	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	1	1	0	1	1	0	0	0	0	0	-	12

Small et al., 2013	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Tremblay et al., 2013	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Tremblay et al., 2019	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	8
Vasilevskaya et al., 2020	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Wang et al., 2017	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	1	0	0	0	0	0	-	11
Ware et al., 2020	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10
Wilde et al., 2016	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	9
Zivadinov et al., 2018	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	-	10

Note: Power was not rated due to lack of clarity about the power criteria for the Downs and Black checklist.

APPENDIX C

Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies.

Reporting (1-10)

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the interventions of interest clearly described?
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristics of patients lost to follow-up been described?
10. Have the probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

External Validity (11-13)

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

Internal Validity-Bias (14-20)

14. Was an attempt made to blind study subjects to the intervention they have received?
15. Was an attempt made to blind those measuring the main outcomes of the intervention?
16. If any of the results of the study were based on "data dredging", was this made clear?
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time-period between the intervention and outcome the same for cases and controls?
18. Were the statistical tests used to assess the main outcomes appropriate?
19. Was compliance with the intervention/s reliable?
20. Were the main outcome measures used accurate (valid and reliable)?

Internal Validity Confounding-Selection Bias

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies)

recruited over the same period of time?
23. Were the study subjects randomised to intervention groups?
24. Was the randomised intervention assignment concealed from both patients and health are staff until recruitment was complete and irrevocable?
25. Was there adequate adjustment for confounding in the statistical analyses from which the main findings were drawn?
26. Were losses of patients to follow-up taken into account?

Power

27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

APPENDIX D

Summary of Studies.

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Bryant et al., 2020)	31587599	Cross Sectional Study	64 retired fighters and 442 active fighters	Age of Experimental Group: 47.8 (9.53) for retired fighters and 29.05 (5.44) for active fighters	Sex of Experimental Group: 61:3 for retired fighters and 407:35 for active fighters	10	Level 4
Aim of Study: To examine the relationship between age of first exposure (AFE) to fighting sports and brain health in later life. **Key Outcome Measures:** Age at first exposure (self-reported), cognitive testing (CNS vital signs), neurologic examination, psychiatric symptom scales (PHQ-9; BIS-11), and a 3 T magnetic resonance imaging (MRI) scan with structural and functional sequences (main outcomes: volumes of the hippocampus, amygdala, caudate, putamen, and thalamus, and the anterior, central, and posterior corpus callosum). **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Not reported. The mean years of fighting exposure was 11.52 (5.64) for retired fighters and 5.27 (4.43) for active fighters **Years of Education:** Median years: 12 for retired fighters and 13 for active fighters; **Race (%):** African American (27%), White (67%), Other (6%); **Population Type:** Athletes **Diagnosis of Concussion:** Not Reported. This study used years of fighting as proxy for exposure to repetitive head injury (RHI). **Key Findings:** Brain MRI data showed significant correlations between earlier AFE and smaller bilateral hippocampal and posterior corpus callosum volumes for both retired and active fighters. There was no correlation between AFE and left amygdala volume for retired fighters. However, active fighters showed a correlation between earlier AFE and smaller left amygdala volume. Conversely, there was a correlation between earlier AFE and smaller right amygdala volume for retired fighters, while active fighters showed no correlation. There were no significant correlations between AFE and thalamus, caudate, or putamen volume on either side in either cohort. Likewise, there was no correlation between anterior or central corpus callosum volume and AFE in either cohort.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Casson et al., 2014)	25177413	Cross Sectional Study	45	Age of Experimental Group: 45.6 (8.9)	Sex of Experimental Group: 45:0	8	Level 3
Aim of Study: To assess whether objective clinical abnormalities can be observed in 30- to 60- year-old retired National Football League (NFL) players. **Key Outcome Measures:** MRI (1.5 T MRI; susceptibility weighted imaging [SWI], diffusion tensor imaging [DTI]), neuropsychological (MMSE, BDI, PHQ, ImPACT) and neurological examinations, interviews, blood tests, BMI (mean: 31.4, SD: 4.8), and APOE genotyping. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Mean of 6.8 (3.2) years of NFL experience earlier in life (ages not explicitly stated). **Years of Education:** 15.5 (1.1); **Race (%):** Not Reported; **Population Type:** Athletes							

Diagnosis of Concussion: Self-reported mTBIs obtained through detailed neurological and concussion history screening. Participants were provided a standard definition of concussion.
Key Findings: The retired players had 6.8 ± 3.2 years (maximum, 14 years) of NFL play and reported 6.9 ± 6.2 concussions (maximum, 25) in the NFL. The majority of retired players had normal clinical mental status and central nervous system (CNS) neurological examinations. Four players (9%) had microbleeds in brain parenchyma identified in SWI, and 3 (7%) had a large cavum septum pellucidum with brain atrophy. The number of concussions/ "dings" was associated with abnormal results in SWI and DTI. SWI detected 4 cases with microbleeds. Anatomical MRI: Two cases were found with abnormally enlarged ventricles and thin corpus callosum, suggesting brain atrophy. Neuropsychological testing revealed isolated impairments in 11 players (24%), but none met criteria for dementia. Nine players (20%) endorsed symptoms of moderate or severe depression on the BDI and/or met criteria for depression on PHQ; however, none had dementia, dysarthria, parkinsonism, or cerebellar dysfunction. The number of football-related concussions was associated with isolated abnormalities on the clinical neurological examination, suggesting CNS dysfunction. There was a statistical association between the presence of abnormalities on the clinical CNS examination and the total number of football concussions sustained at all levels of play.

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Chong et al., 2018)	30913910	Cross Sectional Study	131 total (138 before exclusions due to imaging abnormalities)	Age of Experimental Group: Migrane group: 39.1 (10.7) and PPTH group: 37.7 (10.6) Age of Control Group: 38.1 (10.2)	Sex of Experimental Group: Migrane group: (15:26) and PPTH group: (32:17) Sex of Control Group: 22:19	9	Level 4

Aim of Study: To determine changes in fibertract profiles that are unique to either migraine or to persistent post-traumatic headache (PPTH), and to better understand whether these changes relate to disease characteristics, by exploring the relationships between headache frequency and alterations in fibertract profiles.
Key Outcome Measures: Headache history, the Beck Depression Inventory (BDI), the State Anxiety Inventory, and the Ohio State University TBI Identification questionnaire. DTI and a novel method for detecting subtle changes in fibertract integrity by measuring node-by-node parameters along each tract to compare fibertract profiles between those with migraine and those with PPTH, and compared both cohorts to a group of controls. Node-by-node diffusion parameters of mean diffusivity (MD) and radial diffusivity (RD) were calculated along each tract.
Age at Head Injury: Not Reported, **Years Since Head Injury:** 10 (8.1) for the PPTH group
Years of Education: Not Reported; **Race:** Not Reported; **Population Type:** General Population
Diagnosis of Concussion: Ohio State University TBI Identification questionnaire for determining history of TBI was used.
Key Findings: There were significant differences between migraine and persistent post-traumatic headache cohorts for quartile measurements of MD or RD in the bilateral anterior thalamic radiations, cingulum (angular bundles and cingulate gyri), inferior longitudinal fasciculi, and uncinate fasciculi, the left corticospinal tract, and the right superior longitudinal fasciculi-parietal portion. For migraine patients, there was a significant positive correlation between headache frequency and forceps major MD, whereas for persistent post-traumatic headache there was a positive correlation between headache frequency and cingulum angular bundle MD and RD.

Lead Author	PMID	Study Design	Sample Size	Age: mean (SD)	Sex	Risk of	Level of

and Study Year					M:F	Bias	Evidence
(Clark et al., 2018)	29087238	Cross Sectional Study	61	Age of Experimental Group: Professional players: 3/more TBI (n = 15): 57.9 (3.74); 0-1 TBI (n=15): 59.2 (3.55). Age of Control Group: College players: 3/more TBI (n = 16): 58.2 (3.43); 0-1 TBI (n=15): 58.9 (4.12).	Sex of Experimental Group: College players: 31:0 and professional players: 30:0	14	Level 4
Aim of Study: To better understand the relationship between exposure to concussive and subconcussive head impacts, white matter integrity, and functional task-related neural activity in former U.S. football athletes (NFL and college players). **Key Outcome Measures:** Participants were stratified across three crossed factors: career duration, concussion history, and primary playing position. Fractional anisotropy (FA) and blood oxygen level-dependent (BOLD) percent signal change (PSC) were measured with diffusion-weighted and task-related functional MRI (fMRI), respectively. Analyses of variance of FA and BOLD PSC were used to determine main or interaction effects of the three factors. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Estimated (>10) based on years of exposure to football which for the professional players in the 3 or more concussions group (n = 15) was: 17.6 (3.86), and for the 0-1 concussions group (n = 15) was: 17.7 (2.53); college players in the 3 or more concussions group (n = 16): 8.06 (0.68), and the 0-1 concussions group (n = 15): 8.05 (0.60). **Years of Education:** Professional players: the 3 or more concussions group (n = 15): 16.7 (0.976) and the 0-1 concussions group (n = 15): 16.7 (1.45). For the College players: the 3 or more concussions group (n = 16): 16.6 (1.03) and the 0-1 concussions group (n = 15): 16.4 (0.828); **Race (%):** Not Reported; **Population Type:** Athletes **Diagnosis of Concussion:** Self-reported while provided a standard definition of concussion (McCrory et al., 2013). Exposure to subconcussive impacts was estimated by football career duration (i.e., retired after college football or coninuied to professional foooball for 5+ years.) **Key Findings:** A significant interaction between career duration and concussion history was observed; former college players with more than three concussions had lower FA in a broadly distributed area of white matter compared with those with zero to one concussion ($t(29) = 2.774$; adjusted $p = .037$), and the opposite was observed for former professional players ($t(29) = 3.883$; adjusted $p = .001$). A separate interaction between concussion history and position was observed: Nonspeed players (i.e., offensive or defensive linemen) with more than three concussions had lower FA in frontal white matter compared with those with zero to one concussion ($t(25) = 3.861$; adjusted $p = .002$). Analysis of working memory-task BOLD PSC revealed a similar interaction between concussion history and position (all adjusted $p < .004$). Former football athletes who played a nonspeed position (ie, offensive or defensive linemen) and reported three or more concussions had lower FA ($t(25) = 3.861$; adjusted $p = .002$) and lower blood oxygen level-dependent percent signal change during a working memory task ($t(25) = 3.537$; adjusted $p = .004$) than did those with zero to one concussion.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(De Beaumont et al., 2013)	23972282	Cross Sectional	30	Age of Experimental Group: 60.87 (7.51)	Sex of Experimental Group: 15:0	10	Level 4

		Study		Age of Control Group: 58.13 (5.28)	Sex of Control Group: 15:0		
Aim of Study: To examine how aging combined with a history of remote concussions interact to affect M1 metabolism and function in former university-level athletes. This study also sought to determine whether neurometabolic abnormalities are observed in M1 of former concussed athletes, and if so, whether they relate to possibly reduced M1-dependent motor sequence learning. **Key Outcome Measures:** They used proton magnetic resonance spectroscopy (3 T MRI) to detect metabolic abnormalities in the primary motor cortex and the serial reaction time task (SRTT) to evaluate motor learning. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** 37.07 (7.93) **Years of Education:** Controls: 17.27 (3.45), concussed group: 16.67 (4.07); **Race (%):** Not Reported; **Population Type:** Athletes (former university level hockey and football athletes) **Diagnosis of Concussion:** Self-reported and collected by a certified neuropsychologist (according to the American Academy of Neurology practice parameters). All classified as mild traumatic brain injury on the Glasgow Coma Scale (scoring between 13 to 15). **Key Findings:** Among concussed athletes, they found that the number of concussions sustained was negatively correlated with relative M1 glutamate/H_2O levels (r = -.631; P = .021) as well as sequence-specific motor learning (r = -.597; p = .029). They also found a significant Age by Group interaction for M1 glutamate concentration (F1, 24= 4.616; P = .048; ηp2 = 0.755), indicating that the effect of aging on M1 glutamate levels was significantly exacerbated in former concussed athletes. In contrast, the Age by Group interaction for NAA levels in M1 did not reach significance (F1, 24 = 3.50; P = .074; ηp2 = 0.132).						
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Ford et al., 2013)	23679098	Cross Sectional Study	41	Age of Experimental Group: 62.6 (5) for the high concussion group and 64.1 (6.8) for the low concussion group). Age of Control Group: 62.2 (6.3)	Sex of Experimental Group: 12:0 in the high concussion group and 15:0 in the low concussion group Sex of Control Group: 14:0	11	Level 4
Aim of Study: To use event-related fMRI to examine long-term neural changes associated with multiple sport-related concussions. **Key Outcome Measures:** Event-related fMRI was used to examine long-term differences in neural activity during memory tasks in former athletes who sustained multiple sport-related concussions. Cognitive measures included: the telephone interview for cognitive status, MMSE, WAIS, COWA, TMT-B, BNT, WTAR, and GDS. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Not Reported (more than 10) **Years of Education:** Controls: 16.4 (1.1), low-concussion group: 16.4 (1.4), and high-concussion group: 16.2 (1.3); **Race (%):** Not Reported; **Population Type:** Athletes (former professional NFL players with minimum two seasons of play and healthy aged matched controls) **Diagnosis of Concussion:** Self-reported (method not described) **Key Findings:** Concussion history was not significantly associated with cognitive performance. In contrast, the two groups of former players demonstrated different neural recruitment patterns during relational memory retrieval. In addition, the number of previous concussions						

significantly correlated with functional activity in a number of brain regions, including the medial temporal lobe and inferior parietal lobe.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(R.C. Gardner et al., 2016)	25970145	Cross Sectional Study	34	Age of Experimental Group: 54.6 (15.8) Age of Control Group: 54.7 (15.8)	Sex of Experimental Group: 17:0 Sex of Control Group: 17:0	13	Level 4
Aim of Study: To characterize neuroimaging features of the septum pellucidum in a cohort of retired American pro-football players presenting with cognitive/behavioral symptoms compared with similar memory clinic patients without a history of TBI. **Key Outcome Measures:** CSP grade was measured with 3 T structural MRI (CSP rated as 0-absent, 1-equivocal, 2-mild, 3-moderate, 4-severe) and length was measured according to a standard protocol. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Not Reported. Average number of years since retired from pro-football: 24.5 (15.5). Total lifetime exposure to football since childhood (in years): 17.3 (4.5). **Years of Education:** Controls: 17.3 (5.2) and players: 17.7 (3.3); **Race (%):** Not Reported; **Population Type:** Athletes (retired pro-football players with at least one season of play) **Diagnosis of Concussion:** Self-reported (method not described) **Key Findings:** They retrospectively assessed retired American pro-football players presenting to a memory clinic with cognitive/behavioral symptoms. Each player was matched to a memory clinic control patient with no history of TBI. Sixteen of 17 (94%) players had a CSP graded >2 compared with 3 of 17 (18%) controls. CSP was significantly higher grade ($p < 0.001$) and longer in players than controls (mean length-standard deviation: 10.6 mm-5.4 vs. 1.1 mm-1.3, $p < 0.001$). Results were similar for CSP length, total septal cyst length, and their ratios, suggesting that results were not confounded by larger head sizes among players. CSP >2 distinguished players from controls with 94% sensitivity (95% confidence interval [CI] 71-100%) and 82% specificity (95% CI 57-96%). CSP length of 5 mm distinguished players from controls with 82% sensitivity (95% CI 57-96%) and 100% specificity (95% CI 81-100%).							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Gilmore et al., 2020)	33351088	Longitudinal Cohort Study	139	Age of Experimental Group: 50 (10.3) Age of Control Group: 49.9 (11.9)	Sex of Experimental Group: 62:7 Sex of Control Group: 55:15	10	Level 4
Aim of Study: To identify evidence of neurodegeneration through longitudinal evaluation of structural and functional changes in the visual nervous system and CNS in veterans with a history of mild TBI. **Key Outcome Measures:** Change over time of retinal nerve fibre layer (RNFL) thickness using optical coherence tomography. Cognitive tests: CogState battery and Groton Maze Learning Test (GMLT). **Age at Head Injury:** Not Reported, **Years Since Head Injury:** median: 17 years **Years of Education:** Not Reported in number of years; **Race (%):** Not Reported; **Population Type:** Veterans **Diagnosis of Concussion:** mTBI was diagnosed according to the Mayo TBI Severity Classification System.							

Key Findings: Veterans with mTBI showed significantly greater RNFL thinning compared with controls. RNFL tissue loss was significantly correlated with both worsening performance on the GMLT over time (Spearman ρ = −0.20; p =.03) and mTBI severity (Spearman ρ = −0.25; p = .006). The more severe the mTBI (larger Minnesota Blast Exposure Screening Tool severity score), the faster the reduction in RNFL thickness (i.e., the more negative the slope) across time.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Goswami et al., 2016)	25721800	Case Series	36	Age of Experimental Group: 50 (12) Age of Control Group: 46 (10)	Sex of Experimental Group: 19:0 Sex of Control Group: 17:0	9	Level 4
Aim of Study: The first aim was to determine the relationship between response inhibition and related psychological factors to the structural and functional properties of the uncinate fasciculus (UF) and frontotemporal gray matter in retired professional athletes (CFL players) with a chronic history of multiple concussions. Machine learning was also used to test the predictive power of diffusion imaging metrics within the UF to discriminate these concussed athletes from controls. **Key Outcome Measures:** Used MRI (DWI and rs-fMRI) to examine the UF and connected gray matter as it relates to impulsivity (SART: go/no go task) and aggression (the PAI). Examined cortical thickness, diffusion, probabilistic tractography (including registration of tractography maps for machine learning analysis), resting state fMRI, and machine learning for DTI metrics. **Age at Head Injury:** Not Reported. Almost half reported their first concussion was in high school, **Years Since Head Injury:** Not Reported **Years of Education:** Experimental group: 17 (1.8), controls: 16 (1.9); **Race (%):** Not Reported; **Population Type:** Athletes **Diagnosis of Concussion:** Self-reported. Concussion was operationally defined in accordance with the guidelines agreed upon by the International Consensus statements (McCrory et al., 2013; Tator, 2013). **Key Findings:** Behaviourally, athletes had faster reaction times and an increased error rate on a go/no-go task, and increased aggression and mania on the PAI compared to controls. MRI revealed that the athletes had (1) cortical thinning of the anterior temporal lobe (ATL), (2) negative correlations of orbital frontal cortex (OFC) thickness with aggression and task errors, indicative of impulsivity, (3) negative correlations of UF axial diffusivity with error rates and aggression, and (4) elevated resting-state functional connectivity between the ATL and OFC. Using machine learning, they found that UF diffusion imaging differentiates athletes from healthy controls with significant classifiers based on UF MD and RD showing 79-84 % sensitivity and specificity, and 0.8 areas under the ROC curves. The spatial pattern of classifier weights revealed hot spots at the orbitofrontal and temporal ends of the UF.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Haglund & Bergstrand, 1990)	2281746	Cross Sectional Study	100	Age of Experimental Group: HM-boxers (mean: 32.6 years), LM-boxers (mean: 33.6 years) Age of Control Group: SP mean age: 33, TF mean age:	Sex of Experimental Group: HM-group: 25:0, LM-group 25:0 Sex of Control Group: SP group: 25:0, TF group 25:0	8	Level 4

				33.4			
Aim of Study: To find out if morphological changes could be found in former amateur (low match and high match) boxers using CT and MRI. **Key Outcome Measures:** CT and MRI for evaluation of a cavum septum pellucidum (CSP). **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Average length of career for HM group: 8.3 years and 3.4 years for LM group. **Years of Education:** Not Reported; **Race (%):** Not Reported; **Population Type:** Athletes (former amateur boxers, soccer and track and field players as controls). **Diagnosis of Concussion:** Not described. Years of fighting experience was used as a proxy for repetitive brain injury. **Key Findings:** No significant differences in the width of the ventricular system, anterior horn index, width of cortical sulci, signs of vermian atrophy, or the occurrence of a CSP were found between boxers and controls. A higher incidence of CSP was found in track and field athletes than in the other two groups who sustained repeated head trauma (i.e. boxers and soccer players). The authors state that a CSP is probably an anatomical normal variation and that it can not be concluded from this study that it is a sign of earlier head trauma. Although a correlation existed between the occurrence of a CSP and the number of fights, fights lost, KO/RSC(H) and the length of boxing career, it should be noted that there were only two boxers who had a CSP.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Hampshire et al., 2013)	24135857	Cross Sectional Study	33	Age of Experimental Group: 54 Age of Control Group: 53	Sex of Experimental Group: 13:0 Sex of Control Group: 20:0	6	Level 4
Aim of Study: To assess the performances and functional brain activations of a group of retired NFL players whilst undertaking the One Touch Spatial Planning task, an fMRI-optimised variant of the classical Tower of London paradigm that is widely used to assess executive cognition. **Key Outcome Measures:** Evaluated the performances and brain activation patterns of retired NFL players (NFL alumni) relative to controls using an fMRI-optimised neuropsychological test of executive function. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Not Reported. **Years of Education:** Not Reported; **Race (%):** Not Reported; **Population Type:** Athletes (retired NFL and controls) **Diagnosis of Concussion:** Self-reported number of times that they had been taken out of play due to head impact. **Key Findings:** Retired NFL players showed modest performance deficits on the executive task but demosntrated pronounced hyperactivation and hypoconnectivity of the dorsolateral frontal and frontopolar cortices. The NFL alumni exhibited pronounced hyperactivation within the same DLPFC regions that were engaged by controls during planning and retrieval. This hyperactivation was evident at all levels of planning complexity and for all levels of working-memory load, including those for which there was no significant difference in performance. Moreover, frontopolar regions were selectively recruited in the NFL alumni during more difficult trials whereas in controls no such activation was evident. Abnormal frontal-lobe function was correlated with the number of times that NFL alumni reported having been removed from play after head injury and was evident in individual players.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Hart et al.,	23303193	Cross	48	Age of Experimental Group:	Sex of Experimental	9	Level 4

2013)		Sectional Study		unimpaired retired NFL players mean age: 55.4, cognitively impaired retired NFL players 66.6 Age of Control Group: 60.1	Group: unimpaired retired NFL players: 12:0 and cognitively impaired retired NFL players: 10:0 Sex of Control Group: 26:0		
Aim of Study: To assess cognitive impairment and depression in aging former NFL players and to identify neuroimaging correlates of these dysfunctions. **Key Outcome Measures:** Neuropsychological measures, clinical diagnoses of depression, neuroimaging (3 T MRI) measures of white matter pathology (DTI), and a measure of cerebral blood flow (pseudocontinuous arterial spin labelling and Hemosiderin Scan). **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Estimated (>10) based on years of NFL exposure several decades ago, which was an average of 9.7 years. **Years of Education:** Unimpaired retired NFL players mean years: 16.6, cognitively impaired retired NFL players: 16.1, controls: 16.2; **Race (%):** 23 of the retired NFL players were white and 11 were African American. Control group: 24 were white, 2 were African American.; **Population Type:** Athletes (former NFL and healthy mattched controls) **Diagnosis of Concussion:** Concussion history was obtained retrospectively from participants and informants and classified using the 1997 American Academy of Neurology practice parameter guidelines. **Key Findings:** Of the 34 former NFL players, 20 were without cognitive impairments. Four were diagnosed as having a fixed cognitive deficit; eight, mild cognitive impairment; two, dementia; and eight, depression. Of the subgroup in whom neuroimaging data were acquired, cognitively impaired participants showed the greatest deficits on tests of naming, word finding, and visual/verbal episodic memory. Significant differences were found in white matter abnormalities in cognitively impaired and depressed retired players compared with their respective controls (they found widely distributed reductions of FA in frontal and parietal regions bilaterally as well as along the corpus callosum and in the left temporal lobe). Regional blood flow differences in the cognitively impaired group (impaired players had decreased blood flow to the left temporal pole and increased blood flow to the inferior parietal lobule and superior temporal gyrus) corresponded to regions associated with impaired neurocognitive performance (problems with memory, naming, and word finding).							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(June et al., 2020)	32702483	Longitudinal Cohort Study	153	Age of Experimental Group: 65.14 (11.23) Age of Control Group: 65.2 (11.25)	Sex of Experimental Group: 29:12 Sex of Control Group: 58 (56.9)	11	Level 3
Aim of Study: To examine baseline and longitudinal brain alterations more than 20 years post-concussive event and explore the long-term impact of concussion on subsequent neurodegeneration, in cognitively normal older adults from the Baltimore Longitudinal Study of Aging (BLSA). **Key Outcome Measures:** Participants underwent serial structural MRI and DTI to measure brain structure, as well as 15 O-water PET to							

measure brain function. A battery of neuropsychological tests was also administered.
Age at Head Injury: 33.05 (22.25), **Years Since Head Injury:** 23 (18.64)
Years of Education: Not Reported; **Race (%):** Not Reported by race; **Population Type:** General Population
Diagnosis of Concussion: Self-reported in patient's medical history. If loss of consciousness was reported, only those with reports of < 30 min unconsciousness were included in the analyses.
Key Findings: Compared to those without concussion, participants with a prior concussion had greater brain atrophy in temporal lobe white matter and hippocampus at first imaging visit, which remained stable throughout the follow-up visits. Those with prior concussion also showed differences in white matter microstructure using DTI, including increased RD and axial diffusivity in the fornix/stria terminalis, anterior corona radiata, and superior longitudinal fasciculus at first imaging visit. In 15O-water PET, higher resting cerebral blood flow was seen at first imaging visit in orbitofrontal and lateral temporal regions, and both increases and decreases were seen in prefrontal, cingulate, insular, hippocampal, and ventral temporal regions with longitudinal follow-up. There were no significant differences in neuropsychological performance between groups.

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Kelman et al., 2020)	31691473	Cross Sectional Study	13	Age of Experimental Group: mean age of 60	Sex of Experimental Group: 13:0	9	Level 4

Aim of Study: To evaluate retinal nerve fibre layer (RNFL) thickness in professional rugby league players, with RNFL thinning serving as a potential proxy for wider white matter degeneration.
Key Outcome Measures: RNFL thickness of each eye (using binocular RNFL thickness as measured by spectral domain optical coherence tomography [OCT]) were compared with a normative database. Other measures included the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25). The Quick Mild Cognitive Impairment ("QMCI") screen was used to assess cognitive domains. The Depression Anxiety Stress Scale ("DASS-21") survey was used to assess mood. Alcohol consumption and drinking behaviours were assessed through clinical interview using the Alcohol Use Disorders Identification Test ("AUDIT").
Age at Head Injury: The average age of first concussion was 18, with the earliest reported concussion being at age 11, **Years Since Head Injury:** All participants had competed in Rugby League at a professional club level for 18 years on average. Mean age of introduction to the sport was nine. Average number of years (at testing) since last professional play was 28. Average training per week was four days whilst active, with ten participants reporting weekly games and three participants reporting fortnightly games.
Years of Education: Not Reported; **Race (%):** All caucasian; **Population Type:** Athletes
Diagnosis of Concussion: Self-reported concussion exposure was evaluated in line with guidelines from the third International Conference on Concussion in Sport (McCrory et al., 2009). A detailed medical and sporting history was taken using a standardized questionnaire.
Key Findings: Participants reported sustaining 15 sports-related concussions throughout their career. The RNFL in participants was four micrometres thinner than that of matched normative data. Cohort average RNFL thickness was reduced in 12 out of 14 optical coherence testing parameters. These findings were statistically significant in the left inferonasal [p = .013] and left nasal [p = .006] sectors.

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Koerte, Lin,	25843317	Cross	25	Age of Experimental Group:	Sex of Experimental	10	Level 4

Muehlmann, et al., 2015)		Sectional Study		52 (6.8) Age of Control Group: 46.9 (7.9)	Group: 11:0 Sex of Control Group: 14:0		
Aim of Study: To evaluate neurochemistry by using MRS in former professional soccer players without a known history of concussion, but with a history of extensive heading and associated repetitive subconcussive head injury (RSHI), compared with former professional, age-matched, non-contact sport athletes. In addition, the association between brain chemical concentrations, neurocognitive performance, and estimated number of headers was assessed. **Key Outcome Measures:** 3T magnetic resonance spectroscopy (MRS) neurochemicals quantified: NAA, creatine (Cr), Cho, Glu, GSH, and mI. In addition, lipid and macromolecule resonances were also characterized at 0.9, 1.3, and 2.0 ppm. 11 study participants underwent a brief neurocognitive and balance examination by an examiner who was blinded to the athlete's sport. Other tests: Trailmaking Test (TMT) parts A and B, Rey-Osterrieth Complex Figure (ROCF) test, and Balance Error Scoring System (BESS). **Age at Head Injury:** Mean age when soccer training started was 11.5 (4.3), **Years Since Head Injury:** Not Reported **Years of Education:** Not Reported; **Race (%):** Not Reported; **Population Type:** Athletes **Diagnosis of Concussion:** Lifetime exposure to soccer was used as an indicator of RSHI exposure (only used players without a history of suspected/diagnosed concussion). **Key Findings:** In the soccer players a significant increase was observed in both choline (Cho), a membrane marker, and myo-inositol (ml), a marker of glial activation, compared with control athletes. Additionally, ml and glutathione (GSH) were significantly correlated with lifetime estimate of RSHI within the soccer group. It is noteworthy that GSH/Cr levels were significantly correlated with exposure to RSHI.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Koerte, Hufschmidt, et al., 2016)	26414478	Cross Sectional Study	86	Age of Experimental Group: 54.53 (8.03) Age of Control Group: former professional noncontact sport athletes: 57.14 (7.62)	Sex of Experimental Group: 72:0 Sex of Control Group: former professional noncontact sport athletes: 14:0	10	Level 4
Aim of Study: The aims of this study were (1) to characterize neuroimaging features of CSP in former NFL players who presented with cognitive, mood, and behavioral symptoms compared with asymptomatic noncontact sports athletes, and (2) to evaluate the association between CSP and cognitive and behavioral functioning in former NFL players who present with cognitive, mood, and behavioral symptoms. **Key Outcome Measures:** High-resolution structural 3T MRI for characterization of CSP. All subjects were administered: Neuropsychological Assessment Battery (NAB) List Learning; Map Reading; Naming; ROCF; TMT, Parts A and B; WAIS-R Digit Symbol; WRAT-4 Reading Test; and the Wisconsin Card Sort Test (WCST). The Hamilton Depression Rating Scale (HAM-D), Brown-Goodwin Lifetime History of Aggression (LHA), Barratt Impulsivity Scale (BIS), and Modified Scale for Suicidal Ideation (MSSI) were assessed as part of the psychiatric interview, while the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A), BDI, Beck HopelessnessInventory (BHI), and Buss-Durkee Hostility Inventory (BDHI) were self-completed by each subject. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Estimated (>10) based on years of football exposure from several decades ago.							

Total years of football = 18.11 (3.49) and total years in the NFL = 7.8 (2.67). Also reported the number of concussions: 446.9 (1077.4)
Years of Education: NFL players:16.39 (0.87), controls: 17.64 (2.1); **Race (%):** Not Reported; **Population Type:** Athletes
Diagnosis of Concussion: Self-reported after receiving a definition of concussion using methods described by Robbins et al (2014).
Key Findings: A higher rate of CSP, a greater length of CSP, as well as a greater ratio of CSP length to septum length was found in symptomatic former professional football players compared with athlete controls. In addition, a greater length of CSP was associated with decreased performance on a list learning task (NAB List A Immediate Recall, p = 0.04) and decreased test scores on a measure of estimate verbal intelligence (WRAT-4, p = 0.02).

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Koerte, Mayinger, et al., 2016)	26286826	Cross Sectional Study	30	Age of Experimental Group: 49.3 (5.1) Age of Control Group: former professional non-contact sport athletes: 49.6 (6.4)	Sex of Experimental Group: 15:0 Sex of Control Group: former professional non-contact sport athletes: 15:0	10	Level 4

Aim of Study: To evaluate the association between cortical thickness and estimated exposure to repetitive subconcussive head impact, as well as to cognitive performance in former professional soccer players compared to age-matched non-contact sport athletes.
Key Outcome Measures: Cortical thickness analyses from images obtained from a 3 T MRI scanner (using voxel-based statistics). All study participants were evaluated on cognitive, behavioral, and motor functioning by an examiner who was blinded to their sport. Tests included: Trail making Test (TMT) parts A and B, Rey Osterrieth Complex Figure (ROCF), Barrett Impulsivity Score (BIS), and the BESS. TMT parts A and B were performed to quantify the athlete's psychomotor speed, visual search, and mental flexibility.
Age at Head Injury: Not Reported: soccer exposure since childhood was reported in all players, **Years Since Head Injury:** Not Reported
Years of Education: Not Reported; **Race (%):** Not Reported; **Population Type:** Athletes
Diagnosis of Concussion: Years of playing soccer and estimated ball heading exposure was used as a proxy for repetitive subconcussive head injury.
Key Findings: Soccer players demonstrated greater cortical thinning with increasing age compared to controls in the right inferolateral-parietal, temporal, and occipital cortex. Cortical thinning was associated with lower cognitive performance as well as with estimated exposure to RSHI. Neurocognitive evaluation revealed decreased memory performance in the soccer players compared to controls.

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Kuhn et al., 2017)	30043690	Cross Sectional Study	45	Age of Experimental Group: 46.7 (9.1)	Sex of Experimental Group: 45:0	10	Level 4

Aim of Study: To assess the relationships among 3 neuroimaging findings (cavum septum pellucidum, FA global mean, and microhemorrhages) and neuropsychological test performance and symptom endorsement in a relatively large sample of retired NFL athletes.
Key Outcome Measures: MRI was performed (anatomical to check for CSP, DTI, and SWI) in 45 retired NFL players. Three neuroanatomical

parameters were assessed: (1) the absence or presence of small or large cavum septum pellucidum, (2) a global mean score of FA, and (3) the presence or absence of microhemorrhages. The subjects underwent a battery of 9 neuropsychological tests (i.e., TOMM; BVMT-R; CVLT-II; TMT A and B, WAIS-3 Digit Symbol and Letter Number Sequencing ; COWAT; WTAR, a computerized neurocognitive test (ImPACT), and multiple symptom and depression scales.
Age at Head Injury: Not Reported, **Years Since Head Injury:** Not Reported: data not available (but players began their career in their 20's).
Years of Education: Not Reported; **Race (%):** Not Reported; **Population Type:** Athletes
Diagnosis of Concussion: Self-reported: number of concussions and number of "dings" (defined as "a momentary abnormal sensation in the head occurring immediately upon head impact, with complete resolution within a few seconds and no residual effects").
Key Findings: The 45 subjects reported a mean 6.9 (±6.2) concussions and 13.0 (±7.9) "dings" in the NFL. Ten (22%) did not have a cavum septum pellucidum, while 32 (71%) had a small and 3 (7%) had a large one. Four (9%) had microhemorrhages. Global FA mean was 0.459 (±0.035). The majority (50.8%) of correlations among the neuroimaging parameters and neurocognitive/symptom scores fell below the threshold of "small" effect size ($r < 0.10$). The remaining (49.2%) correlations were between "small" and "medium" effect sizes ($0.1 < r < 0.3$). However, all correlations were statistically nonsignificant. The MRI measures of cavum septum pellucidum, FA mean, and microhemorrhaging accounted for between 0.0009% and 6.53% of the variance observed.

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Lepage et al., 2019)	29779184	Cross Sectional Study	108	Age of Experimental Group: 54.86 (7.9) Age of Control Group: 57.3 (7)	Sex of Experimental Group: 86:0 Sex of Control Group: 22:0	10	Level 4

Aim of Study: To compare the volumes of the amygdala, hippocampus, and cingulate gyrus in symptomatic former NFL players, relative to asymptomatic controls without a history of RHI or brain trauma.
Key Outcome Measures: Neuroimaging data (volumetric) was acquired on a 3-Tesla MRI Scanner. Regions of interest included the cingulate gyrus, hippocampus, and amygdala. As part of DETECT, participants completed: TMT A and B; Digit Span and Digit Symbol Coding (from the WAIS-R); Wisconsin Card Sorting Test (WCST); Controlled Oral Word Association Test (COWAT); Animal Fluency; Color-Word Interference subtest (DKEFS); ROCF; and Story Learning, List Learning, Naming, and Map Reading, from the NAB. Mood/behavior measures: Apathy Evaluation Scale (AES), BIS-11, BDI-II, Beck Hopelessness Scale (BHS), BRIEF-A, LHA, Center for Epidemiologic Studies - Depression Scale (CES-D), Buss-Durkee Inventory, HAM-D, and the MSSI.
Age at Head Injury: Not Reported, **Years Since Head Injury:** Not Reported. Estimated (>10) based on NFL exposure of at least 12 years earlier in life.
Years of Education: NFL players: 16.4 (0.96) and for the controls: 17.4 (2.2); **Race (%):** Not Reported; **Population Type:** Athletes
Diagnosis of Concussion: Based on self-report after being provided a definition of concussion (Robbins et al., 2014)
Key Findings: They compared select limbic brain regional volumes (the amygdala, hippocampus, and cingulate gyrus) between symptomatic former NFL players (n = 86) and controls (n = 22). Compared to controls (with no TBI or contact-sport exposure), former NFL players exhibited reduced volumes bilaterally of the amygdala, hippocampus, and cingulate gyrus. Within the NFL group (n = 75), reduced bilateral cingulate gyrus volume was associated with worse attention and psychomotor speed ($r = 0.4$ (right), $r = 0.42$ (left); both $p < 0.001$), while decreased right

hippocampal volume was associated with worse visual memory (r = 0.25, p = 0.027).

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(A. P. Lin et al., 2015)	25780390	Cross Sectional Study	10	Age of Experimental Group: 43.6 (10.8) Age of Control Group: 45.2 (12.6)	Sex of Experimental Group: 5:0 Sex of Control Group: 5:0	7	Level 4

Aim of Study: To report the results of a pilot study, using the Localized COrrelated SpectroscopY (L-COSY) method, on chronic sports-induced repetitive head injury in elite athletes compared with healthy age-matched controls with no history of head injury.
Key Outcome Measures: MRI and MRS - the posterior cingulate gyrus was chosen for examination due to evidence that this area is sensitive to TBI in addition to this area being implicated in receiving higher tau deposition with CTE.
Age at Head Injury: Not Reported, **Years Since Head Injury:** Average of 17.4 (7.2) years of exposure to repetitive TBI in contact sports.
Years of Education: Not Reported; **Race (%):** Not Reported; **Population Type:** Athletes
Diagnosis of Concussion: Based on self-reported number of professional years and total number of years played in their sport as a proxy for RHI
Key Findings: None of the athletes showed structural MRI abnormalities using conventional imaging metrics. The variation of the method was calculated by repeated examination of a healthy control and phantom and found to be 10% and 5%, respectively, or less. The L-COSY measured large and statistically significant differences ($p \leq 0.05$), between healthy controls and athletes with RHI. Men with RHI showed higher levels of glutamine/glutamate (31%), choline (65%), fucosylated molecules (60%) and phenylalanine (46%). The results were evaluated and the sample size of five found to achieve a significance level p = 0.05 and a power of 90%. Differences in N-acetyl aspartate and myo-inositol between RHI and controls were small and were not statistically significant.

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Lipton et al., 2013)	23757503	Cross Sectional Study	37	Age of Experimental Group: Low-heading group: 32.4 (6.2), Medium-heading group: 31.4 (5.5), and High-heading group: 28.7 (6.2)	Sex of Experimental Group: Low-heading group: 6:3, Medium-heading group: 15:4 and High-heading group: 8:1	10	Level 4

Aim of Study: To investigate the association of soccer heading with subclinical evidence of TBI.
Key Outcome Measures: Diffusion-tensor magnetic resonance (MR) imaging at 3T was performed (32 directions; b value, 800 sec/mm2; 2 3 2 3 2-mm voxels). Computerized battery of tests for cognitive functioning and questionnaire to quantify heading in the prior 12 months and lifetime concussion history.
Age at Head Injury: Not Reported, **Years Since Head Injury:** Not Reported. Estimated (>10) based on years of exposure to soccer: Low-heading group: 27 (6.1) years, Medium-heading group: 21.6 (7.9) years, and High-heading group: 19.9 (6.9) years
Years of Education: Low-heading group: 16.2 (1.6), Medium-heading group: 16.5 (1.5) and High-heading group: 15.3 (1.7); **Race (%):** Not Reported; **Population Type:** Athletes

Diagnosis of Concussion: Self-reported: subjects were asked to quantify heading in the prior 12 months and lifetime concussion exposure. **Key Findings:** Participants had headed 32–5400 times (median, 432 times) over the previous year. Heading was associated with lower FA at three locations in temporo-occipital white matter with a threshold that varied according to location (885–1550 headings per year) ($p < .00001$). Lower levels of FA were also associated with poorer memory scores ($p < .00001$), with a threshold of 1800 headings per year.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Misquitta et al., 2018)	29984163	Cross Sectional Study	399	Age of Experimental Group: 55.6 (12.9) Age of Control Group: Study controls: 50.8 (10) and Cam-CAN controls: 58.1 (16)	Sex of Experimental Group: 53:0 Sex of Control Group: Study controls: 25:0 and Cam-CAN controls: 321:0	10	Level 4
Aim of Study: To use structural segmentation and deformation-based morphometry (DBM) analyses to compare the effect of multiple concussions on regional brain volumes in retired professional athletes from the Canadian Football League (ex-CFL) with non-athlete control subjects with no history of concussion. **Key Outcome Measures:** DBM analysis of subcortical structures using 3T MRI, APOE genotyping, the PAI, Rey Auditory Verbal Learning Test, and the Rey Visual Design Learning Test. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Estimated (>10) based on number of years in CFL: average of 9 years, earlier in life. **Years of Education:** 16.7 (1.7) for Ex-CFL players and 16 (1.9) for study controls; **Race (%):** Not Reported; **Population Type:** Athletes **Diagnosis of Concussion:** Concussion exposure was based on players' recall of injury during a semi-structured interview in accordance with the Zurich Guidelines on Concussions (McCrory et al., 2013). **Key Findings:** Volumetric analyses revealed greater hippocampal atrophy than expected for age in former athletes with multiple concussions than controls and smaller left hippocampal volume was associated with poorer verbal memory performance in the former athletes. DBM confirmed smaller bilateral hippocampal volume that was associated with poorer verbal memory performance in athletes. Number of years playing professional football was significantly related to smaller left and right hippocampus and left and right amygdala volumes, but not with ventricular volume. After Bonferroni correction for multiple comparisons, only correlations with the left and right amygdala remained significant ($p < 0.01$). There was no correlation between career years and self-reported number of concussions ($r = -0.01$, $p = 0.93$).							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Monti et al., 2013)	23986698	Cross Sectional Study	44	Age of Experimental Group: young mTBI group: 22.4 (2), middle-aged mTBI group: 52.9 (9.4) Age of Control Group: young control group: 22.3 (2.6),	Sex of Experimental Group: young mTBI group: 7:5, middle-aged mTBI group: 4:6 Sex of Control Group: young control group:	10	Level 4

				middle-aged control group: 52.5 (7.9)	7:5, middle-aged control group: 4:6		
Aim of Study: To examine structural and functional brain aberrations in individuals who had sustained mTBI several decades ago in the brain regions and networks subserving relational memory. **Key Outcome Measures:** fMRI study: 3T MRI was used. Subcortical volume analyses and functional analyses were done. Participants completed an event-related relational memory task during fMRI scanning where the goal was to form an association between a face and scene. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** young mTBI group: 4 (3.1), middle-aged mTBI group: 39 (12.6) **Years of Education:** young mTBI group: 15.4 (0.52), middle-aged mTBI group: 17.3 (3.9), young control group: 15.6 (0.9), middle-aged control group: 17.3 (3.6); **Race (%):** Not Reported; **Population Type:** General Population **Diagnosis of Concussion:** Only those participants whose mTBIs were diagnosed by a medical professional and/or resulted in LOC for less than 30 minutes were included in the mTBI groups; based on criteria from the Mild Traumatic Brain Inury Committee (1993) at the American Congress of Rehabilitation Medicine. **Key Findings:** Results indicated that middle-aged adults with a head injury in their remote past had impaired memory compared to sex-, age-, and education- matched control participants. The present study demonstrated that these individuals also had smaller bilateral hippocampi, and had reduced neural activity during memory performance in cortical regions important for memory retrieval. Reduced neural activity in multiple regions of the PFC was found for the MI group relative to the MC group, including the right inferior frontal gyrus, right medial PFC (mPFC), bilateral frontopolar cortex, and middle and superior frontal gyri.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Multani et al., 2016)	27142715	Cross Sectional Study	35	Age of Experimental Group: 49.6 (12) Age of Control Group: 46.7 (10)	Sex of Experimental Group: 18:0 Sex of Control Group: 17:0	10	Level 4
Aim of Study: To examine the effect of multiple concussions on whole-brain white-matter integrity in retired professional football players. **Key Outcome Measures:** DTI: Whole brain tract-based spatial statistics analysis were performed to examine white matter tract integrity (tractography on the SLF was performed using the probabilistic tractography [probtrackx] in FSL) and to compare findings with neuropsychological outcomes. Assessment measures: PAI, RDVLT, and WTAR. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** 16.2 (13) **Years of Education:** Players: 17.3 (2), controls: 16.4 (2); **Race (%):** Not Reported; **Population Type:** Athletes **Diagnosis of Concussion:** The history of concussions was determined by the player's ability to recall injuries caused by a blow to the head or body that resulted in concussion symptoms, including at least one of the following: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, and trouble concentrating. **Key Findings:** Whole brain tract-based spatial statistics analysis revealed increased axial diffusivity in the right hemisphere of retired players in the (1) superior longitudinal fasciculus (SLF), (2) corticospinal tract, and (3) anterior thalamic radiations, suggesting chronic axonal degeneration in these tracts. TBSS results were not significantly different for FA, RD, and MD between retired players and controls. Moreover, retired players reported significantly higher neuropsychiatric and cognitive symptoms than controls, and worsening symptoms since their last concussion.							

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Rajesh et al., 2017)	28726543	Case Control Study	44	Age of Experimental Group: 20-65 years post-injury group: 52.9 (9.4) and 1-10 years post-injury group: 22.42 (2.02). Age of Control Group: 20-65 years controls: 52.5 (7.86) and 1-10 years controls: 22.55 (2.58).	Sex of Experimental Group: 20-65 years post-injury group: 6:4 and 1-10 years post-injury group: 5:7 Sex of Control Group: 20-65 years controls: 6:4 and 1-10 years controls: 5:7	9	Level 4
Aim of Study: To examine two groups of cognitively resolved remote-mTBI individuals with 1-10 years or 20-65 years time post-injury. **Key Outcome Measures:** Examined resting state functional connectivity and structure (volumetric and thickness-based morphometry, and FA). **Age at Head Injury:** Not Reported, **Years Since Head Injury:** 20-65 years group: 39 (12.57), 1-10 years group: 4 (3.19) **Years of Education:** 20-65 years post-injury group: 17.3 (3.86), 1-10 years post-injury group: 15.42 (0.51), 20-65 years age-matched control group: 17.3 (3.6) and 1-10 years age-matched control group: 15.73 (0.79); **Race (%):** Not Reported; **Population Type:** General Population **Diagnosis of Concussion:** Diagnosis of mTBI was made by a medical professional and/or those who had LOC <30 min and/or who had a post-traumatic amnesia <24 h. **Key Findings:** Abnormalities in brain architecture were only found in the TBI 1-10 years post-injury group and were characterized by functional hypoactivation in the right frontal pole, smaller superior frontal gyrus and frontal pole volume, and less FA in the genu of the corpus callosum that extended near the right frontal pole compared with matched controls. For the resting state DMN data, only the comparison for Control > mTBI 1-10 years post-injury showed significant differences, and only for the seed placed in the PCC. Specifically, the PCC region in healthy controls showed significantly greater correlation with the right frontal pole/anterior prefrontal cortex relative to mTBI 1-10 years post-injury group ($p < 0.05$ cluster corrected). In secondary analysis within the combined group of mTBI ($n = 22$), age at last injury did not correlate with magnitude of functional activation n the right frontal pole ($r = -0.20$; $p = 0.38$).						
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Rowland et al., 2018)	29634322	Cross Sectional Study	16	Age of Experimental Group: PTSD group: 34.9 (4.7) Age of Control Group: No PTSD group: 43.4 (7.8)	Sex of Experimental Group: 7:0 Sex of Control Group: 9:0	12	Level 4
Aim of Study: To determine differences in whole-brain resting-state functional networks associated with the development of PTSD following deployment-acquired mild TBI. **Key Outcome Measures:** Graph theory metrics, including small-worldness, clustering coefficient, and modularity, were calculated from individually constructed whole-brain networks based on 5-min eyes-open resting-state magnetoencephalography (MEG) recordings. Tests: the Structured Clinical Interview for DSM-IV Diagnosis, Clinician-Administered PTSD Scale-5, Test of Premorbid Function, neurobehavioral							

symptom inventory (NSI), and PTSD Checklist-5 (PCL-5).
Age at Head Injury: Not Reported, **Years Since Head Injury:** PTSD group: 9.07 (3.77) years and no PTSD group: 13.1 (7.7)
Years of Education: PTSD group: 15.1 (1.6) years and no PTSD group: 16.6 (2.2); **Race (%):** 14.3% minorities in the PTSD group and 28.6% in the no PTSD group; **Population Type:** Veterans
Diagnosis of Concussion: A structured clinician-administered interview was used to determine mTBI history according to the American Congress of Rehabilitation Medicine criteria (Menon et al., 2010). Severity was based on VA/DoD consensus criteria (2009), with mTBI displaying LOC <30 min, alteration of consciousness (AOC) < 24 h, and/or post traumatic amnesia (PTA) <24 h.
Key Findings: Results demonstrated that participants with current PTSD displayed higher levels of small-worldness, $F(1,12) = 5.364$, $p < 0.039$, partial eta squared = 0.309, and Cohen's d = 0.972, and clustering coefficient, $F(1, 12) = 12.204$, $p < 0.004$, partial eta squared = 0.504, and Cohen's d = 0.905, than those without PTSD. There were no between-group differences in modularity or the number of modules present.

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Small et al., 2013)	23343487	Cross Sectional Study	10	Age of Experimental Group: median age: 59, Range: 45-73 Age of Control Group: median age: 60, Range: 45-66	Sex of Experimental Group: 5:0 Sex of Control Group: 5:0	10	Level 4

Aim of Study: To perform PET scans after intravenous injections of FDDNP and explore whether brain tau deposits can be detected in a small group of retired NFL players with cognitive and mood symptoms in comparison with a group of male controls of comparable age, educational achievement, and body mass index (BMI).
Key Outcome Measures: Neuropsychiatric evaluations and FDDNP-PET. PET signals in subcortical (caudate, putamen, thalamus, subthalamus, midbrain, cerebellar white matter) and cortical (amygdala, frontal, parietal, posterior cingulate, medial and lateral temporal) regions were examined. Subjects had screening laboratory tests and structural imaging scans (computed tomography [CT] or magnetic resonance imaging) to rule out other causes of mental symptoms (e.g., stroke, tumor) and for co-registration with PET scans for region-of-interest (ROI) analyses. The MMSE, Hamilton Rating Scale for Depression (HAM-D), and neuropsychological tests were administered to confirm diagnoses.
Age at Head Injury: Not Reported, **Years Since Head Injury:** Not Reported, but the athletes all played between 10 - 16 years (median: 14).
Years of Education: Players**:** median years of education: 17, controls: 15; **Race (%):** 4 white, 1 African American; **Population Type:** Athletes
Diagnosis of Concussion: Not described
Key Findings: FDDNP signals were higher in players (median BMI = 32) compared with controls (median BMI = 34) in all subcortical regions and the amygdala, areas that produce tau deposits following trauma. Players had significantly higher FDDNP signals compared with controls in caudate (median levels:1.48 versus 1.23, $p = 0.03$), putamen (1.47 versus 1.20, $p = 0.05$), thalamus (1.48 versus 1.29, $p=0.03$), subthalamus (1.45 versus 1.25, $p = 0.03$) midbrain (1.31 versus 1.14, $p = 0.03$), and cerebellar white matter (1.15 versus 1.09, $p = 0.05$) regions. The two groups did not differ significantly in FDDNP binding in cortical regions except for the amygdala (1.30 versus 1.14, $p = 0.03$). Although none of the Spearman correlations reached statistical significance (as expected due to the small sample size), the plots show an increase in FDDNP binding levels with increase in number of concussions.

Lead Author	PMID	Study Design	Sample Size	Age: mean (SD)	Sex	Risk of	Level of

and Study Year					M:F	Bias	Evidence
(Tremblay et al., 2013)	22581847	Cross Sectional Study	30	Age of Experimental Group: 60.87 (7.51) Age of Control Group: 58.13 (5.28)	Sex of Experimental Group: 15:0 Sex of Control Group: 15:0	10	Level 4
Aim of Study: To document possible structural anomalies of brain tissue in vivo in retired athletes who sustained sports concussions in early adulthood and to establish neurocognitive links between hypothesized structural and neurometabolic anomalies in retired concussed athletes with cognitive decline. **Key Outcome Measures:** 3T MRI (VBM for hippocampal volume and corical thickness): 1H MR spectra were obtained from the voxels localized in the bilateral medial temporal lobes and bilateral prefrontal cortices. The following metabolites were quantified: N-acetylaspartate (NAA), myo-inositol (mI), choline-containing compounds (Cho), as well as H_2O for an internal reference. Genotyping was done and cognitive measures included: the MMSE, BDI-II, Taylor complex figure test (TCFT), RAVLT, verbal fluency, TMT A and B, and SDMT. **Age at Head Injury:** Sustained their last sports concussion in early adulthood 24 (4.55), **Years Since Head Injury:** 37.08 (7.10) **Years of Education:** controls: 17.27 (3.45) and concussion history group: 16.67 (4.06); **Race (%):** Not Reported; **Population Type:** Athletes **Diagnosis of Concussion:** A standardized concussion history questionnaire was administered in an interview with a sports physician. Concussion was defined according to the 2009 Consensus Statement on Concussion in Sports (McCrory et al., 2009). **Key Findings:** Compared to controls, former athletes exhibited: 1) Abnormal enlargement of the lateral ventricles, 2) cortical thinning in regions more vulnerable to the aging process, 3) various neurometabolic anomalies found across regions of interest, 4) episodic memory and verbal fluency decline that correlated with neuroimaging findings in concussed participants. 1H MRS examination detected a significant elevation of mI/H_2O in the left medial temporal lobe of formerly concussed participants that correlated strongly with the TCFT delayed recall score, after FDR correction for multiple comparisons. The same ROI also exhibited an abnormal reduction in Cho, while the right prefrontal cortex presented a significant increase in the same metabolite, when referenced to H_2O. When the age variable was introduced in addition to the group, lateral ventricular volume presented a significant age by group interaction, suggesting that ventricular volume expansion was further exacerbated with the advancing age in the group with a history of concussion.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Tremblay et al., 2019)	31233955	Cross Sectional Study	74	Age of Experimental Group: Recent mTBI: 62.89 (4.92), remote mTBI: 60.87 (7.51) Age of Control Group: Controls for recent mTBI: 61.76 (6.6), controls for remote mTBI: 58.13 (5.28)	Sex of Experimental Group: Recent mTBI group: 7:12 and remote mTBI group: 15:0 Sex of Control Group: Controls for recent mTBI group: 11:14 and controls for remote mTBI group: 15:0	8	Level 4
Aim of Study: To determine whether patients who sustain a mTBI earlier in life fare better than patients who sustain a mTBI at an older age.							

Key Outcome Measures: 3T MRI (DWI): Deformation-based morphometry (DBM) provides an estimate of volume changes across the entire T1-weigthed brain image for assessment of white and grey matter atrophy. Tract-based spatial statistics (TBSS) was done to compare various DWI metrics across groups to localise brain changes in diffusion at a voxel-wise level.
Age at Head Injury: Recent mTBI group: 61.05 (4.9) and remote mTBI group: 24.6 (6.34), **Years Since Head Injury:** Recent group (in months): 22.06 (13.12) and remote group (in months): 443.20 (77.30)
Years of Education: Recent mTBI group: 16.67 (1.97) and remote mTBI group: 16.67 (4.06). Controls for recent mTBI group: 16.92 (2.25) and controls for remote mTBI group: 17.27 (3.45); **Race (%):** The entire sample was 100% Caucasian; **Population Type:** Other: Athletes for remote group and general population for recent group.
Diagnosis of Concussion: A standardized concussion history questionnaire was administered in an interview setting by an experienced sports physician. A concussion was defined according to the 2009 Consensus Statement on Concussion in Sports (McCrory et al., 2009).
Key Findings: Results showed a significant interaction on DWI measures indicating larger anomalies in adults who sustained a mTBI at a younger age ($F_{1,70}$, $p < .05$, FDR corrected). Total brain volume did not differ between mTBI and control participants in the recent and remote cohort. Analyses of MD images revealed a significant Group by Cohort interaction effect following correction for multiple comparisons. Regions affected included primarily the anterior aspect of the corpus callosum and frontal white matter. Decomposition of the interaction term into simple effects revealed large areas of increased MD in patients from the remote mTBI cohort relative to controls.

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Vasilevskaya et al., 2020)	32097865	Cross Sectional Study	38	Age of Experimental Group: 55.08 (13.39) Age of Control Group: 51.36 (14.44)	Sex of Experimental Group: 37:1 (for the whole sample; n = 13 for APOE4 group and n = 25 for APOE4 non-carriers)	10	Level 4

Aim of Study: To examine the effect of the APOE4 allele and MAPTH1H1 on SUVRs of PET tau-specific [F-18]AV-1451 tracer in former professional contact sport athletes (CFL) at risk for CTE.
Key Outcome Measures: PET tau imaging with 5mCi of [F-18]AV-1451 tracer was performed (imaged using 3T MRI). A sandwich ELISA method was used to measure Aβ42, phosphorylated tau (p-tau) and total tau (t-tau) levels in CSF. Blood was collected from all participants and genomic DNA was extracted using a Qiagen kit from whole blood. The APOE genotypes and MAPT haplotypes were determined. Cognitive tests used: TMT A and B, RAVLT, RVDLT, SDMT, PAI, digit span forward and backward.
Age at Head Injury: Not Reported, **Years Since Head Injury:** APOE4 Carriers: 19.58 (21.59) and APOE4 Non-Carriers: 21.59 (15.82)
Years of Education: APOE4 Carriers: 15.92 (1.61), APOE4 Non-Carriers: 15.36 (1.73); **Race (%):** Not Reported; **Population Type:** Athletes
Diagnosis of Concussion: Concussion exposure was determined based on the player's recall of injury using the concussion definition provided by the Concussion in Sport Group (Meeuwisse et al., 2017). All players had a semi-structured interview to verify information and to jog memory.
Key Findings: Cortical grey matter PET tau SUVR values were significantly higher in APOE4 carriers compared to non-carriers ($p = 0.020$). There was no significant difference in SUVR between MAPTH1H1 vs non-H1H1 carrier genes ($p = 1.00$). There was a significantly higher

APOE4 allele frequency in the high cortical grey matter PET tau group, compared to the low cortical grey matter PET tau group (p = 0.048).							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(M.-L. Wang et al., 2017)	28689050	Cross Sectional Study	90	Age of Experimental Group: mTBI group: 67.63 (6.65), preclinical mTBI: 73.5 (6.2), MCI to AD mTBI: 73.65 (6.86), and AD mTBI: 72.8 (8.31) Age of Control Group: mTBI controls: 68.63 (5.26), preclinical controls: 72.7 (4.81), MCI to AD controls: 72.18 (6.12), and AD controls: 72.3 (10.32)	Sex of Experimental Group: mTBI group: 4:4, preclinical mTBI: 6:4, MCI to AD mTBI: 15:2, and AD dementia mTBI: 6:4 Sex of Control Group: mTBI controls: 4:4, preclinical controls: 6:4, MCI to AD controls: 15:2, and AD dementia controls: 6:4	11	Level 4
Aim of Study: To investigate whether self-reported mTBI is associated with decreased AD-vulnerable cortical thickness, and to assess the relationship between AD-vulnerable cortical thickness and AD-related biomarker in ADNI subjects. **Key Outcome Measures:** 3T Structural MRI, 18FAV45 PET, and cerebrospinal fluid (CSF) data. Cortical thickness of eight AD-vulnerable regions, mean AD-vulnerable cortical thickness, 18F-AV45 PET mean amyloid SUVR, CSF Aβ42, CSF total tau (T-tau), and CSF phosphorylated tau (P-tau) were compared between mTBI and non-TBI groups. **Age at Head Injury:** normal mTBI group: 29.88 (23.2), preclinical mTBI group: 30 (23.66), MCI to AD mTBI group: 37.1 (27.35), and AD dementia mTBI group: 36.4 (21.37), **Years Since Head Injury:** Not reported **Years of Education:** normal mTBI group: 17.5 (1.69), preclinical mTBI group: 17.2 (2.35), MCI to AD mTBI group: 17 (3.04), AD dementia mTBI group: 15.6 (2.27), normal control group: 17.13 (3.04), preclinical control group: 17 (2.11), MCI to AD control group: 16.94 (2.84), and AD dementia control group: 16.1 (1.97); **Race (%):** Not Reported; **Population Type:** General Population **Diagnosis of Concussion:** Identified 45 mild closed head injury subjects from the ADNI cohort according to the Mayo Clinic TBI standards. **Key Findings:** Of the 45 subjects, eight subjects were healthy; ten were preclinical AD; seventeen had MCI due to AD; ten had AD. Preclinical AD subjects with self-reported mTBI had decreased cortical thickness in mean (p = 0.038) and three AD-vulnerable cortical regions than non-TBI subjects (p < 0.05). The mean cortical thickness of all identified AD-vulnerable regions was correlated with CSF T-tau (r = -0.81, p = 0.001). The regions included when examining mean differences between groups were: superior parietal cortex, inferior parietal cortex, middle temporal gyrus, inferior temporal gyrus, precuneus, posterior cingulate cortex, entorhinal cortex, and temporal pole. The three individual regions that were significant in this study were the inferior parietal cortex (p = 0.005), superior parietal cortex (p = 0.009), and precuneus (p = 0.015). The CSF P-tau was also higher in the preclinical AD with self-reported mTBI group (p = 0.028). Among all the preclinical AD subjects, the mean AD-vulnerable cortical thickness was correlated with CSF T-Tau (r = -0.55, p = 0.018) and CSF P-Tau (r = -0.60, p = 0.007). There was no statistical difference in the comparison of normal, MCI due to AD, and AD groups.							
Lead Author	PMID	Study Design	Sample Size	Age: mean (SD)	Sex	Risk of	Level of

and Study Year					M:F	Bias	Evidence
(Ware et al., 2020)	30565025	Cross Sectional Study	19	Age of Experimental Group: 45.7 (9.71) Age of Control Group: 43.4 (9.11)	Sex of Experimental Group: 10:0 Sex of Control Group: 9:0	10	Level 4
Aim of Study: To determine the specificity of microstructural changes in subregions of the corpus callosum in chronic, repetitive boxing-related TBI relative to noncontact sport athlete controls. The second aim was to identify any group differences on commonly reported psychiatric and neuropsychological difficulties. For the third aim, the clinical implications of white matter microstructural findings were examined. **Key Outcome Measures:** Deterministic DTI of different regions of the corpus callosum. Anxiety using the BAI, depression using the Centre for Epidemiological Studies-Depression, executive function (TMT), and fine motor dexterity using the Grooved Pegboard. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Not Reported. Estimated (>10) based on ages they started boxing: 10 (4.5) **Years of Education:** Experimental group: 13 (1.49), control group: 13.78 (1.92); **Race (%):** Only Hispanic % was given: experimental group: 40%, control group: 22%; **Population Type:** Athletes **Diagnosis of Concussion:** Not described, however history of boxing was used as a proxy for RHI. In addition, number of professional bouts, years sparring and professional knockouts with and without loss of consciousness were collected. **Key Findings:** Quantitative DTI metrics were estimated for corpus callosum subregions. Group by Region interaction effects were observed on FA ($\eta 2p \geq .21$). Follow-up indicated large effects of group ($\eta 2p \geq .26$) on splenium FA (boxers<comparisons) and genu MD (boxers > comparisons), but not RD. In boxers, years sparring, professional bouts, and knockout history correlated strongly ($r > .40$) with DTI metrics and fine motor dexterity. A similar pattern was observed between total number of professional knockouts (with and without associated LOC) and diffusion metrics in the body of the corpus callosum; greater number of professional knockouts was strongly associated with lower FA and higher MD and RD values in the body of the corpus callosum, respectively. Number of professional knockouts with LOC was strongly, negatively correlated with FA in splenium of the corpus callosum; greater number of knockouts with LOC was strongly associated with lower FA values in the splenium of the corpus callosum.							
Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Wilde et al., 2016)	26414735	Cross Sectional Study	19	Age of Experimental Group: 45.7 (9.71) Age of Control Group: 43.4 (9.11)	Sex of Experimental Group: 10:0 Sex of Control Group: 9:0	9	Level 4
Aim of Study: To evaluate imaging and cognitive indications of neurodegeneration after RHI and mTBI associated with extended exposure to boxing. **Key Outcome Measures:** 3T MRI: DTI, particularly bilateral uncinate fasciculus; inferior longitudinal fasciculus; ventral striatum; and cerebral peduncle. Cognitive measures: verbal selective reminding test and the serial reaction time test. **Age at Head Injury:** Not Reported, **Years Since Head Injury:** Not Reported. Estimated (>10) based on the average number of years boxing which was 35.70 (9.15), indicating that participants began boxing early in life. **Years of Education:** Experimental group: 13.00 (1.49); Controls: 13.78 (1.92); **Race (%):** Not Reported; **Population Type:** Athletes							

Diagnosis of Concussion: Not described, however they asked about knockouts during fights (M = 0.89, SD = 0.60) including knockouts with loss of consciousness (M = 0.67, SD = 0.71).
Key Findings: Evans Index (maximum width of the anterior horns of the lateral ventricles/maximal width of the internal diameter of the skull) was significantly larger in the boxers (F = 4.52; p = 0.050; Cohen's f = 0.531). FA and the apparent diffusion coefficient (ADC) measured by tractography did not significantly differ between groups. Years of boxing had the most consistent, negative correlations with FA, ranging from -0.65 for the right ventral striatum to -0.92 for the right cerebral peduncle. Years of boxing was negatively related to the number of words consistently recalled over trials (r = -0.74; p = 0.02), delayed recall (r = -0.83; p = 0.003), and serial RT (r = 0.66; p = 0.05). Of the measures of exposure, years of boxing had the most significant, negative correlations with FA, including for the right uncinate fasciculus (r = -0.807; p = 0.026) and the right cerebral peduncle (r = -0.827; p = 0.022). Convergent with the correlations for FA, years of boxing was positively related to ADC, reaching significance for the left inferior longitudinal fasciculus (r = 0.798; p = 0.032) and left uncinate fasciculus (r = -0.763; p = 0.046).

Lead Author and Study Year	PMID	Study Design	Sample Size	Age: mean (SD)	Sex M:F	Risk of Bias	Level of Evidence
(Zivadinov et al., 2018)	30080799	Cross Sectional Study	42	Age of Experimental Group: 56.7 (9.5) Age of Control Group: 55.4 (9.3)	Sex of Experimental Group: 21:0 Sex of Control Group: 21:0	10	Level 4

Aim of Study: To investigate multimodal metabolic and structural brain MRI differences in retired professional contact sport athletes compared with noncontact sport athletes.
Key Outcome Measures: 3T MRI (structural and functional analyses); white matter signal abnormalities; global and regional atrophy measures; DTI measures; cerebral microbleeds; quantitative susceptibility mapping; MR spectroscopy measures; PWI measures.
Age at Head Injury: Not Reported. Athletes were NFL players and NHL players who entered into their respective leagues in their 20s, **Years Since Head Injury:** Not Reported
Years of Education: Experimental group: high school = 36.4%, some college = 18.2%, college degree = 31.8%, associate's degree = 9.1%, postgraduate degree = 4.5%; Control group: high school = 9.5%, some college = 0%, college degree = 42.9%, associate's degree = 9.5%, postgraduate degree = 38.1%; **Race (%):** Experimental = 100% Caucasian; Controls = 86.4% Caucasian, 13.6% African American; **Population Type:** Athletes (retired NFL and NHL athletes)
Diagnosis of Concussion: Not Reported. Contact sport play used as proxy for RHI.
Key Findings: No significant differences were found for structural or functional MRI measures between retired contact sport athletes and noncontact sport athletes. This multimodal imaging study did not show any microstructural, metabolic brain tissue injury differences in retired contact versus non-contact sport athletes.

APPENDIX E

Tables 15 – 19 showing the main effects of age in four brain regions.

Table 15

Exploratory Regression Results Predicting Cortical Thickness in the Right Fusiform Cortex

	B	**S.E.**	**β**	***p***	***Corrected p***
mTBI	0.055	0.031	0.147	0.083	1.134
MCI Status	-0.002	0.037	-0.004	0.964	1.040
Age	-0.013	0.003	-0.356	<0.001***	0.002**
Education	0.007	0.007	0.085	0.328	0.841
CAPS Lifetime	0.001	0.000	0.167	0.060	0.820
R^2	0.197				

Note. B = unstandardized betas, β = standardized betas, and $p < 0.01$ = **, $p < 0.001$ = ***. ****p* = <0.001 before the FDR correction. ***p* = 0.002 after the FDR correction.

Table 16

Exploratory Regression Results Predicting Cortical Thickness in the Left Fusiform Cortex

	B	**S.E.**	**β**	***p***	***Corrected p***
mTBI	0.001	0.323	0.003	0.970	0.994
MCI Status	-0.011	0.383	-0.025	0.784	1.005
Age	-0.011	0.003	-0.304	0.001***	0.013*
Education	0.010	0.007	0.127	0.172	0.882
CAPS Lifetime	-0.000	0.000	-0.037	0.692	1.090
R^2	0.095				

Note. B = unstandardized betas, β = standardized betas, and p <0.05 = *, $p < 0.001$ = ***. ****p* = 0.001 before the FDR correction. **p* = 0.013 after the FDR correction.

Table 17

Exploratory Regression Results Predicting Cortical Thickness in the Left Lingual Cortex

	B	**S.E.**	**β**	***p***	***Corrected p***
mTBI	-0.005	0.171	-0.021	0.801	0.887
MCI Status	-0.045	0.022	-0.140	0.092	0.943
Age	-0.012	0.027	-0.446	<0.001***	0.004**
Education	-0.005	0.002	-0.092	0.285	0.974
CAPS Lifetime	0.000	0.000	0.006	0.948	1.022
R^2	0.241				

Note. B = unstandardized betas, β = standardized betas, and $p < 0.01$ = **, $p < 0.001$ = ***. ****p* = <0.001 before the FDR correction. ***p* = 0.004 after the FDR correction.

Table 18

Exploratory Regression Results Predicting Cortical Thickness in the Left Pericalcarine Cortex

	B	**S.E.**	**β**	***p***	***Corrected p***
mTBI	0.020	0.026	0.071	0.439	0.818
MCI Status	-0.012	0.030	-0.036	0.691	1.011
Age	-0.008	0.003	-0.284	0.003**	0.031*
Education	-0.011	0.006	-0.179	0.057	0.779
CAPS Lifetime	-0.000	0.000	-0.065	0.492	1.261
R^2	0.122				

Note. B = unstandardized betas, β = standardized betas, and p <0.05 = *, $p < 0.01$ = **. ***p* = 0.003 before the FDR correction. **p* = 0.031 after the FDR correction.

Table 19

Exploratory Regression Results Predicting Cortical Thickness in the Right Pericalcarine Cortex

	B	**S.E.**	**β**	***p***	***Corrected p***
mTBI	0.025	0.025	0.087	0.324	0.949
MCI Status	-0.059	0.030	-0.169	0.055	1.128
Age	-0.007	0.002	-0.251	0.006**	0.049*
Education	-0.003	0.005	-0.054	0.548	0.977
CAPS Lifetime	-0.000	0.000	-0.021	0.822	1.087
R^2	0.102				

Note. B = unstandardized betas, β = standardized betas, and $p < 0.05$ = *, $p < 0.01$ = **. **$p = 0.006$ before the FDR correction. *$p = 0.049$ after the FDR correction.