

# Soccer Heading Exposure–Dependent Microstructural Injury at Depths of Sulci in Adult Amateur Players

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## Abstract

### Background and Objectives

Repetitive head impacts (RHIs) in sports are associated with adverse clinical and neuropathologic outcomes, but there is limited evidence from in vivo human imaging studies to inform risk assessment, exposure standards, and interventions. We tested the association of RHI with in vivo microstructural disruption at the depths of cerebral sulci, a region vulnerable to trauma.

### Methods

We examined the relationship between soccer-related RHI exposure over 12 months and imaging measures. Participants included amateur soccer players and noncollision sport athletes aged 18–55 years from the Greater New York City area. We analyzed diffusion MRI measures specifically within the juxtacortical white matter at the depths of cortical sulci and crests of gyri, as well as within deep white matter. Cognitive function was assessed using components of the CogState computerized battery, focusing on verbal learning and memory performance.

### Results

A total of 352 soccer players (mean [SD] age, 25.6 [7.5] years; 245 men [70%]) and 77 controls (22.8 [5.1] years; 30 men [39%]) were included. In multivariable regression, greater RHI was associated with lower fractional anisotropy (FA) (standardized  $\beta = -0.234$ ;  $p < 0.001$ ) and higher orientation dispersion index (ODI) ( $\beta = 0.156$ ;  $p = 0.008$ ), averaged over depths of cerebral sulci, in an RHI exposure-dependent manner. Worse cognitive performance on verbal learning and memory tests was associated with lower FA (Pearson  $r = 0.16$  to  $0.24$ ,  $p < 0.001$ ) and higher ODI ( $r = -0.25$  to  $-0.17$ ,  $p < 0.001$ ) at depths of sulci in the orbitofrontal region. Diffusion measures from deep white matter were not associated with RHI or cognitive measures. Mediation analyses revealed that orbitofrontal depths of sulci microstructural disruption (lower FA and higher ODI) partially mediated the relationship between RHI exposure and poorer performance on verbal learning (indirect effects =  $-0.26$  to  $-0.25$ ,  $p < 0.001$ ), weighted verbal learning ( $-0.51$  to  $-0.48$ ,  $p < 0.001$ ), and verbal memory ( $-0.05$  to  $-0.04$ ,  $p = 0.04$ ).

### Discussion

Higher RHI exposure was associated with MRI measures of microstructural disruption at the depths of sulci in an exposure-dependent manner. By contrast, deep white matter regions were relatively insensitive to RHI effects. Diffusion MRI at the depths of sulci may serve as a more specific marker of RHI-related brain injury.

## Introduction

The associations of repetitive head impacts (RHIs) in sports with cognitive dysfunction<sup>1,2</sup> and neurodegenerative diseases<sup>3–5</sup> are well established, but specific mechanisms and in vivo

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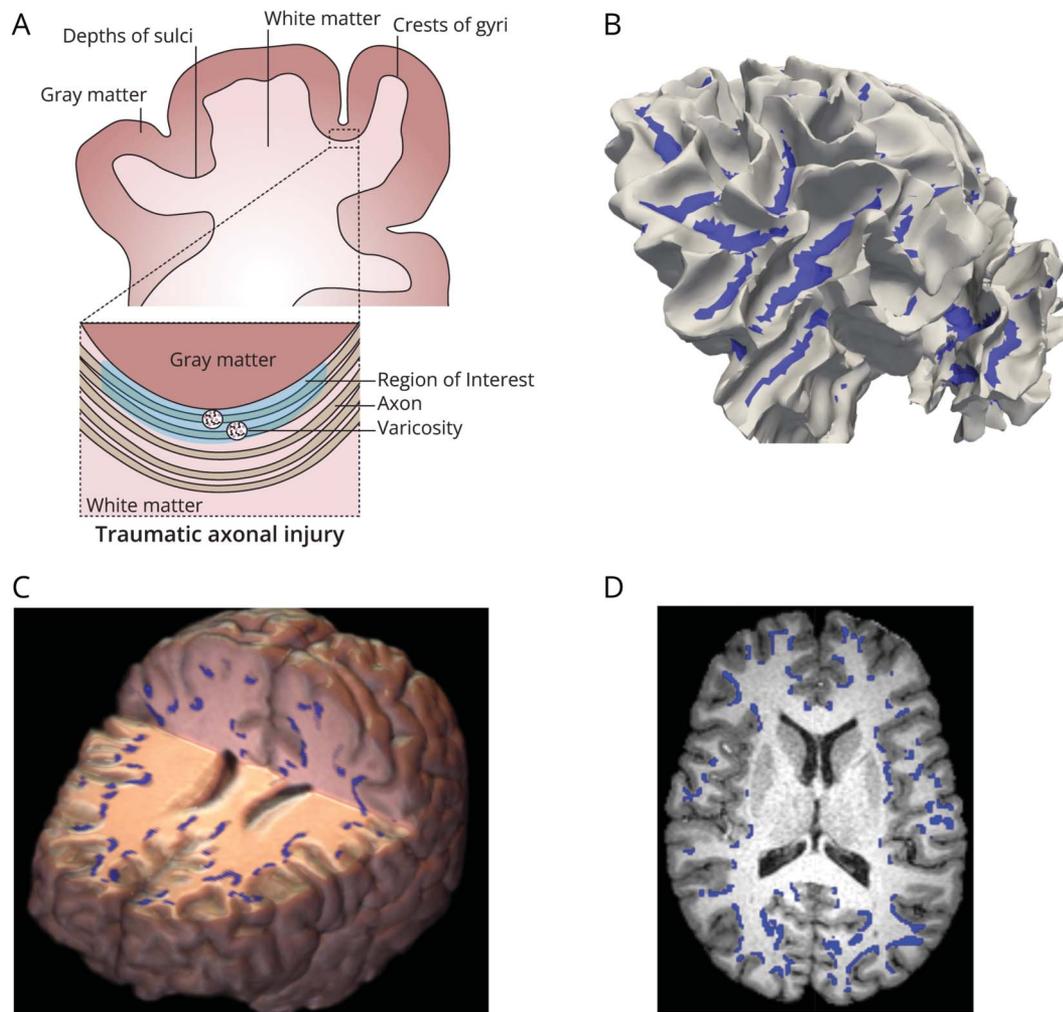
## Glossary

**CTE** = chronic traumatic encephalopathy; **dmMRI** = diffusion MRI; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FITBIR** = Federal Interagency Traumatic Brain Injury Repository; **FSL** = FMRIB software library; **ISL** = International Shopping List; **ISRL** = ISL Delayed Recall; **NODDI** = neurite orientation dispersion density imaging; **ODI** = orientation dispersion index; **RHI** = repetitive head impact; **ROI** = region of interest; **TBI** = traumatic brain injury; **TE** = echo time; **TI** = inversion time; **TR** = repetition time; **wISL** = weighted ISL; **WM** = white matter.

biomarkers remain elusive. Converging evidence implicates the juxtacortical white matter (WM) at the depths of sulci as a key site of RHI-related injury. Finite element modelling<sup>6,7</sup> identifies the biomechanical vulnerability of the depths of sulci (Figure 1A), which are also the pathognomonic site of tauopathy in chronic traumatic encephalopathy (CTE). Although RHI exposure has been linked to increased risk of CTE in some individuals,<sup>8</sup> most who are exposed to RHI do not develop CTE. CTE represents a specific neuropathologic

diagnosis that has been reported in a small subset of individuals with a history of RHI, including some young adult amateur soccer players.<sup>9-11</sup> Postmortem findings of injury to juxtacortical WM in RHI include axonal degeneration, microglial activation, and astrogliosis.<sup>9,12</sup> Ex vivo neuroimaging has identified MRI correlates of juxtacortical injury in CTE brains. Specifically, fractional anisotropy (FA) at the depths of sulci correlated with severity of collocated histologic axonal disruption.<sup>13</sup> This constellation of findings indicates

**Figure 1** Localization of Juxtacortical White Matter at Depths of Sulci in an Individual Brain



Schematic (A) demonstrating RHI-associated traumatic axonal injury, indicated by varicosity formation, occurring in juxtacortical white matter at the depth of a sulcus. Data from one individual participant's brain showing (B) surface rendering of the gray matter-white matter boundary (white) with overlaid depths of sulci ROI (blue), (C) 3D volume rendering of the depths of sulci ROI on the T1-weighted brain, and (D) a single slice from the T1-weighted axial brain volume shown in (C), with portions of the depths of sulci ROI (blue) that intersect the slice. RHI = repetitive head impact; ROI = region of interest.

that RHI-associated juxtacortical WM injury could be detected in vivo using diffusion MRI (dMRI).

dMRI including diffusion tensor imaging (DTI)<sup>14</sup> and neurite orientation dispersion density imaging (NODDI)<sup>15</sup> are widely used to study the microstructural properties of brain tissue injury and have been applied to investigate adverse effects of sport-related RHI. Most dMRI studies focus on deep WM regions of interest (ROIs) or use whole-brain techniques, which typically exclude the juxtacortical WM.<sup>16</sup> dMRI findings in sport-related RHI are inconsistent, ranging from lower FA in RHI to no detectable WM disruptions.<sup>17</sup> Notably, these studies excluded the juxtacortical WM from their analytic approach.<sup>17</sup> As a result, existing studies cannot address potential adverse effects of RHI on juxtacortical WM subjacent to the depths of sulci, which is particularly vulnerable to and therefore a plausible location of detectable axonal injury.<sup>18,19</sup> We addressed this knowledge gap in an observational study of active soccer players by examining whether estimated RHI exposure was directly associated with dMRI parameters derived from the depths of sulci.

We localized juxtacortical WM at the depths of sulci in individual soccer players in vivo, based on the curvature of each individual's gray matter-WM boundary (Figure 1, B and C), and assessed the association of dMRI measures from these regions with prior RHI exposure. Building on previously reported associations of greater RHI with lower deep WM FA, and worse cognitive performance in this cohort,<sup>1,20,21</sup> we hypothesized an exposure-dependent relation of RHI with microstructure at the depths of sulci, and of juxtacortical WM microstructure with cognitive performance.

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

The study and procedures were approved by the Institutional Review Boards of Albert Einstein College of Medicine and Columbia University Irving Medical Center. Written informed consent was obtained from all participants before study enrollment. The study adhered to ethical standards for research involving human participants in accordance with the Declaration of Helsinki.

### Study Design

Our prospective observational study of active adult amateur soccer players and noncollision sport athletes is described in detailed elsewhere.<sup>22</sup> Participants were recruited from the greater New York City region as soccer players or athletes in noncollision sports, aged 18–55 years at the time of study enrollment, active in their sport for  $\geq 5$  years, currently active for  $\geq 6$  months per year, and fluent in English. Inclusion and exclusion criteria can be found in eMethods. All participants underwent the same data collection protocol during their visit.

## RHI Exposure Assessment

RHI was estimated using HeadCount-12m, a structured, web-based questionnaire, the details and validation of which have been previously described.<sup>23</sup> HeadCount-12m estimates heading over the prior 12 months based on a structured questionnaire that assesses exposure during practice and games. Owing to positive skew of heading exposure, it was represented as approximately equal quartiles of 12-month RHI. Lifetime concussion history was collected as a separate variable through HeadCount-12m, with participants indicating “the number of head injuries experienced throughout their lifetime for which they sought or were advised to seek medical attention.” We treated concussion as a categorical variable (0, 1, or  $\geq 2$ ). Accounting for concussion allowed us to distinguish effects of RHI and the potentially distinct effects of recognized concussion when conducting our multivariable analyses.

## Neuroimaging

Data collection used a 3T Philips Achieva TX scanner with a 32-channel head coil. The protocol included T1-weighted 3D magnetization prepared rapid gradient echo (repetition time [TR]/echo time [TE]/inversion time [TI] = 9.9/4.6/900 milliseconds, flip angle = 8°, 1 × 1 × 1 mm resolution), multishell diffusion imaging (6 directions at  $b = 300$  s/mm<sup>2</sup>, 32 at  $b = 800$  s/mm<sup>2</sup>, 60 at  $b = 2000$  s/mm<sup>2</sup>, 7  $b = 0$  s/mm<sup>2</sup> images, TR/TE = 10,000/95 milliseconds, 2 × 2 × 2 mm resolution), and field mapping (field of view = 250 mm, 3 × 3 × 3 mm resolution, TR/TE/ $\Delta$ TE = 26/2.5/2.3 milliseconds) for susceptibility correction. All participants underwent identical imaging protocols. All images were reviewed for structural abnormalities or visible evidence of prior trauma by a board-certified neuroradiologist (M.L.L.). Brain extraction was performed using SynthStrip<sup>24</sup> for T1-weighted images and the Brain Extraction Tool from the FMRIB software library (FSL)<sup>25</sup> for field map images. A rigorous manual quality assurance examination was undertaken to confirm image and brain extraction quality, as well as exclude artifacts and aberrant images. Diffusion data were corrected for head motion and eddy current effects using FSL *EddyCorrect* with the  $b = 0$  s/mm<sup>2</sup> image as the target image. Brain extraction of diffusion images was performed by transferring the T1-weighted image's brain mask and distorting it to match echo planar imaging distortions of the diffusion scan based on the field map. FA, radial diffusivity, axial diffusivity, and mean diffusivity maps were obtained using FSL *DTIFit*. Orientation dispersion index (ODI), intracellular volume fraction, and isotropic diffusion maps were obtained using accelerated microstructure imaging via convex optimization.<sup>26</sup> T1-weighted images were processed and segmented using FreeSurfer 7.3.2's surface reconstruction to identify depths of sulci and crests of gyri (details in eMethods). Metrics were averaged within juxtacortical WM at depths of sulci, crests of gyri, and within deep WM regions and tracts.

## Neuropsychological Performance

Verbal learning and memory were assessed using components of the CogState computerized battery, a validated and reliable

set of cognitive tests (eMethods). The International Shopping List (ISL) task evaluated immediate verbal recall through a 12-item list learning paradigm. The examiner read aloud a list of grocery items and asked the participant to recall them immediately, with the process repeated over three trials. A weighted score (wISL) was derived from these trials to account for learning effects. In the International Shopping List Delayed Recall (ISRL), task participants were asked to recall the same items 20 minutes after initial presentation.

## Statistical Analysis

The relationship of 12-month RHI with dMRI measures was analyzed through multiple linear regression adjusted for age, sex, and lifetime concussions. A significance threshold of  $p_{\text{adjusted}} < 0.01$  was used, with Bonferroni correction for multiple comparisons. Effect sizes were calculated using Cohen  $f^2$  to assess the association between RHI quartiles and dMRI measures across different ROIs in the linear regression models. Cohen  $d$  was used to compare measures between RHI quartiles and control groups. Monotonic trends across RHI exposure quartiles were assessed first among soccer players (Q1–Q4) and then including noncollision athlete controls as the lowest exposure group. Pearson partial correlation coefficients ( $r$ ) were calculated to assess associations between cognitive scores and depths of sulci microstructure adjusted for age, sex, years of education, and lifetime concussions. Based on the results of these partial correlation analyses, dMRI measures showing significant associations were selected for subsequent mediation analyses to examine whether dMRI measures mediate the relationships between RHI exposure and cognitive performance, adjusted for age, sex, years of education, and lifetime concussions. All analyses followed the causal steps approach of Baron and Kenny,<sup>27</sup> extended with bootstrapped CIs for significance testing.<sup>28</sup> Details are included in eMethods.

## Data Availability

All data reported in this paper are publicly available through the Federal Interagency Traumatic Brain Injury Repository (FITBIR) accessible at: [fitbir.nih.gov/](https://fitbir.nih.gov/). The study page on FITBIR is [fitbir.nih.gov/study\\_profile/220](https://fitbir.nih.gov/study_profile/220).

## Results

### Demographics

The study included 352 currently active adult amateur soccer players, divided into four quartiles (Q1–Q4) based on prior 12-month heading and 77 controls who were currently active in a noncollision sport and had no history of organized collision sport play (Table 1). Of 352 soccer players (245 [70%] male; mean [SD] age, 25.6 [7.5] years), 127 (36%) reported at least 1 lifetime concussion. Among 77 controls (30 [39%] male; mean [SD] age, 22.8 [5.1] years), 6 (8%) reported at least 1 lifetime concussion. The controls were not matched for sex or age; multiple linear regression models were used

to adjust for these variables in all analyses. No visible MRI evidence of prior trauma or structural abnormalities was detected.

## Identifying Parameters of Interest

We planned a priori that, based on analyses of 12-month RHI associations with each diffusion parameter at each anatomic region (depths of sulci, crests of gyri, and deep WM structures), the diffusion metrics showing the largest effect sizes would be the focus of subsequent analyses. The initial linear regression analyses revealed, for all regions, the largest Cohen  $f^2$  effect sizes for FA and ODI (Figure 2A, eTables 1–8). Therefore, FA and ODI were the focus of subsequent analyses.

## Effect Magnitude Across Brain Regions

Effect sizes for deep WM regions and tracts, and for juxtacortical WM at the crests of gyri were smaller compared with depths of sulci. For instance, at crests of gyri, the FA effect size ( $f^2 = 0.166$ ) was less than half that observed at depths of sulci ( $f^2 = 0.367$ ). In deep WM, FA at the uncinate fasciculus showed the largest effect size ( $f^2 = 0.0317$ ), which was an order of magnitude smaller than in depths of sulci.

## Group Comparison of Soccer Players and Noncollision Athletes

We first compared FA and ODI between soccer players and noncollision athletes. Soccer players showed significantly lower FA values across multiple brain regions, with the most pronounced differences observed in the depths of sulci (Figure 2B). The largest effects were seen in all depths of sulci and depths of sulci in the temporal region, followed by substantial differences in the orbitofrontal, parietal, frontal, and occipital regions. Less pronounced and significant differences were observed in the crests of gyri and deep WM. Complementing these findings, ODI measurements showed corresponding increases in soccer players compared with noncollision athletes (Figure 2C). The largest effects were again observed in the depths of sulci regions.

## Association of RHI With dMRI Metrics

Figure 3, A and B illustrates significant adjusted linear trends of brain microstructure with RHI in soccer players. Greater RHI was associated with lower FA (standardized  $\beta = -0.234$ ;  $p < 0.001$ ) and higher ODI ( $\beta = 0.156$ ;  $p = 0.008$ ) across all cerebral depths of sulci. Associations were strongest and most prevalent in depths of sulci, with fewer significant findings in crests of gyri and weakest effects in deep WM structures ( $p > 0.05$ ).

## Noncollision Athlete Comparisons

Comparisons of RHI quartiles against noncollision athlete controls revealed significantly lower FA (Figure 4A) and significantly higher ODI (Figure 4B) at depths of sulci in soccer players, with stronger associations in those with greater RHI exposure. The largest differences were seen in the highest exposure quartile (Q4), where depths of sulci FA was

**Table 1** Characteristics of the Participants

	Controls (n = 77)	Total soccer (n = 352)	Quartiles for RHI count in previous 12 mo			
			Q1 (n = 88)	Q2 (n = 88)	Q3 (n = 88)	Q4 (n = 88)
Age, y, median (IQR)	21 (20–24)	23 (20.75–28)	26.5 (22.75–34)	24 (22–28.25)	22 (20–28)	21 (20–23)
Male sex, n (%)	30 (39)	245 (70)	47 (53)	60 (68)	70 (80)	68 (77)
No. of RHI in previous 12 mo, median (IQR)	0 (0–0)	684.5 (296–1877)	105 (43–212)	491 (391–595.25)	1,160 (857.75–1,435)	3,152 (2,386–4,787.25)
<b>Lifetime concussion(s), n (%)</b>						
0	71 (92)	225 (64)	58 (66)	53 (60)	57 (65)	57 (65)
1	6 (8)	58 (16)	17 (19)	17 (19)	15 (17)	9 (10)
≥2	0 (0)	69 (20)	13 (15)	18 (20)	16 (18)	22 (25)
<b>Race, n (%)</b>						
American Indian/Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asian	4 (5)	13 (4)	1 (1)	4 (5)	6 (7)	2 (2)
Black/African American	12 (16)	56 (16)	6 (7)	14 (16)	13 (15)	23 (26)
Native Hawaiian/Pacific Islander	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
White	51 (66)	225 (64)	68 (77)	59 (67)	56 (64)	42 (48)
<b>Ethnicity, n (%)</b>						
Hispanic or Latino	10 (13)	83 (24)	13 (15)	19 (22)	24 (27)	27 (31)
Not Hispanic or Latino	66 (86)	252 (72)	72 (82)	66 (75)	60 (68)	54 (61)
Unknown/not reported	1 (1)	17 (5)	3 (3)	3 (3)	4 (5)	7 (8)

Abbreviations: IQR = interquartile range; RHI = repetitive head impact.

markedly lower (Figure 4A) and ODI was substantially higher (Figure 4B). Regional analysis showed that temporal, orbitofrontal, and parietal depths of sulci showed RHI-associated lower FA and higher ODI.

Trend analysis revealed regional differences in FA and ODI across RHI exposure quartiles. Exposure-dependent decline of FA was greater at depths of sulci than in crests of gyri or in corpus callosum (Figure 5A). Similarly, ODI demonstrated exposure-dependent increase of ODI at depths of sulci compared with both crests of gyri and corpus callosum (Figure 5B). Exposure-dependent trends in crests of gyri differed significantly from the corpus callosum for ODI, but not for FA.

QQ plots comparing all analyzed brain regions revealed exposure-dependent departures from the theoretical null distribution for both FA and ODI, with the most pronounced deviations observed at the depths of sulci for the highest RHI exposure quartile (eFigure 1). This demonstrates that the disruptions are unlikely to occur by chance. Finally, we performed a post hoc sensitivity analysis by excluding the non-collision athletes with any history concussion and observed that none of the findings changed.

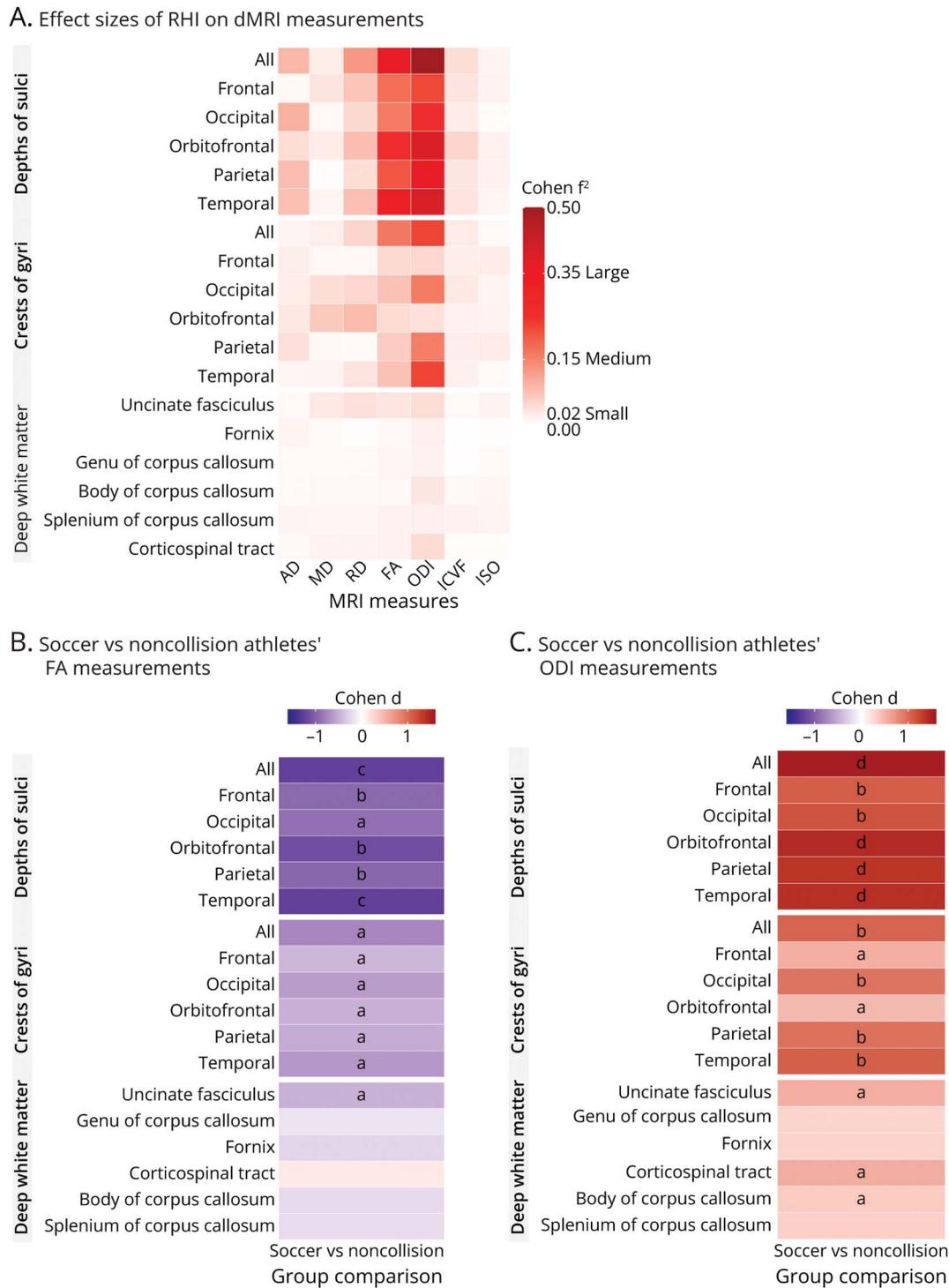
## Post Hoc Analysis of Alternative Exposure Metrics

To address the possibility that other aspects of exposure could explain the associations of RHI with dMRI, we added the following variables to the regression model: 12-month unintentional head impacts and years of soccer play (eTable 11). The association of 12-month RHI with depths of sulci FA remained significant ( $p = 0.002$ ,  $\Delta R^2 = 0.040$ , standardized  $\beta = -0.315$ ). Significance of ODI was somewhat attenuated in a similar multivariable analysis ( $p = 0.076$ ,  $\Delta R^2 = 0.019$ , standardized  $\beta = 0.236$ ) but showed a stronger trend than the alternative predictors (12-month unintentional head impacts [ $p = 0.657$ ,  $\Delta R^2 = 0.004$ , standardized  $\beta = 0.116$ ] and years of play [ $p = 0.808$ ,  $\Delta R^2 < 0.001$ , standardized  $\beta = 0.219$ ]).

## Cognition

The orbitofrontal depths of sulci demonstrated the strongest partial correlations with cognitive performance among all brain regions examined (Figure 6A and eTable 12). In this region, both FA and ODI measures showed significant partial correlations with verbal learning (ISL, wISL) and verbal memory (ISRL). FA showed positive partial correlations (Pearson  $r = 0.16$  to  $0.24$ ,  $p < 0.001$ ), while ODI showed negative partial correlations ( $r = -0.25$  to  $-0.17$ ,  $p < 0.001$ ).

**Figure 2** Juxtacortical White Matter Microstructure in Depths of Sulci Associated With RHI Exposure



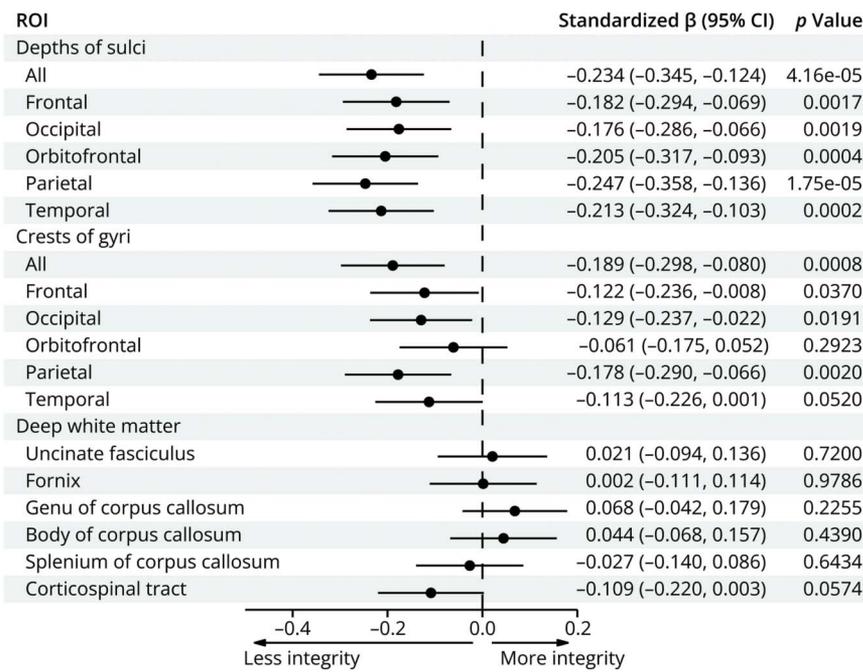
The effect size of RHI on diffusion metrics (Cohen  $f^2$  values of 0.02, 0.15, and 0.35 representing small, medium, and large effects, respectively) was largest for the depths of sulci (A; for numerical results see eTable 1). Group-level analysis comparing soccer players with noncollision athletes demonstrates differences in FA (B) and ODI (C) were largest for the depths of sulci. <sup>a</sup> $p_{\text{adjusted}} < 0.01$ . <sup>b</sup> $p_{\text{adjusted}} < 10^{-10}$ . <sup>c</sup> $p_{\text{adjusted}} < 10^{-16}$ . <sup>d</sup> $p_{\text{adjusted}} < 10^{-18}$ . AD = axial diffusivity; FA = fractional anisotropy; ISO = isotropic diffusion; MD = mean diffusivity; ODI = orientation dispersion index; RD = radial diffusivity; RHI = repetitive head impact.

with cognitive performance. Similar but slightly weaker partial correlations were observed when examining all depths of sulci combined, with FA showing positive partial correlations and ODI showing negative partial correlations with verbal

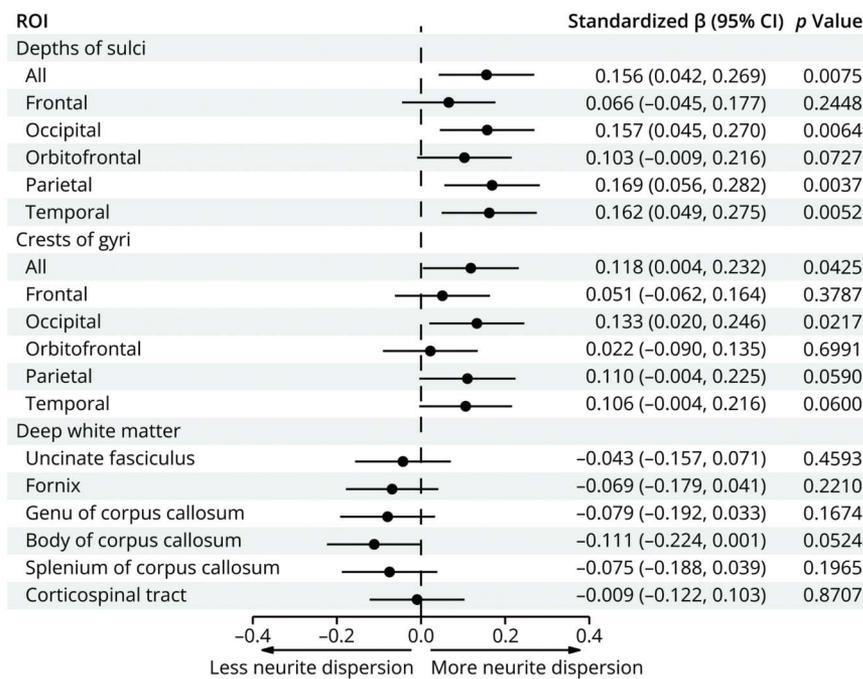
learning (ISL, wISL). Notably, deep WM regions and tracts showed no significant partial correlation with cognitive performance after correction for multiple comparisons (eTable 12).

**Figure 3** Juxtacortical White Matter Microstructure at Depths of Sulci Associated With Greater 12-Month RHI Exposure

**A.** Trend analysis of RHI quartiles with FA among soccer players



**B.** Trend analysis of RHI quartiles with ODI among soccer players



Among soccer players only, a linear test of trend across quartiles of 12-month RHI exposure as a continuous predictor of FA (A) and ODI (B) demonstrate an exposure-dependent association of greater RHI with greater microstructural disruption at the depths of sulci. "All" indicates the aggregate of all regions. FA = fractional anisotropy; ODI = orientation dispersion index; RHI = repetitive head impact.

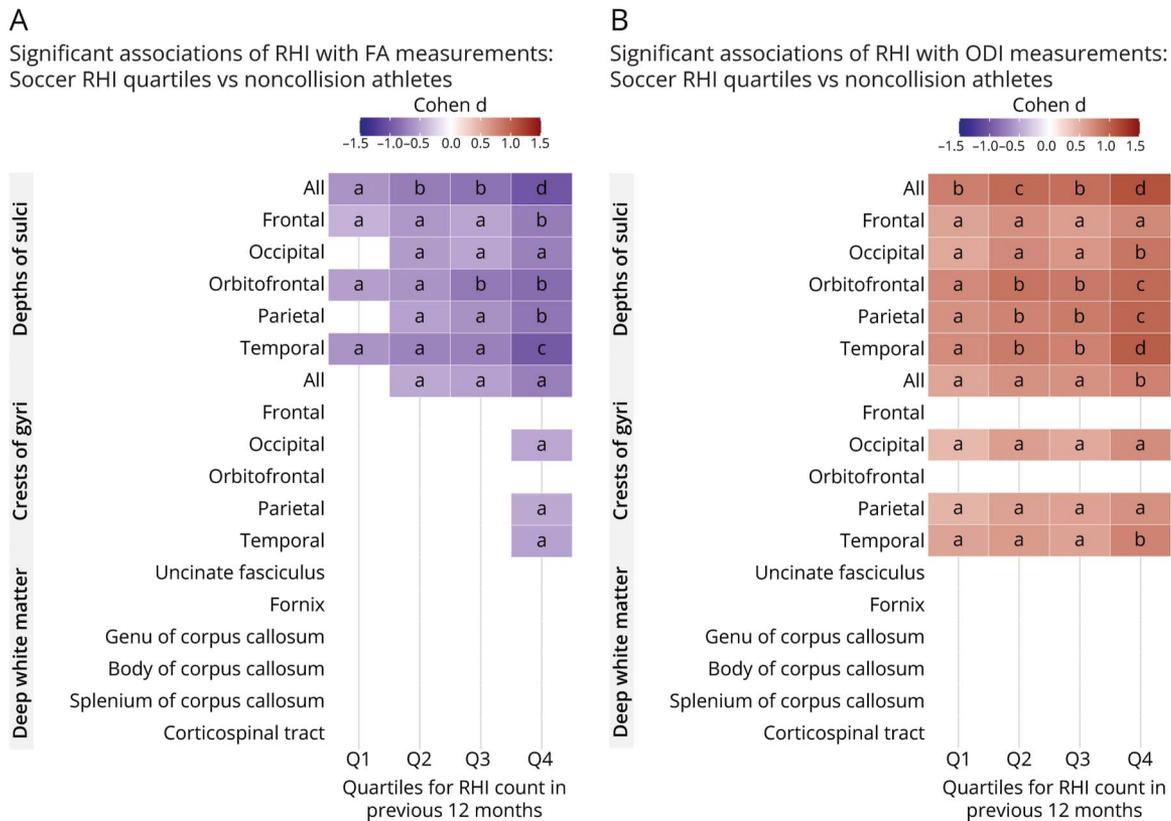
**Mediation**

Mediation analyses were conducted to examine the role of brain microstructural alterations in the relationship between soccer heading exposure and cognitive performance (Figure 6B). For these analyses, noncollision athlete controls were included the reference group, with soccer players in categorized by 12-month RHI quartiles representing

increasing levels of exposure. RHI exposure had significant total effects on ISL ( $\beta = -0.487, p < 0.001$ ), ISRL ( $\beta = -0.086, p < 0.001$ ), and wISL ( $\beta = -0.927, p < 0.001$ ).

Consistent with the Cohen effect size analyses, the regression coefficients from mediation analyses showed that higher RHI exposure was significantly associated with microstructural

**Figure 4** Soccer Heading Exposure-Dependent Microstructural Disruption of Juxtacortical White Matter Microstructure at Depths of Sulci



Multiple linear regression analysis of soccer players grouped by quartiles of 12-month RHI exposure, compared with noncollision athlete controls, adjusted for concussion history, age, and sex. Q1–Q4 = 12-month RHI quartiles. For numerical results, see eTables 9 and 10. <sup>a</sup> $p_{\text{adjusted}} < 0.01$ . <sup>b</sup> $p_{\text{adjusted}} < 10^{-10}$ . <sup>c</sup> $p_{\text{adjusted}} < 10^{-16}$ . <sup>d</sup> $p_{\text{adjusted}} < 10^{-18}$ . FA = fractional anisotropy; ODI = orientation dispersion index; RHI = repetitive head impact.

disruption at the depths of sulci. In the orbitofrontal region, greater RHI exposure was associated with lower FA ( $\beta = -0.162, p < 0.001$ ) and higher ODI ( $\beta = 0.211, p < 0.001$ ). Similar associations were observed across all depths of sulci (FA:  $\beta = -0.130, p < 0.001$ ; ODI:  $\beta = 0.166, p < 0.001$ ).

Microstructural measures at the depths of sulci were significantly associated with cognitive performance in regression analyses, similar to our findings discussed above. In the orbitofrontal region, lower FA was associated with worse performance on ISL ( $\beta = 1.616, p < 0.001$ ), ISRL ( $\beta = 0.299, p = 0.001$ ), and wISL ( $\beta = 3.112, p < 0.001$ ). Similarly, higher ODI was associated with worse performance on ISL ( $\beta = -1.200, p < 0.001$ ), ISRL ( $\beta = -0.204, p = 0.007$ ), and wISL ( $\beta = -2.263, p < 0.001$ ). Across all depths of sulci, FA and ODI were significantly associated with worse performance on ISL (FA:  $\beta = 1.418, p < 0.001$ ; ODI:  $\beta = -1.244, p < 0.001$ ) and wISL (FA:  $\beta = 2.606, p < 0.001$ ; ODI:  $\beta = -2.352, p < 0.001$ ), but not on ISRL (FA:  $p = 0.095$ ; ODI:  $p = 0.106$ ).

The direct effects of RHI on cognitive measures remained significant ( $p < 0.001$ ) after controlling for FA or ODI, indicating partial mediation. In the orbitofrontal region, FA significantly mediated the relationship between RHI and ISL

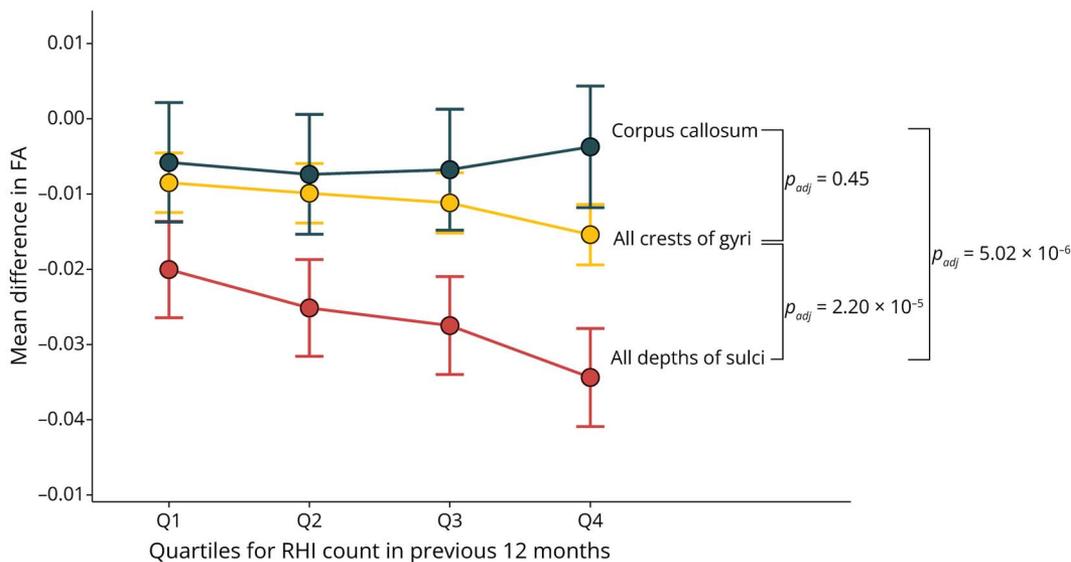
(indirect effect =  $-0.262, 95\% \text{ CI } -0.442 \text{ to } -0.118, p < 0.001$ ), ISRL (indirect effect =  $-0.049, 95\% \text{ CI } -0.114 \text{ to } -0.003, p = 0.04$ ), and wISL (indirect effect =  $-0.505, 95\% \text{ CI } -0.842 \text{ to } -0.225, p < 0.001$ ). Similarly, ODI significantly mediated the effect of RHI on ISL (indirect effect =  $-0.253, 95\% \text{ CI } -0.422 \text{ to } -0.114, p < 0.001$ ), ISRL (indirect effect =  $-0.043, 95\% \text{ CI } -0.097 \text{ to } -0.004, p = 0.04$ ), and wISL (indirect effect =  $-0.478, 95\% \text{ CI } -0.781 \text{ to } -0.223, p < 0.001$ ). Across all depths of sulci, both FA and ODI mediated the effect of RHI on ISL (FA: indirect effect =  $-0.185, 95\% \text{ CI } -0.355 \text{ to } -0.034, p = 0.02$ ; ODI: indirect effect =  $-0.207, 95\% \text{ CI } -0.371 \text{ to } -0.068, p = 0.004$ ) and wISL (FA: indirect effect =  $-0.340, 95\% \text{ CI } -0.653 \text{ to } -0.063, p = 0.02$ ; ODI: indirect effect =  $-0.391, 95\% \text{ CI } -0.697 \text{ to } -0.128, p = 0.004$ ).

## Discussion

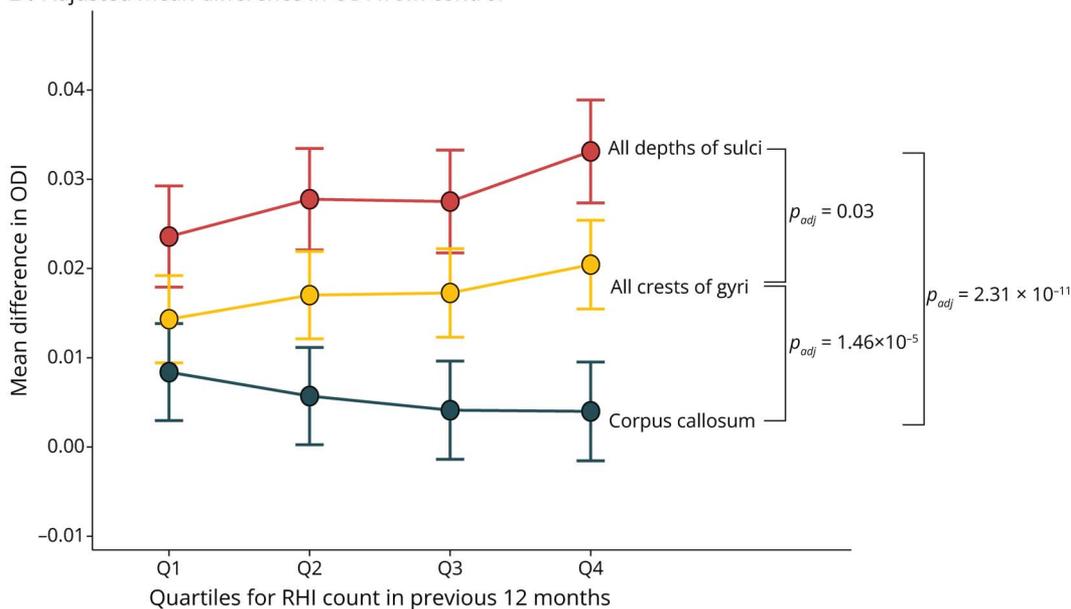
Based on regression analyses, adult amateur soccer players with highest exposure to heading over the prior 12 months had significantly greater microstructural disruption within juxtacortical WM at the depths of sulci compared with soccer players in the lowest RHI quartile, and compared with noncollision athletes. Minimal juxtacortical WM microstructural

**Figure 5** RHI Linked to Depths of Sulci, But Not Corpus Callosum Microstructural Disruption

**A.** Adjusted mean difference in FA from control



**B.** Adjusted mean difference in ODI from control

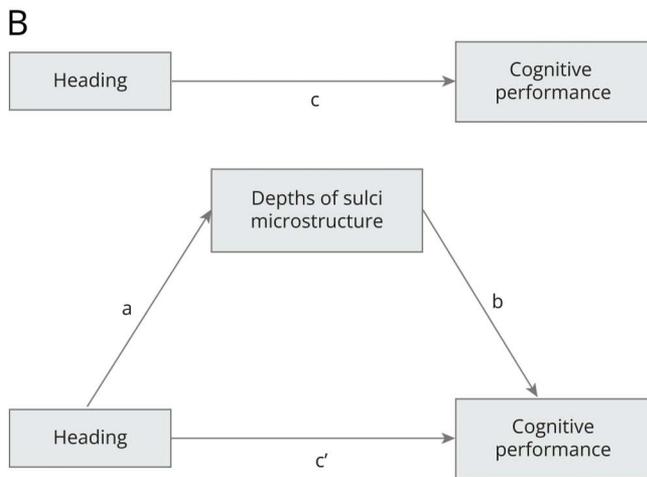
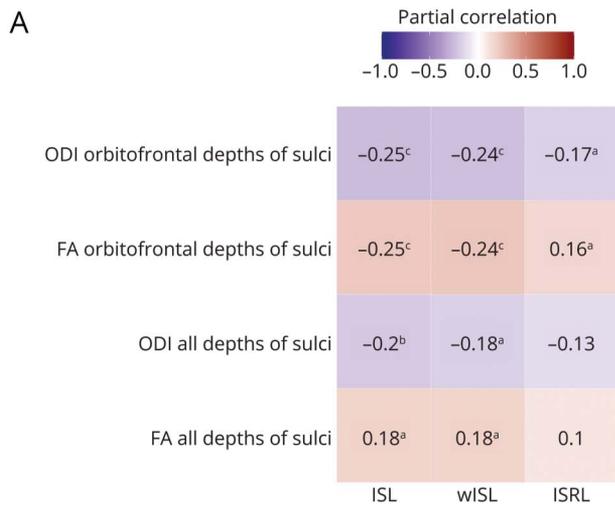


Adjusted mean differences, controlling for age, sex, and lifetime history of concussions, for FA (A) and ODI (B) from all depths of sulci (red), all crests of gyri (yellow) and corpus callosum (black). Higher RHI exposure is associated with greater axonal disruption at the depths of sulci (blue), and to a lesser extent the crests of gyri (gold), but not in the corpus callosum (grey). Error bars show 95% CI of the estimate.  $p_{adjusted}$  values reflect difference in slope across RHI quartiles between two regions. Q1–Q4 = 12-month RHI quartile. For numerical results, see eTables 2 and 3. FA = fractional anisotropy; ODI = orientation dispersion index; RHI = repetitive head impact.

disruption was observed at the crests of gyri, and even less within deep WM regions and tracts. These findings highlight the specificity of RHI-related disruptions to the depths of sulci, with associations that were as much as an order of magnitude greater than those observed in other brain regions. Depths of sulci microstructure may serve as a more specific imaging biomarker for RHI-related brain injury, warranting further investigation as a potential mediator of the association of RHI with neurocognitive function.

Our findings expand existing knowledge in several ways. First, we report on microstructure of the juxtacortical WM in vivo in humans. Postmortem human<sup>9,12</sup> studies demonstrate prediction of injury for juxtacortical WM, which is also evident in clinical imaging of more severe brain trauma.<sup>29,30</sup> In vivo human studies of RHI and traumatic brain injury (TBI), however, have explicitly excluded the juxtacortical WM from analysis.<sup>16</sup> Second, we reveal specific vulnerability of the depths of sulci and contrast this location with crests of gyri

**Figure 6** Depths of Sulci Microstructure and Cognitive Performance



(A) Cognitive tests included international shopping list (ISL), trial-weighted ISL (wISL), and ISL recall (ISRL). The Pearson partial correlation of cognitive performance among all participants with FA or ODI from orbitofrontal depths of sulci or all depths of sulci. For complete results, see eTable 12. (B) Path diagram of the single-mediator model. <sup>a</sup> $p_{\text{adjusted}} < 0.01$ . <sup>b</sup> $p_{\text{adjusted}} < 0.001$ . <sup>c</sup> $p_{\text{adjusted}} < 0.0001$ . FA = fractional anisotropy; ODI = orientation dispersion index.

and deeper WM regions that have been extensively studied. Importance of the depths of sulci is evident from biomechanical<sup>6,7</sup> and postmortem studies, and we now show its specific vulnerability in vivo. Third, we delineate ROI in the individual's native anatomic space, without transformation to a template space, as is common across dMRI studies. This personalized approach is important because interindividual variation of cortical anatomy can introduce errors or preclude accurate coregistration of gyri and sulci altogether. Moreover, it enables potential future use of our method to extract measurements from individuals for clinical assessment. We note that one previous in vivo human study has reported on FA from the entirety of cortical sulci, using a template-based ROI approach.<sup>31</sup> We expand on these findings by discriminating the sulcal and gyral regions, showing that they have

distinct sensitivity to RHI effects, and address the significant limitation of transformation to a template.

An important consideration in any ROI analysis is whether partial volume effects could create bias leading to false inference. There are several reasons, and this is highly unlikely to explain our findings. First, the juxtacortical WM ROI did not visibly overlap the gray matter-WM boundary (Figure 1D). Second, partial volume effects alone would not be expected to covary with RHI exposure in such a robust exposure-dependent way (eFigure 2). Third, the associations we identified were far stronger for depths of sulci compared with weaker or absent effects for crests of gyri and in deep WM regions. Deep WM ROI would be least affected by partial volume effects. Because partial volume effects would likely dampen associations with RHI rather than enhance them, the finding of greatest effects in sulcal juxtacortical locations but not in gyral juxtacortical or deep WM militates against our findings being driven by partial volume effects.

Another important consideration in the evaluation of DTI is the potential for biased voxel-level metrics due to intravoxel crossing fiber effects. As for partial volume effects, it is implausible that crossing fiber effects would covary systematically with RHI exposure and more likely that these effects would dampen true associations with RHI. Our use of NODDI, which accounts for crossing fiber effects and complex fiber orientations, also addresses the potential susceptibility of FA to these effects and might explain why higher ODI, of all dMRI parameters tested, exhibited the strongest association with RHI exposure.

Our approach can be applied to any standard 3D T1-weighted and dMRI data set. It does not require specialized MRI acquisition protocols. This makes depths of sulci diffusion measures a potentially valuable biomarker because they could be readily extracted from existing data sets and easily incorporated into future studies. The relative sensitivity of these measures, compared with those from the deep WM regions and tracts, can advance clinical utility in assessing concussion, blast injuries, and other forms of TBI.

We have previously established association of greater RHI with worse cognitive performance in this cohort.<sup>1,20,21</sup> The high density of interstitial WM neurons at the depths of sulci<sup>32</sup> and their role in modulating corticocortical connectivity<sup>33</sup> could be a substrate for worse cognitive performance associated with greater RHI.<sup>1,2</sup> Associations of depths of sulci microstructure with cognitive performance suggest that RHI-induced microstructural disruption at the depths of sulci may disrupt the neural circuitry critical for cognitive processing. The orbitofrontal region, which showed the strongest correlations between depths of sulci microstructure and cognitive measures, is known to play a crucial role in decision-making, emotional regulation, and memory formation.<sup>34</sup>

The regression-based mediation results align with the effect size and correlation analyses, confirming that RHI exposure is associated with microstructural disruption at depths of sulci, which in turn relates to poorer verbal learning and memory performance. Particularly strong mediation effects were observed for the orbitofrontal depths of sulci where lower FA and higher ODI significantly mediated the effects of RHI on all cognitive measures. This regional specificity aligns with the orbitofrontal depths of sulci's vulnerability to traumatic forces<sup>35</sup> and its role in learning and memory integration.<sup>34</sup> The inclusion of noncollision athletes as controls allowed us to examine a more complete exposure spectrum, demonstrating exposure-dependent relationships along the pathway from RHI exposure through brain microstructure to cognitive performance. The observed partial rather than complete mediation suggests that the microstructural disruption reflected in dMRI signals represents a significant mechanism, but other factors likely contribute to adverse effects of RHI on cognitive performance. The stronger mediation for ISL and wISL compared with ISRL is consistent with differential effects of RHI-related orbitofrontal injury on distinct elements probed by our tests of learning and memory. The known role of orbitofrontal cortex in strategic encoding, value-based information integration, and salience detection during active learning<sup>34</sup> aligns with the mediating role of orbitofrontal dMRI in the association of RHI and ISL/wISL. The comparatively weaker mediating role of orbitofrontal dMRI in the association of RHI and ISRL may reflect that delayed recall predominantly engages hippocampal-cortical networks for memory trace retrieval,<sup>36</sup> which were not directly assessed in our study.

Soccer heading is a major source of RHI for more than 250 million active players worldwide.<sup>37</sup> Although physical exercise through sport participation reduces risk for early mortality and neurologic syndromes such as dementia,<sup>38</sup> Parkinson disease,<sup>39</sup> and age-related cognitive decline,<sup>40</sup> RHI exposure could offset these benefits.<sup>41</sup> Early-stage CTE has been detected in young soccer players,<sup>11</sup> although it can only be diagnosed post-mortem. The biomechanics of soccer heading creates pressure gradients<sup>35</sup> and shear forces<sup>18,19</sup> which concentrate at the gray matter-WM boundary,<sup>6</sup> supporting its vulnerability to RHI.

The specificity of depths of sulci diffusion measures to RHI which we observe supports the biological hypothesis that these regions are uniquely vulnerable to injury.<sup>7,10</sup> Lower FA and higher ODI at the depths of sulci are consistent with axonal injury,<sup>42</sup> demyelination,<sup>43</sup> and loss of fiber coherence and neurite density in the juxtacortical WM, which is primarily composed of U-fibers.<sup>44</sup> However, pathologic mechanisms related to RHI are incompletely understood, and our findings are from otherwise healthy young individuals. dMRI does not identify, for example, hyperphosphorylated tau deposition, a hallmark of CTE. We cannot infer that the observed microstructural effects will necessarily lead to CTE or other chronic adverse outcomes, although the findings indicate need for further study and longer follow-up.

Although lifetime RHI exposure is associated with altered sulcal morphology and cortical thinning in retired athletes,<sup>45</sup> previous analysis of our cohort demonstrated no association of 12-month RHI with regional volume or cortical thickness.<sup>46</sup> Finite element modeling consistently shows peak mechanical strain occurs in the depths of sulci during impact, despite variations in sulcal geometry (e.g., depth, width, and radii), indicating that the basic pattern of strain concentration is independent of specific anatomical morphology.<sup>7</sup> Clustering of microstructural injury at the depths of sulci in young healthy adults with high exposure to RHI may be a general feature of trauma, not necessarily specific to CTE, and offers a potentially powerful biomarker for assessing the consequences of RHI on brain health.

The RHI exposure measures we use are based on a structured self-report of prior exposure. Given the findings that increased RHI is associated with poorer cognitive performance, particularly in verbal learning and memory, there is potential for recall bias. That is, participants with greater exposure-related cognitive effects might have systematically overestimated their RHI levels relative to others who did not experience RHI-related cognitive effects. Notwithstanding the inherent potential for bias in self-report measures, our approach has been validated and used across multiple independent cohorts.<sup>23,47</sup> The structured nature of the HeadCount-12m questionnaire, which systematically assesses exposure during different contexts (practice and games) over defined timeframes, helps mitigate some recall limitations. Moreover, individual errors in self-reporting RHI exposure would most likely attenuate the associations we identified. The inclusion of heading exposure from practices, drills, scrimmages, and games in our estimates provides a more complete picture of total RHI exposure compared with studies focused on heading during competitive matches.

The observed microstructural disruptions at the depths of sulci are based on a single time point and do not provide insight into the temporal evolution of these changes in relation to the timing of RHI exposure. This limitation is particularly relevant in the context of the hypothesized window of vulnerability to reinjury. We had limited information about exposure before the year assessed, but did not find that years of play altered the associations we report. Moreover, we have previously reported that age at first exposure to heading does not modify the effects of prior 12-month RHI.<sup>48</sup> Future longitudinal RHI studies would be needed to understand the relationship of the timing of RHI with the onset, persistence, and progression of microstructural injury.

Our study examined the largest cohort to date of amateur soccer players for RHI-related brain microstructural changes. This focus on amateur players is particularly relevant given that they represent the largest population worldwide exposed to RHI through soccer,<sup>37</sup> suggesting significant public health implications. Although our cohort's demographic composition reflects the diverse amateur soccer population in the

Greater New York City area, findings may not generalize to other locations and contexts such as professional play.

The cognitive assessments examined in this study were restricted to verbal learning and memory tasks. This focus was deliberate because changes in these domains have demonstrated sensitivity to RHI exposure in previous studies of contact sport athletes.<sup>49</sup> However, other domains such as executive function (e.g., inhibition, flexibility, and planning) linked to WM microstructure were not evaluated. Future studies that incorporate broader neuropsychological testing could reveal other domains associated with orbitofrontal injury and more fully characterize the functional significance of our observed RHI-related microstructural disruptions at the depths of sulci.

In conclusion, RHI is associated, in an exposure-dependent fashion, with microstructural disruption at the depths of cerebral sulci, predominantly affecting the orbitofrontal region, and with relative sparing of deep WM regions. These in vivo findings reflect vulnerability of the depths of sulci to repetitive trauma and may serve as sensitive biomarkers for detecting and monitoring RHI-related brain injury. Leveraging these indicators of RHI-related injury could be used to characterize injury mechanisms and develop targeted approaches to early detection, harm reduction, and ultimately treatment of sport-related head trauma.

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## Author Contributions

B. DeMessie: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. W.F. Stewart: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R.B. Lipton: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Kim: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K. Ye: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M.E. Zimmerman: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. T.W. Kaminski: drafting/revision of the manuscript for content, including medical writing for content. R. Fleysher: major role in the acquisition of data. M.L. Lipton: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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