Received: 12 September 2024 | Revised: 3 February 2025 | Accepted: 3 February 2025

DOI: 10.1002/alz.70085

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Does white matter and vascular injury from repetitive head impacts lead to a novel pattern on T2 FLAIR MRI? A hypothesis proposal and call for research

Annalise E. Miner[1] | **Jenna R. Groh**[1] | **Chad Farris**[1,2] | **Sarina Hattiangadi**[3] | **Anna Cui**[1] | **Adam M. Brickman**[4,5] | **Mohamad Alshikho**[4,5] | **Gil D. Rabinovici**[6,7] | **Howie J. Rosen**[6,7] | **Yann Cobigo**[6,7] | **Breton Asken**[8,9] | **Christopher J. Nowinski**[1,10] | **Samantha Bureau**[1,10] | **Fereydoun Shahrokhi**[11] | **Yorghos Tripodis**[1,12] | **Monica Ly**[1,11,13] | **Caroline Altaras**[1,11,13] | **Steven Lenio**[1,11,13] | **Robert A. Stern**[1,11,14,15] | **Grace Rosen**[1,13,16,17] | **Hunter Kelley**[1,16,17] | **Bertrand Russell Huber**[1,16,17,18,19] | **Thor D. Stein**[1,15,16,17] | **Jesse Mez**[1,11] | **Ann C. McKee**[1,11,16,18,19] | **Michael L. Alosco**[1,11,13,14]

[1]Boston University Alzheimer's Disease Research Center and Boston University CTE Center, Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts, USA

[2]Department of Radiology, Boston Medical Center, Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts, USA

[3]Convent of the Sacred Heart, New York, New York, USA

[4]The Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Vagelos College of Physicians and Surgeons, Columbia University, New York, New York, USA

[5]Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, New York, USA

[6]Department of Radiology & Biomedical Imaging, University of California San Francisco, San Francisco, California, USA

[7]Department of Neurology, Alzheimer's Disease Research Center, Memory & Aging Center, University of California San Francisco, San Francisco, California, USA

[8]Department of Clinical and Health Psychology, University of Florida, Gainesville, Florida, USA

[9]1Florida Alzheimer's Disease Research Center, Gainesville, Florida, USA

[10]Concussion Legacy Foundation, Boston, Massachusetts, USA

[11]Department of Neurology, Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts, USA

[12]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA

[13]Department of Neurology, Boston Medical Center, Boston, Massachusetts, USA

[14]Department of Anatomy and Neurobiology, Boston University Chobanian and Avedisian School of Medicine, Boston, Massachusetts, USA

[15]Department of Neurosurgery, Boston University Chobanian and Avedisian School of Medicine, Boston, Massachusetts, USA

[16]Department of Veterans Affairs Medical Center, Boston, Massachusetts, USA

[17]National Center for PTSD, US Department of Veterans Affairs, Boston, Massachusetts, USA

[18]Department of Veterans Affairs Medical Center, Bedford, Massachusetts, USA

[19]Department of Pathology and Laboratory Science, Boston University Chobanian & Avedisian School of Medicine, Boston University, Boston, Massachusetts, USA

Correspondence
Michael L. Alosco, 72 E Concord Street, L5 Instructional Building, Boston, MA 02118, USA.
Email: malosco@bu.edu

Annalise E. Miner and Jenna R. Groh are shared first authors.

Funding information
BU-CTSI, Grant/Award Number: 1UL1TR001430; NIA, Grant/Award Number: P30AG072978; NINDS/NIA, Grant/Award Number: R01NS122854

Abstract

The goal of this paper is to introduce the hypothesis that white matter (WM) and vascular injury are long-term consequences of repetitive head impacts (RHI) that result in a novel T2 fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging pattern. A non-systematic literature review of autopsy and FLAIR studies of RHI-exposed adults was first conducted as a foundation for our hypothesis. A case series of RHI-exposed participants is presented to illustrate the unique FLAIR WM hyperintensities (WMH) pattern. Current literature shows a direct link between RHI and later-life WM/vascular neuropathologies, and that FLAIR WMH are associated with RHI, independent of modifiable vascular risk factors. Initial observations suggest a distinctive pattern of WMH in RHI-exposed participants, termed RHI-associated WMH (RHI-WMH). RHI-WMH defining features are as follows: (1) small, punctate, non-confluent, (2) spherical, and (3) proximal to the gray matter. Our hypothesis serves as a call for research to empirically validate RHI-WMH and clarify their biological and clinical correlates.

KEYWORDS
chronic traumatic encephalopathy, contact and collision sports, fluid attenuated inversion recovery neuroimaging biomarkers, FLAIR MRI, head trauma, neurodegenerative disease, repetitive head impact-associated white matter hyperintensities, RHI-WMH, repetitive head impacts, traumatic brain injury, traumatic encephalopathy syndrome, white matter hyperintensities

Highlights

- Repetitive head impacts (RHI) have been associated with later-life white matter (WM) and vascular neuropathologies.
- T2 FLAIR MRI of RHI-exposed participants reveals a potentially unique WM hyperintensity (WMH) pattern that is termed RHI-associated WMH (RHI-WMH).
- RHI-WMH are characterized as (1) small, punctate, and non-confluent, (2) spherical, and (3) proximal to the gray matter at an area anatomically susceptible to impact injury, such as the depths of the cortical sulci.

1 | INTRODUCTION

Repetitive head impacts (RHI) refer to recurrent hits, blows, or forces applied to the head that can result in symptomatic concussion and/or non-concussive injury.[1–3] RHI exposure can occur through contact and collision sports (CCS), military combat and training activities, and physical violence, all of which are linked to later-life neuropathological consequences.[4–10] Exposure to RHI has been studied extensively in the setting of CCS, particularly in American football. Youth, high school, college, and professional football players can be exposed to thousands of head impacts over a single season.[2, 11–15] Other CCS athletes, such as soccer players, can be exposed to hundreds of head impacts per season.[16, 17] With tens of millions of people in the United States alone having been exposed to RHI from participation in CCS,[15] later-life neurological disorders associated with RHI exposure are a major public health concern.

Exposure to RHI is associated with the development of neurodegenerative diseases including but not limited to chronic traumatic encephalopathy (CTE).[18–22] CTE is uniquely characterized by the perivascular deposition of hyper-phosphorylated tau (p-tau) in neurons distributed around blood vessels at the depths of the cerebral sulci.[23–27] CTE can manifest as a combination of diverse symptoms, including cognitive impairment.[24, 28, 29] Neurobehavioral dysregulation is a common clinical feature in RHI-exposed cohorts, but it is weakly correlated with CTE p-tau pathology.[30, 31] As shown in Alzheimer's disease (AD) and AD and related dementias (ADRD), cognitive decline and dementia are often consequences of mixed neuropathologies as opposed to a single proteinopathy.[28, 32–35] Among individuals exposed to RHI, there is a heterogeneous accumulation of various neurodegenerative disease proteins, such as the presence of Lewy bodies,[36] alpha synuclein,[37] amyloid beta (Aβ),[29] and transactive response DNA-binding protein with 43 kDa (TDP-43) deposits,[38, 39]

and structural white matter (WM) changes.[32, 40–42] Co-morbid neuropathology could explain the diverse clinical presentations observed in the setting of RHI and CTE.[43]

The cardinal pathologies of acute traumatic brain injury (TBI) include WM and vascular injury.[44–48] For this review, we define WM injury as damage to the myelinated axons of the brain's neurons, whereas vascular injury pertains to damage to the blood vasculature in the brain, including but not limited to endothelial damage and blood–brain barrier (BBB) leakage.[49] It is important to note that while vascular and WM injury are highly interrelated, they represent separate pathologies that differ in the structure, that is, injured or compromised.[50] Diffusion magnetic resonance imaging (dMRI) studies demonstrate that a single season of CCS play can result in WM changes across age groups, from childhood to adulthood.[8, 51–67] A nascent but growing literature demonstrates that WM and vascular changes are present in older participants years after exposure to RHI has ended and that these pathologies contribute to symptoms.[49, 68] We hypothesize that WM and vascular changes begin during active exposure to RHI and progress with aging, independent of and/or in parallel with p-tau accumulation and potentially other neurodegenerative disease pathologies. We further hypothesize that WM and vascular pathologies contribute to clinical outcomes (Figure 1). Additionally, we propose that T2 fluid attenuated inversion recovery (FLAIR) MRI can capture these WM and vascular pathologies as WM hyperintensities (WMH) and that RHI may result in a unique pattern of WMH. We refer to these as RHI-associated WMHs (RHI-WMH).

The objective of this paper is to introduce our hypothesis of RHI-WMH and to ignite research on this observation. We first provide a non-systematic review of the literature surrounding WM and vascular injury neuropathology among brain donors exposed to RHI. This literature directly informed the start of research on the association between RHI and WMH. We then present literature on the association between RHI and WMH on T2 FLAIR MRI, followed by presentation of a case series to illustrate the unique pattern of WMH that we have anecdotally observed in participants exposed to RHI (i.e., RHI-WMH). We conclude with a discussion on differential diagnostic considerations and several targets for future research on RHI-WMH.

2 | METHODS

In this hypothesis proposal and accompanying supportive literature review, we do not focus on the role of p-tau accumulation as that has been reviewed elsewhere,[18, 40, 69] with the exception of when we provide context to CTE neuropathology. Our current knowledge surrounding the long-term effects of exposure to RHI is focused on neuropathological and in vivo research in older male American football players. This population is featured in this review; however, data from other populations exposed to RHI (e.g., former soccer players, military veterans, survivors of intimate partner violence) are presented when appropriate. As this paper is focused on the long-term consequences of RHI, we highlight research in older populations years after RHI exposure has ended, rather than in active athletes or participants who have not yet reached at least middle age. While there is documented evidence that a single TBI or concussion can lead to both acute and persistent WM changes,[70, 71] we do not include studies specifically focused on symptomatic TBI, single incident concussions, or post-concussion syndrome, but rather focus on the cumulative effects of RHI. We acknowledge that there are many MRI techniques for the evaluation of WM and vascular injury, such as dMRI, arterial spin labeling (ASL), single-photon emission computed tomography (SPECT), susceptibility weighted imaging (SWI), and dynamic contrast-enhanced MRI

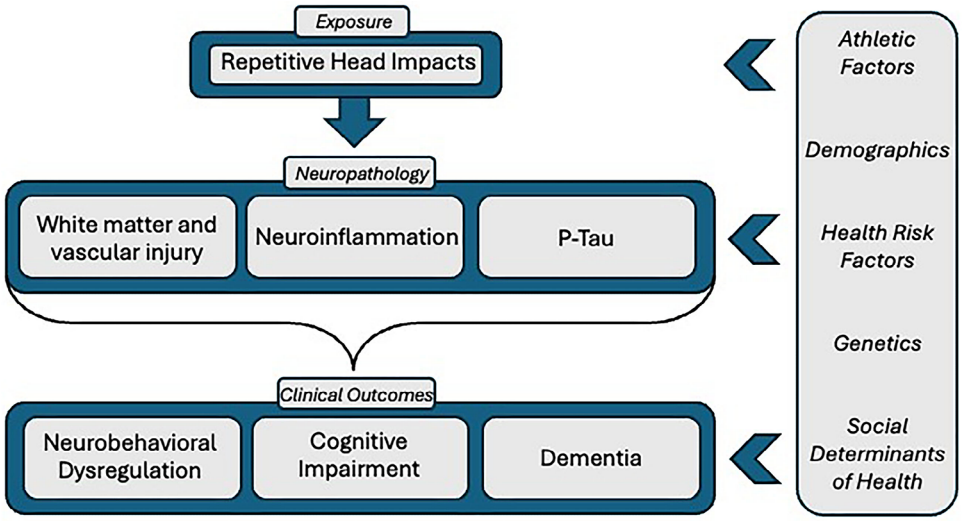

FIGURE 1 Conceptual framework of the associations between repetitive head impacts (RHI), neuropathologies, clinical outcomes, and modifiers. The lists of pathologies, clinical outcomes, and modifiers are not exhaustive. Neuropathologies not included in this figure but that are still associated with RHI include, but are not limited to, presence of Lewy bodies, alpha synuclein, amyloid beta (Aβ), and transactive response DNA-binding protein with 43 kDa (TDP-43) deposits.

(DCE-MRI). However, these techniques are either not applied routinely in clinical practice in memory disorder settings, or they are applied routinely clinically but are relatively insensitive for the WM and vascular injury (e.g., SWI) that is easily captured by T2 FLAIR imaging. We focus our review on T2 FLAIR MRI because it is routine in both clinical care and research in neurodegenerative disorders.

Our non-systematic review of the literature was conducted using relevant key words in medical search engines (e.g., PubMed), including but not limited to, "repetitive head impacts," "sub-concussion," "concussion," "traumatic brain injury," "contact sport athletes," "American football," "white matter," "white matter degeneration," "white matter rarefaction," "white matter loss," "white matter integrity," "microstructural integrity," "white matter hyperintensities," "white matter injury," "diffusion tensor imaging," "FLAIR," "vascular changes," "vascular damage," "vascular injury," "SPECT," "arterial spin labeling," "ASL," "susceptibility weighted imaging," "SWI," "chronic traumatic encephalopathy," and "CTE." References of research articles and connected papers were also used for identifying relevant studies for this review.

The illustrative case series presented comes from a visual review of scans during weekly multidisciplinary consensus conferences at the Boston University Alzheimer's Disease Research Center (ADRC).[72–74] Some of these participants are also part of the National Institute of Neurological Disorders and Stroke (NINDS)/National Institute on Aging (NIA) funded collaborative study between the Boston University and University of California San Francisco ADRCs known as the "Study of Axonal and Vascular Effects of Head Impacts (Project SAVE)." The Boston University ADRC is one of > 30 ADRCs in the United States that are funded by the NIA and contributes standardized data to the National Alzheimer's Coordinating Center (NACC). The Boston University ADRC supports high-impact, innovative research on AD and ADRD, including CTE and other long-term consequences of RHI. The center follows participants who complete annual visits that include clinical interviews, neuropsychological testing, neurological exams, blood draws, as well as a baseline and 3-year MRI and an optional lumbar puncture. Approximately one third of the cohort includes participants exposed to RHI whereas the remaining participants are those who span the AD continuum. Multidisciplinary diagnostic consensus conferences are conducted for all participants to adjudicate clinical syndromes and suspected etiologies. Syndromic diagnoses are made blinded to biomarkers, but RHI exposure details are known prior to clinical and biomarker data review. Biomarkers, including T2 FLAIR MRI, are reviewed to determine etiologic diagnoses.

3 | NEUROPATHOLOGY OF CTE

The neuropathology of CTE, a disease specific to RHI exposure,[1, 2, 20, 24, 69] provides impetus for the study of WM and vascular injury pathology. Historically, CTE has been described in boxers as "punch drunk" or "dementia pugilistica" before "chronic traumatic encephalopathy" was introduced.[75–81] Since Corsellis et al. published a case series in 1973 describing CTE neuropathology in boxers, CTE neuropathology has been documented in American football players, ice hockey players, soccer players, rugby players, and military veterans.[24, 82–87] More recently, CTE has been neuropathologically diagnosed in both male and female Australian rules football players.[88–91]

The first modern description of unusual tau pathology in a former National Football League (NFL) player was published by Omalu et al. in 2005,[83] which noted characteristic neurofibrillary tangles and neuropil threads, without the presence of neuritic plaques, suggesting a separate etiology from AD.[83, 92] Subsequently, criteria for the neuropathological diagnosis of CTE and a staging system for grading pathologic severity was proposed by McKee et al. in 2013.[24, 25, 27] The pathognomonic CTE lesion is shown in Figure 2 and is characterized by the aggregation of neuronal p-tau around small blood vessels at the depths of the cortical sulci. The staging scheme proposed by McKee et al. described the severity of CTE pathology from stage I (low severity) to stage IV (high severity).[24, 25, 27] In stages I and II, the p-tau lesions are patchy and located in the frontal and temporal cortices. In stage III, p-tau aggregates are observed in the medial temporal lobes before becoming more widespread in stage IV. Higher stages are associated with more severe neuroinflammation, older age at death, and proxies of RHI exposure, including level of American football play (i.e., high school, college, semi-professional, professional) and longer duration of football career.[20, 24, 28, 40, 93]

3.1 | White Matter Neuropathology

WM injury is difficult to quantify and exists on a spectrum. WM injury can be described as pallor, wherein visible changes to the WM are seen through histological staining techniques, such as hematoxylin and eosin, which stain nuclear and cytoplasmic components respectively.[94] Damage is assessed by determining the degree of pallor after staining and comparing it to healthy tissue samples. Some stains, such as Luxol fast blue, are used to stain myelin directly to determine whether there are demyelinating processes or cellular damage.[28] In CTE, there is evidence to suggest the presence of both oligodendrocyte[21, 95] and myelin[96] damage; thus, a combination of stains is required to understand the complex presentation of the disease. Figure 3 demonstrates these myelin staining techniques in the context of CTE and shows examples of histochemical staining of myelin in a former American football player diagnosed with CTE.

Neurons are uniquely susceptible to damage by traumatic injury. Focal, multifocal, or diffuse injury to neurons due to trauma is termed traumatic axonal injury (TAI).[97, 98] TAI is related to insidiously progressive axonal pathology following TBI.[99] Buée et al. was one of the first studies to demonstrate a link between CTE (then termed "dementia pugilistica") and TAI in 1994.[100] This study examined two boxers with "dementia pugilistica" in their 60s and found extensive TAI that correlated with neurofibrillary tangle distribution. Recent studies have shown that an increased presence of axonal spheroids and distorted axonal varicosities, hallmarks of TAI, are associated with increasing CTE severity.[24, 97] The prevalence of WM pathology in CTE may be related to its primary risk factor: exposure to RHI.

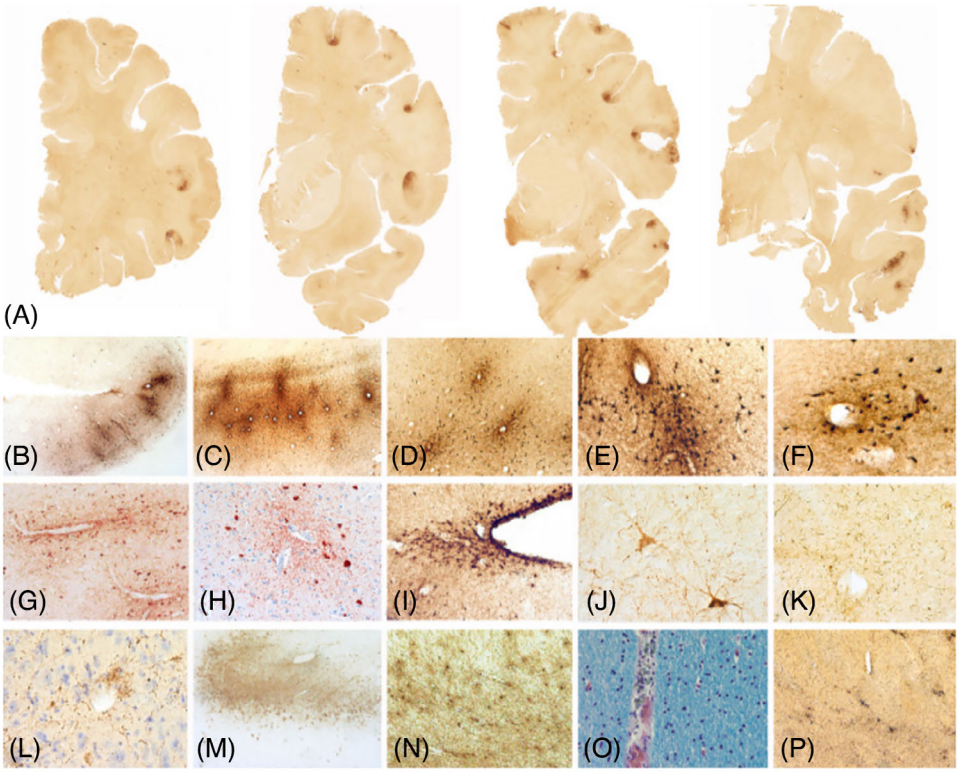

FIGURE 2 Pathognomonic lesion of chronic traumatic encephalopathy (CTE). This figure, taken from McKee et al., shows microscopic findings in stage II CTE.[26] A, Whole mount coronal sections in stage II CTE show multiple foci of phosphorylated tau (p-tau) pathology primarily located at the depths of the cortical sulci of the frontal and temporal lobes (free floating 50 μ sections, AT8 immunostain). B–H, The p-tau pathology consists of neurofibrillary tangles and dot-like and thread-like dystrophic neurites and is characteristically found around small blood vessels (B–F, free floating 50 μ sections, AT8 immunostain, G, H, 10 μ paraffin embedded sections, AT8 immunostain). I, Subpial astrocytic tangles are also found at the cortical depths (free floating 50 μ sections, AT8 immunostain). Other pathologies include pretangles (J), dystrophic neurites in the white matter (K), and occasional p-tau astrocytes (L; free floating 50 μ sections, AT8 immunostain). There may be marked astrocytosis of the white matter (M, N; free floating 50 μ sections, glial fibrillary acidic protein immunostain). Hemosiderin-laden macrophages (O; 10 μ paraffin section, Luxol fast blue hematoxylin and eosin stain) and multiple perivascular foci of reactive microglia (P) are found around small vessels in the cerebral white matter (free floating 50 μ sections, LN3 immunostain). Text taken from McKee et al.[26]

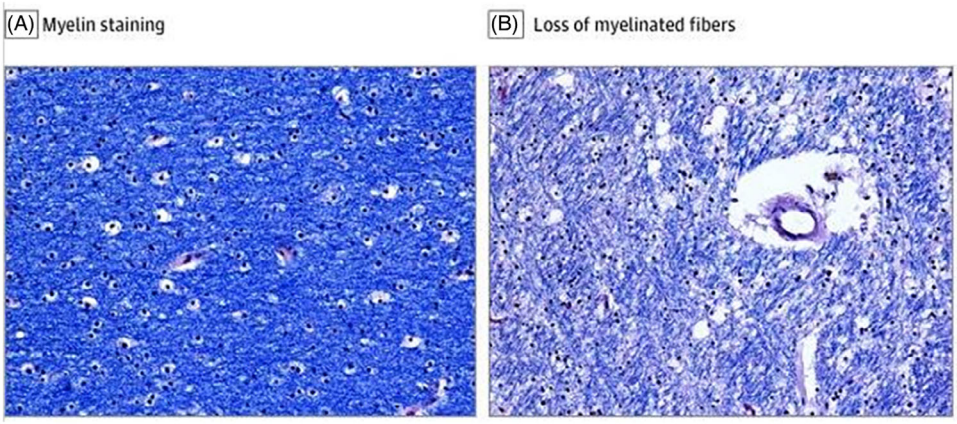

FIGURE 3 White matter rarefaction in a participant with chronic traumatic encephalopathy. Figure from Alosco et al.[28] A, Luxol fast blue with hematoxylin–eosin histochemical staining shows robust myelin staining (blue) in a former US football college player in his early 40s who was neuropathologically diagnosed with chronic traumatic encephalopathy (CTE; stage I/II) who was not determined to have had antemortem dementia. B, A man who had played professional US football, was in his mid-80s, had been neuropathologically diagnosed with CTE (stage III/IV), and was determined by consensus to have dementia, there was severe loss (3+) of myelinated fibers. Text adapted from Alosco et al.[28]

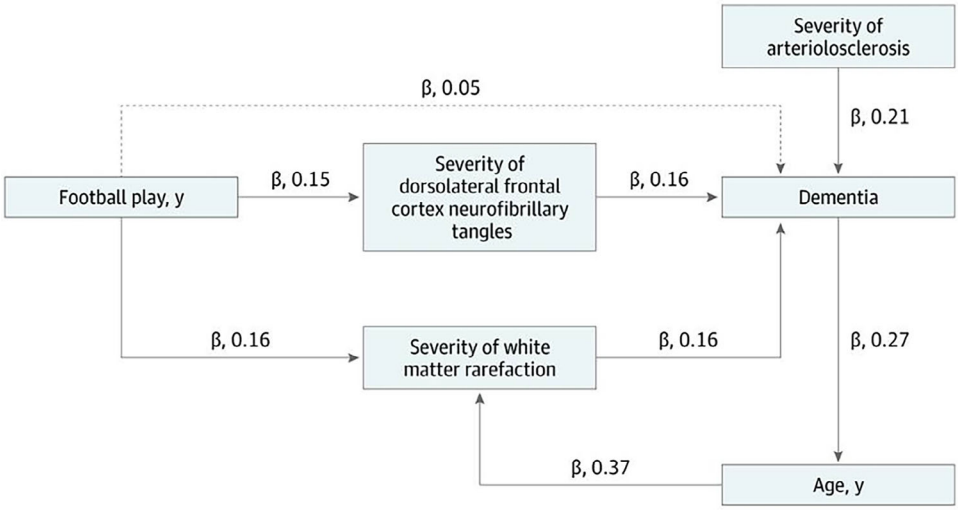

FIGURE 4 Cross-sectional model on the contributions of white matter rarefaction, arteriolosclerosis, and phosphorylated tau to dementia in chronic traumatic encephalopathy (CTE). Figure from Alosco et al.[28] Simultaneous equations regression models tested the association of pathological markers of cerebrovascular disease with dementia in older deceased individuals who had played football and had CTE. Not all variables or pathways are displayed for ease of presentation. The β values shown are standardized estimates, and each path shown is significant at an $\alpha < 0.05$. Standardized estimates permit direct comparison of the effect sizes across pathways. The dashed line between years of football play and dementia denotes a significant indirect effect in which the association of years of football play with dementia was mediated by dorsolateral frontal cortex neurofibrillary tangles and severity of white matter rarefaction. Text adapted from Alosco et al.[28].

Historically, neuropathological studies investigating the effects of RHI on WM have been qualitative in nature. A 2019 empirical autopsy-based study examined the associations among exposure to RHI, WM vascular pathologies, and dementia in 180 deceased male American football players (aged 40+) with neuropathologically confirmed CTE.[28] The study found that moderate to severe WM rarefaction was independently associated with dementia in CTE.[28] Additionally, greater duration of football play, a proxy metric for RHI exposure, was associated with more severe WM rarefaction. A conceptual summary of the relationship among WM rarefaction, vascular disease, and tau in CTE-related dementia is shown in Figure 4. This figure demonstrates the results of simultaneous regression models that tested the associations of pathological markers of WM rarefaction, arteriolosclerosis, and tau with dementia. This study was one of the first to examine WM and vascular changes as later-life consequences of RHI exposure.[28]

A more refined method for the assessment of myelin integrity in post-mortem brain tissue compares the concentrations of two proteins that contribute to the structure and maintenance of myelin, myelin-associated glycoprotein (MAG), and proteolipid protein-1 (PLP-1).[101] Both proteins are produced in oligodendrocytes; MAG is located distally from the cell body whereas PLP is distributed throughout the myelin sheath.[102, 103] MAG is susceptible to reduced tissue oxygenation due to its epi-distal location, while PLP-1 is relatively resistant. The ratio of these two proteins is consistently reduced in cerebrovascular disease and vascular injury, which are highly interrelated with WM injury.[104, 105] The decline in this ratio in the context of vascular disease suggests pathological hypoperfusion, which can have clinical consequences.[104] A neuropathological analysis of CTE-confirmed post-mortem brain tissue demonstrated that oligodendrocyte-specific proteins, including MAG, were reduced in both gray matter and WM in CTE.[106] MAG was further reduced in moderate to advanced stages of CTE. A neuropathological examination of CTE cases from Boston University found both a reduced number of oligodendrocytes, the progenitor of MAG and PLP, as well as a unique oligodendrocyte profile compared to controls.[95] In an RHI-exposed cohort, more years of football play and younger age at first exposure were associated with decreased MAG and PLP.[96] Myelin degeneration, as measured by these proteins, could be a potential marker of WM and vascular injury from RHI.

WM injury can be examined through ex vivo dMRI. Diffusion tensor imaging enables the in vivo or ex vivo spatial evaluation of WM integrity by assessing the fractional anisotropy and radial, axial, and longitudinal diffusivity of an estimated diffusion tensor.[107–109] Evidence from a post-mortem dMRI analysis of brains with neuropathologically-confirmed CTE found that axonal disruption and tau pathology were closely associated.[107] Evidence of axonal injury was found in WM directly adjacent to gray matter at the sulcal depths, where CTE p-tau pathology is located,[107] demonstrating that WM changes are closely associated and potentially co-localized with both RHI- and CTE-related pathology.

WM pathologies have been found in other forms of RHI exposure besides CCS, such as intimate partner violence.[110] Survivors of intimate partner violence are susceptible to RHI-related pathological changes and are at risk of negative long-term health outcomes.[10, 111] A study from Dams-O'Connor et al. used ex vivo imaging of 14 donated brains to investigate the relationship between intimate partner violence and CTE.[112] While none of the participants met criteria for CTE, there were substantial documented vascular and WM pathologies.[112] Exposure to RHI through military blast is also associated with increased markers of astrogliosis at the boundaries of

gray and WM in the dorsolateral frontal cortex.[113] This was the case even in participants with no CTE pathology,[113] indicating that regional alterations in astrogliosis may occur independently of CTE.

3.2 | Vascular Neuropathology

Vascular injury encompasses arteriolosclerosis, endothelial cell damage, BBB disruption, increased BBB permeability, and any further damage to the blood architecture of the brain. It has high comorbidity with neurodegenerative diseases and contributes to cognitive decline.[114–117] Vascular injury is commonly associated with aging and cardiovascular disease,[118, 119] and certain subgroups of former American football players have higher rates of cardiovascular disease than non-CCS athlete controls.[120–122] Kahriman et al.'s longitudinal research in mouse models demonstrated that mice subjected to closed head TBIs developed progressive tau pathology, as well as substantial microvascular injury.[123] Neuropathological analysis of post-mortem brains and an ultrastructural analysis of a mouse model by Goldstein et al. indicated that RHI from blast exposure was associated with microvascular injury pathology and subcortical WM injury.[124] Autopsy evidence of human brain donors also supports vascular injury as a consequence of RHI.[40, 49, 125] Parsing out the differing contributions of aging, cardiovascular disease, and RHI to vascular injury will be critical moving forward.[121, 122]

A post-mortem examination by Doherty et al. of participants exposed to RHI with neuropathologically diagnosed CTE found damage to the BBB, loss of endothelial junctions, and axonal injury.[126] A recent 2023 post-mortem investigation using 156 donated brains found that levels of intercellular adhesion molecule 1 (ICAM1), vascular cellular adhesion molecule 1 (VCAM1), C-reactive protein (CRP), and all vascular injury-associated markers were higher in RHI-exposed brain tissue compared to controls with no history of RHI exposure.[49] Both ICAM1 and CRP levels increased with longer duration of RHI exposure. ICAM1 levels increased with CTE severity. Overall, the study concluded that vascular injury markers were associated with RHI exposure and CTE, and worsened with increased disease severity.[49]

3.3 | Summary of Neuropathology Literature

CTE is caused in part by exposure to RHI and is characterized by an accumulation of p-tau centered around small blood vessels at the depths of the cortical sulci. Autopsy studies have shown associations between exposure to RHI and long-term WM and vascular pathologies. The neuropathological literature has provided neuroimaging targets for the in vivo investigation of the long-term effects of RHI on the brain, including areas of WM and vascular injury. Next, we provide contextual literature regarding T2 FLAIR WMH and present an illustrative case series that demonstrates our proposed hypothesis of an RHI-specific WMH pattern.

4 | WHITE MATTER NEUROIMAGING MODALITIES

The effects of RHI on the WM and vasculature of the brain have been studied using various in vivo neuroimaging techniques.[127–131] Investigations into later-life consequences of RHI in older adults using dMRI have found significant reductions in WM integrity.[127–131] While dMRI can provide information on subtle microstructural changes, it is not always used in routine clinical practice. Alternatively, T2 FLAIR MRI is a practical and routinely used MRI sequence in the work-up for neurological disease, including in the setting of dementia. On T2 FLAIR images, WMHs appear as bright spots and signal non-specific injury.[132, 133] The variability in WMH appearance has been proposed to be reflective of differences in both etiology and pathological severity.[134] T2 FLAIR has the potential to show unique patterns of WMH by disease, suggesting it could have value as a supportive diagnostic tool.[135, 136] T2 FLAIR MRI has served as an accessible neuroimaging method to detect and study WM pathologies in AD/ADRD (as reviewed next) and we hypothesize similar utility in neurological conditions related to RHI.

4.1 | T2 FLAIR WMH in Aging and AD/ADRD

T2 FLAIR WMH have historically been presumed to indicate small vessel disease from aging and cardiovascular disease,[137, 138] but this is a simplistic conceptualization as their etiology is multifactorial. WMH can also occur in midlife,[139, 140] and prevalence of subcortical WMH has been found to increase by 0.2% per year of age.[141] In cognitive aging samples, WMH burden predicts accelerated cognitive decline and risk for developing dementia.[142–148] Robust and unique associations between WMH and the different AD/ADRDs have been established. Patterns of WMH found in AD are different from those found in participants without AD in terms of their spatial distribution.[149–151] There is increased WMH burden in participants with autosomal dominant AD, even before symptom onset, suggesting WMH (and their underlying pathologies) occur early in the AD pathogenic cascade.[152, 153] WMH are associated with known AD biomarkers, including hippocampal atrophy, high levels of cerebrospinal fluid (CSF) total tau, and amyloid deposition in positron emission tomography (PET) imaging.[144, 154, 155] Research has found that frontal and posterior WMH are associated with amyloid burden in AD.[156] Regional patterns of WM degradation in AD are different from those in diseases such as frontotemporal dementia (FTD).[157] Research in autosomal dominant FTD due to pathogenic variants in the granulin gene demonstrated severe WMH in cortical regions, specifically in the intermediate cortical layers of the left frontal pole and anterior frontal lobe.[158] The study noted severe WM pathology but no or minimal vascular pathology in areas of high WMH burden, and determined that WMH was not related to vascular pathology, separating the two pathologies etiologically.[158]

Overall, the nature and causal pathways of WMH in aging and AD/ADRD remain controversial. Some propose that WM changes occur early in disease and may initiate some AD/ADRD-related pathologic changes; others consider disease pathologic accumulation and WM changes as separate processes; still others propose that WM injury is downstream from AD/ADRD pathologic accumulation and represents a secondary phenomenon, such as Wallerian degeneration.[159, 160] More research is needed to understand the consequences of WM changes in AD and ADRD.

4.2 | RHI as a Novel Risk Factor for T2 FLAIR WMH

There is a growing body of research that has used T2 FLAIR MRI to study the association between RHI and WM pathologies. In 2013, Hart et al. conducted a cross-sectional neuroimaging study of 34 retired NFL players and 26 controls with no history of concussion or exposure to football, aged 41 to 79.[127] Participants underwent cognitive and neuropsychological testing; a neurologic assessment; and completed a 3-Tesla (3T) MRI that included T2 FLAIR, dMRI, and ASL sequences. There were no differences in vascular risk factors in the cognitively impaired and unimpaired former players. The study found that total WMH was greater in former players with cognitive deficits than in age-matched controls, but periventricular lesion volume did not differ between the two groups. Additionally, there was a greater burden of deep WMH in former players with cognitive deficits, alluding to a potential relationship of WMH spatial distribution with cognitive outcomes among RHI-exposed individuals.

The association among WM hypointensities, RHI, and clinical function was examined in a study of former NFL players.[161] This study examined WM changes through T1-weighted images, wherein WM lesions present as hypointense. The study included 86 former NFL players and 23 asymptomatic men with no history of CCS participation, military service, or TBI (aged 40–69). Participants underwent a 3T T1-weighted MRI. Participants also underwent neuropsychological testing, and their cumulative head impact index (CHII) and modified Framingham Stroke Risk Profile (FSRP) were calculated.[14, 162] The study found that former football players had a larger volume of WM hypointensities compared to controls. Greater RHI exposure in former football players was associated with higher volume of WM hypointensities. WM hypointensities also corresponded to worse performance on neuropsychological tests of psychomotor speed and executive function in former players. A 2024 study by Esagoff et al. expanded on these findings by examining WM signal abnormalities in a cohort of 90 active professional fighters from the Professional Fighters Brain Health Study.[163] This study compared T1-weighted 3T MRI findings between fighters with and without a history of football/rugby play and unexposed controls. The study found an increased burden of WM hypointensities in active fighters compared to unexposed controls. Additionally, there was greater WM hypointensity volume in fighters with former football/rugby exposure compared to fighters without additional exposure and controls, demonstrating a potential dose-dependent relationship of these MRI findings with RHI exposure.

In 2023, Alosco et al. investigated the burden and distribution of T2 FLAIR WMH and their association with metrics of RHI exposure and clinical function.[164] This study leveraged a sample of 149 former college and professional football players and 53 unexposed male participants, aged 45 to 74, from the Diagnostics, Imaging and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE) cohort.[164, 165] Participants completed T2 FLAIR MRI, neuropsychological testing, and self-reported neuropsychiatric measures. The study found that older former football players had greater total, frontal, temporal, and parietal WMH compared to the same-age, unexposed controls. Younger age of first exposure was associated with greater WMH in the older cohort (> 60 years) but not in the younger cohort of former players. There was no association between WMH and total years of play. Finally, higher WMH burden was associated with worse performance on tests of executive function and verbal memory in the total sample of former players.

Recent investigations used T2 FLAIR MRI to examine the relationship of RHI exposure with WM changes in younger cohorts. Brett et al. leveraged multiple imaging modalities, including FLAIR and dMRI, to investigate WM changes in an adolescent (average age of 18 years) and early midlife (average age of 38 years) cohort with a history of participation in CCS.[166] The study did not find an association between years of participation and WMH volume but did find greater WMH burden in former professional football players over the age of 60 compared to asymptomatic men of the same age.[166] Additionally, global WM changes associated with years of football participation were broadly similar from adolescence through early midlife, suggesting that any reported WM changes due to RHI may manifest later in life. Similarly, Glikstein et al. used T2 FLAIR, gradient recalled echo (GRE), and dMRI to investigate MRI findings in military personnel that were exposed to RHI through repeated blasts.[167] The participating cohort in this 5-year longitudinal study included 92 men, aged 24 to 42, with an average of 9.4 years of blast exposure.[167] This study reported volume loss and WM changes, along with enlarged Virchow–Robin (perivascular) spaces over a 5-year period. Vascular lesions and an increased number of WMH were also noted.

Some studies have not found a connection between WMH burden and RHI exposure. A 2014 investigation by Casson et al. examined 45 retired NFL players who underwent comprehensive neuropsychological and neurological examinations, blood tests, and an MRI protocol that included FLAIR, dMRI, and SWI.[168] The study found four former players with microbleeds and one with a vascular malformation, as well as some evidence of WMH on FLAIR MRI. Scores on the Mini-Mental State Examination (MMSE) ranged from 25 to 30. Overall, the study concluded that the majority of NFL players did not display chronic brain damage that could be detected by neuroimaging but was limited by its lack of a control population and the slightly younger age of its participating cohort (aged 30–60). A 2018 study of 21 male CCS athletes and 21 age-matched non-CCS athletes incorporated multimodal imaging metrics, including T2 FLAIR, dMRI, and SWI

along with measures of cerebral microbleeds, MR spectroscopy, and perfusion-weighted imaging.[169] The study did not find any metabolic, functional, or structural differences on brain MRI between the groups.

4.3 | Biological Correlates of T2 FLAIR WMH

While the underlying pathology that results in T2 FLAIR WMH is variable and non-specific, we propose that WM and vascular injury resulting from RHI exposure manifests as a unique WMH pattern. In 2022, Uretsky et al. examined the association between WMH and neuropathologic correlates in brain donors exposed to RHI (67 professional football players and 8 other CCS athletes or military veterans).[68] This imaging–pathologic correlation study leveraged antemortem T2 FLAIR scans from medical records and post-mortem neuropathological evaluations, along with informant interviews regarding detailed histories of cognitive, behavioral, mood, and motor symptomatology.[68] CTE was present in 70% of the examined brains. Years of American football play were independently associated with greater WMH volume, even after controlling for CTE stage, dorsolateral frontal cortex p-tau severity, and Aβ neuritic plaque scores. Greater WMH were associated with WM rarefaction, arteriolosclerosis, and CTE stage. Greater total WMH volume was also associated with worse informant-reported cognitive and functional difficulties. Overall, the study concluded that FLAIR WMH may capture pathologic changes from RHI exposure, including WM rarefaction, p-tau accumulation, and microvascular disease.

Ly et al. evaluated associations between T2 FLAIR WMH and CSF biomarkers of amyloid, p-tau, neuroinflammation, axonal injury, and neurodegeneration.[170] Participants included 180 former football players (120 former NFL players, 60 former college players) and 60 asymptomatic unexposed male controls from the DIAGNOSE CTE cohort.[165] The study found that WMH were associated with greater vascular risk, higher levels of CSF p-tau$_{181}$, lower fractional anisotropy on dMRI, and reduced cortical thickness in former football players.[170] The magnitudes of these associations were stronger in former football players than in asymptomatic, non-RHI exposed men. There was no association found between WMH burden and CSF markers of amyloid (A$\beta_{1\text{-}42}$), neuroinflammation (soluble triggering receptor expressed on myeloid cells 2 [sTREM2]), or axonal injury (neurofilament light chain [NfL]). The results of this study also demonstrated that WMH burden correlated with CSF p-tau$_{181}$ in RHI-exposed participants. That study emphasized the multifaceted etiologies of WMH in the setting of RHI that include but are not limited to factors related to aging and cardiovascular disease.

5 | RHI-WMH: A NOVEL PATTERN OF T2 FLAIR WMH

Next, we present anecdotal evidence of a potentially unique pattern of WMH in participants exposed to RHI. This evidence comes from a visual review of scans during weekly multidisciplinary consensus conferences at the Boston University ADRC.[72–74] Using T2 FLAIR MRI scans of RHI-exposed participants, we have observed a consistent pattern of WMH with the following characteristics: (1) small, punctate, and non-confluent, (2) spherical, and (3) proximal to the cortical gray matter. We hypothesize that the closer the WMH are to the gray–WM junction the more specific they are to RHI-related pathology, but the diagnostic implications of this distance are unclear. It is the combination of each of these features that makes the pattern unique as opposed to any one of them in isolation. These WMH can be distributed throughout the cerebrum but can also be focal. The localization of RHI-WMH is in areas anatomically susceptible to impact injury, specifically at the depths of cortical sulci (i.e., at the gray–WM junction). The total burden of WMH in RHI-exposed participants is variable but is often low, particularly in younger aged individuals. There may or may not be confluent periventricular WMH that are often seen in aging. We have observed RHI-WMH in young (e.g., 50–60) and otherwise healthy individuals where this number of WMH might not be expected.

Previously, we described how neurons are susceptible to TAI by impact damage due to their inherent morphology, and how the brain is susceptible to damage from linear or rotational mechanical forces.[97, 98, 171] Research in both mouse and human models has demonstrated that forces from blunt trauma or blast shock are amplified near tissue heterogeneities, such as cerebral sulci, vessels, and axons.[124, 172–174] We propose that this pattern of RHI-WMH at the sulcal depths is due to injury sustained at the most susceptible part of the brain to linear and rotational forces of head trauma. Figure 5 shows the distribution of WMH described above. This figure depicts pathology in brain areas susceptible to RHI, such as the depths of the cerebral sulci through the methods of (Figure 5Aa) low magnification immunohistochemistry, (Figure 5Ac) myelin staining, (Figure 5Ae) ex vivo dMRI imaging, and (Figure 5B) a post-mortem brain slice stained to show three-repeat tau deposition. These methodologies demonstrate a localization of RHI-related pathology in the depths of the cortical sulci, where we see the characteristic RHI-WMH pattern on FLAIR MRI (Figure 5C,D). It is important to note that this figure is not intended to imply that WMH are related to p-tau pathology outside of similarities in localization.

6 | ILLUSTRATIVE CASE EXAMPLES

What follows is a presentation of a series of eight cases that are exemplary illustrations of the RHI-WMH pattern. These cases were selected from research participants who completed research T2 FLAIR MRIs at the Boston University ADRC. These participants were selected as exemplary examples of the RHI-WMH pattern we describe. This was not a systematic empirical selection, and therefore RHI-exposed participants without this pattern, or participants who have this pattern along with comorbidities or substantial vascular risk factors, are not presented.

Case summaries are presented in Table 1. These participants ranged from 50 to 75 years of age and included seven male participants and one female. These participants were middle aged and had minimal to no modifiable vascular risk factors, including hypertension,

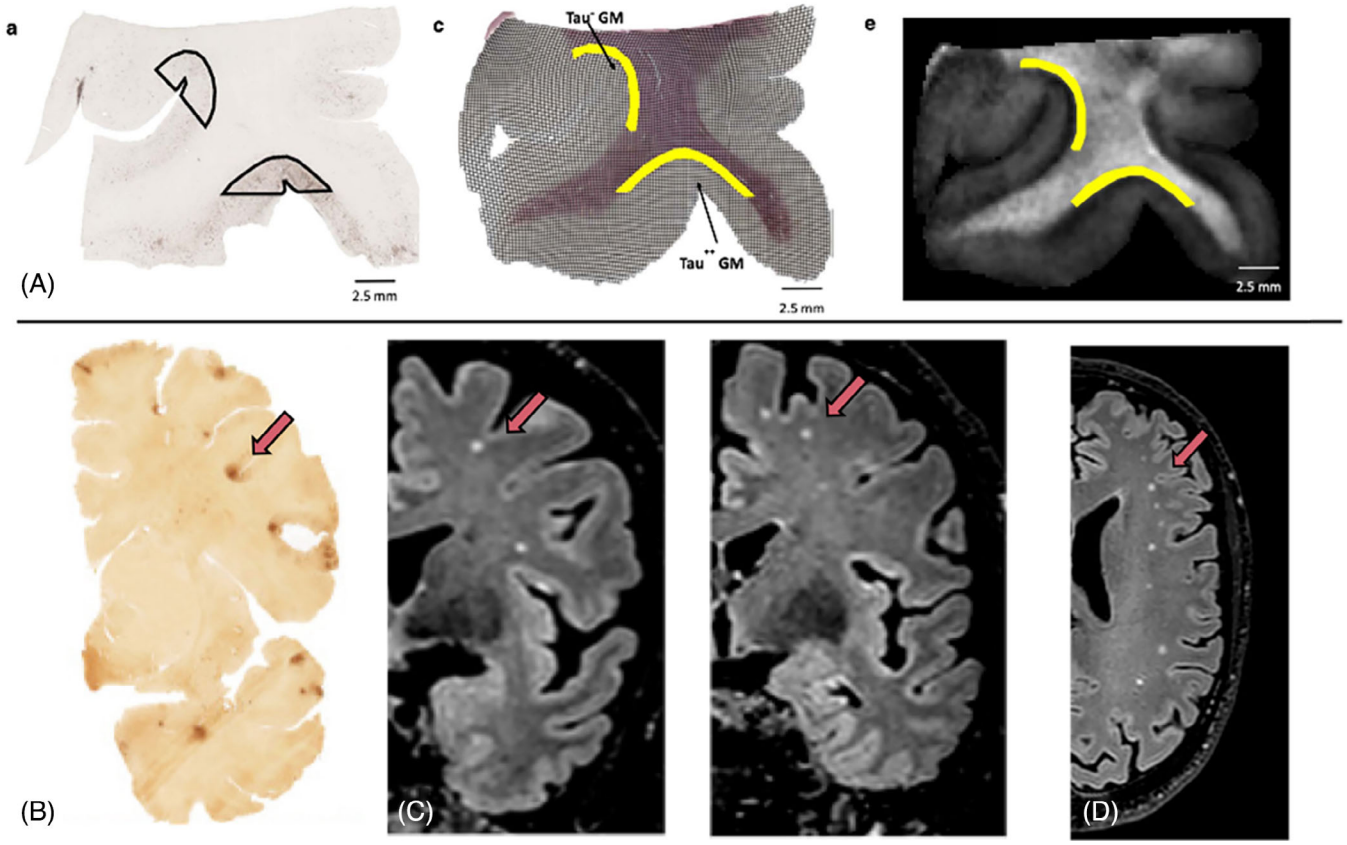

FIGURE 5 Pathology in brain areas susceptible to damage by repetitive head impact (RHI). A, Figure taken from Holleran et al.[107] Phosphorylated tau (p-tau), myelin black gold II, and high-resolution ex vivo diffusion tensor imaging in chronic traumatic encephalopathy (CTE) tissue. **a**, Low magnification immunohistochemistry using AT8 p-tau antibody demonstrating high tau pathology in the depth of one sulcus and lower tau pathology in another sulcus. **c**, Myelin black gold II staining in an adjacent slice from the same CTE brain tissue sample. The overlayed grid demonstrates the individual regions of interest analyzed for power coherence measurements. The arrows indicate the tau-negative and tau-positive sulcal depths. **e**, Diffusion tensor imaging fractional anisotrophy map from the corresponding region of the same CTE brain tissue sample. The yellow outlines indicate 0.5 mm white matter regions of interest immediately adjacent to the sulcal depths. B, Figure taken from McKee et al.[26] Whole mount coronal sections in stage II CTE show multiple foci of p-tau pathology primarily located at the depths of the cortical sulci of the frontal and temporal lobes (free floating 50 μ sections, AT8 immunostain). C, Coronal slices of fluid attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) of two RHI-exposed participants demonstrating round white matter hyperintensities (WMH) scattered throughout the cerebrum at the base of the cerebral sulci. D, Axial slice of FLAIR MRI of an RHI-exposed participant exhibiting the RHI-WMH pattern. Text adapted from Holleran et al.[107] and McKee et al.[26]

hypercholesterolemia, diabetes, history of smoking or history of heart attack, congestive heart failure, stroke, or transient ischemic attack. No participants had imaging evidence of cardiovascular disease outside of WMH findings, including no evidence of microhemorrhages. One participant reported a remote/inactive history of alcohol use disorder and one participant reported a history of adult marijuana use as a young adult. No other participants reported substance use history. All cases were exposed to RHI through a range of CCS, including American football, mixed martial arts, ice hockey, soccer, rugby, and horse jockeying. They all had substantial exposure to RHI, many of whom participated at elite levels.

Participants' diagnoses included normal cognition (n = 6) and amnestic single-domain mild cognitive impairment (MCI; n = 2). On the self-report Cognitive Change Index (CCI) questionnaire, seven participants reached the threshold for subjective cognitive impairment (i.e., CCI score > 16). In a formal consensus review by a panel of experts, four participants were found to meet research diagnostic criteria for traumatic encephalopathy syndrome (TES), the research diagnostic term for the clinical syndrome of CTE.[175] Of these four participants, two were determined to meet TES-CTE possible criteria and two were determined to meet TES-CTE suggestive criteria. The two participants who were TES-CTE possible also had MCI. The remaining four participants did not meet criteria for a TES diagnosis because they either did not present with the core clinical features of cognitive impairment or neurobehavioral dysregulation, or they did not demonstrate a progressive course of symptoms. None of the participants had other neurological conditions (e.g., history of multiple sclerosis, history of stroke, moderate to severe TBI, headaches).

Of the three participants with available amyloid biomarker data, two had CSF assessed (participants A, H) and the third completed

TABLE 1 Illustrative case series participant profiles.

	Case study participants							
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
Age range (5 years)	60–65	65–70	50–55	65–70	55–60	70–75	55–60	60–65
Sex	Male	Male	Male	Male	Female	Male	Male	Male
Education (years)	16	18	14	18	22	19	12	20
RHI exposure	American football, ice hockey, rugby	American football, ice hockey, karate	Mixed martial arts, soccer	Ice hockey, lacrosse	Rugby, soccer	American football	Horse jockey, youth American football	American football, rugby
Vascular risk factors	Hypertension	None	None	None	Mild CV valve disease	None	None	None
Substance use disorder history	Remote alcohol use	None	Remote young adult marijuana use	None	None	None	None	None
TES diagnosis	TES-CTE possible	TES-CTE suggestive	TES negative	TES negative	TES negative	TES negative	TES-CTE suggestive	TES-CTE possible
TES neurobehavioral dysregulation	No	Yes	Yes	No	No	No	Yes	No
TES cognitive diagnoses	Amnestic single domain MCI	Normal cognition	Normal cognition	Normal cognition	Normal cognition	Normal cognition	Normal cognition	Amnestic single domain MCI
CCI total score	46	29	36	24	21	13	44	31
MRI findings	Mild parietal atrophy; slightly enlarged lateral ventricles	Mild parietal atrophy; small cavum; slight asymmetrical right hippocampal atrophy	Enlarged ventricles; some atrophy in posterior, anterior, and temporal lobes	Mild temporal, posterior atrophy	Mild ventricle asymmetry	Temporal and posterior atrophy; cavum atrophy	Small anterior cavum	Small cavum
Amyloid findings: CSF	Inconsistent with AD	N/A	N/A	N/A	N/A	N/A	N/A	Inconsistent with AD
Amyloid findings: PET	N/A	Negative	N/A	N/A	N/A	N/A	N/A	N/A
Tau findings: PET	Negative	Negative	N/A	N/A	N/A	N/A	N/A	N/A
Hippocampal atrophy present	Yes	No	Yes	No	No	Yes	No	No

Notes: Cognitive Change Index (CCI)—a self-report instrument used to determine an individual's perception of changes in cognitive ability over time. The first 12 items of the CCI were scored, with potential scores ranging from 12 to 60. Higher numbers indicate higher burden of cognitive symptoms. Subject cognitive impairment is determined at a score of >16.

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; CTE, chronic traumatic encephalopathy; CV, cardiovascular; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; RHI, repetitive head impact; TES, traumatic encephalopathy syndrome.

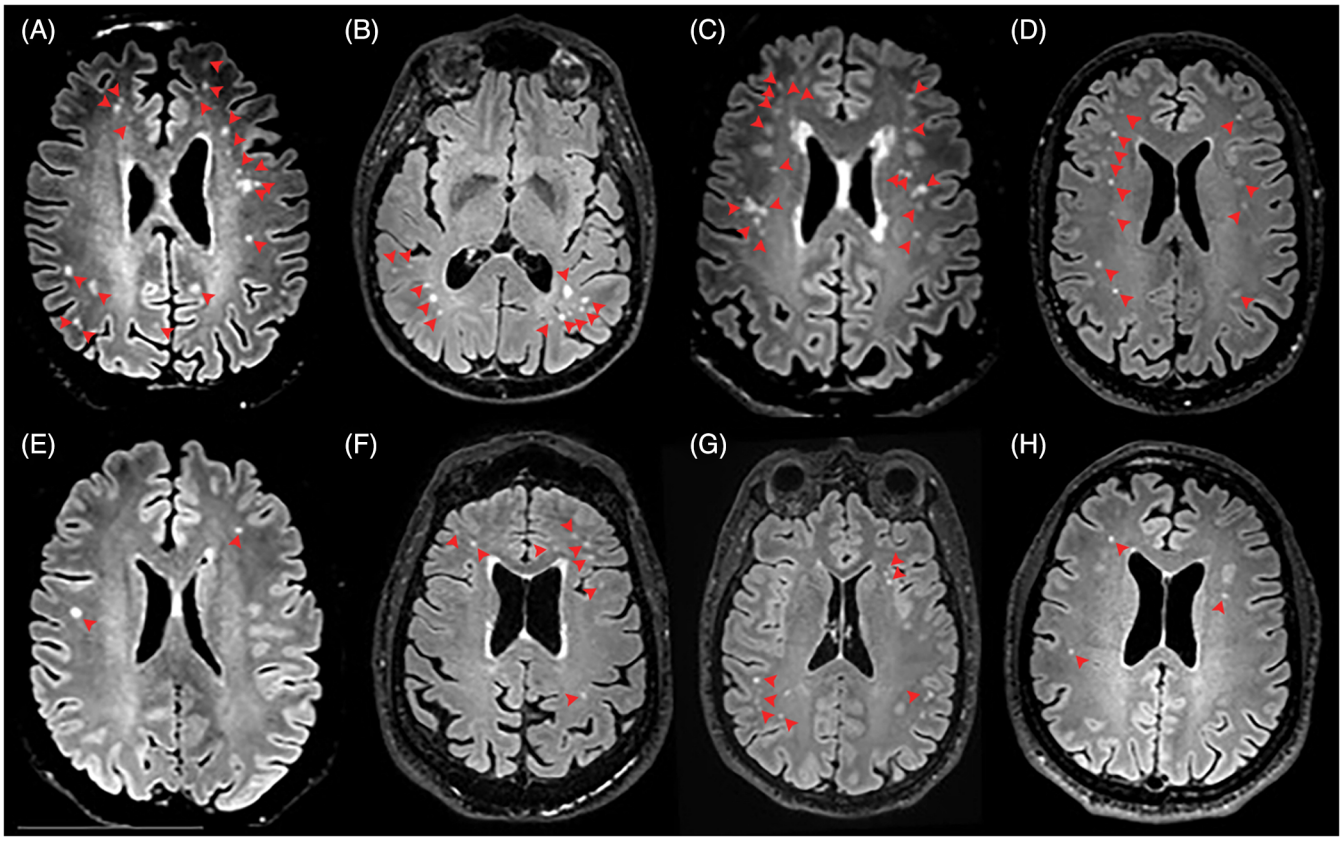

FIGURE 6 RHI-WMH: T2 FLAIR MRI images of eight RHI-exposed cases. Axial images demonstrate the pattern of RHI-WMH scattered throughout the cerebrum at the depths of the cerebral sulci. Includes images from participants A to H.

an amyloid PET scan (participant B). None of the three participants demonstrated elevated or abnormal amyloid biomarker results. Of the two participants with available tau PET imaging (participants A, B), neither had tau PET evidence for AD. Three participants had hippocampal atrophy on an MRI.

Each of the eight cases had a consistent pattern of small, punctate, non-confluent, spherical, WMH proximal to the gray matter, most in the absence of significant periventricular burden (Figure 6).

Participant D demonstrated an exemplary case of the RHI-WMH pattern being described. We have included a series of images from participant D's T2 FLAIR MRI, demonstrating the dissemination of RHI-WMH throughout the brain (Figure 7).

Overall, the participants examined in this illustrative case series present with minimal to no modifiable vascular risk factors and have substantial RHI exposure through a diverse range of CCS. All participants demonstrate the RHI-WMH pattern that we describe.

7 | DIFFERENTIAL DIAGNOSIS OF RHI-WMH

There are several competing differential etiologies that could give rise to WMH including aging, multiple sclerosis, AD/ADRD, vascular risk factors, migraine, and index TBIs. RHI-WMH are distinct from the hyperintensities with periventricular extensions (Dawson's fingers) seen in multiple sclerosis,[176, 177] as well as from the perivascular and often confluent (with more severe disease) lesions in aging and AD.[178, 179] Figure S1 in supporting information illustrates the characteristic WMH patterns seen in AD and normal aging through FLAIR MRI of one non-RHI participant with AD dementia (male, 80–85 years) and one female participant with normal cognition (70–75 years). Age-related WMH frequently present around the lateral ventricles. AD and ADRD can have a distinct topography that mirrors the distribution of their characteristic pathology.[180] WMH co-localize with atrophy and proteinopathy in AD and frontotemporal lobar degeneration (FTLD); we expect that a similar phenomenon is happening in RHI.[181–183] WMH burden has also been found to be elevated in older participants with vascular risk factors, and has been associated with clinical outcomes like depression.[184] The updated Boston criteria for the diagnosis of cerebral amyloid angiopathy has recently incorporated WM characteristics into the diagnostic criteria.[185] WMH in cerebral amyloid angiopathy are numerous and punctate and are associated with lobar cerebral microbleeds.[186] Punctate and non-confluent T2 FLAIR WMH are also a consistent finding in participants with migraines.[187, 188] The periventricular location of these lesions and smaller overall numbers is different from RHI-WMH.[189] We note that post-traumatic migraines could be quite frequent in this setting and cannot be ruled out as a differential diagnosis; however, even if migraine is the driver of these lesions, it is still potentially reflective of RHI exposure.

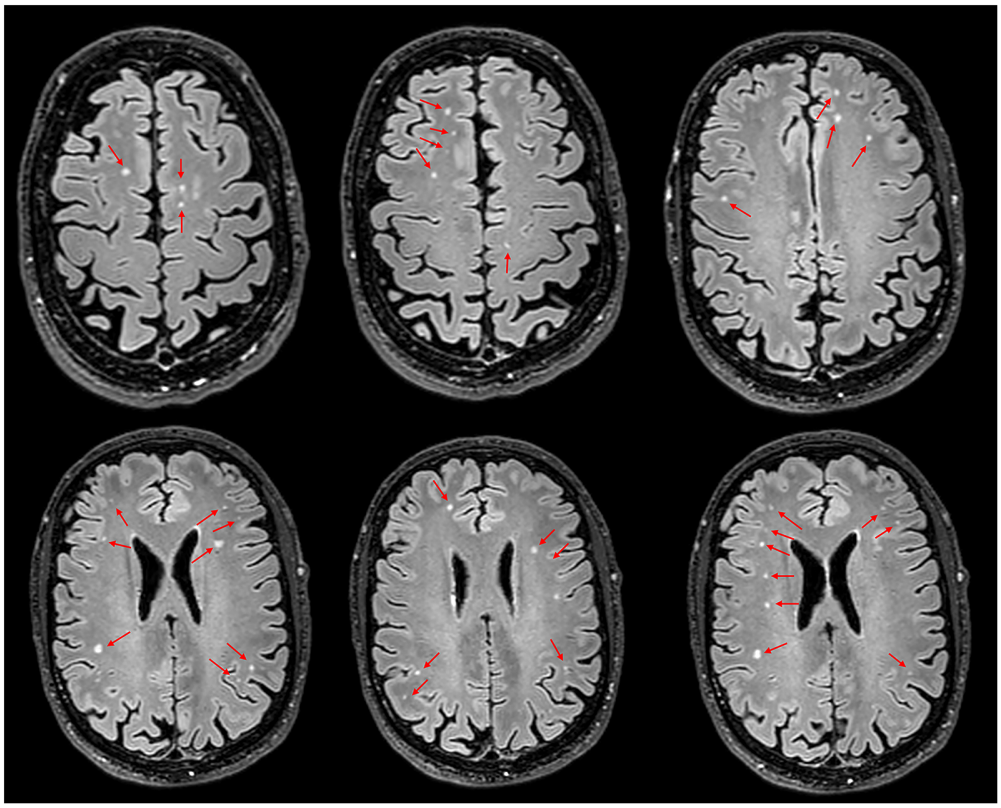

FIGURE 7 RHI-WMH: T2 FLAIR MRI slices from illustrative case participant D. A series of axial images taken from one participant demonstrate the pattern of WMH throughout the cerebrum. These RHI-WMH are consistently located at the depths of the cerebral sulci and demonstrate the same small, punctate, non-confluent, and spherical morphometry. Images taken from participant D's FLAIR MRI.

Perhaps most similar to RHI-WMH are the WMH seen in TBI.[190, 191] The mechanical forces applied to the head in TBI may also cause microbleeds, axonal shearing, and TAI.[192] These injuries, like in RHI exposure, may appear as hyperintensities on T2 FLAIR MRI along with a hemosiderin footprint.[193] The number of discrete WMH increases with higher TBI severity.[190, 191] TBI-related WMH are subcortical and close to the gray–WM junction,[191, 194] and are visually similar to RHI-WMH. This distribution may be due to RHI and TBI resulting in similar patterns of axonal injury.[192] Incidence of TBI tends to be higher in individuals with RHI exposure,[195] which may be the reason for the similar WMH presentation. Additionally, evidence from computational modeling has shown that TBI cause brain tissue injury in areas of high strain, such as the sulcal depths.[196] Overall, RHI-WMH may be capturing TAI that occur because of TBIs from RHI.

8 | DISCUSSION

The neuropathological literature suggests that WM and vascular neuropathologies may be long-term consequences of RHI. Guided by these autopsy studies, an increasing number of in vivo neuroimaging studies have investigated the relationship between RHI and WM and vascular injury in individuals with RHI exposure. WMH on T2 FLAIR MRI are a common finding in RHI-exposed participants, independent of modifiable vascular risk factors. Initial visual observations of T2 FLAIR MRIs from RHI-exposed participants who are part of the Boston University ADRC suggest a distinctive pattern of WMH in this population. Taken together, we hypothesize that exposure to RHI can lead to long-term WM and vascular injury, inducing a potentially unique pattern of WMH on T2 FLAIR MRI that we refer to as RHI-WMH. RHI-WMH are small, punctate, non-confluent, spherical, and proximal to the gray matter and appear commonly at the depths of cortical sulci.

In RHI-exposed participants, WM pathology encompasses damage to oligodendrocytes[21, 95] and the myelin sheath,[96] reduced MAG and PLP proteins,[96] increased WM rarefaction,[28] and TAI.[24, 97] Vascular pathology presents as damage to endothelial cells, BBB disruption,[126] and arteriolosclerosis.[28] While etiologically separate, WM and vascular injury are both associated with post-mortem CTE p-tau pathology.[24, 25, 49, 97, 197] We hypothesize that RHI may initiate WM and vascular injury at the time of exposure, and these pathologies potentially progress over time. The co-localization of RHI-WMH and p-tau accumulation raises the question of whether WM injury may precipitate or occur in parallel with p-tau lesion development. While p-tau has been linked with cognitive symptoms in the setting of RHI and CTE, there is a weak correlation between p-tau pathology and neurobehavioral dysregulation.[20, 30] As WM and vascular injury are associated with cognitive changes in the setting of CTE,[28, 129, 198, 199] we propose

that these pathologies may also be potential drivers of neurobehavioral dysregulation.

We hypothesize that RHI-WMH have potential specificity to RHI given (1) their anatomical location in areas susceptible to traumatic injury (gray–WM junction); (2) the presentation is inconsistent with what is typically observed in cognitive aging; (3) the growing empirical evidence that links RHI and WMH; and (4) absence of other conditions that might fully explain the presence, phenotype, and distribution of these WMH. However, we acknowledge the non-specificity of WMH. This review represents a first step toward defining the patterns of WMH that exposure to RHI might induce and a call for future research into this potential phenomenon.

8.1 | A Call for Future Research

Our hypothesis surrounding RHI-WMH and the accompanying literature review and illustrative case series is an initial step and raises several directions for future research including an improved understanding of the following: (1) the specificity of RHI-WMH, (2) the clinical meaning of RHI-WMH, (3) the biological correlates of RHI-WMH, and (4) the standard measurement of the anatomical features of WMH. Currently, our observations of RHI-WMH are based on anecdotal evidence from research participants with agreement among content experts. These illustrative case examples were chosen to be exemplary of the pattern to guide future research. Empirical studies are needed to validate this pattern as being unique to RHI, as well as demonstrate how the pattern may progress in these participants longitudinally and across the lifespan including from time of injury. A critical question is if these WMH arise at the time of injury and persist and/or progress with age. There is an ongoing collaboration between the Boston University and the University of California San Francisco ADRCs that is conducting a comprehensive investigation on the relationships between exposure to RHI, WM and vascular injury, and corresponding clinical sequelae in aging former CCS athletes. This collaborative study, titled, "Project SAVE," involves WM and vascular imaging, fluid biomarker analyses of WM and vascular proteins, and clinical phenotyping. As part of Project SAVE, there are ex vivo aims to comprehensively characterize WM and vascular pathologies in tissue, including through the use of 3D techniques known as CLARITY.[200] This study will also seek to conduct imaging-to-autopsy studies to improve our understanding of the neuropathological underpinnings of RHI-WMH. Other ongoing initiatives are also uniquely positioned to study RHI-WMHs in different cohorts and age groups, including the National Collegiate Athletic Association (NCAA)–Department of Defense (DOD) Concussion Assessment, Research and Education (CARE) Consortium;[201] the Prospective, Longitudinal, and Translational Study for Former National Football League Players (NFL-LONG);[202–205] the Football Players' Health Study (FPHS) at Harvard University;[206] and the Neurodegeneration: Traumatic Brain Injury as Origin of the Neuropathology (NEwTON) study.[207]

In conclusion, we hypothesize that exposure to RHI leads to long-term WM and vascular changes that manifest in a unique pattern on T2 FLAIR MRI that we now refer to as RHI-WMH. Future research that empirically validates RHI-WMH and establishes their specificity, explores their association with cognitive and neurobehavioral outcomes, and identifies pathologies associated with these hyperintensities will shed light on this pattern's utility as a neuroimaging consequence of RHI exposure.

ACKNOWLEDGMENTS

We would like to acknowledge William Collatos for his generous philanthropic support, which made this research possible. This work is supported by the NIA (P30AG072978), NINDS/NIA (R01NS122854), and through the BU-CTSI Grant Number 1UL1TR001430.

CONFLICT OF INTEREST STATEMENT

G.D.R. has received grants from Genentech, the NIH, the Alzheimer's Association, and Rainwater Charitable Foundation outside the submitted work, and is an associate editor for *JAMA Neurology*.

C.J.N. is a volunteer member of the Mackey–White Committee of the National Football League Players Association for which he receives travel support; an advisor and options-holder with Oxeia Biopharmaceuticals, LLC, and StataDx; and has received travel support from the NFL, NFL Players Association, World Rugby, WWE, and AEW for lectures or conferences. C.J.N. has served as an expert witness in cases related to concussion and CTE and is compensated for speaking appearances and serving on the Players Advocacy Committee for the NFL Concussion Settlement. C.J.N. is employed by the Concussion Legacy Foundation, a 501(c)(3) non-profit which receives charitable donations. R.A.S. is a member of the board of directors of King-Devick Technologies, Inc. (Chicago, IL, USA), and he receives royalties for published neuropsychological tests from Psychological Assessment Resources, Inc. (Lutz, FL, USA), and consulting fees from Eisai. A.C.M. is a member of the Mackey–White Health and Safety Committee of the National Football League Players Association and reported receiving grants from the National Institutes of Health and Department of Veteran Affairs and other funding from the Buoniconti Foundation and MacParkman Foundation during the conduct of the study. M.L.A. receives royalties from Oxford University Press Inc. and has received honorarium from the Michael J. Fox Foundation for services unrelated to this study. He also reports research support from Life Molecular Imaging Inc. and Rainwater Charitable Foundation Inc. The other authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided necessary informed consent to participate in this research study.

ORCID

Annalise E. Miner https://orcid.org/0000-0002-9336-2419

REFERENCES

1. Nowinski CJ, Bureau SC, Buckland ME, et al. Applying the Bradford Hill Criteria for causation to repetitive head impacts and chronic traumatic encephalopathy. *Front Neurol*. 2022;13:938163.

2. Daneshvar DH, Nair ES, Baucom ZH, et al. Leveraging football accelerometer data to quantify associations between repetitive head impacts and chronic traumatic encephalopathy in males. *Nat Commun*. 2023;14(1):3470.
3. Nowinski CJ, Rhim HC, McKee AC, et al. "Subconcussive" is a dangerous misnomer: hits of greater magnitude than concussive impacts may not cause symptoms. *Br J Sports Med*. 2024;58(14):754-756.
4. Lipton ML, Kim N, Zimmerman ME, et al. Soccer heading is associated with white matter microstructural and cognitive abnormalities. *Radiology*. 2013;268(3):850-857.
5. Montenigro PH, Corp DT, Stein TD, Cantu RC, Stern RA. Chronic traumatic encephalopathy: historical origins and current perspective. *Annu Rev Clin Psychol*. 2015;11:309-330.
6. Rubin TG, Catenaccio E, Fleysher R, et al. MRI-defined white matter microstructural alteration associated with soccer heading is more extensive in women than men. *Radiology*. 2018;289(2):478-486.
7. Wright DK, O'Brien TJ, Shultz SR. Sub-acute changes on MRI measures of cerebral blood flow and venous oxygen saturation in concussed Australian rules footballers. *Sports Med Open*. 2022;8(1):45.
8. Bahrami N, Sharma D, Rosenthal S, et al. Subconcussive head impact exposure and white matter tract changes over a single season of youth football. *Radiology*. 2016;281(3):919-926.
9. McKee AC, Robinson ME. Military-related traumatic brain injury and neurodegeneration. *Alzheimers Dement J Alzheimers Assoc*. 2014;10(30):S242-53.
10. Karr JE, Leong SE, Ingram EO, Logan TK. Repetitive head injury and cognitive, physical, and emotional symptoms in women survivors of intimate partner violence. *J Neurotrauma*. 2024;41(3-4):486-498.
11. Broglio SP, Eckner JT, Martini D, Sosnoff JJ, Kutcher JS, Randolph C. Cumulative head impact burden in high school football. *J Neurotrauma*. 2011;28(10):2069-2078.
12. Kercher KA, Steinfeldt JA, Macy JT, Seo DC, Kawata K. Drill intensity and head impact exposure in adolescent football. *Pediatrics*. 2022;150(5):e2022057725.
13. Choi GB, Smith EP, Duma SM, et al. Head impact exposure in youth and collegiate American football. *Ann Biomed Eng*. 2022;50(11):1488-1497.
14. Montenigro PH, Alosco ML, Martin BM, et al. Cumulative head impact exposure predicts later-life depression, apathy, executive dysfunction, and cognitive impairment in former high school and college football players. *J Neurotrauma*. 2017;34(2):328-340.
15. Daneshvar DH, Nowinski CJ, McKee AC, Cantu RC. The epidemiology of sport-related concussion. *Clin Sports Med*. 2011;30(1):1-17.
16. Spiotta AM, Bartsch AJ, Benzel EC. Heading in soccer: dangerous play? *Neurosurgery*. 2012;70(1):1-11. Discussion 11.
17. Beaudouin F, Demmerle D, Fuhr C, Tröß T, Meyer T. Head impact situations in professional football (soccer). *Sports Med Int Open*. 2021;5(2):E37-E44.
18. McKee AC, Alosco M, Huber BR. Repetitive head impacts and chronic traumatic encephalopathy. *Neurosurg Clin N Am*. 2016;27(4):529-535.
19. Alosco ML, Cherry JD, Huber BR, et al. Characterizing tau deposition in chronic traumatic encephalopathy (CTE): utility of the McKee CTE staging scheme. *Acta Neuropathol (Berl)*. 2020;140(4):495-512.
20. Mez J, Daneshvar DH, Abdolmohammadi B, et al. Duration of American football play and chronic traumatic encephalopathy. *Ann Neurol*. 2020;87(1):116-131.
21. Bieniek KF, Ross OA, Cormier KA, et al. Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. *Acta Neuropathol (Berl)*. 2015;130(6):877-889.
22. Bieniek KF, Blessing MM, Heckman MG, et al. Association between contact sports participation and chronic traumatic encephalopathy: a retrospective cohort study. *Brain Pathol Zurich Switz*. 2020;30(1):63-74.
23. Falcon B, Zivanov J, Zhang W, et al. Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules. *Nature*. 2019;568(7752):420-423.
24. McKee AC, Stein TD, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*. 2013;136(1):43-64.
25. McKee AC, Cairns NJ, Dickson DW, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol (Berl)*. 2016;131:75-86.
26. McKee AC, Stein TD, Kiernan PT, Alvarez VE. The neuropathology of chronic traumatic encephalopathy. *Brain Pathol*. 2015;25(3):350-364.
27. Bieniek KF, Cairns NJ, Crary JF, et al. The second NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2021;80(3):210-219.
28. Alosco ML, Stein TD, Tripodis Y, et al. Association of white matter rarefaction, arteriolosclerosis, and tau with dementia in chronic traumatic encephalopathy. *JAMA Neurol*. 2019;76(11):1298-1308.
29. Mez J, Daneshvar DH, Kiernan PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA*. 2017;318(4):360-370.
30. Mez J, Alosco ML, Daneshvar DH, et al. Validity of the 2014 traumatic encephalopathy syndrome criteria for CTE pathology. *Alzheimers Dement*. 2021;17(10):1709-1724.
31. Alosco ML, White M, Bell C, et al. Cognitive, functional, and neuropsychiatric correlates of regional tau pathology in autopsy-confirmed chronic traumatic encephalopathy. *Mol Neurodegener*. 2024;19(1):10.
32. Stein TD, Montenigro PH, Alvarez VE, et al. Beta-amyloid deposition in chronic traumatic encephalopathy. *Acta Neuropathol (Berl)*. 2015;130(1):21-34.
33. Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific contribution of neuropathologies to cognitive loss in old age. *Ann Neurol*. 2018;83(1):74-83.
34. Buchman AS, Yu L, Wilson RS, et al. Progressive parkinsonism in older adults is related to the burden of mixed brain pathologies. *Neurology*. 2019;92(16):e1821-e1830.
35. Saltiel N, Tripodis Y, Menzin T, et al. Relative contributions of mixed pathologies to cognitive and functional symptoms in brain donors exposed to repetitive head impacts. *Ann Neurol*. 2024;95(2):314-324.
36. Adams JW, Alvarez VE, Mez J, et al. Lewy body pathology and chronic traumatic encephalopathy associated with contact sports. *J Neuropathol Exp Neurol*. 2018;77(9):757-768.
37. Acosta SA, Tajiri N, de la Pena I, et al. Alpha-synuclein as a pathological link between chronic traumatic brain injury and Parkinson's disease. *J Cell Physiol*. 2015;230(5):1024-1032.
38. Nicks R, Clement NF, Alvarez VE, et al. Repetitive head impacts and chronic traumatic encephalopathy are associated with TDP-43 inclusions and hippocampal sclerosis. *Acta Neuropathol (Berl)*. 2023;145(4):395-408.
39. McKee AC, Gavett BE, Stern RA, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2010;69(9):918-929.
40. Cherry JD, Tripodis Y, Alvarez VE, et al. Microglial neuroinflammation contributes to tau accumulation in chronic traumatic encephalopathy. *Acta Neuropathol Commun*. 2016;4(1):112.
41. Standring OJ, Friedberg J, Tripodis Y, et al. Contact sport participation and chronic traumatic encephalopathy are associated with altered severity and distribution of cerebral amyloid angiopathy. *Acta Neuropathol (Berl)*. 2019;138(3):401-413.
42. Brett BL, Koch KM, Muftuler LT, Budde M, McCrea MA, Meier TB. Association of head impact exposure with white matter macrostructure and microstructure metrics. *J Neurotrauma*. 2021;38(4):474.
43. Montenigro PH, Baugh CM, Daneshvar DH, et al. Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed

research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimers Res Ther*. 2014;6(5):68.
44. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery*. 2014;75 Suppl 4(0 4):S24-33.
45. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train*. 2001;36(3):228-235.
46. Armstrong RC, Sullivan GM, Perl DP, et al. White matter damage and degeneration in traumatic brain injury. *Trends Neurosci*. 2024;47(9):677-692.
47. Kenney K, Amyot F, Haber M, et al. Cerebral Vascular Injury in Traumatic Brain Injury. *Exp Neurol*. 2016;275 Pt 3:353-366.
48. Salehi A, Zhang JH, Obenaus A. Response of the cerebral vasculature following traumatic brain injury. *J Cereb Blood Flow Metab*. 2017;37(7):2320-2339.
49. Kirsch D, Shah A, Dixon E, et al. Vascular injury is associated with repetitive head impacts and tau pathology in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2023;82(2):127-139.
50. Pansieri J, Hadley G, Lockhart A, Pisa M, DeLuca GC. Regional contribution of vascular dysfunction in white matter dementia: clinical and neuropathological insights. *Front Neurol*. 2023;14:1199491. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10313211/
51. Johnson B, Walter AE, Wilkes JR, Papa L, Slobounov SM. Changes in white matter of the cervical spinal cord after a single season of collegiate football. *Neurotrauma Rep*. 2021;2(1):84-93.
52. Barber Foss KD, Yuan W, Diekfuss JA, et al. Relative head impact exposure and brain white matter alterations after a single season of competitive football: a pilot comparison of youth versus high school football. *Clin J Sport Med*. 2019;29(6):442-450.
53. Brett BL, Savitz J, Nitta M, et al. Systemic inflammation moderates the association of prior concussion with hippocampal volume and episodic memory in high school and collegiate athletes. *Brain Behav Immun*. 2020;89:380-388.
54. Koerte IK, Ertl-Wagner B, Reiser M, Zafonte R, Shenton ME. White matter integrity in the brains of professional soccer players without a symptomatic concussion. *JAMA*. 2012;308(18):1859-1861.
55. Bazarian JJ, Zhu T, Zhong J, et al. Persistent, long-term cerebral white matter changes after sports-related repetitive head impacts. *PloS One*. 2014;9(4):e94734.
56. Merz ZC, Flashman LA, Ford JC, McDonald BC, McAllister TW. Comparison of season-long diffusivity measures in a cohort of non-concussed contact and non-contact athletes. *J Clin Exp Neuropsychol*. 2020;42(8):811-821.
57. Champagne AA, Peponoulas E, Terem I, et al. Novel strain analysis informs about injury susceptibility of the corpus callosum to repeated impacts. *Brain Commun*. 2019;1(1):fcz021.
58. Asselin PD, Gu Y, Merchant-Borna K, et al. Spatial regression analysis of MR diffusion reveals subject-specific white matter changes associated with repetitive head impacts in contact sports. *Sci Rep*. 2020;10:13606.
59. Orr CA, Albaugh MD, Watts R, et al. Neuroimaging biomarkers of a history of concussion observed in asymptomatic young athletes. *J Neurotrauma*. 2016;33(9):803-810.
60. Koerte IK, Kaufmann D, Hartl E, et al. A prospective study of physician-observed concussion during a varsity university hockey season: white matter integrity in ice hockey players. Part 3 of 4. *Neurosurg Focus*. 2012;33(6):E3:1-7.
61. Sasaki T, Pasternak O, Mayinger M, et al. Hockey Concussion Education Project, Part 3. White matter microstructure in ice hockey players with a history of concussion: a diffusion tensor imaging study. *J Neurosurg*. 2014;120(4):882-890.
62. Cubon VA, Murugavel M, Holmes KW, Dettwiler A. Preliminary evidence from a prospective DTI study suggests a posterior-to-anterior pattern of recovery in college athletes with sports-related concussion. *Brain Behav*. 2018;8(12):e01165.
63. Sollmann N, Echlin PS, Schultz V, et al. Sex differences in white matter alterations following repetitive subconcussive head impacts in collegiate ice hockey players. *NeuroImage Clin*. 2018;17:642-649.
64. Strauss SB, Fleysher R, Ifrah C, et al. Framing potential for adverse effects of repetitive subconcussive impacts in soccer in the context of athlete and non-athlete controls. *Brain Imaging Behav*. 2021;15(2):882-895.
65. Hoffman LJ, Mis RE, Brough C, et al. Concussions in young adult athletes: no effect on cerebral white matter. *Front Hum Neurosci*. 2023;17:1113971.
66. Charney MF, Ye KQ, Fleysher R, et al. Age of first exposure to soccer heading: associations with cognitive, clinical, and imaging outcomes in the Einstein Soccer Study. *Front Neurol*. 2023;14:1042707.
67. Helmer KG, Pasternak O, Fredman E, et al. Hockey Concussion Education Project, Part 1. Susceptibility-weighted imaging study in male and female ice hockey players over a single season. *J Neurosurg*. 2014;120(4):864-872.
68. Uretsky M, Bouix S, Killiany RJ, et al. Association between antemortem FLAIR white matter hyperintensities and neuropathology in brain donors exposed to repetitive head impacts. *Neurology*. 2022;98(1):e27-e39.
69. McKee AC, Stein TD, Huber BR, et al. Chronic traumatic encephalopathy (CTE): criteria for neuropathological diagnosis and relationship to repetitive head impacts. *Acta Neuropathol (Berl)*. 2023;145(4):371-394.
70. Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain J Neurol*. 2013;136(pt 1):28-42.
71. Bazarian JJ, Zhu T, Blyth B, Borrino A, Zhong J. Subject-specific changes in brain white matter on diffusion tensor imaging after sports-related concussion. *Magn Reson Imaging*. 2012;30(2):171-180.
72. Jefferson AL, Wong S, Bolen E, Ozonoff A, Green RC, Stern RA. Cognitive correlates of HVOT performance differ between individuals with mild cognitive impairment and normal controls. *Arch Clin Neuropsychol*. 2006;21(5):405-412.
73. Sugarman MA, Zetterberg H, Blennow K, et al. A longitudinal examination of plasma neurofilament light and total tau for the clinical detection and monitoring of Alzheimer's disease. *Neurobiol Aging*. 2020;94:60-70.
74. Frank B, Ally M, Brekke B, et al. Plasma p-tau181 shows stronger network association to Alzheimer's disease dementia than neurofilament light and total tau. *Alzheimers Dement*. 2022;18(8):1523-1536.
75. Martland HS. Punch drunk. *J Am Med Assoc*. 1928;91(15):1103-1107.
76. Critchley M. Medical aspects of boxing, particularly from a neurological standpoint. *Br Med J*. 1957;1(5015):357-362.
77. Critchley M. Punch-drunk syndromes: the chronic traumatic encephalopathy of boxers. *Hommage a Clovis Vincent*. 1949:131-141.
78. Parker HL. Traumatic encephalopathy ('Punch Drunk') of professional pugilists. *J Neurol Psychopathol*. 1934;15(57):20-28.
79. Millspaugh J. Dementia pugilistica. *US Nav Med Bull*. 1937;35(303):297-261.
80. Bowman KM, Blau A. Psychotic states following head and brain injury in adults and children. In: *Injuries of the Skull, Brain and Spinal Cord: Neuro-psychiatric, Surgical, and Medico-legal Aspects*. Williams & Wilkins Co; 1940:309-360.
81. Jordan B. Chronic traumatic brain injury associated with boxing. *Semin Neurol*. 2000;20:179-185.
82. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol*. 2009;68(7):709-735.
83. Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH. Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery*. 2005;57(1):128-134. Discussion 128-134.

84. Priemer DS, Iacono D, Rhodes CH, Olsen CH, Perl DP. Chronic traumatic encephalopathy in the brains of military personnel. *N Engl J Med*. 2022;386(23):2169-2177.
85. Roberts GW, Whitwell HL, Acland PR, Bruton CJ. Dementia in a punch-drunk wife. *Lancet Lond Engl*. 1990;335(8694):918-919.
86. Corsellis JA, Bruton CJ, Freeman-Browne D. The aftermath of boxing. *Psychol Med*. 1973;3(3):270-303.
87. Stewart W, Buckland ME, Abdolmohammadi B, et al. Risk of chronic traumatic encephalopathy in rugby union is associated with length of playing career. *Acta Neuropathol (Berl)*. 2023;146(6):829-832.
88. Pearce AJ, Sy J, Lee M, et al. Chronic traumatic encephalopathy in a former Australian rules football player diagnosed with Alzheimer's disease. *Acta Neuropathol Commun*. 2020;8(1):23.
89. Suter CM, Affleck AJ, Pearce AJ, Junckerstorff R, Lee M, Buckland ME. Chronic traumatic encephalopathy in a female ex-professional Australian rules footballer. *Acta Neuropathol (Berl)*. 2023;146(3):547-549.
90. Buckland ME, Sy J, Szentmariay I, et al. Chronic traumatic encephalopathy in two former Australian National Rugby League players. *Acta Neuropathol Commun*. 2019;7(1):97.
91. Suter CM, Affleck AJ, Lee M, et al. Chronic traumatic encephalopathy in a routine neuropathology service in Australia. *J Neuropathol Exp Neurol*. 2022;81(10):790-795.
92. Omalu BI, DeKosky ST, Hamilton RL, et al. Chronic traumatic encephalopathy in a national football league player: part II. *Neurosurgery*. 2006;59(5):1086-1092. Discussion 1092-1093.
93. Alosco ML, Mez J, Tripodis Y, et al. Age of first exposure to tackle football and chronic traumatic encephalopathy. *Ann Neurol*. 2018;83(5):886-901.
94. Rosario A, Howell A, Bhattacharya SK. A revisit to staining reagents for neuronal tissues. *Ann Eye Sci*. 2022;7:6.
95. Chancellor KB, Chancellor SE, Duke-Cohan JE, et al. Altered oligodendroglia and astroglia in chronic traumatic encephalopathy. *Acta Neuropathol (Berl)*. 2021;142(2):295-321.
96. Alosco ML, Ly M, Mosaheb S, et al. Decreased myelin proteins in brain donors exposed to football-related repetitive head impacts. *Brain Commun*. 2023;5(2):fcad019.
97. Stein TD, Alvarez VE, McKee AC. Chronic traumatic encephalopathy: a spectrum of neuropathological changes following repetitive brain trauma in athletes and military personnel. *Alzheimers Res Ther*. 2014;6(1):4.
98. Bruggeman GF, Haitsma IK, Dirven CMF, Volovici V. Traumatic axonal injury (TAI): definitions, pathophysiology and imaging—a narrative review. *Acta Neurochir (Wien)*. 2021;163(1):31-44.
99. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Exp Neurol*. 2013;246:35-43.
100. Buée L, Hof PR, Bouras C, et al. Pathological alterations of the cerebral microvasculature in Alzheimer's disease and related dementing disorders. *Acta Neuropathol (Berl)*. 1994;87(5):469-480.
101. Miners JS, Palmer JC, Love S. Pathophysiology of hypoperfusion of the precuneus in early Alzheimer's disease. *Brain Pathol Zurich Switz*. 2016;26(4):533-541.
102. Schnaar RL, Lopez PHH. Myelin-associated glycoprotein and its axonal receptors. *J Neurosci Res*. 2009;87(15):3267-3276.
103. Ruskamo S, Raasakka A, Pedersen JS, et al. Human myelin proteolipid protein structure and lipid bilayer stacking. *Cell Mol Life Sci*. 2022;79(8):419.
104. Thomas T, Miners S, Love S. Post-mortem assessment of hypoperfusion of cerebral cortex in Alzheimer's disease and vascular dementia. *Brain J Neurol*. 2015;138(pt 4):1059-1069.
105. McAleese KE, Miah M, Graham S, et al. Frontal white matter lesions in Alzheimer's disease are associated with both small vessel disease and AD-associated cortical pathology. *Acta Neuropathol (Berl)*. 2021;142(6):937-950.
106. Bi B, Choi HP, Hyeon SJ, et al. Quantitative proteomic analysis reveals impaired axonal guidance signaling in human postmortem brain tissues of chronic traumatic encephalopathy. *Exp Neurobiol*. 2019;28(3):362-375.
107. Holleran L, Kim JH, Gangolli M, et al. Axonal disruption in white matter underlying cortical sulcus tau pathology in chronic traumatic encephalopathy. *Acta Neuropathol (Berl)*. 2017;133(3):367-380.
108. Pierre K, Molina V, Shukla S, et al. Chronic traumatic encephalopathy: diagnostic updates and advances. *AIMS Neurosci*. 2022;9(4):519-535.
109. Winklewski PJ, Sabisz A, Naumczyk P, Jodzio K, Szurowska E, Szarmach A. Understanding the physiopathology behind axial and radial diffusivity changes-what do we know? *Front Neurol*. 2018;9:92.
110. Tiemensma M, Byard RW, Vink R, Affleck AJ, Blumbergs P, Buckland ME. Chronic traumatic encephalopathy (CTE) in the context of longstanding intimate partner violence. *Acta Neuropathol (Berl)*. 2024;148(1):1.
111. Liu LY, Bush WS, Koyutürk M, Karakurt G. Interplay between traumatic brain injury and intimate partner violence: data driven analysis utilizing electronic health records. *BMC Womens Health*. 2020;20:269.
112. Dams-O'Connor K, Seifert AC, Crary JF, et al. The neuropathology of intimate partner violence. *Acta Neuropathol (Berl)*. 2023;146(6):803-815.
113. Babcock KJ, Abdolmohammadi B, Kiernan PT, et al. Interface astrogliosis in contact sport head impacts and military blast exposure. *Acta Neuropathol Commun*. 2022;10(1):52.
114. Alosco ML, Duskin J, Besser LM, et al. Modeling the relationships among late-life body mass index, cerebrovascular disease, and Alzheimer's disease neuropathology in an autopsy sample of 1,421 subjects from the National Alzheimer's Coordinating Center Data Set. *J Alzheimers Dis JAD*. 2017;57(3):953-968.
115. Deramecourt V, Slade JY, Oakley AE, et al. Staging and natural history of cerebrovascular pathology in dementia. *Neurology*. 2012;78(14):1043-1050.
116. Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. *Alzheimer Dis Assoc Disord*. 1999;13(suppl 3):S115-123.
117. Toledo JB, Arnold SE, Raible K, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain J Neurol*. 2013;136(pt 9):2697-2706.
118. Dallaire-Théroux C, Saikali S, Richer M, Potvin O, Duchesne S. Histopathological analysis of cerebrovascular lesions associated with aging. *J Neuropathol Exp Neurol*. 2022;81(2):97-105.
119. Love S, Miners JS. Cerebrovascular disease in ageing and Alzheimer's disease. *Acta Neuropathol (Berl)*. 2016;131(5):645-658.
120. Okoh AK, Amponsah MKD, Cheffet-Walsh S, et al. Prevalence of cardiovascular disease and risk factors among former National Football League players. *J Am Coll Cardiol*. 2024;83(19):1827-1837.
121. Tucker AM, Vogel RA, Lincoln AE, et al. Prevalence of cardiovascular disease risk factors among National Football League players. *JAMA*. 2009;301(20):2111-2119.
122. Baron SL, Hein MJ, Lehman E, Gersic CM. Body mass index, playing position, race, and the cardiovascular mortality of retired professional football players. *Am J Cardiol*. 2012;109(6):889-896.
123. Kahriman A, Bouley J, Smith TW, Bosco DA, Woerman AL, Henninger N. Mouse closed head traumatic brain injury replicates the histological tau pathology pattern of human disease: characterization of a novel model and systematic review of the literature. *Acta Neuropathol Commun*. 2021;9:118.
124. Goldstein LE, Fisher AM, Tagge CA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci Transl Med*. 2012;4(134):134ra60.
125. McKee AC, Daneshvar DH, Alvarez VE, Stein TD. The neuropathology of sport. *Acta Neuropathol (Berl)*. 2014;127(1):29-51.

126. Doherty CP, O'Keefe E, Wallace E, et al. Blood-brain barrier dysfunction as a hallmark pathology in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2016;75(7):656-662.
127. Hart J, Kraut MA, Womack KB, et al. Neuroimaging of cognitive dysfunction and depression in aging retired NFL players: a cross-sectional study. *JAMA Neurol*. 2013;70(3):326-335.
128. Tremblay S, Henry LC, Bedetti C, et al. Diffuse white matter tract abnormalities in clinically normal ageing retired athletes with a history of sports-related concussions. *Brain J Neurol*. 2014;137(pt 11):2997-3011.
129. Multani N, Goswami R, Khodadadi M, et al. The association between white-matter tract abnormalities, and neuropsychiatric and cognitive symptoms in retired professional football players with multiple concussions. *J Neurol*. 2016;263(7):1332-1341.
130. Coughlin JM, Wang Y, Minn I, et al. Imaging of glial cell activation and white matter integrity in brains of active and recently retired National Football league players. *JAMA Neurol*. 2017;74(1):67-74.
131. Wright DK, Gardner AJ, Wojtowicz M, et al. White matter abnormalities in retired professional Rugby League players with a history of concussion. *J Neurotrauma*. 2021;38(8):983-988.
132. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838.
133. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol*. 2023;22(7):602-618.
134. Alber J, Alladi S, Bae HJ, et al. White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): knowledge gaps and opportunities. *Alzheimers Dement Transl Res Clin Interv*. 2019;5(1):107-117.
135. Weidauer S, Wagner M, Hattingen E. White matter lesions in adults—a differential diagnostic approach. *ROFO Fortschr Geb Rontgenstr Nuklearmed*. 2020;192(12):1154-1173.
136. Wildner P, Stasiołek M, Matysiak M. Differential diagnosis of multiple sclerosis and other inflammatory CNS diseases. *Mult Scler Relat Disord*. 2020;37:101452.
137. Dadar M, Mahmoud S, Zhernovaia M, et al. White matter hyperintensity distribution differences in aging and neurodegenerative disease cohorts. *NeuroImage Clin*. 2022;36:103204.
138. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18(7):684-696.
139. d'Arbeloff T, Elliott ML, Knodt AR, et al. White matter hyperintensities are common in midlife and already associated with cognitive decline. *Brain Commun*. 2019;1(1):fcz041.
140. Wang ML, Zhang XX, Yu MM, Li WB, Li YH. Prevalence of white matter hyperintensity in young clinical patients. *Am J Roentgenol*. 2019;213(3):667-671.
141. de Leeuw FE, de Groot JC, Oudkerk M, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain J Neurol*. 2002;125(pt 4):765-772.
142. Brickman AM, Sneed JR, Provenzano FA, et al. Quantitative approaches for assessment of white matter hyperintensities in elderly populations. *Psychiatry Res*. 2011;193(2):101-106.
143. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13(6):614-629.
144. Tosto G, Zimmerman ME, Carmichael OT, Brickman AM, Alzheimer's Disease Neuroimaging Initiative. Predicting aggressive decline in mild cognitive impairment: the importance of white matter hyperintensities. *JAMA Neurol*. 2014;71(7):872-877.
145. Bilello M, Doshi J, Nabavizadeh SA, et al. Correlating cognitive decline with white matter lesion and brain atrophy magnetic resonance imaging measurements in Alzheimer's disease. *J Alzheimers Dis*. 2015;48(4):987-994.
146. Brickman AM, Zahodne LB, Guzman VA, et al. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiol Aging*. 2015;36(1):27-32.
147. Maillard P, Carmichael O, Fletcher E, Reed B, Mungas D, DeCarli C. Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology*. 2012;79(5):442-448.
148. Carmichael O, Schwarz C, Drucker D, et al. Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. *Arch Neurol*. 2010;67(11):1370-1378.
149. Lindemer ER, Greve DN, Fischl B, Augustinack JC, Salat DH. Alzheimer's disease neuroimaging initiative. differential regional distribution of juxtacortical white matter signal abnormalities in aging and Alzheimer's disease. *J Alzheimers Dis*. 2017;57(1):293-303.
150. Lee DY, Fletcher E, Martinez O, et al. Vascular and degenerative processes differentially affect regional interhemispheric connections in normal aging, mild cognitive impairment, and Alzheimer disease. *Stroke*. 2010;41(8):1791-1797.
151. Yoshita M, Fletcher E, Harvey D, et al. Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology*. 2006;67(12):2192-2198.
152. Lee S, Viqar F, Zimmerman ME, et al. White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network. *Ann Neurol*. 2016;79(6):929-939.
153. Schoemaker D, Zanon Zotin MC, Chen K, et al. White matter hyperintensities are a prominent feature of autosomal dominant Alzheimer's disease that emerge prior to dementia. *Alzheimers Res Ther*. 2022;14(1):89.
154. Fiford CM, Manning EN, Bartlett JW, et al. White matter hyperintensities are associated with disproportionate progressive hippocampal atrophy. *Hippocampus*. 2017;27(3):249-262.
155. Grimmer T, Faust M, Auer F, et al. White matter hyperintensities predict amyloid increase in Alzheimer's disease. *Neurobiol Aging*. 2012;33(12):2766-2773.
156. Lorenzini L, Ansems LT, Lopes Alves I, et al. Regional associations of white matter hyperintensities and early cortical amyloid pathology. *Brain Commun*. 2022;4(3):fcac150.
157. Zhang Y, Schuff N, Du AT, et al. White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. *Brain*. 2009;132(9):2579-2592.
158. Woollacott IOC, Bocchetta M, Sudre CH, et al. Pathological correlates of white matter hyperintensities in a case of progranulin mutation associated frontotemporal dementia. *Neurocase*. 2018;24(3):166-174.
159. Maxwell WL, Bartlett E, Morgan H. Wallerian degeneration in the optic nerve stretch-injury model of traumatic brain injury: a stereological analysis. *J Neurotrauma*. 2015;32(11):780-790.
160. Koliatsos V, Alexandris A. Wallerian degeneration as a therapeutic target in traumatic brain injury. *Curr Opin Neurol*. 2019;32(6):786-795.
161. Alosco ML, Koerte IK, Tripodis Y, et al. White matter signal abnormalities in former National Football League players. *Alzheimers Dement Amst Neth*. 2018;10:56-65.
162. Dufouil C, Beiser A, McLure LA, et al. A revised framingham stroke risk profile to reflect temporal trends. *Circulation*. 2017;135(12):1145-1159.
163. Esagoff AI, Gifford MK, Narapareddy BR, et al. Prior football or rugby exposure and white matter signal abnormalities in professional male mixed martial arts fighters. *Phys Sportsmed*. 2025;53(1):42-46.
164. Alosco ML, Tripodis Y, Baucom ZH, et al. White matter hyperintensities in former American football players. *Alzheimers Dement J Alzheimers Assoc*. 2023;19(4):1260-1273.

165. Alosco ML, Mariani ML, Adler CH, et al. Developing methods to detect and diagnose chronic traumatic encephalopathy during life: rationale, design, and methodology for the DIAGNOSE CTE Research Project. *Alzheimers Res Ther*. 2021;13(1):136.
166. Brett BL, Klein AP, Vazirnia P, et al. White matter hyperintensities and microstructural alterations in contact sport athletes from adolescence to early midlife. *J Neurotrauma*. 2024;41(19-20):2307-2322.
167. Glikstein R, Melkus G, Portela de Oliveira E, et al. Five-year serial brain MRI analysis of military members exposed to chronic subconcussive overpressures. *J Magn Reson Imaging*. 2025;61(1):415-423.
168. Casson IR, Viano DC, Haacke EM, Kou Z, LeStrange DG. Is there chronic brain damage in retired NFL players? Neuroradiology, neuropsychology, and neurology examinations of 45 retired players. *Sports Health*. 2014;6(5):384-395.
169. Zivadinov R, Polak P, Schweser F, et al. Multimodal imaging of retired professional contact sport athletes does not provide evidence of structural and functional brain damage. *J Head Trauma Rehabil*. 2018;33(5):E24-E32.
170. Ly MT, Tuz-Zahra F, Tripodis Y, et al. Association of vascular risk factors and CSF and imaging biomarkers with white matter hyperintensities in former American football players. *Neurology*. 2024;102(2):e208030.
171. Mckee AC, Daneshvar DH. The neuropathology of traumatic brain injury. *Handb Clin Neurol*. 2015;127:45-66.
172. Cloots RJH, Gervaise HMT, van Dommelen JaW, Geers MGD. Biomechanics of traumatic brain injury: influences of the morphologic heterogeneities of the cerebral cortex. *Ann Biomed Eng*. 2008;36(7):1203-1215.
173. Cloots RJH, van Dommelen JaW, Nyberg T, Kleiven S, Geers MGD. Micromechanics of diffuse axonal injury: influence of axonal orientation and anisotropy. *Biomech Model Mechanobiol*. 2011;10(3):413-422.
174. Povlishock JT. Pathobiology of traumatically induced axonal injury in animals and man. *Ann Emerg Med*. 1993;22(6):980-986.
175. Katz DI, Bernick C, Dodick DW, et al. National Institute of Neurological Disorders and Stroke Consensus diagnostic criteria for traumatic encephalopathy syndrome. *Neurology*. 2021;96(18):848-863.
176. Dawson JW. The histology of disseminated sclerosis. *Edinb Med J*. 1916;17(5):311-344.
177. Lassmann H. Multiple sclerosis pathology. *Cold Spring Harb Perspect Med*. 2018;8(3):a028936.
178. Rezek DL, Morris JC, Fulling KH, Gado MH. Periventricular white matter lucencies in senile dementia of the Alzheimer type and in normal aging. *Neurology*. 1987;37(8):1365-1368.
179. Prins ND, van Dijk EJ, den Heijer T, et al. Cerebral white matter lesions and the risk of dementia. *Arch Neurol*. 2004;61(10):1531-1534.
180. Garnier-Crussard A, Bougacha S, Wirth M, et al. White matter hyperintensity topography in Alzheimer's disease and links to cognition. *Alzheimers Dement*. 2022;18(3):422-433.
181. Desmarais P, Gao AF, Lanctôt K, et al. White matter hyperintensities in autopsy-confirmed frontotemporal lobar degeneration and Alzheimer's disease. *Alzheimers Res Ther*. 2021;13:129.
182. Alban SL, Lynch KM, Ringman JM, et al. The association between white matter hyperintensities and amyloid and tau deposition. *NeuroImage Clin*. 2023;38:103383.
183. Huynh K, Piguet O, Kwok J, et al. Clinical and biological correlates of white matter hyperintensities in patients with behavioral-variant frontotemporal dementia and Alzheimer disease. *Neurology*. 2021;96(13):e1743-e1754.
184. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963-974.
185. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol*. 2022;21(8):714-725.
186. Charidimou A, Boulouis G, Haley K, et al. White matter hyperintensity patterns in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology*. 2016;86(6):505-511.
187. Cheng CY, Cheng HM, Chen SP, et al. White matter hyperintensities in migraine: clinical significance and central pulsatile hemodynamic correlates. *Cephalalgia*. 2018;38(7):1225-1236.
188. Hamedani AG, Rose KM, Peterlin BL, et al. Migraine and white matter hyperintensities: the ARIC MRI study. *Neurology*. 2013;81(15):1308-1313.
189. Chong CD, Schwedt TJ, Trivedi M, Chong BW. The characteristics of white matter hyperintensities in patients with migraine. *Front Pain Res*. 2022;3:852916.
190. Riedy G, Senseney JS, Liu W, et al. Findings from structural MR imaging in military traumatic brain injury. *Radiology*. 2016;279(1):207-215.
191. Trifan G, Gattu R, Haacke EM, Kou Z, Benson RR. MR imaging findings in mild traumatic brain injury with persistent neurological impairment. *Magn Reson Imaging*. 2017;37:243-251.
192. Andriessen TMJC, Jacobs B, Vos PE. Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. *J Cell Mol Med*. 2010;14(10):2381-2392.
193. Liu W, Soderlund K, Senseney JS, et al. Imaging cerebral microhemorrhages in military service members with chronic traumatic brain injury. *Radiology*. 2016;278(2):536-545.
194. Jarrett M, Tam R, Hernández-Torres E, et al. A prospective pilot investigation of brain volume, white matter hyperintensities, and hemorrhagic lesions after mild traumatic brain injury. *Front Neurol*. 2016;7:11.
195. Selassie AW, Wilson DA, Pickelsimer EE, Voronca DC, Williams NR, Edwards JC. Incidence of sport-related traumatic brain injury and risk factors of severity: a population-based epidemiologic study. *Ann Epidemiol*. 2013;23(12):750-756.
196. Fagan BT, Satapathy SS, Rutledge JN, Kornguth SE. Simulation of the strain amplification in sulci due to blunt impact to the head. *Front Neurol*. 2020;11:998.
197. Buee L, Bussiere T, Buee-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res Brain Res Rev*. 2000;33(1):95-130.
198. Strain JF, Didehbani N, Spence J, et al. White matter changes and confrontation naming in retired aging National football league athletes. *J Neurotrauma*. 2017;34(2):372-379.
199. Veeramuthu V, Narayanan V, Kuo TL, et al. Diffusion tensor imaging parameters in mild traumatic brain injury and its correlation with early neuropsychological impairment: a longitudinal study. *J Neurotrauma*. 2015;32(19):1497-1509.
200. Chung K, Wallace J, Kim SY, et al. Structural and molecular interrogation of intact biological systems. *Nature*. 2013;497(7449):332-337.
201. Broglio SP, McCrea M, McAllister T, et al. A National Study on the effects of concussion in collegiate athletes and US military service academy members: the NCAA-DoD concussion assessment, research and education (CARE) consortium structure and methods. *Sports Med Auckl NZ*. 2017;47(7):1437-1451.
202. Brett BL, Walton SR, Kerr ZY, et al. Distinct latent profiles based on neurobehavioural, physical and psychosocial functioning of former National Football League (NFL) players: an NFL-LONG Study. *J Neurol Neurosurg Psychiatry*. 2021;92(3):282-290.
203. Kuenze C, Pietrosimone B, Currie KD, et al. Joint injury, osteoarthritis, and cardiovascular disease risk factors in former National Football League athletes: an NFL-LONG study. *J Athl Train*. 2023;58(6):528-535.

204. Walton SR, Kerr ZY, Brett BL, et al. Health-promoting behaviours and concussion history are associated with cognitive function, mood-related symptoms and emotional-behavioural dyscontrol in former NFL players: an NFL-LONG Study. *Br J Sports Med*. 2021;55(12):683-690.
205. Lempke LB, Walton SR, Brett BL, et al. Relating American football age of first exposure to patient-reported outcomes and medical diagnoses among former National football league players: an NFL-LONG study. *Sports Med Auckl NZ*. 2023;53(5):1073-1084.
206. Zafonte R, Pascual-Leone A, Baggish A, et al. The football players' health study at Harvard University: design and objectives. *Am J Ind Med*. 2019;62(8):643-654.
207. van Amerongen S, Caton DK, Ossenkoppele R, et al. Rationale and design of the "NEurodegeneration: traumatic brain injury as Origin of the Neuropathology (NEwTON)" study: a prospective cohort study of individuals at risk for chronic traumatic encephalopathy. *Alzheimers Res Ther*. 2022;14(1):119.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Miner AE, Groh JR, Farris C, et al. Does white matter and vascular injury from repetitive head impacts lead to a novel pattern on T2 FLAIR MRI? A hypothesis proposal and call for research. *Alzheimer's Dement*. 2025;21:e70085. https://doi.org/10.1002/alz.70085