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ORIGINAL PAPER

Characterizing white matter and vascular pathologies in brain donors exposed to repetitive head impacts

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Abstract

Chronic traumatic encephalopathy (CTE) is a progressive brain disease linked to repetitive head impacts (RHI), often incurred from contact sports, and can lead to dementia. Here, we investigated the association between RHI and white matter/vascular neuropathologies and their relative contribution to dementia status in deceased men 50 + years old with and without exposure to RHI from various types of contact and collision sports. Our sample included two RHI groups from the UNITE brain bank: (1) American Football players (RHI-AF, $n = 79$), and (2) non-AF contact and collision sport athletes (e.g., boxing, rugby; RHI-CCS, $n = 49$). Controls included similarly aged (± 5 years) male brain donors without RHI. A modified ischemic injury scale (mIIS) served as a global measure of white matter and vascular neuropathologies, encompassing nine subcomponents. Dementia was determined through diagnostic consensus conference based on interviews with families. Using linear regression models controlling for age at death, mIIS was different in RHI-AF versus non-RHI only ($p = 0.036$). Subsequent logistic regression of each mIIS subcomponent, controlling for age at death, demonstrated that worse white matter rarefaction (RHI-AF; Beta = 1.42, [95% CI 2.03–8.43]; RHI-CCS; Beta = 1.93, [95% CI 2.35–20.17]) and hippocampal sclerosis (RHI-AF; Beta = 2.01, [95% CI 2.69–20.81]; RHI-CCS; Beta = 2.19, [95% CI 2.49–32.10]) was more common in RHI groups from their controls. Further, logistic regressions found that higher global mIIS correlated with increased odds of dementia in only the RHI-AF group ($p = 0.02$), driven by white matter rarefaction ($\beta = 0.94$, [95% CI 1.66–4.00]) and hippocampal sclerosis ($\beta = 1.08$, [95% CI 1.35–6.42]). There were similar findings in RHI-CCS group for odds of dementia ($p = 0.048$), including white matter rarefaction ($\beta = 0.68$, [95% CI 1.22–3.21], $p = 0.05$). Overall, these results demonstrate that white matter rarefaction and hippocampal sclerosis are linked to RHI exposure across all types of contact sports. Further, these pathologies contribute to dementia independent of p-tau pathology in American football players.

Keywords Repetitive head impacts · Cerebrovascular disease · Hippocampal sclerosis · White matter rarefaction · Dementia

Introduction

Chronic traumatic encephalopathy (CTE) is a progressive brain disease associated with repetitive head impacts (RHIs), often incurred during contact and collision sports, military service, interpersonal violence, and other sources [40]. CTE can only be diagnosed postmortem and is characterized by the aggregation of phosphorylated-tau (p-tau) proteins in neurons around small blood vessels at the depths of the cortical sulci [12, 40]. Elucidating the specific clinical correlates of CTE is an area of ongoing investigation. The clinical syndrome of CTE, known as traumatic encephalopathy syndrome (TES), describes cognitive impairment and neurobehavioral dysregulation as core clinical features of the disease [35]. Supportive psychiatric features include anxiety, depression, apathy, and paranoia [35]. CTE p-tau pathology strongly correlates with the cognitive symptoms observed in CTE [7, 41], while the relationship between CTE p-tau pathology and neurobehavioral symptoms is less clear [7, 41]. In

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addition to symptom heterogeneity, there is variability in the age of symptom onset and course. Similar to other neurodegenerative diseases [55], the clinical heterogeneity could be explained by the mixed neuropathologies that often co-occur in the setting of RHI [5, 40]. Exposure to RHI can have a lasting impact on white matter (WM) and blood vessel integrity. This link is supported by in vivo fluid-attenuated inversion recovery (FLAIR) and diffusion tensor imaging (DTI) magnetic resonance imaging (MRI) studies among former contact and collision sport athletes, particularly American football players [6, 39, 65]. Immunoassay-based measurements of myelin and vascular proteins in autopsy cohorts of contact and collision sport athletes similarly relate exposure to RHI with myelin and vascular injury [2, 36]. Exposure to RHI may result in a wide range of WM and vascular pathologies independent of, synergistically, and/or in parallel to CTE that could explain the different symptom profiles.

Alosco et al. (2019) examined different types of WM and vascular pathologies in 180 former football players with autopsy-confirmed CTE [5] using data from the Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) brain bank. Greater years of football play, a proxy for the duration of exposure to RHI, was associated with worse WM rarefaction and increased neurofibrillary tangle (NFT) aggregates of p-tau in the dorsolateral frontal cortex (DLFC). WM rarefaction and NFTs were associated with increased odds of having antemortem dementia. Comparatively, while arteriolosclerosis did not correlate with the years of football play, it was associated with increased odds of having a dementia diagnosis [5]. That study was among the first to establish tau and non-tau pathologies, particularly WM and vascular injury, as pathological contributors to dementia in CTE. Other studies have since supported the associations between WM and vascular injury and clinical symptoms in people exposed to RHI [2].

The study by Alosco et al. (2019) and the broader literature on the association between RHI and WM and vascular neuropathologies did not include comparison groups, have an isolated focus on American football players, and/or have restricted pathological assessments. As a result of these limitations, it remains unclear if WM and vascular pathologies are more common in those exposed to RHI (across different sources) compared to those not exposed to RHI, and in the context of other neurodegenerative diseases. Moreover, while CTE p-tau pathology is associated with cognitive symptoms, similar to other neurodegenerative diseases like Alzheimer's disease (AD), vascular and WM changes also likely contribute to cognitive symptoms in RHI [2, 5, 6]. In fact, recent studies from our group showed that decreased myelin in the frontal lobes and WM rarefaction in individuals with RHI contribute to cognitive symptoms [2, 5]. However, no study to date has thoroughly examined the range of vascular/WM pathologies and its association with dementia in individuals with RHI.

The objective of this study was to comprehensively characterize vascular and WM pathologies in two groups of brain donors exposed to RHI: (1) American football players and (2) non-football contact and collision sport athletes. Each RHI group had its respective similarly aged and sex-matched comparison group of brain donors without RHI, many of whom had other types of neurodegenerative diseases. We compared the RHI and non-RHI groups across nine types of WM and vascular pathologies. We additionally investigated the contribution of these pathologies to dementia. We hypothesized that WM and vascular pathologies would be associated with RHI compared to non-RHI controls and that the presence of WM and vascular pathologies would increase the odds of a dementia diagnosis in this cohort.

Materials and methods

Study design

Our goal was to investigate the relationship between types of contact and collision sports (American Football versus other types of contact sports), neuropathology, and dementia outcomes. Therefore, our RHI cohort included athletes who came to autopsy, while our non-RHI controls included participants who denied RHI and came to autopsy. Participants included 79 deceased male American football (AF; RHI-AF) and 49 deceased male non-AF contact and collision sports (CCS; RHI-CCS) athletes from the UNITE brain bank [41, 63]. For each RHI group, we included a group of similarly aged (±5 years) male brain donors without RHI from the Boston University Alzheimer's Disease Research Center (BU ADRC) ($n=20$) and Framingham Heart Study (FHS) ($n=61$) brain banks. All procedures were approved by the Boston University Medical Campus and/or the Bedford VA Hospital institutional review board. Written informed consent was obtained from informants of brain donors and participants from the BU ADRC and FHS. A description of the methods for UNITE [5, 42], BU ADRC [18, 25, 44], and FHS [8, 62] can be found elsewhere, and we provide a brief overview here:

UNITE is designed to characterize the long-term clinical and neuropathological effects of RHI including but not limited to CTE. Brain donors are required to have a history of RHI from contact and collision sports, military service, physical violence or other sources. Symptomatic status is not part of the eligibility criteria. Brain donors are excluded for poor tissue quality. Brain donations are made by next of kin, referrals from medical examiners, the Concussion Legacy Foundation, or by the individuals prior to death. Comprehensive neuropathological evaluations are

conducted, blinded to clinical data. Brain donors are not followed prospectively during life. Therefore, semi-structured and unstructured interviews with informants of brain donors are conducted in addition to medical record review to ascertain a history of cognitive, behavioral, mood, functional, and motor symptoms.

The BU ADRC follows ~ 400+ older adults with and without cognitive impairment longitudinally. It is one of more than 30 Centers in the U.S. that is funded by the NIA that contributes harmonized data to the National Alzheimer's Coordinating Center to facilitate research on AD and related dementias. Participants are English speaking and have adequate vision and hearing. Each year, participants complete clinical history interviews, neuropsychological testing, and measures of activities of daily living. Participants are also asked for brain donation through their participation in the BU ADRC.

The FHS began in 1948 and is a longitudinal community-based study of the original 1948 cohort along with their children (generation 2) and grandchildren (Generation 3). A second cohort, OMNI1, was created in 1994 to expand the study to include a better representation of the ethnic and racial composition of the Framingham, MA community. While FHS is currently examining a third cohort, OMNI2, these individuals have not come to autopsy. Medical, physical, neurological, and laboratory examinations are completed every 2 years for the Generation 1 cohort, and approximately every 4 years for the Generation 2 and OMNI1 cohorts.

Brain donors and RHI status determination

All participants were required to be at least 50 years old at death to increase the likelihood of meaningful neuropathology and dementia presence [5, 40], and to facilitate similarly aged participants across the brain banks. For the BU ADRC, history of RHI was not routinely assessed until ~ 2018. However, informants of brain donors in the BU ADRC and FHS have been contacted to ascertain history of exposure to RHI. Informants completed the Boston University Repetitive Head Impact Exposure Assessment (BU-RHIEA) questionnaire to determine RHI status and related exposure variables [4, 13]. The BU-RHIEA asks participants, "Have you ever participated in organized sports, which includes membership on a team with scheduled practices and games (excluding pick-up or neighborhood games)?" If they select yes, the questionnaire proceeds to query the type of sport played and proxies for RHI. Subsequent questions about CCS play are asked regarding age of first exposure, years or seasons of play, and highest level of play (youth, high school, college, professional) [13]. If informants denied *any* history of CCS play, military enrollment, or physical violence resulting in head injury, brain donors were classified as non-RHI. If participation in CCS was endorsed, brain donors were classified into one of the RHI groups (RHI-AF or RHI-CCS) based on their primary sport, as determined by the sport they played the longest. The RHI-AF group included all brain donors who played football as their primary sport, whereas the RHI-CCS group included brain donors who identified their primary contact/collision sport to be non-football. Note that the RHI-CCS group was permitted to have a history of American football play, but play must have been less than 5 years, a level below when CTE is less likely to occur [35].

Our rationale for separating AF players from other CCS is due to the substantial differences in the type and extent of exposure in RHI across the individual sports. In AF, RHI exposure within and across players is relatively homogeneous, while less is known in non-AF CCS athletes. Our knowledge is also much more advanced on the late effects of AF compared to other CCS. By separating AF and non-AF CCS, it allows us to better understand the long-term effects of the other CCS independent of AF.

Neuropathological diagnoses

Neuropathological processing and evaluation methods follow established procedures and have been published elsewhere [5]. Neuropathologists (T.D.S., B.R.H., A.C.M.) were blinded to clinical data. The neuropathological diagnosis of CTE was made using the National Institutes of Neurological Disease and Stroke and National Institute of Biomedical Imaging and Bioengineering consensus panel criteria [12]. The pathognomonic lesion of CTE is defined as 'phosphorylated-tau aggregates in neurons, with or without glia tau in thorn-shaped astrocytes, at the depth of a cortical sulcus around a small blood vessel, in deeper cortical layers not restricted to subpial and superficial regions of the sulcus' [12]. CTE stage (0-IV) [40] and severity of neurofibrillary tangle (NFT) burden in the dorsolateral frontal cortex (DLFC; 0–3, with 0 denoting no NFTs and 3 indicating severe NFTs) served as semi-quantitative scales of phosphorylated-tau severity [5, 7]. The DLFC was selected because it is an initial site of phosphorylated-tau deposition in CTE that becomes severely affected with disease progression, is densely populated with tau aggregates, and is associated with dementia [5, 7] Studies from our group found that compared to participants with low DLFC NFT burden, those with high levels of DLFC NFT had increased odds of having a dementia [5, 7]. Therefore, this brain region was selected as a covariate. Other neurodegenerative diseases including Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), and Lewy Body disease (LBD) were diagnosed using established neuropathological diagnostic criteria [11].

Modified ischemic injury scale (mIIS): The mIIS was used as a global composite of WM and vascular injury [8]. The individual scores of various vascular and WM pathologies are combined to yield an overall mIIS score (possible

range: 0–17) that reflects the level of WM and vascular injury in the brain [8]. Unlike the original ischemic injury scale, cribriform was not included because it was not rated in more remote cases from our brain bank. The mIIS consists of 9 pathologies:

1. Chronic infarcts/lacunes [11, 16] (presence/absence): old small tissue cavities > 2 mm that result from an obstruction of blood flow, or infarction, in the brain.
2. Microinfarcts [59] (presence/absence): brain lesions (2 mm or less) caused by infarction.
3. Laminar Necrosis [32] (presence/absence): measure of neuronal loss and gliosis in the cortical mantle.
4. Cerebral microbleeds [32] (CMB; presence/absence): measures of lesions ranging from 2 to 10 mm that mark an accumulation of blood and hemosiderin in the brain.
5. Atherosclerosis [29, 32, 64] (0–3 score): resultant buildup of cholesterol/fats within the arteries, with intima thickening and monocyte recruitment.
6. Arteriolosclerosis [29, 64] (0–3 score): measure of hypertension-associated, hyaline thickening of arterioles.
7. White matter rarefaction [5] (WM rarefaction; 0–3 score): measure of WM integrity as defined by myelin loss, small blood vessel vacuolization, and increased density of reactive astrocytes.
8. Hippocampal sclerosis [47] (0–3 score): marked by gliosis and neuronal loss within the hippocampal regions, often seen in CA1, CA2, and subiculum, with greater involvement of CA4, and hilum in severe cases. Note that growing research shows transactive response DNA-binding protein of 43 kDa (TDP-43) to be the underlying cause of hippocampal sclerosis. However, the cause continues to be multifactorial and include vascular contributions [60]. Therefore, for this reason and because it was originally part of the IIS, we retained hippocampal sclerosis.
9. Cerebral amyloid angiopathy [29, 64] (CAA; 0–3 score): measure of Beta-amyloid accumulation within the parenchymal and/or leptomeningeal blood vessels.

Arteriolosclerosis, atherosclerosis, cerebral amyloid angiopathy, and WM rarefaction were rated on a semi-quantitative scale (0 = none, 3 = severe). Hippocampal sclerosis was rated as none (0), unilateral (1), bilateral (2), and present but laterality not assessed (3) in CA1 and/or subiculum. The remaining pathologies were rated as absent/present. WM rarefaction and arteriolosclerosis were assessed using slides stained with luxol fast blue and hematoxylin–eosin [11]. For both WM rarefaction and arteriolosclerosis, scoring was based on the evaluation of the subcortical WM in the middle frontal, inferior parietal, superior temporal, and occipital cortices, as well as deep WM of the basal ganglia. The presence or absence of infarcts, microinfarcts, and microbleeds was evaluated in the cerebral cortex, subcortical WM, deep WM, basal ganglia, brainstem, and cerebellum using hematoxylin–eosin stains. CAA was assessed using thioflavin-S-stained sections in the hippocampus, midfrontal cortex, inferior parietal cortex, and superior temporal gyrus [52]. Luxol fast blue with hematoxylin and eosin-stained hippocampal sections were used to generate quantifications for hippocampal sclerosis. Gross examination was used to determine atherosclerosis. Finally, laminar necrosis measurement was assessed via cellular loss in the cerebral cortex using hematoxylin–eosin stains.

Dementia diagnosis

Dementia diagnoses for participants were determined by diagnostic consensus conferences. In the UNITE study, informants complete structured and semi-structured interviews that probe the donor's cognitive, functional, behavioral, mood, and motor symptoms [42]. This information is presented to a multidisciplinary panel of clinicians who then adjudicate dementia diagnoses following the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) criteria. More information can be found in eMethods 2 of Alosco et al. [5]. Comparatively, the FHS collects medical and physical examinations, neurological and neuropsychological evaluations, and laboratory assessments from generations in families. A consensus panel reviews the information to determine a donor's dementia status [4]. For participants who were part of the BU ADRC, clinical and medical history interviews, neurological examinations, neuropsychological testing, and measures of functional independence were collected and used for adjudication during diagnostic consensus conference [4]. A total of 3 individuals in our study did not have a reported dementia status.

Statistical analyses

Statistical significance was defined by false-discovery rate (FDR)-adjusted (using the Benjamini–Hochberg procedure for primary analyses only) p value less than or equal to 0.05 for primary analyses (i.e., all analyses with each mIIS subcomponent as an outcome), and less than or equal to 0.05 for secondary analyses. Data analysis was completed with SAS version 9.4 (SAS Institute Inc) and SPSS (version 28) under the oversight of study co-author and biostatistician (YT).

The primary independent grouping variables included: (1) RHI-AF versus similarly aged male non-RHI controls, and (2) non-AF RHI-CCS athletes versus similarly aged non-RHI males. Models were performed separately for each group (each RHI group with their respective non-RHI control). Group differences for demographic factors and medical conditions were examined using independent sample t-tests

for continuous variables, Fisher's exact test, or Chi-squared ($\chi 2$) tests for categorical variables. In separate models, linear regression analyses tested the association between RHI status (predictor) and mIIS (outcome). Binary logistic regressions tested the association between RHI status (predictor) and each individual mIIS subcomponent (binarized to 0 or 1). Binary logistic regression also tested the association between global mIIS and the mIIS subcomponents and odds of having a dementia diagnosis. Sample sizes varied due to missing data across the standardized scales and model variables. All models were adjusted for age at death.

For statistically significant findings, we conducted secondary sensitivity analyses that controlled for additional medical conditions (diabetes, hypertension, myocardial infarction/coronary artery disease, and hypercholesterolemia). For statistically significant dementia outcome findings, secondary sensitivity analyses included semi-quantitative rating of tau in the DLFC, to control for the independent contribution of tau pathology on dementia. Post-hoc binary logistic regression models, controlling for age, also explored associations between the mIIS and CTE neuropathology (CTE status, CTE severity).

Results

Sample characteristics

Table 1 presents sample characteristics. T-tests, Fisher's exact test, and $\chi 2$ tests examined differences in demographic and medical variables between RHI groups (RHI-AF and RHI-CCS) versus non-RHI controls (Table 1). Average years of football play were 12.51 (standard deviation [SD] = 5.58). The RHI-CCS group was predominantly made up of boxers

Table 1 Sample demographics and medical conditions

	RHI-AF ($n=79$)	Non-RHI ($n=79$)	p value	RHI-CCS ($n=49$)	Non-RHI ($n=49$)	p value
Demographic and medical characteristics						
Age at time of death, mean (SD)	78.7 (11.0)	83.6 (10.9)	0.005	74.3 (10.2)	77.8 (9.83)	0.09
Race, Black % (n)	7.6 (6)	2.5 (2)	0.28	6.1 (3)	0.0	0.24
Education level (highest) % (n)			<0.001			0.28
No high school	0.0	3.8 (3)		2.0 (1)	2.0 (1)	
Some high school	0.0	3.8 (3)		4.1 (2)	2.0 (1)	
High school Diploma/GED	3.8 (3)	21.5 (17)		28.6 (14)	22.4 (11)	
Some college	13.9 (11)	11.4 (9)		24.5 (12)	6.1 (3)	
College degree	49.4 (39)	25.3 (20)		18.4 (9)	26.5 (13)	
More than college	2.5 (2)	11.4 (9)		4.1 (2)	14.3 (7)	
Graduate degree	30.4 (24)	11.4 (9)		18.4 (9)	14.3 (7)	
Missing % (n)	–	11.4 (9)		–	12.2 (6)	
MI/coronary artery disease			0.05			0.12
Yes % (n)	32.9 (26)	8.9 (7)		16.3 (8)	4.1 (2)	
Missing % (n)	1.3 (1)	46.8 (37)		14.3 (7)	36.7 (18)	
Hypertension			0.08			0.66
Yes % (n)	55.7 (44)	69.6 (55)		49.0 (24)	59.2 (29)	
Missing % (n)	3.8 (3)	2.5 (2)		12.2 (6)	2 (1)	
Hypercholesterolemia			0.003			0.11
Yes % (n)	43.0 (34)	65.8 (52)		38.8 (19)	63.3 (31)	
Missing % (n)	2.5 (2)	2.5 (2)		18.4 (9)	2 (1)	
Diabetes			0.05			0.61
Yes % (n)	22.8 (18)	11.4 (9)		16.3 (8)	14.3 (7)	
Missing % (n)	3.8 (3)	2.5 (2)		12.2 (6)	2 (1)	
Clinical diagnosis						
Dementia diagnosis			< .001			0.009
Yes % (n)	89.9 (71)	49.4 (39)		75.5 (37)	49.0 (24)	
Missing % (n)	1.3 (1)	1.3 (1)		–-	2.0 (1)	

The repetitive head impact (RHI) groups were age (±5 years) and sex-matched to the non-RHI control groups. RHI-AF = brain donors who reported American style football as their primary sport. RHI-CCS = brain donors who reported a non-football primary sport. *mIIS* modified ischemic injury scale, *MI* myocardial infarct. Ns denote number of participants with data for specific variable. T-tests were used to assess age and education level; Fisher's exact test was used for race, and all other analyses were employed using Pearson $\chi 2$

($n=16$, 32.7%; mean years of play = 14.31, SD = 9.3), ice hockey players ($n=15$, 30.6%; mean years of play = 24.20, SD = 9.8), and soccer players ($n=9$, 18.4%; mean years of play = 22.0, SD = 10.3). Primary sport (sport played the longest) for the remaining 9 participants included rugby ($n=2$), amateur wrestling ($n=4$), entertainment wrestling ($n=1$), lacrosse ($n=1$), and snow skiing ($n=1$, who also boxed). The RHI-CCS included people who played multiple CCS sports. Although we attempted to make the groups similar in age, non-RHI controls were 4.9 years older at time of death compared with the RHI-AF group ($p=0.005$), on average. The RHI-AF participants also had higher levels of education ($p<0.001$). There was no difference in race between groups. No significant differences between groups across any demographic variables (ps > 0.05) were found when comparing the RHI-CCS group to their respective non-RHI controls. While education was higher in the RHI-AF group, we did not have questionnaires to assess quality of education in this group, which is an obstacle faced by athletes and an important factor in dementia risk. Therefore, we did not control for education in our models.

The RHI-AF group was more likely to have a diagnosis of hypercholesterolemia ($p=0.003$), myocardial infarction/coronary artery disease ($p=0.05$), and diabetes ($p=0.05$) compared to their non-RHI control group (Table 1). There were no other statistically significant differences in medical conditions, including stroke or hypertension. The RHI-CCS group versus non-RHI controls did not display statistically significant differences in any medical conditions, including myocardial infarction/coronary artery disease, stroke, hypertension, and diabetes.

Neuropathology and dementia characteristics

RHI-AF. In the RHI-AF group, 11.4% ($n=9$) had CTE stage I/II and 72.1% ($n=57$) had CTE stage III/IV (Table 2). CTE pathology was not present in the non-RHI group. 32.9% ($n=26$) had LBD, and 32.9% ($n=26$) had AD in the RHI-AF participants. Comparatively, 22.8% ($n=18$) of the non-RHI counterparts had LBD and 36.7% ($n=29$) had AD. 13.9% ($n=11$) of the RHI-AF group had FTLD pathology, compared with 4.1% ($n=2$) in the non-RHI controls. 89.9% ($n=71$) of the RHI-AF group and 49.4% ($n=39$) of the non-RHI group had a dementia diagnosis by a consensus panel of experts (Table 1).

RHI-CCS. In the RHI-CCS group, 16.3% ($n=8$) had CTE stage I/II and 42.9% ($n=21$) had CTE stage III/IV. The non-RHI control group for the RHI-CCS did not have CTE. In the RHI-CCS group, 30.6% ($n=15$) had LBD and 34.7% ($n=17$) had AD pathology. Comparatively, 20.4% ($n=10$) of the non-RHI counterparts had LBD and 34.7% ($n=17$) had AD. 18.4% ($n=9$) of the RHI-CCS group had FTLD pathology compared to 2% ($n=1$) of non-RHI controls. 75.5% ($n=37$) of the RHI-CCS group and 49% ($n=24$) of the non-RHI group had a dementia diagnosis.

As mentioned in the Methods, hippocampal sclerosis can have TDP-43 and vascular causes, among others. In the RHI-AF versus non-RHI data set, hippocampal sclerosis was associated with hippocampal TDP-43 inclusions ($p<0.001$) and WM rarefaction ($p=0.047$), but not arteriolosclerosis. In the RHI-CCS versus non-RHI data set, hippocampal sclerosis was associated with hippocampal TDP-43 inclusions ($p<0.001$), trending towards significance with WM rarefaction ($p=0.08$), and was not associated with arteriolosclerosis.

RHI and modified ischemic injury scale

Two individuals in the non-RHI control group (for the RHI-CCS group) had missing mIIS information. A linear regression model with RHI (RHI-AF and RHI-CCS) vs non-RHI controls as the predictor and mIIS as the outcome, controlling for age was statistically significant for both RHI groups (RHI-AF; $R^2=28.7\%$, F (2, 150) = 30.1, $p<0.001$; RHI-CCS; $R^2=45.9\%$, F (2, 93) = 39.45, $p<0.001$) (Table 3; Supplemental Table 1 for sensitivity analysis). While each overall model was statistically significant, there was a main effect for the RHI-AF group only ($p=0.036$), where the RHI-AF group had higher mIIS scores compared to the non-RHI control group (Table 3). Classification of RHI status was no longer statistically significant (RHI-AF vs. non-RHI control, $p=0.24$; RHI-CCS vs non-RHI control, $p=0.21$) after medical conditions (myocardial infarction/coronary artery disease, hypertension, hypercholesterolemia, and diabetes) were added as covariates (Table S1). Sample size was reduced due to missingness of medical covariates. Effect size for RHI vs non-RHI was similar for the RHI-CCS analysis only.

We next examined RHI status in relation to mIIS subcomponents, controlling for age of death using a binary logistic regression model. Of the mIIS subcomponents, WM rarefaction (RHI-AF; Beta = 1.42, $padj=0.005$; RHI-CCS; Beta = 1.93, $padj=0.005$) and hippocampal sclerosis (RHI-AF; Beta = 2.01, $padj=0.005$; RHI-CCS; Beta = 2.19, $padj=0.005$) were the only statistically significant mIIS subcomponent for both RHI-AF and RHI-CCS groups (Table 4). The RHI groups had more severe WM rarefaction and hippocampal sclerosis compared to non-RHI controls (Table 2). See Supplemental Table 2 where all mIIS subcomponents remained statistically significant after inclusion of medical condition covariates.

Modified ischemic injury scale and dementia

Logistic regression examined the association between mIIS scores and dementia status, controlling for age of death.

Table 2 Sample neuropathology characteristics

	RHI-AF ($n=79$)	Non-RHI ($n=79$)	RHI-CCS ($n=49$)	Non-RHI ($n=49$)
mIIS total and components				
mIIS score, mean (SD)	6.6 (2.8)	6.3 (3.1)	6.17 (2.76)	6.02 (3.29)
Missing % (n)	–	–	4.1 (2)	–
White matter rarefaction, % (n)				
None	3.8 (3)	45.6 (36)	8.2 (4)	44.9 (22)
Mild	35.4 (28)	22.8 (18)	24.5 (12)	18.4 (9)
Moderate	46.8 (37)	25.3 (20)	38.8 (19)	26.5 (13)
Severe	11.4 (9)	6.3 (5)	22.4 (11)	10.2 (5)
Missing % (n)	2.5 (2)	–	6.1 (3)	–
Cerebral amyloid angiopathy % (n)				
None	40.5 (32)	20.3 (16)	46.9 (23)	28.6 (14)
Mild	25.3 (20)	41.8 (33)	28.6 (14)	30.6 (15)
Moderate	19.0 (15)	30.4 (24)	12.2 (6)	32.7 (16)
Severe	12.7 (10)	7.6 (6)	8.2 (4)	8.2 (4)
Missing % (n)	2.5 (2)	–	4.1 (2)	–
Infarct/lacune, % yes (n)	26.6 (21)	35.4 (28)	22.4 (11)	30.6 (15)
Missing % (n)	1.3 (1)	–	4.1 (2)	–
Microinfarct, % yes (n)	39.2 (31)	57.0 (45)	30.6 (15)	51.0 (25)
Missing % (n)	1.3 (1)	–	4.1 (2)	–
Atherosclerosis % (n)				
None	35.4 (28)	26.6 (21)	30.6 (15)	30.6 (15)
Mild	34.2 (27)	39.2 (31)	34.7 (17)	51 (25)
Moderate	16.5 (13)	21.5 (17)	16.3 (8)	8.2 (4)
Severe	11.4 (9)	12.7 (10)	12.2 (6)	10.2 (5)
Missing % (n)	2.5 (2)	–	6.1 (3)	–
Arteriolosclerosis % (n)				
None	13.9 (11)	11.4 (9)	12.2 (6)	12.2 (6)
Mild	12.7 (10)	21.5 (17)	30.6 (15)	24.5 (12)
Moderate	53.2 (42)	44.3 (35)	38.8 (19)	42.9 (21)
Severe	17.7 (14)	22.8 (18)	14.3 (7)	20.4 (10)
Missing % (n)	2.5 (2)	–	4.1 (2)	–
Cerebral microbleeds, % yes (n)	3.8 (3)	6.3 (5)	2.0 (1)	8.2 (4)
Missing % (n)	1.3 (1)	–	4.1 (2)	–
Hippocampal sclerosis % (n)				
None	68.4 (54)	88.6 (70)	59.2 (29)	87.8 (43)
Unilateral	0.0	3.8 (3)	0.0	4.1 (2)
Bilateral	10.1 (8)	1.3 (1)	12.2 (6)	2.0 (1)
Present but laterality not assessed	20.3 (16)	6.3 (5)	20.4 (10)	6.1 (3)
Missing % (n)	1.3 (1)	–	8.2 (4)	–
Laminar necrosis, % yes (n)	0.0	7.6 (6)	0.0	8.2 (4)
Missing % (n)	1.3 (1)	–	4.1 (2)	–
Neurodegenerative diseases				
Frontotemporal lobar degeneration-TDP-43				
% present (n)	9.0 (7)	4.1 (2)	17.0 (8)	0
Missing % (n)	1.3 (1)	–	4.1 (2)	–
Hippocampal TDP-43 inclusions				
% present (n)	46.1 (35)	14.3 (10)	34.0 (16)	12.2 (5)
Missing % (n)	3.8 (3)	11.4 (9)	4.1 (2)	16.3 (8)
Alzheimer's disease pathology, % yes (n)	32.9 (26)	36.7 (29)	34.7 (17)	34.7 (17)
Missing % (n)	1.3 (1)	–	10.2 (5)	–

Table 2 (continued)

	RHI-AF ($n=79$)	Non-RHI ($n=79$)	RHI-CCS ($n=49$)	Non-RHI ($n=49$)
Lewy bodies pathology, % yes (*n*)				
None	65.8 (52)	70.9 (56)	65.3 (32)	71.4 (35)
Brainstem predominant	13.9 (11)	8.9 (7)	10.2 (5)	6.1 (3)
Limbic/neocortical	19 (15)	13.9 (11)	20.4 (10)	14.3 (7)
Missing % (*n*)	1.3 (1)	6.3 (5)	4.1 (2)	8.2 (4)
CTE, % yes (*n*)	83.5 (66)	0.0	59.2 (29)	0.0
Missing % (*n*)	–	–	–	–
CTE stage, % yes (*n*)				
None	15.2 (12)	–	38.8 (20)	–
Stage I	6.3 (5)	–	6.1 (3)	–
Stage II	5.1 (4)	–	10.2 (5)	–
Stage III	39.2 (31)	–	14.3 (7)	–
Stage IV	32.9 (26)	–	28.6 (14)	–
Missing % (*n*)	1.3 (1)	–	–	–

The repetitive head impact (RHI) groups were age (±5 years) and sex-matched to the non-RHI control groups. RHI-AF = brain donors who reported American style football as their primary sport. RHI-CCS = brain donors who reported a non-football contact and collision sport as their primary sport and was made up of boxers, ice hockey players, soccer players, wrestlers, rugby players, and lacrosse players. TDP-43 = Transactive response DNA binding protein 43 kDa, *mIIS* = modified ischemic injury scale, *CTE* = chronic traumatic encephalopathy. Ns denote number of participants with data for specific variable

Table 3 Linear regression model (modified ischemic injury scale) ~ age of death + RHI vs non-RHI control

	RHI-AF vs. non-RHI control ($n=153$)				RHI-CCS vs. non-RHI control ($n=96$)			
Model 1	$R^2=0.270$, F (1, 151) = 54.5, $p<.001$				$R^2=0.440$, F (1, 94) = 73.4, $p<.001$			
Model 2	$R^2=0.290$, F (2, 150) = 30.1, $p<.001$				$R^2=0.460$, F (2, 93) = 39.4, $p<.001$			
Variable	Unstandardized Beta	SE	*p* value	95% CI	Unstandardized Beta	SE	*p* value	95% CI
Age of death	0.14	0.02	**<.001**	0.11–0.18	0.20	0.02	**<.001**	0.16–0.25
RHI vs non-RHI control	0.87	0.41	**.04**	0.06–1.68	0.88	0.47	0.06	0.05–1.80

Linear regression model with RHI (RHI-AF or RHI-CCS) versus non-RHI control as the predictor and mIIS as the continuous outcome, controlling for age of death. Model 1 denotes age of death as the only predictor in the model. Model 2 includes both age of death and RHI vs non-RHI controls as predictors.

SE = standard error, *CI* = confidence interval

Two separate analyses were completed: one combining mIIS in the RHI-AF group and their non-RHI controls (overall model 2, $p=0.04$) and another combining mIIS of the RHI-CCS group and their non-RHI controls (overall model 2, $p=0.002$). In the combined RHI-AF and non-RHI control group, mIIS was statistically significant (Beta = 0.18, $p=0.02$) and was able to classify dementia diagnosis with 70.9% accuracy (Table 5). Similarly, in the combined RHI-CCS and non-RHI control groups, mIIS was statistically significant (Beta = 0.21, $p=0.048$) and was able to classify dementia diagnosis with 70.5% accuracy. In a sensitivity analysis controlling for both age at death and semi-quantitative DLFC rating of tau, mIIS remained statistically significant for the RHI-AF vs non-RHI group only (RHI-AF, $n=146$; main effect for mIIS, Beta = 0.17, SE = 0.09, $p=0.05$; DLFC, Beta = 1.30, SE = 0.24, $p=<0.001$; RHI-CCS, $n=89$; main effect for mIIS, Beta = 0.17, SE = 0.12, $p=0.14$; DLFC, Beta = 1.04, SE = 0.25, $p=<0.001$).

For post-hoc analyses, we repeated the logistic regression analyses between mIIS score and dementia stratified by RHI status. For these analyses, emphasis is place on change in effect sizes given the sample size is significantly reduced. Overall, the effect sizes of mIIS on dementia for the RHI-AF (Beta = 0.19) and RHI-CCS (Beta = 0.29) were greater than those observed in the entire sample (above) and larger than the non-RHI controls (Beta = 0.11 for both control groups). Findings suggest that the association between mIIS and dementia was indeed driven by the RHI group.

We then investigated each mIIS subcomponent in relation to a dementia diagnosis, controlling for age of death. When

Table 4 Logistic regression (mIIS subcomponent) ~ age of death + (RHI vs. non-RHI controls)

	RHI-AF vs. non-RHI controls ($n=158$)					
	Beta	SE	Wald χ^2	p-value	Odds Ratio	95% CI
Infarct/lacune ($n=157$)	− 0.09	0.37	0.06	0.91	0.91	0.44–1.90
Microinfarct ($n=157$)	− 0.45	0.35	1.67	0.45	0.64	0.33–1.26
Atherosclerosis ($n=156$)	0.14	0.38	0.14	0.91	1.15	0.55–2.44
White matter rarefaction ($n=156$)	1.42	0.36	15.26	**0.005**	4.13	2.03–8.43
Arteriolosclerosis ($n=156$)	0.63	0.39	2.68	0.30	1.88	0.88–4.00
Cerebral amyloid angiopathy ($n=156$)	− 0.10	0.35	0.08	0.91	0.91	0.46–1.80
Cerebral microbleeds ($n=157$)	− 0.53	0.77	0.48	0.90	0.59	0.13–2.64
Hippocampal sclerosis ($n=157$)	2.01	0.52	14.87	**0.005**	7.48	2.69–20.81
Laminar necrosis ($n=157$)	− 18.43	4480.42	0.00	1.00	0.00	0.00
RHI-CCS vs. non-RHI controls ($n=98$)						
Infarct/lacune ($n=96$)	− 0.06	0.50	0.01	1.00	0.94	0.35–2.54
Microinfarct ($n=96$)	− 0.58	0.46	1.60	0.38	0.56	0.23–1.38
Atherosclerosis ($n=95$)	1.03	0.53	3.75	0.16	2.81	0.99–8.00
White matter rarefaction ($n=95$)	1.93	0.55	12.35	**0.005**	6.88	2.35–20.17
Arteriolosclerosis ($n=96$)	− 0.08	0.45	0.03	1.00	0.93	0.38–2.24
Cerebral amyloid angiopathy ($n=96$)	− 0.77	0.48	2.59	0.25	0.46	0.18–1.18
Cerebral microbleeds ($n=96$)	− 1.34	1.15	1.35	0.38	0.26	0.03–2.51
Hippocampal sclerosis ($n=94$)	2.19	0.65	11.29	**0.005**	8.94	2.49–32.10
Laminar necrosis ($n=96$)	− 18.28	5248.04	0.00	1.00	0.00	0.00

Logistic regression model with RHI (RHI-AF or RHI-CCS) versus non-RHI controls as the predictor and each mIIS component as the outcome, controlling for age of death. Each mIIS component was dichotomized to none-mild (0) or moderate to severe (1); hippocampal sclerosis was dichotomized to none-unilaterally present (0) and at minimum, unilateral (laterality not assessed), or bilateral (1). Ns denote number of participants with data for specific variable. *All p values are FDR corrected.*

SE = standard error, *CI* = confidence interval, χ^2 = Chi-square

Table 5 Logistic regression (dementia diagnosis [yes/no]) ~ age of death + mIIS

RHI-AF vs. non-RHI controls ($n=151$)								
Model 2	$\chi 2$ (2) = 6.25, $p=0.04$							
	Beta	SE	Wald χ^2	p value	Odds ratio	95% CI	-2 Log likelihood	% correct
mIIS	0.18	0.08	5.48	**0.02**	1.19	1.03–1.38	179.40	70.90
	RHI-CCS vs. non-RHI controls ($n=95$)							
Model 2	$\chi 2$ (2) = 12.67, $p=0.002$							
mIIS	0.21	0.11	3.90	**0.048**	1.23	1.00–1.52	112.37	70.50

Logistic regression with mIIS as the predictor and dementia diagnosis as the outcome variable, controlling for age of death in Model 2. SE = Standard Error. *CI* = confidence interval, χ^2 = Chi-squared test, *mIIS* = modified ischemic injury scale

combining the RHI-AF with their non-RHI controls, both WM rarefaction (Beta = 0.94, SE = 0.22, *padj* = 0.009) and hippocampal sclerosis (Beta = 1.08, SE = 0.40, *padj* = 0.03) were associated with increased odds for having dementia (see Table 6). There were no associations between a dementia diagnosis and any mIIS component in the RHI-CCS and non-RHI group, with the exception of WM rarefaction (Beta = 0.68, SE = 0.25 *padj* = 0.05). To determine whether these mIIS subcomponents contributed to a dementia diagnosis beyond DLFC p-tau burden, we conducted sensitivity analyses of WM rarefaction and hippocampal sclerosis controlling for age at death and DLFC p-tau burden. Both WM rarefaction (Beta = 1.29, SE = 0.30, $p = < 0.001$) and hippocampal sclerosis (Beta = 0.86, SE = 0.45, $p = 0.05$) remained statistically significant for the RHI-AF vs non-RHI group, and WM rarefaction (Beta = 0.72, SE = 0.35, $p = 0.04$) in the RHI-CCS vs non-RHI group. Note that Chi-square analyses also showed that WM rarefaction and hippocampal sclerosis were not associated with DLFC p-tau severity in the RHI-AF group (ps > 0.05). See Supplemental Table 3 for

Table 6 Logistic regression (dementia diagnosis [yes/no]) ~ age of death + mIIS subcomponent

RHI-AF vs. non-RHI controls ($n=158$)						
	Beta	Standard error	Wald χ^2	p value	Odds ratio	95% CI
Infarct/lacune ($n=155$)	0.27	0.41	0.43	0.71	1.31	0.59–2.94
Microinfarct ($n=155$)	− 0.20	0.38	0.29	0.71	0.82	0.39–1.71
Atherosclerosis ($n=154$)	0.07	0.20	0.13	0.71	1.10	0.73–1.58
White matter rarefaction ($n=154$)	0.94	0.22	18.01	**0.009**	2.56	1.66–4.00
Arteriolosclerosis ($n=154$)	− 0.09	0.21	0.18	0.71	0.92	0.61–1.38
Cerebral amyloid angiopathy ($n=154$)	0.13	0.19	0.44	0.71	1.14	0.78–1.65
Cerebral microbleeds ($n=155$)	− 0.91	0.84	1.17	0.71	0.40	0.08–2.09
Hippocampal sclerosis ($n=155$)	1.08	0.40	7.34	**0.03**	2.94	1.35–6.42
Laminar necrosis ($n=155$)	0.74	1.12	0.44	0.71	2.09	0.23–18.60
RHI-CCS vs. non-RHI controls ($n=98$)						
Infarct/lacune ($n=95$)	0.03	0.56	0.003	0.96	1.03	0.35–3.08
Microinfarct ($n=95$)	0.39	0.50	0.63	0.65	1.48	0.56–3.94
Atherosclerosis ($n=94$)	0.25	0.28	0.83	0.65	1.29	0.75–2.22
White matter rarefaction ($n=94$)	0.68	0.25	7.62	**0.05**	1.98	1.22–3.21
Arteriolosclerosis ($n=95$)	− 0.18	0.28	0.41	0.67	0.84	0.48–1.45
Cerebral amyloid angiopathy ($n=95$)	0.35	0.25	1.86	0.38	1.41	0.86–2.32
Cerebral microbleeds ($n=95$)	− 2.11	1.26	2.81	0.27	0.12	0.01–1.43
Hippocampal sclerosis ($n=93$)	0.49	0.27	3.42	0.27	1.64	0.97–2.77
Laminar necrosis ($n=95$)	− 0.21	1.22	0.31	0.96	0.81	0.07–8.74

Logistic regression with mIIS predicting dementia diagnosis (outcome variable) and controlling for age of death. *All p-values are FDR corrected*. *SE* = standard error, *CI* = confidence interval, χ^2 = Chi-squared test

other sensitivity analyses with inclusion of medical conditions, where global mIIS, WM rarefaction, and hippocampal sclerosis all survived their respective models for the RHI-AF group and WM rarefaction for the RHI-CCS group.

Post-hoc: modified ischemic injury scale and CTE neuropathology

mIIS scores were not associated with CTE status or CTE severity (high versus low) in the RHI-AF or RHI-CCS groups (all ps > 0.05).

Discussion

This study aimed to characterize WM and vascular neuropathologies in brain donors with and without different RHI types and test their relationship to dementia status (see Fig. 1). Our groups of interest included both AF players and non-AF CCS athletes. When comparing the RHI-AF group to their respective controls, higher global mIIS differentiated those with and without RHI. WM rarefaction and hippocampal sclerosis emerged as the pathologies that best distinguished these groups. Additionally, higher mIIS was associated with increased odds of having a dementia diagnosis in both RHI-AF and non-RHI control group, even when controlling for p-tau pathology in the DLFC, with WM rarefaction and hippocampal sclerosis driving the effects. When comparing RHI-CCS group to their similarly aged and male-matched non-RHI controls, there was no group difference in the mIIS ($p=0.06$). However, WM rarefaction and hippocampal sclerosis in isolation did distinguish RHI-CCS from their non-RHI counterparts. Higher global mIIS was also associated with increased odds of having a dementia diagnosis in the RHI-CCS group and their controls. Importantly, both WM rarefaction and hippocampal sclerosis remained statistically significant in both RHI-AF and RHI-CCS groups, even when controlling for medical conditions. Overall, these results demonstrate that WM rarefaction and hippocampal sclerosis are linked to RHI exposure across all types of contact sports. Further, mIIS contributes to dementia independent of p-tau pathology in the DLFC in American football players. Nonetheless, association between RHI-AF and mIIS did not survive analysis when other medical conditions were included.

Our study expands on previous research on the association between RHI and WM and vascular injury [2, 5, 6, 39] through the inclusion of a non-RHI comparison, many of whom had other neurodegenerative diseases. In addition, the current study examined non-AF CCS athletes, an understudied group, and indeed observed that, similar to the RHI-AF group, WM rarefaction was more severe compared to their

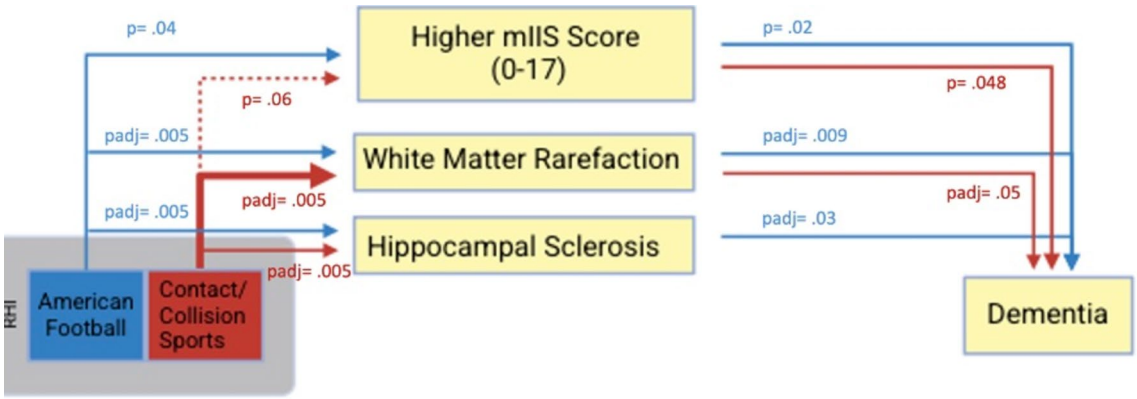

Fig. 1 Conceptual summary of findings. Separate regression models tested the association between mIIS and dementia in older deceased individuals exposed to repetitive head impacts, separated by type of sport play (American Football [AF] and contact and collision sports [CCS]). This figure provides an illustrative conceptual summary of the primary significant findings. Each solid path shown is significant at a p-value less than or equal to 0.05 (FDR-correction depicted with 'padj'), with thicker lines reflecting higher unstandardized beta estimates. Dotted lines depict p-values that may be trending towards significance. WM rarefaction was dichotomized to none-mild (0) or moderate to severe (1); hippocampal sclerosis was dichotomized to none-unilaterally present (0) and at minimum, unilateral (laterality not assessed), or bilateral (1). Models are controlled for age at death. padj = FDR-corrected p-value

non-RHI counterparts. In fact, the strength of WM rarefaction was greater in the CCS group vs non-RHI controls (Unstandardized Beta = 1.93) compared to the AF group vs non-RHI controls (unstandardized Beta = 1.42). Our findings thereby add to the extant literature by demonstrating that RHI-CCS, similar to RHI-AF with proposed more heterogenous levels of RHI exposures [5, 13], still incur WM loss that is potentially due to RHI. These results align with other neuropathological studies showing WM rarefaction, including axonal loss and astrogliosis in the dorsolateral prefrontal cortex and gray-WM junction in those with RHI/TBI, regardless of a CTE diagnosis [9, 31, 34]. Therefore, it is possible that dysregulation within the gray-WM junction, likely including u-fibers, as well as axonal loss, together elicit disrupted or disconnected cortico-cortical networks that might result in cognitive and behavioral symptoms. This disruption/disconnection has been shown in 'frontal-subcortical' syndrome, where psychomotor speed and executive functions are impaired, accompanied by mood symptoms such as depression [6, 37]. Importantly, the same symptoms are frequently observed in TES, the clinical syndrome of CTE [35].

Hippocampal sclerosis was more severe in both RHI groups compared to their controls and was associated with antemortem dementia in the RHI-AF group. Previous studies have also shown an association between RHI and hippocampal sclerosis [51]. To our knowledge, our study is the first to confirm a higher prevalence of hippocampal sclerosis in RHI when compared to similarly aged non-RHI male controls with various neurodegenerative diseases. Hippocampal sclerosis has been linked to pathological changes in the context of increased age (e.g., limbic-predominant age-related TDP-43 encephalopathy; LATE) [46] and other neurological disorders such as epilepsy [66] and FTLD [57], and is mainly associated with an amnestic profile. Our cohort was comprised of relatively younger individuals (RHI groups were on average < 80 years of age) compared to those with LATE; therefore our findings are likely influenced by the nature of RHI, as described by a recent paper from our group [51]. In that study, a cohort of 401 individuals with a history of RHI and CTE at autopsy was compared to 33 individuals with hippocampal sclerosis aging without CTE. Hippocampal sclerosis and TDP-43 pathology were common in CTE (hippocampal sclerosis, 23.4%; TDP-43 inclusions, 43.3%) and linked to duration of play [51]. An overall model found that age, hippocampal TDP-43 inclusions and CTE stage ($p < 0.001$) were related to hippocampal sclerosis, demonstrating a strong link between hippocampal sclerosis in CTE and TDP-43 pathology. Limbic and frontal TDP-43 were much higher in the CTE/hippocampal sclerosis group (41.5%) compared to controls (18.2%), despite a lower age of death in the experimental group. These neuroanatomical regions are often associated with impairments in executive functions and memory and are often the site of neurobehavioral dysregulation commonly observed in people with RHI [35]. Therefore, it is likely that our measure of hippocampal sclerosis is tightly linked to TDP-43 pathology and is an area of further exploration in relation to mIIS.

Hippocampal sclerosis has also been linked to small blood vessel changes in older individuals [48, 49, 60] as well as younger individuals with FTLD, many of whom have TDP-43 as the underlying pathology [57]. It is plausible that RHI may damage blood vessels in the hippocampus, which appear particularly vulnerable to hypoperfusion/

hypoxia [61], thus leading to hippocampal sclerosis. CA1 neurons appear to be vulnerable to ischemic conditions [57] and chronic vascular conditions can modulate perivascular TDP-43 pathology [26], therefore, demonstrating how hippocampal sclerosis can have different causes, including vascular changes, TDP-43 and a feed-forward process occurring in these two pathologies. Given this information, we do not fully understand the etiology of hippocampal sclerosis in our cohort, and it is likely multifactorial.

Our design is unique in that we have similar-aged non-RHI males who came to autopsy. These individuals had a variety of neurodegenerative diseases, including AD, FTLD, and LBD, and may have had increased levels of cerebrovascular disease [22, 23, 27, 30, 56]. Therefore, our results stress that RHI can lead to WM and vascular injury, above and beyond what is typically observed in other neuropathological diseases. One possible mechanism may be that microvascular injury or damage to the neurovascular unit increases permeability and neuroinflammation acutely following RHI and, with persistence of permeability, CTE pathogenesis and progression follow [36]. Further, serum leakage into the parenchyma would likely activate microglia and reactive astrocytes, consistent with our findings of WM rarefaction as a primary factor in RHI [45, 53, 54]. Longitudinal studies examining WM injury, especially in younger individuals with RHI, will help elucidate our understanding of the interplay between RHI and cerebrovascular disease, disease course, and treatment options.

P-tau pathology has been commonly described in people with high exposure to RHI. It contributes to some, but not all, clinical symptoms of CTE, with a particular disconnect between p-tau and neurobehavioral dysregulation [7, 41]. Regarding cognition, multiple studies describe the importance of vascular contributions to cognitive impairment and dementia [17, 19, 22–24]. Given the prevalence of cerebrovascular disease in AD and frontotemporal dementia (FTD), the clinical syndrome associated with FTLD [17, 19, 22–24], the pathological similarities (i.e., tau) between these diseases, and the clinical symptoms seen throughout life, it may be the case that WM and vascular injury play a significant role in dementia outcome for those with RHI. Drawing from research on other neurodegenerative diseases, like AD, there is evidence of an association between p-tau and cerebral small vessel disease, including hypoperfusion promoting tau pathology and, in turn, tau pathology disrupting vessel architecture that worsens neurodegeneration [15, 21, 33, 38] and cognitive impairment [22, 38]. In our study, post-hoc analyses revealed no association between severity of p-tau in the DLFC and WM rarefaction or between mIIS scores and CTE neuropathology. Additional research is needed to elucidate the relationships between WM and vascular injury and p-tau pathology and their unique contribution to clinical outcomes. Finally, the explanation for why specific WM and vascular injuries were associated with dementia in the RHI-AF group but not the RHI-CCS group may be related to the smaller sample size in our RHI-CCS group. Further exploration is needed.

This study is not without limitations. First, our study included males only. Therefore, our findings are not generalizable to females with RHI. Selection biases associated with brain donation should be considered as another limitation as individuals with RHI exposure and symptoms are more likely to donate to the UNITE brain bank. Similarly, our non-RHI group was comprised of individuals spanning across two separate cohorts with different inclusion/exclusion criteria, target population, and dementia rates. Further, mIIS and tau pathology in DLFC were based on a semi-quantitative approach that restricts the range of pathology. Future studies with quantitative measures of other neurodegenerative pathologies may further elucidate the unique contribution of mIIS in RHI. In addition, despite our findings showing an association between mIIS and dementia outcome controlling for p-tau pathology in the DLFC, and lack of association between CTE stage and severity with mIIS score, it remains possible that CTE could be driving both mIIS and dementia outcome given the prevalence of CTE in our cohort (72.1% with Stage III\IV in the RHI-AF group). Some of our results were no longer statistically significant in our sensitivity analysis, likely due to low power given the relatively equivalent effect sizes as well as statistically significant differences in myocardial infarction/CAD, diabetes, and hypercholesterolemia between groups. The differences in cardiovascular disease between RHI versus non-RHI groups are not entirely clear, with conflicting reports of equal [43] and lower [10] mortality rates due to cardiovascular disease, as well as lower [58] and higher [1, 28] prevalence of cardiovascular diseases in professional athletes compared to non-athletes. When compared to professional athletes less prone to RHI (e.g., baseball), football players had significantly elevated cardiovascular mortality rates, perhaps hinting at a relationship between RHI and prevalence of cardiovascular disease [50]. Mortality and prevalence of cardiovascular disease in professional athletes is also influenced by factors such as age, body mass index and player position, thus complicating rates [10, 28]. We acknowledge that this study is unable to disentangle the relationship between RHI and cardiovascular disease as well as whether RHI-related mIIS is independent of other cardiovascular conditions. While effects of our findings were similar with the inclusion of medical conditions as covariates, larger epidemiological studies are needed to address these important questions. Future studies should also consider matching groups based on medical conditions that can modulate vascular/WM changes. Finally, we did not examine neurobehavioral or cognitive symptoms in this study, and dementia diagnosis was based on retrospective interviews with families for UNITE. While the focus of this

study was on dementia outcome, it is possible that WM and vascular injuries are also associated with neurobehavioral symptoms, another clinical symptom often seen in individuals with RHI, and should be a target of additional research.

Conclusion

In conclusion, we show that both WM rarefaction and hippocampal sclerosis were more common in people exposed to RHI from AF and other CCS compared to similarly aged individuals and sex-matched non-RHI controls of individuals who had varying amounts of neurodegenerative disease pathologies. Similarly, we found an association between WM rarefaction, hippocampal sclerosis, and antemortem dementia status in the RHI groups. Our findings stress exposure to RHI as a risk factor for mixed neuropathologies, particularly WM and vascular injury that contribute to clinical symptoms.

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Declarations

Conflict of interest The authors declare no competing interests.

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