

Longitudinal change in regional brain volumes with exposure to repetitive head impacts

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Abstract

Objective

This study tests the hypothesis that certain MRI-based regional brain volumes will show reductions over time in a cohort exposed to repetitive head impacts (RHI).

Methods

Participants were drawn from the Professional Fighters Brain Health Study, a longitudinal observational study of professional fighters and controls. Participants underwent annual 3T brain MRI, computerized cognitive testing, and blood sampling for determination of neurofilament light (NfL) and tau levels. Yearly change in regional brain volume was calculated for several predetermined cortical and subcortical brain volumes and the relationship with NfL and tau levels determined.

Results

A total of 204 participants who had at least 2 assessments were included in the analyses. Compared to controls, the active boxers had an average yearly rate of decline in volumes of the left thalamus ($102.3 \text{ mm}^3/\text{y}$ [$p = 0.0004$], mid anterior corpus callosum ($10.2 \text{ mm}^3/\text{y}$ [$p = 0.018$]), and central corpus callosum ($16.5 \text{ mm}^3/\text{y}$ [$p = <0.0001$]). Retired boxers showed the most significant volumetric declines compared to controls in left ($32.1 \text{ mm}^3/\text{y}$ [$p = 0.002$]) and right ($30.6 \text{ mm}^3/\text{y}$ [$p = 0.008$]) amygdala and right hippocampus ($33.5 \text{ mm}^3/\text{y}$ [$p = 0.01$]). Higher baseline NfL levels were associated with greater volumetric decline in left hippocampus and mid anterior corpus callosum.

Conclusion

Volumetric loss in different brain regions may reflect different pathologic processes at different times among individuals exposed to RHI.

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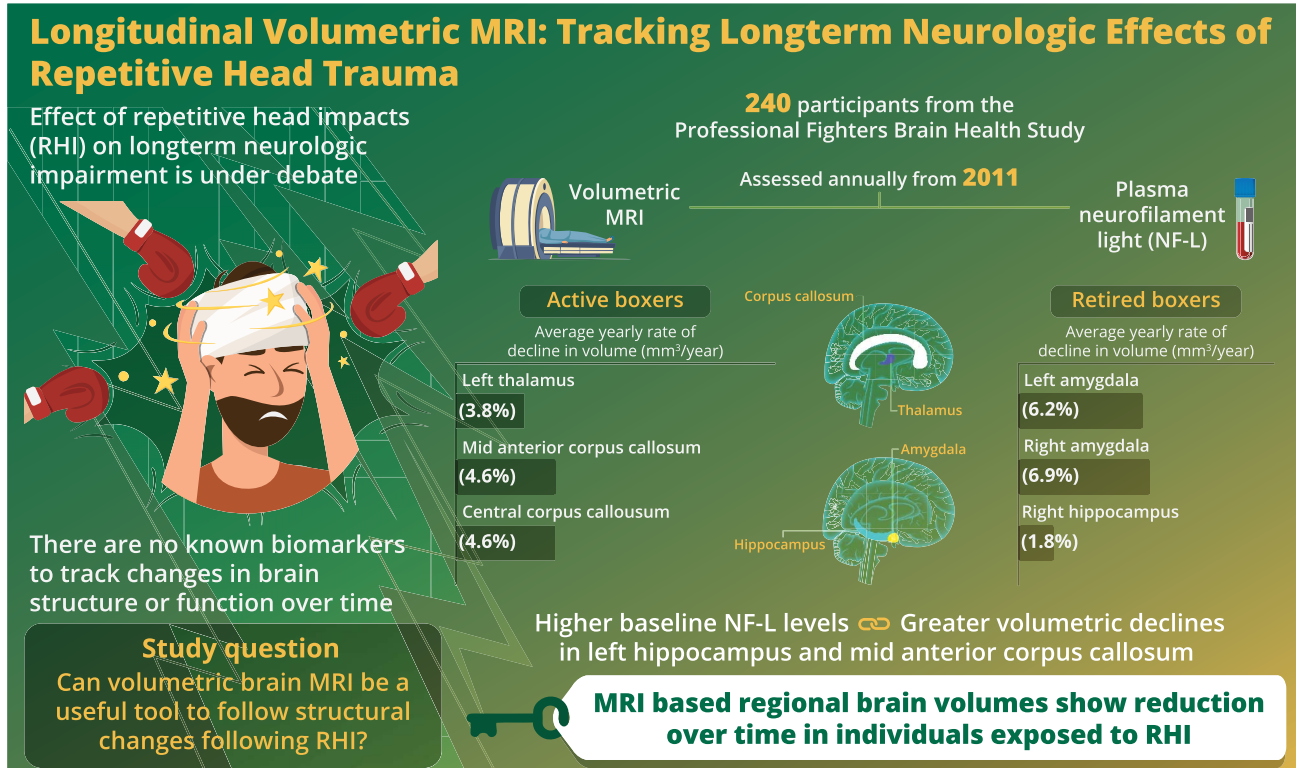
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Glossary

AD = Alzheimer disease; CTE = chronic traumatic encephalopathy; MMA = mixed martial arts; NfL = neurofilament light; PFBHS = Professional Fighters Brain Health Study; RHI = repetitive head impacts; SNR = signal-to-noise ratio.



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The relationship between high levels of exposure to repetitive head impacts (RHI) and long-term neurologic impairment has garnered much attention and debate in both the medical and lay literature. How often this exposure, or which level or severity of exposure, leads to a progressive neurodegenerative condition such as chronic traumatic encephalopathy (CTE) is unknown (figure 1).^{1,2} Hindering our ability to determine the natural history of exposure to RHI is the lack of biomarkers that can track change in brain structure and function over time.

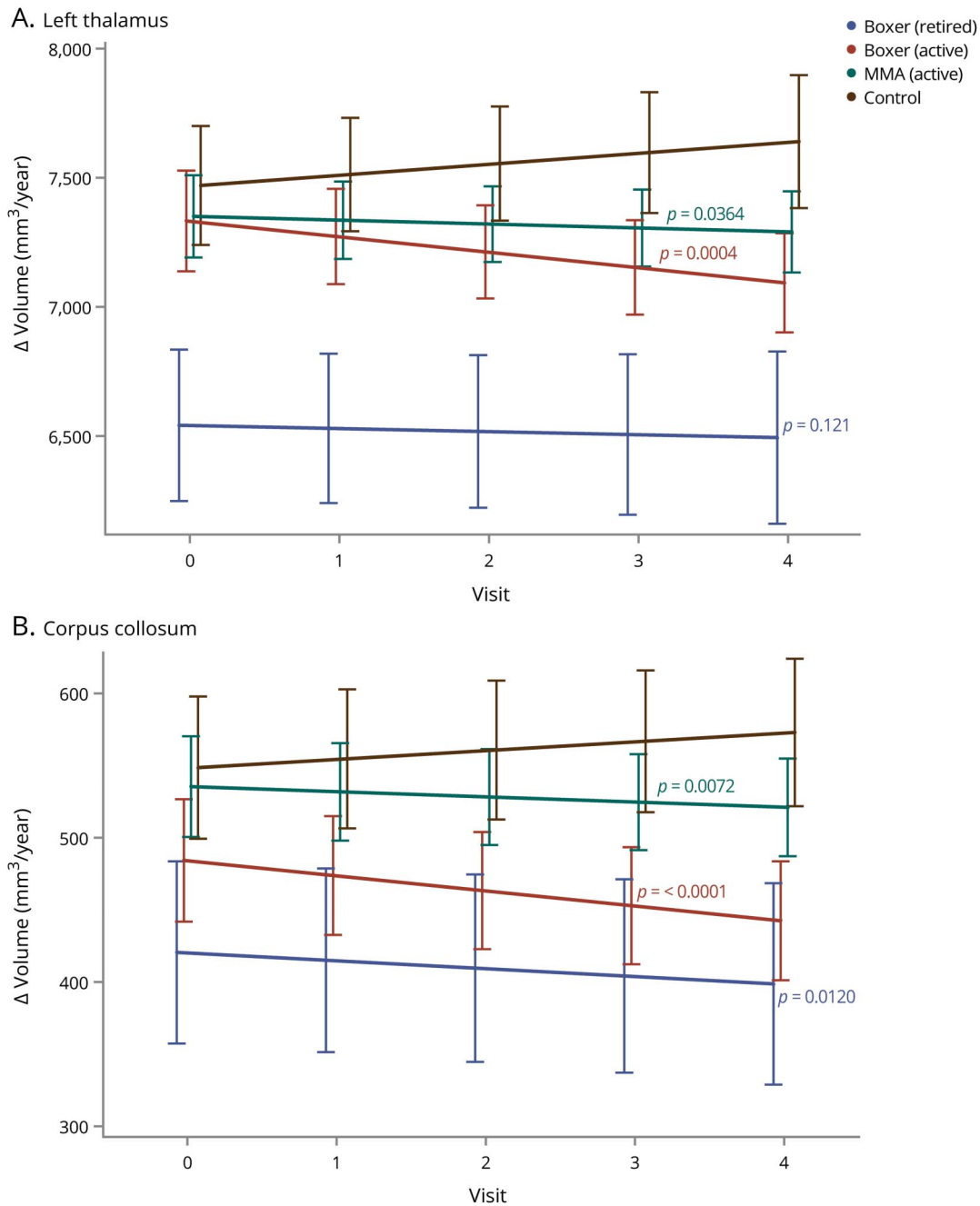
Previous work has suggested that monitoring regional brain volumes through MRI may serve as a potential tool to recognize and follow structural brain changes.³ Measurement of hippocampal volumes has been well-studied in Alzheimer disease (AD) and is commonly used as a secondary outcome measure in AD clinical trials.⁴ Similarly, we and others have reported associations between volumes of certain brain regions and exposure to RHI as well as clinical outcomes in cross-sectional studies.^{5,6} Less is known about using volumetric MRI techniques in a longitudinal manner in those exposed to RHI.

The Professional Fighters Brain Health Study (PFBHS) is a longitudinal study of professional fighters intended to better understand the long-term effects of exposure to RHI. Utilizing this cohort, where MRI is completed annually, we test the hypothesis that certain regional brain volumes will show reductions over time in those exposed to RHI and explore factors that are associated with or modify the effect of those reductions.

Methods

Participants in the PFBHS consist of active and retired professional fighters (boxers and mixed martial arts [MMA] fighters), along with age- and education-matched controls. Active fighters were required to have at least 1 professional fight within 2 years of enrollment and be training with the intent to compete; information about the study was disseminated by the Nevada Athletic Commission, fight promoters, and local training facilities. Retired fighters were included if they had been boxers, had a minimum of 10 professional fights, had no sanctioned fights for at least 2 years, and did not intend to return to competition (there were too few retired MMA

Figure 1 Average yearly change in left thalamic and central corpus callosum (CC) volumes among retired fighters, active boxers, active mixed martial arts (MMA) fighters, and control group



Average yearly change in (A) left thalamic and (B) central CC volumes (mL/y) among retired fighters, active boxers, active MMA fighters, and control group.

fighters to include as a separate group). Control participants were recruited from outreach efforts in the community and could not have any history of neurologic disorders, head trauma, military service, or participation at a high school level or higher in a combat sport or a sport in which head trauma can be anticipated to occur, such as football, wrestling, hockey, rugby, soccer, or rodeo. Enrollment in the PFBHS began in 2011 and has been continuous since then. Each participant is seen on an annual basis, and for active fighters, not sooner than 45 days from a sanctioned fight. The PFBHS was approved by the

Cleveland Clinic Institutional Review Board and written informed consent was obtained from all participants. More detailed methods of recruitment and study procedures have been described previously.⁷

At baseline and each annual visit, a battery of tests and information are acquired including MRI brain, computerized cognitive testing, and exposure history. Participants answer questionnaires with the assistance of the study coordinator that collect information on demographics; educational

attainment; medical history including concurrent illnesses and prescribed medications; previous head trauma, both related and unrelated to athletic activities; and prior involvement in other contact sports. Number of professional fights was ascertained by review of commonly recognized databases (boxrec.com for boxers, sherdog.com for MMA fighters). Information on the amount of sparring the participant has engaged in, as well as whether there have been any concussions or head injuries within the 2 weeks prior to the study visit, is obtained through a structured questionnaire.

Cognitive function was assessed by 2 computerized cognitive test batteries. One consists of 4 subtests of the CNS Vital Signs including verbal memory, symbol digit coding, Stroop, and a finger-tapping test. CNS Vital Signs offers robust and reliable measurements of cognition, which are computerized, but are supervised by a technician.⁸ Results from these tests are used to make up scores in various clinical domains: verbal memory, processing speed, psychomotor speed, and reaction time. The other cognitive assessment is the C3, an iPad-based test that includes symbol digit, Trails A and B, simple and choice reaction time, and a balance measure.⁹

A high-resolution T1-weighted anatomical MRI was obtained on all fighters at each visit. A 3T MRI scanner (Siemens [Munich, Germany] Verio from April 2011 through October 2015 and Siemens Skyra from December 2016 to the present) with a 32-channel head coil was used to acquire structural 3D T1-weighted magnetization-prepared rapid acquisition gradient echo images (repetition time ms/echo time ms, 2,300/2.98; resolution, $1 \times 1 \times 1.2 \text{ mm}^3$). Only data with high-quality cortical reconstruction from FreeSurfer were utilized. This was ensured through a quality control procedure outlined by FreeSurfer's quality analysis tools (surfer.nmr.mgh.harvard.edu/fswiki/QATools), and only data with signal-to-noise ratio (SNR) of at least 16 were included in this study (surfer.nmr.mgh.harvard.edu/pub/dist/freesurfer/tutorial_packages/OSX/freesurfer/bin/wm-anat-snr). This SNR number was decided upon based on our observation from randomly selected participants that the segmented images with an SNR of 16 or above yielded maps that require no operator-controlled edits. Therefore, no manual edits were performed.

Volumes of the hippocampus and amygdala and subcortical gray matter including thalamus, caudate, and putamen, along with corpus callosum, were calculated using the automated full brain segmentation process in Freesurfer v.6 software. These regions have been shown in pathologic series and our prior work to be affected in those with extensive RHI.^{5,10} The volumes of each structure were measured in both hemispheres separately and adjusted for total intracranial volume.

Blood samples were collected annually in EDTA tubes and centrifuged at 3,200 rpm for 10 minutes to separate plasma from blood cells. The supernatant was aliquoted in 2 mL portions that were immediately frozen and stored at -80° pending analysis. Plasma tau and neurofilament light (NfL)

concentrations were measured using ultrasensitive single molecule array (Simoa) assays as previously described in detail.^{11,12} The lower limits of quantification for tau and NfL were 1.22 and 6.9 pg/mL, respectively, and intra-assay coefficients of variation were just above or below 10%. All analyses were performed by board-certified laboratory technicians who were blinded to clinical data.

Statistical analysis

In the table for the characteristics of the study cohort (table 1), mean and SD were computed for continuous variables (e.g., age, number of fights) and the number of events and proportion were calculated for dichotomous variables. Analysis of variance was used to compare the group difference for each continuous variable, nonparametric Kruskal-Wallis test was used for comparing groups when the outcome is ordinal, and the χ^2 test was used when the outcome is dichotomized.

Linear mixed models were used for the repeated measurements. When the 4 groups (retired boxer, active boxer, active MMA, and control) were compared with regards to each brain volume, the main effects were visit, group, and their interaction, after adjustment for age, education years, ethnicity, scanner type, and total intracranial volume. The variable scanner type was added in the model because the scanner was upgraded during the study. When only the fighters were included in the model, the number of fights was added as another covariate.

Yearly percentage change of volume for each brain region was determined by calculating the slope of all MRI time points; this value was utilized for all the analyses. However, to categorize the active fighters by rate of volume decline of the caudate, only the volume at the first visit and that at the last visit from the same scanner was used. A 1.5% yearly percentage decrease was considered as the cutoff to separate the participants into 2 subgroups: a stable group with the decreasing rate being less than the cutoff and a declining group with the decreasing rate being more than 1.5% yearly. The repeated cognitive measurements were assessed in linear mixed models with the main effects of group (decliner or not), visit, and their interaction, adjusted by age, education years, ethnicity, scanner type, and number of fights.

All these tests were 2-sided at α level of 0.05. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC).

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

In total, 204 participants who had at least 2 assessments and complete data for those visits were included in the analyses.

Table 1 Characteristics of the study cohort

	Boxer, retired	Boxer, active	MMA, active	Control	p Value
No.	23 (11)	50 (25)	100 (49)	31 (15)	
Age, y	45.48 (9.97)	28.56 (6.04)	29.19 (4.81)	30.55 (10.53)	<0.0001
Education, y	12 (12–15)	12 (12–14)	14 (12–16)	14 (12–17)	<0.0001
No. of fights	38 (23–56)	5 (0–18)	7.5 (1–16.5)	0	<0.0001
Years of fighting	10.47 (5.71)	4.89 (5.08)	4.89 (4.44)	0	<0.0001
Years of follow-up	2.61 (1.53)	3.02 (1.63)	2.56 (1.58)	2.29 (1.37)	0.1915
Male	22 (96)	48 (96)	90 (90)	26 (84)	0.2360
Race					0.0588
African American	7 (30)	13 (26)	25 (25)	5 (16)	
White	13 (57)	22 (44)	63 (64)	22 (71)	
Asian	0 (0)	2 (4)	4 (4)	2 (6)	
Other	3 (13)	13 (26)	7 (7)	2 (6)	

Abbreviation: MMA = mixed martial arts.
For ordinal outcomes (education year and number of fights), median (interquartile range) are reported. Other values are n (%).

Characteristics of the study group are shown in table 1. As expected, the retired boxers were older and had more professional fights and years of fighting. Demographics for active boxers and MMA fighters were similar. The controls were matched for age but tended to have a higher level of education and were more likely to be Caucasian.

Compared to controls, the active boxers had a notable average yearly rate of decline in volumes of the left thalamus (102.3 mm³/y [*p* = 0.0004]), mid anterior corpus callosum (10.2 mm³/y [*p* = 0.018]), and central corpus callosum (16.5 mm³/y [*p* < 0.0001]) (figure 1). For the MMA fighters, the pattern was similar but to a slightly lesser extent in left thalamic decline (57.5 mm³/y [*p* = 0.036]) and central corpus callosum (9.7 mm³/y [*p* = 0.007]). Retired boxers, on the other hand, showed the most significant volumetric declines compared to controls in left (32.1 mm³/y [*p* = 0.002]) and right (30.6 mm³/y [*p* = 0.008]) amygdala and right hippocampus (33.5 mm³/y [*p* = 0.01]). Several other structures showed a trend toward decreasing volumes compared to controls (table 2).

To assess whether degree and timing of exposure to RHI was influencing the pattern of regional volumetric decline seen between active and retired fighters, we compared the different fighter groups, controlling for number of professional fights. Among types of fighters, with active MMA fighters as the reference, active boxers showed greater yearly volumetric decline in left thalamus (44.7 mm³/y [*p* = 0.0211]), right hippocampus (19.1 mm³/y [*p* = 0.0067]), and central (7.17 mm³/y [*p* = 0.0053]), mid anterior (7.36 mm³/y [*p* = 0.0114]), and mid posterior corpus callosum (6.30 mm³/y [*p* = 0.0007]); retired

fighters showed greater decline in left amygdala (27.4 mm³/y [*p* = 0.0011]), left hippocampus (32.7 mm³/y [*p* = 0.0055]), and right hippocampus (36.9 mm³/y [*p* = 0.0002]).

There were no significant differences in trajectory of cognitive test scores between controls and active or retired fighters at a group level. However, after separating the active fighters into those with and without yearly caudate volumetric decline as described above, one additional variable (dichotomized variable: decliner or nondecliner) was created and included in the repeated measures statistical model with all visits included. We found that decliners had significant yearly worsening in both Trails A (2.67 s/y [*p* = 0.004]) and Trails B (4.72 s/y [*p* = 0.015]) tests (figure 2). No differences in symbol digit or simple or choice reaction time tests were seen between decliners and nondecliners.

Higher baseline NfL levels were associated with greater volumetric decline in left hippocampus (33.2 mm³/y, *p* < 0.001) and mid anterior corpus callosum (7.68 mm³, *p* = 0.015), with a trend seen in the left amygdala, right thalamus, and mid corpus callosum. Higher baseline tau levels were not correlated with regional volumetric changes. Moreover, there was no difference in change over time in plasma tau or NfL levels between the active fighter decliners and nondecliners.

Discussion

Identifying biomarkers that can track change in brain structure or function over time in those exposed to RHI may have important implications prognostically and in clinical trials as a means to select cohorts or as a possible outcome measure.

Table 2 Average regional yearly rate of volume change in mm³

Region	Baseline, total volume of control	Yearly rate of change from the fitted statistical model			
		Control	Retired boxer	Active boxer	Active MMA
Left thalamus	3,773.0	42.5	-96.8 (0.121)	-144.8 (0.001)	-100.0 (0.036)
Left putamen	2,853.1	-26	38.3 (0.605)	60.9 (0.077)	58.7 (0.081)
Left hippocampus	2,282.5	-6.6	-18.7 (0.080)	4.9 (0.889)	14.0 (0.512)
Left amygdala	771.8	16.2	-48.2 (0.002)	-26.5 (0.231)	-21.2 (0.540)
Left caudate	1,446.3	-9.5	2.0 (0.465)	0.2(0.271)	6.1 (0.676)
Right thalamus	3,405.9	4.7	-16.9 (0.612)	-33.6 (0.149)	-9.8 (0.787)
Right putamen	3,163.2	13.8	-7.7 (0.814)	-17.5 (0.860)	-16.8 (0.881)
Right hippocampus	2,349.5	9.7	-43.2 (0.010)	-25.1 (0.152)	-6.0 (0.714)
Right amygdala	795.6	24.7	-55.3 (0.008)	-43.2 (0.051)	-43.0 (0.043)
Right caudate	1,164.3	3.7	-17.3 (0.302)	-22.5 (0.084)	-17.5 (0.183)
Anterior CC	285.1	-0.3	-6.7 (0.195)	-2.3 (0.558)	-4.1 (0.298)
Central CC	493.2	6.1	-17.6 (0.012)	-22.6 (<0.0001)	-15.8 (0.007)
Mid anterior CC	300.6	3.6	-10.3 (0.196)	-13.8 (0.018)	-6.7 (0.452)
Mid posterior CC	364.7	-5.9	10.1 (0.204)	3.0 (0.282)	9.0 (0.240)
Posterior CC	311.5	-5.4	4.3 (0.877)	10.5 (0.417)	7.1 (0.777)

Abbreviation: CC = corpus callosum; MMA = mixed martial arts.

p Values are presented in parentheses comparing each group with the control group. Estimated regional brain volumes are presented in the column for controls.

One potential modality that is already commercially available is MRI-based regional volumetric measures.¹³ This study examined longitudinal change in MRI volumes in a cohort of active and retired professional fighters. Among the active fighters, thalamic and corpus callosum volumes significantly declined over time compared to controls, whereas in the retired fighters, the amygdala and hippocampus were the structures that showed the most decline, controlling for age. Moreover, the group of fighters that had significant decline in caudate volume also demonstrated reduction in processing speed on a cognitive measure. Higher baseline NFL levels were associated with declining volumes in certain cortical and subcortical volumes.

Previous studies, including our own work, have reported differences compared to controls in thalamic and corpus callosum volumes in disorders that affect the white matter, including traumatic brain injury and multiple sclerosis.^{5,14–16} Animal studies of head trauma indicate that blows to the head can result in physical injury to axons.¹⁷ Because the thalamus has abundant afferent and efferent fibers, the progressive loss of volume seen may reflect Wallerian degeneration of the axons with subsequent neuronal dropout, though other mechanisms that may reduce thalamic volume are also possible.¹⁸

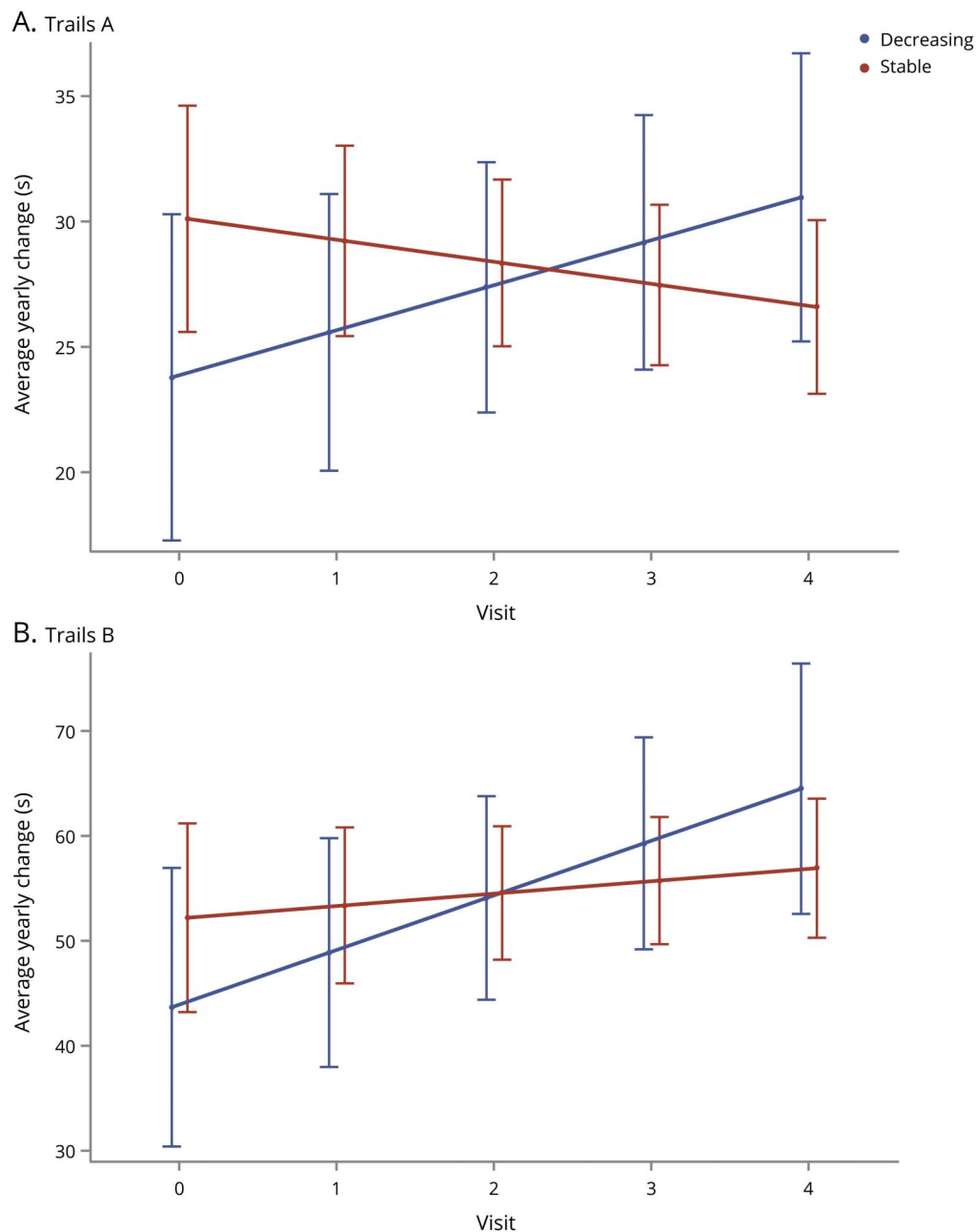
In the retired fighters, the structures that showed the greatest decline in volumes over time differed from those in the

younger, active fighters. In this retired group, who were generally older, the most significant changes were in the amygdala and hippocampus. Postmortem studies of CTE suggest that the characteristic tau pathology is more scattered in frontal and temporal regions in lower stages and with more advanced disease, and tends to accumulate in the temporal lobe structures with accompanying gross atrophy.¹⁹ One interpretation of our findings is that MRI volumetric changes in thalamus and corpus callosum in younger individuals, particularly those actively exposed to RHI, is primarily the result of accumulating axonal injury, whereas in the older, retired cohort, change in hippocampal and amygdala volumes may be reflective of a different process such as CTE or other types of neurodegeneration, such as Alzheimer-type pathology.

The relationship between decline in regional volumes and longitudinal performance on cognitive measures requires scrutiny. We did not find any differences at a group level between active and retired fighters and controls after adjusting for age and education. This may be due to the limited scope of our cognitive test battery, lack of sensitivity to the type of cognitive changes one might encounter in those exposed to head trauma, or variability of the tests themselves.

Experience with other neurodegenerative diseases has shown that more obvious clinically apparent cognitive decline may lag behind structural changes.^{20,21} To investigate this

Figure 2 Average yearly change in performance on Trail-Making Test (TMT) parts A and B between active fighters who showed >1.5% average yearly decline in caudate volumes (decliners) and those who did not exceed this rate of decline



Average yearly change in performance on TMT parts A (A) and B (B) in seconds between active fighters who showed >1.5% average yearly decline in caudate volumes (decliners) compared to those who did not exceed this rate of decline.

possibility in our cohort, we dichotomized the study participants into decliners and nondecliners using a greater than 1.5 SD per year drop in caudate volume compared to controls. The caudate was chosen because damage to this structure can result in cognitive and behavioral impairment; we have previously reported a relationship between caudate volumes and cognitive performance and it provided a reasonable number of participants in each group (decliners and nondecliners).^{5,22,23} Those who had decline in caudate volumes showed a greater

yearly lowering in scores on the Trails A and B tests. Trail-making tests are thought to reflect a wide range of cognitive functions including attention, sequencing and shifting, cognitive flexibility, abstraction, psychomotor speed, and ability to simultaneously maintain 2 trains of thought.²⁴

NfL is highly expressed in large-caliber myelinated axons of the white matter and is an established biochemical marker of axonal injury.^{25,26} Elevations in NfL have been reported not only after

concussion, but also after cardiac arrest, as well as in a number of chronic neurologic disorders.^{27–30} We have previously reported that serum NfL levels are higher in active fighters compared to retired fighters and controls, with very little overlap between NfL levels in active fighters and controls.³¹ Thus, the current finding that, within the active fighter group, those with higher baseline NfL levels were more likely to show regional volumetric decline suggests that this measure may have predictive properties in identifying individuals who may be at risk of ongoing structural brain injury. Whether cessation of exposure to RHI in those who have elevated NfL levels will halt this volume loss over time needs further investigation.

While this study benefits from having well-characterized participants who either are, or have been, exposed to repetitive head impacts, along with a control group free from reported head trauma, there are certain limitations to be acknowledged. For one, the cohort examined was not a random sample of active and retired fighters, introducing potential bias in the results; that is, it may be that participants who are the most symptomatic and have more concern about their health might be more likely to continue in the study. Arguing against this is the finding that only a small proportion showed decline in cognitive function. Though our study group included both men and women, the number of women was small, making it difficult to determine if sex influences volumetric change. However, repeat analyses that were restricted to men did not significantly change any results. The timeframe for follow-up was brief; although some participants had up to 6 years between baseline and last visit, the average follow-up time was 2.6 years. In addition, we used a brief computerized cognitive battery and may have found more correlations between volumetric decline and cognitive change if we employed more exhaustive testing. In a clinical setting, though, it may not be realistic to obtain full neuropsychological testing on a frequent basis, so that identifying brief, readily available tests that correlate with structural change may be more practical.

One major concern with studies using MRI volumetrics is the variability or noise that may occur with repeated measures. Studies of test and retest stability of volumes consistently report a certain amount of variability including gain or loss of volume.^{32,33} Our sample is no exception, though we benefit from including multiple imaging data points to determine yearly rate of change. We employed an automated quality control procedure for the MRI volumetrics in this study and there may be some imperfections in exact reconstruction of the brain regions. However, we speculate that the statistical effects due to lack of manually editing those minor imperfections on brain regions utilized in this study should be minimal.³⁴ In addition, we have processed the longitudinal data with cross-sectional analysis in FreeSurfer. To minimize the effect of brain volume at different time points, this study utilized intracranial volume as a nuisance regressor.

Inclusion of this nuisance variable does not eliminate the bias inherent due to lack of longitudinal reconstruction and future studies will evaluate the effects of cross-sectional and longitudinal reconstruction on the results we report. Finally, the average yearly percentage change in regional brain volumes is relatively small. Yet the magnitude of volume change in the brain regions we found to be significant exceed the within-scanner test–retest variability reported in the literature. Still, it is not known if this reliability would apply in general clinical practice, and further work is needed to determine how useful this could be on an individual basis, or if these small changes are prognostic.

Despite these limitations, this study is one of the largest to longitudinally follow MRI brain volumetric changes among active and retired professional athletes exposed to RHI. The findings reported shed some light on how longitudinal regional volumetric MRI may be employed in tracking the long-term neurologic effects of repetitive head trauma. Volumetric loss in different brain regions may reflect different pathologic processes at different times among individuals exposed to RHI. Further research is needed to determine if this pattern of volumetric change continues over a longer follow-up period and can be replicated in other cohorts exposed to RHI.

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Disclosure

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