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RESEARCH

Soccer heading and white matter microstructural changes: a two-year longitudinal cohort study

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Abstract

Soccer is played by over 265 million people worldwide, with repetitive head impacts from ball heading being common practice. However, the long-term neurological effects of such impacts on amateur players remain poorly understood. This two-year longitudinal cohort study examined whether cumulative soccer ball heading affects white matter microstructure and cognitive performance in adult amateur players from the New York City metropolitan area.

The study followed 159 amateur soccer players (24.3% female, ages 18–53) who completed diffusion MRI scans and cognitive assessments at baseline and two-year follow-up. Heading exposure was quantified using the validated Head-Count-12 m questionnaire administered annually. Changes in DTI and NODDI parameters were analyzed across 10 white matter regions, alongside cognitive performance across six domains using the CogState battery.

Participants were categorized by two-year heading exposure: low ($n = 80$, median 304 headers), medium ($n = 39$, median 808 headers), and high ($n = 40$, median 2,073 headers). After FDR correction across 70 tests (7 diffusion metrics × 10 white matter ROIs), one association exceeded the correction threshold. In the right middle fronto-orbital white matter, low-exposure players showed significant ODI decrease (mean change = -0.020, $P < .001$), whereas high-exposure players showed no significant change (mean change = -0.006, $P = .16$), yielding a significant group difference in covariate-adjusted analyses ($\beta = 0.0132$, 95% CI [0.005, 0.0214]; Cohen d = 0.58; $P = .002$). While no cognitive performance measures showed significant associations with heading after multiple comparisons correction, increased right middle fronto-orbital white matter orientation dispersion index correlated with declining working memory performance ($\beta = -1.35$; 95% CI [-2.45, -0.24]; $P = .018$). These findings provide the first longitudinal evidence linking soccer heading exposure to white matter microstructural changes, highlighting the need for continued assessment of long-term neurological consequences in young adult players.

Keywords soccer heading · white matter microstructure · diffusion tensor imaging · repetitive head impacts · longitudinal neuroimaging

Introduction

Soccer heading involves low magnitude head impacts that cause linear and rotational brain acceleration-deceleration (Spiotta et al., 2012). Amateur league soccer players head the ball with a wide range of frequency (Michael L. Lipton et al., 2013). Heading is most often asymptomatic, but is also associated with CNS symptoms including headache and dizziness (Stewart et al., 2017) that sometimes lead to diagnosis of concussion (Rodrigues et al., 2016).

Cross-sectional studies of professional (Matser et al., 2001; Tysvaer & Løchen, 1991), collegiate (Downs & Abwender, 2002; Rutherford et al., 2009), adult amateur (Michael L. Lipton et al., 2013; Rubin et al., 2018), and high school players (Witol & Webbe, 2003) have, with few exceptions (Koerte et al., 2023), consistently shown greater

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long-term soccer-related repetitive head impact (RHI) exposure correlates with worse cognitive performance (Downs & Abwender, 2002; Matser et al., 1998, 1999; Rutherford et al., 2005). However, these cross-sectional studies cannot establish temporal relationships between RHI exposure and cognitive outcomes. Longitudinal studies better assess risk from continued play. One study found controls improved in sensorimotor function and cognition over one season while players with greater heading showed slower improvement (Koerte et al., 2022). A five-year study of professional players did not identify significant neurological, macrostructural, or neuropsychological changes (Kemp et al. 2016a, b). A recent review noted a paucity of longitudinal evidence regarding heading sequelae (Peek et al., 2023).

Neuroimaging provides an objective method for identifying variation in brain structure that may underlie or precede cognitive effects (Belanger et al., 2007). Cross-sectional studies of active adult amateur soccer players suggest that soccer-related RHI is associated with alterations in white matter microstructure (Michael L. Lipton et al., 2013; Rubin et al., 2018), while studies of former professional players show structural brain changes including cerebral atrophy (Adams et al., 2007; Sortland & Tysvaer, 1989) and cortical thinning (Koerte et al., 2016). Notably, cross-sectional morphometric analyses of active adult amateur players showed no associations of RHI with brain volume or cortical thickness (Oliveira et al., 2020). Diffusion MRI (dMRI), including diffusion tensor imaging (DTI) (Basser & Jones, 2002; Mori & Zhang, 2006) and neurite orientation dispersion density imaging (NODDI) (Zhang et al., 2012), have been used to study the microstructural properties of brain tissue and identify correlates of traumatic axonal injury attributed to RHI (Bahrami et al., 2016; Charney et al., 2023; Kawata et al., 2020; Michael L. Lipton et al., 2013) and to concussion (Hulkower et al., 2013; Niogi & Mukherjee, 2010; Palacios et al., 2020; Shenton et al., 2012). Compared with conventional CT and structural MRI, DTI and NODDI demonstrate higher sensitivity to microstructural injury associated with mild traumatic brain injury (mTBI) and RHI (Suri & Lipton, 2018). This study aimed to determine if 2-year soccer heading exposure is associated with change of brain microstructural and cognitive performance in adult amateur soccer players. We hypothesized that greater cumulative RHI exposure from soccer heading would be associated with altered longitudinal white matter microstructure trajectories. Based on prior cross-sectional evidence of RHI-associated changes in frontal and frontotemporal white matter, regions vulnerable to rotational acceleration forces during heading, we focused on 10 white matter ROIs in these anatomical territories. Given limited prior longitudinal NODDI data in this population, we treated this as an exploratory study examining multiple diffusion metrics with appropriate multiple comparison correction.

Methods

Study participants

Institutional Review Boards at Albert Einstein College of Medicine and Columbia University approved all procedures. Eligible amateur soccer players (aged 18–55) had > 5 years' playing experience and remained active > 6 months annually. Participants completed demographic questionnaires, cognitive assessments, and neuroimaging at baseline and two-year follow-up (recruitment details in eMethods). Clinical trial number: not applicable.

Assessment of repetitive heading impact exposure

HeadCount-12 m, a validated (Catenaccio et al., 2016), structured, computer-administered questionnaire, was used to estimate soccer heading exposure over the prior 12 months at each study visit. The questionnaire assessed soccer play during practice and competition in various settings, with details described in the eMethods. Two-year cumulative heading exposure was estimated and categorized into quartiles, with quartiles one and two combined to define the low heading exposure group, quartile three defining moderate exposure, and quartile four defining high exposure. Lifetime concussion history was also collected, with concussions defined as head injuries for which medical attention was advised or sought. As a sensitivity analysis, we also applied trimmed k-means clustering ($k=3$, $\alpha=0.05$) to identify data-driven exposure groups.

Magnetic resonance imaging

Imaging was performed using a 3.0T Philips Achieva TX scanner with a 32-channel head coil. The protocol included T1-weighted imaging, DTI, and NODDI. Detailed acquisition parameters and image processing protocols are provided in the eMethods. All neuroimaging data underwent detailed quality review by trained research staff. Images with motion artifacts, signal abnormalities, or incomplete acquisitions were excluded from analysis. A board-certified neuroradiologist (M.L.L.) reviewed all images for structural abnormalities or evidence of prior trauma. DTI and NODDI measures were averaged across regions of interest selected from the Johns Hopkins University brain atlas (Faria et al., 2010; Mori et al., 2008; Oishi et al., 2009), based on previous literature demonstrating alterations of dMRI metrics

in studies of RHI and mTBI (Bazarian et al., 2014; Echlin et al., 2021; Rosenbaum & Lipton, 2012). White matter regions comprised fronto-orbital white matter, precuneus white matter, superior corona radiata, superior parietal white matter, and uncinate fasciculus.

Cognitive functioning

Cognitive function was assessed using CogState, a validated computerized neuropsychological battery (Maruff et al., 2009). Tests evaluated working memory (Two Back Test (TWOB), processing speed (Groton Maze Chase Test (GMCT), attention (One Back Test (ONB), Identification Test (IDN), and verbal learning and memory (International Shopping List – Immediate (ISL) and Delayed Recall (ISRL). Details are provided in the eMethods.

Statistical analysis

Analyses were performed in R statistical programming language (version 4.3.2) (R Development Core Team, 2017). All participants underwent MRI and cognitive assessment at baseline (0 months) and follow-up (two years). Change values were computed as the difference between follow-up and baseline measurements; these change values served as dependent variables in linear models. Heading exposure group was included as the primary predictor, with adjustments for baseline measurement, age, sex, and concussion history (categorized as 0, 1, or ≥2 previous concussions).

We assessed exposure-related changes in brain microstructure and cognitive performance between baseline and 24-month follow-up using linear regression:

$$\triangle Y_{i,0-2} = \beta_0 + \beta_1 Medium + \beta_2 High + \beta_3 Y_{i,0} + \beta_4 Age + \beta_5 Sex + \beta_6 Concussion + \varepsilon_i$$

where $\Delta Y_{i,0-2}$ represents change from baseline to two years for participant *i*. Exposure was coded categorically (low = reference). In regression models, Medium and High are binary indicator variables (0/1) representing exposure group membership, with Low exposure as the reference category. Sex is coded as binary (0 = female, 1 = male). All other variables were entered as continuous variables. Coefficients β_1 and β_2 estimate exposure effects adjusted for baseline values and demographics. Models were fit separately for each outcome.

We used the above change score analysis method (24-month minus baseline ODI) as our primary approach, adjusting for baseline outcome values. For two-timepoint data, this approach is statistically equivalent to a linear mixed-effects model with a time × group interaction (Fitzmaurice et al., 2012). As a sensitivity analysis, we confirmed our results using mixed-effects models with random intercepts for subjects and a time × exposure group interaction term. Covariates for the primary analysis were selected a priori based on established associations with brain microstructure: age, sex, prior concussion history, and baseline values of the outcome measure. To evaluate robustness of significant findings to potential confounding, we conducted additional sensitivity analyses using two complementary approaches: (1) E-value analysis to quantify the minimum strength of association that an unmeasured confounder would need with both exposure and outcome to fully explain the observed association; and (2) comparison of nested regression models using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Potential confounders evaluated included smoking history, years of education, and alcohol consumption. We examined heading exposure as a continuous exposure variable (per 1,000 headings over 2 years) using linear regression models adjusted for baseline values, age, sex, and concussion history. We also tested for nonlinearity by comparing linear models to models including a quadratic exposure term using likelihood ratio tests. We tested for effect modification by sex, age (≤25 vs. >25 years), and education (≤16 vs. >16 years) by including interaction terms (exposure group × modifier) in models adjusted for baseline ODI, age, and concussion history. Stratified analyses were conducted within demographic subgroups. All models used robust (HC1) standard errors to account for potential heteroscedasticity. To characterize normative outcome trajectories, we examined participants with minimal heading exposure (≤100 cumulative headings over the 2-year study period, including 10 with zero headings) as an internal reference population. We tested whether age was associated with outcome change within the Low exposure group using linear regression adjusting for sex and concussion history. To examine whether within-person variability in heading exposure was associated with brain microstructure changes beyond cumulative exposure, we calculated two trajectory metrics for subjects with heading data at all three timepoints (baseline, 12-month, and 24-month): (1) coefficient of variation (CV), defined as the standard deviation of heading counts across timepoints divided by the mean, quantifying relative variability in exposure; and (2) non-linearity, defined as the absolute deviation of the 12-month heading count from the linear interpolation between baseline and 24-month values, capturing spike or dip patterns. These metrics were standardized (*z*-scored) and entered as predictors in regression models adjusting for cumulative heading exposure, baseline outcome, age, sex, and concussion history.

To investigate potentially relevant structure-function relationships, we established an a priori analytical plan to examine associations between diffusion metric change and cognitive change. To limit the number of statistical tests, we

only tested correlation of change in cognitive performance with change in microstructure measures from brain regions demonstrating significant associations of change in microstructure measures with RHI (Yadav & Lewis, 2017). For each region showing a significant association of RHI with change in dMRI, we fit:

$$\Delta C_{i,0-2} = \gamma_0 + \gamma_1 \Delta M_{ri,0-2} + \gamma_2 C_{i,0} + \gamma_3 Age + \gamma_4 Sex + \gamma_5 Concussion + v_i$$

Where $\Delta C_{i,0-2}$ represents two-year cognitive change, $\Delta M_{ri,0-2}$ represents microstructural change in region r for participant i showing significant exposure effects, and $\Delta C_{i,0}$ is baseline cognitive performance. The coefficient γ_1 quantifies the structure-function relationship adjusted for baseline performance and demographics.

All reported regression coefficients are unstandardized. *P*-values presented are uncorrected. This study was exploratory in nature, examining associations between RHI exposure and longitudinal change across 7 diffusion MRI metrics (FA, AD, RD, MD, ICVF, ISO, ODI) in 10 white matter ROIs (bilateral middle fronto-orbital white matter, superior corona radiata, uncinate fasciculus, superior parietal white matter, and precuneus white matter). To control for multiple comparisons across these 70 tests, we applied Benjamini-Hochberg false discovery rate (FDR) correction with $\alpha = 0.05$ (Benjamini & Hochberg, 1995). Cognitive outcomes were analyzed as secondary endpoints. To assess potential selection bias from participant attrition, we compared baseline characteristics between participants who completed both study visits with analyzable imaging data ($n = 140$) and those who only completed the baseline visit ($n = 211$). This comparison allowed us to determine whether systematic differences existed between retained and lost-to-follow-up participants that could influence the generalizability of our findings. Wilcoxon rank-sum tests were used for continuous variables and chi-square tests for categorical variables. We conducted post hoc power calculations using a two-sided significance level of $\alpha = 0.05$ and power of 80%. The observed study data had 80% power to detect differences between the groups of Cohen $d = 0.59$ in the neuroimaging outcomes and Cohen $d = 0.55$ in the cognitive outcomes.

Results

The analysis included 159 participants who completed both baseline and two-year follow-up assessments. For the cognitive analysis, all 159 participants were categorized into RHI exposure groups (80 low, 39 medium, 40 high). Cohort characteristics for the cognitive analysis are presented in Table 1. For the neuroimaging analysis, quality inspection

Table 1 Cohort Demographic Characteristics by RHI-Exposure Group

Characteristic[a]	Low	Medium	High	*P* Value
Sample size (n)	80	39	40	
Headers/year, median (IQR)	304.0 (117.0-591.5)	808.0 (461.0–1,464.5)	2,073.0 (1,274.0–3,943.5)	<0.001
Male sex, n (%)	53 (66.2)	32 (82.1)	35 (87.5)	0.02
Age, mean (SD)	28.0 (8.5)	26.6 (7.3)	24.6 (6.1)	0.07
Handedness, No. (%)				0.20
Right	73 (91.2)	35 (89.7)	37 (92.5)	
Left	2 (2.5)	4 (10.3)	2 (5.0)	
Mixed	5 (6.2)	0 (0.0)	1 (2.5)	
Education years, mean (SD)	16.4 (2.2)	15.9 (2.2)	14.9 (2.3)	0.001
Race[b], No. (%)				0.02
White	55 (68.8)	21 (53.8)	15 (37.5)	
Black or African American	13 (16.2)	8 (20.5)	13 (32.5)	
Asian	3 (3.8)	4 (10.3)	1 (2.5)	
Not Reported	7 (8.8)	6 (15.4)	11 (27.5)	
Past or present smoker	22 (27.5)	15 (38.5)	9 (22.5)	0.27
Alcohol consumption, No. (%)				<0.001
0 drinks/week	13 (16.2)	7 (17.9)	21 (52.5)	
1–2 drinks/week	30 (37.5)	18 (46.2)	13 (32.5)	
3–7 drinks/week	27 (33.8)	12 (30.8)	2 (5.0)	
8–14 drinks/week	9 (11.2)	2 (5.1)	3 (7.5)	
>14 drinks/week	1 (1.2)	0 (0)	1 (2.5)	
Concussion History				0.98
0 concussions	54 (67.5)	27 (69.2)	29 (72.5)	
1 concussion	12 (15.0)	6 (15.4)	5 (12.5)	
≥2 concussions	14 (17.5)	6 (15.4)	6 (15.0)	
Baseline Cognitive Performance				
IDN speed, mean (SD)	2.6 (0.5)	2.6 (0.4)	2.7 (0.4)	0.80
ISL correct, mean (SD)	26.6 (3.7)	26.5 (3.4)	24.6 (4.2)	0.02
ISRL correct, mean (SD)	9.5 (1.9)	9.7 (1.6)	8.7 (2.0)	0.03
ONB speed, mean (SD)	2.9 (0.1)	2.8 (0.5)	2.9 (0.1)	0.35
TWOB accuracy, mean (SD)	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	0.41
GMCT speed, mean (SD)	1.5 (0.5)	1.5 (0.4)	1.3 (0.6)	0.08

P values from one-way ANOVA (continuous variables), Kruskal-Wallis (cumulative heading), and chi-square test (categorical variables).Abbreviations: IQR, interquartile range; IDN, Identification; ISL, International Shopping List; ISRL, International Shopping List Delayed Recall; ONB, One Back Test; TWOB, Two Back Test; GMCT, Groton Maze Chase Test.[a] Summary for neuroimaging sub-cohort is provided in eTable 1.[b] Race was captured via participant self-report using fixed categories.

of MRI data identified acceptable images for 140 of the 159 participants (88.1%), who were similarly categorized by exposure (71 low, 35 medium, 34 high). Demographic characteristics for the neuroimaging subcohort are provided in eTable 1. Demographic comparisons between exposure groups revealed that participants in the high-exposure group were younger (mean age 24.6 vs. 28.0 years; $P = .025$), had fewer years of education (14.9 vs. 16.4 years; $P = .001$), and were more likely to be male (87.5% vs. 66.2%; $P = .02$) compared with the low-exposure group (Table 1). Smoking history ($P = .66$) and prior concussion history ($P = .85$) did not differ significantly between high and low exposure groups.

As a descriptive characterization of the cohort, we defined longitudinal trajectory categories based on heading frequency at baseline, 12 months, and 24 months. 56 participants (35%) demonstrated consistently decreasing heading frequency across all assessments (mean [SD] age, 26.3 [7.5] years), whereas nine participants (6%) showed consistently increasing frequency (mean [SD] age, 28.6 [12.0] years). The age difference between these groups was not statistically significant (mean difference, 2.2 years; $P = .60$). The remaining participants exhibited variable trajectories (mean [SD] age, 26.5 [7.4] years), with no significant age difference compared with those showing consistent trajectories (mean difference, −0.2 years; 95% CI, −2.8 to 2.4; $P = .91$).

Regional changes over time in microstructure by RHI exposure group

Among the 10 white matter analyzed, one association exceeded the FDR correction threshold. High versus low heading exposure was associated with attenuated two-year decrease in orientation dispersion index (ODI) in the right middle fronto-orbital white matter ($\beta = 0.0132$, 95% CI, 0.005 to 0.0214; Cohen $d = 0.58$, 95% CI, 0.17 to 0.99; $P = .002$), after adjusting for baseline ODI, age, sex, and concussion history (Fig. 1). Other DTI and NODDI metrics did not reach significance after FDR correction. Within-group analyses (one-sample t-tests) examined whether each exposure group's ODI change differed significantly from zero. In the right middle fronto-orbital white matter, low-exposure players showed significant ODI decrease consistent with developmental maturation (mean change = -0.020, $P < .001$), whereas high-exposure players showed no significant change (mean change = -0.006, $P = .16$), yielding a significant group difference in covariate-adjusted analyses ($\beta = 0.0132$; 95% CI, 0.005 to 0.0214; Cohen d = 0.58; $P = .002$). Among 21 participants with minimal heading exposure (≤100 cumulative headings), ODI trajectories in the fronto-orbital region differed significantly from the High exposure group ($P = .03$). Within the Low exposure group ($n = 70$; age range 18–53 years), age was not significantly associated with 2-year ODI change (β = -0.0002 per year, $P = .55$), indicating that age-related variation does not confound exposure group comparisons.

Treating heading exposure as a continuous variable showed a significant association with ODI change ($\beta = 0.0047$ per 1,000 headings; 95% CI, 0.0015 to 0.0079; $P = .004$), though likelihood ratio tests revealed significant nonlinearity ($P = .008$), supporting the use of categorical exposure groupings (eResults, eTable 2). Sensitivity analysis using linear mixed-effects models with random intercepts and time × exposure group interaction terms yielded equivalent conclusions for the fronto-orbital region ($\beta = 0.019$, SE = 0.006, $P = .003$; eResults), consistent with our primary change score analysis. E-value analysis (E = 4.22) indicated substantial robustness to unmeasured confounding, and model comparison using AIC and BIC favored the parsimonious base model over models including additional covariates (eResults, eTable 3). Results remained significant after adjustment for smoking, education, and alcohol consumption (all $P < .01$). Sensitivity analysis using trimmed k-means clustering to define exposure groups (Low $n = 80$, Medium $n = 66$, High $n = 13$) yielded consistent findings for the fronto-orbital region ($\beta = 0.0222$; 95% CI, 0.0097 to 0.0348; $P < .001$; eResults). Heading trajectory characteristics (coefficient of variation and non-linearity) were not significantly associated with ODI change after adjusting for cumulative exposure (eResults, eTables 4–5).

Tests for effect modification revealed a significant sex × RHI exposure interaction ($P = .01$; eResults, eTable 6). Sex-stratified analyses showed the association was significant among males ($\beta = 0.0169$, $P < .001$) but not females (β = -0.0071, $P = .40$; eResults, eTable 7). Age-stratified analyses showed significant associations among younger participants (≤25 years: $\beta = 0.0133$, $P = .008$) but not older participants (>25 years: $\beta = 0.0086$, $P = .22$). Education-stratified analyses showed significant associations among those with ≤16 years of education ($\beta = 0.0160$, $P < .001$) but not those with >16 years ($\beta = 0.0024$, $P = .77$).

Cognitive change over time by RHI exposure group

Among the six cognitive measures, change of performance over two years did not differ significantly by exposure group after FDR correction (Table 2). These results indicate that the effect of RHI on cognitive metrics is smaller than Cohen $d = 0.55$ at 80% confidence level.

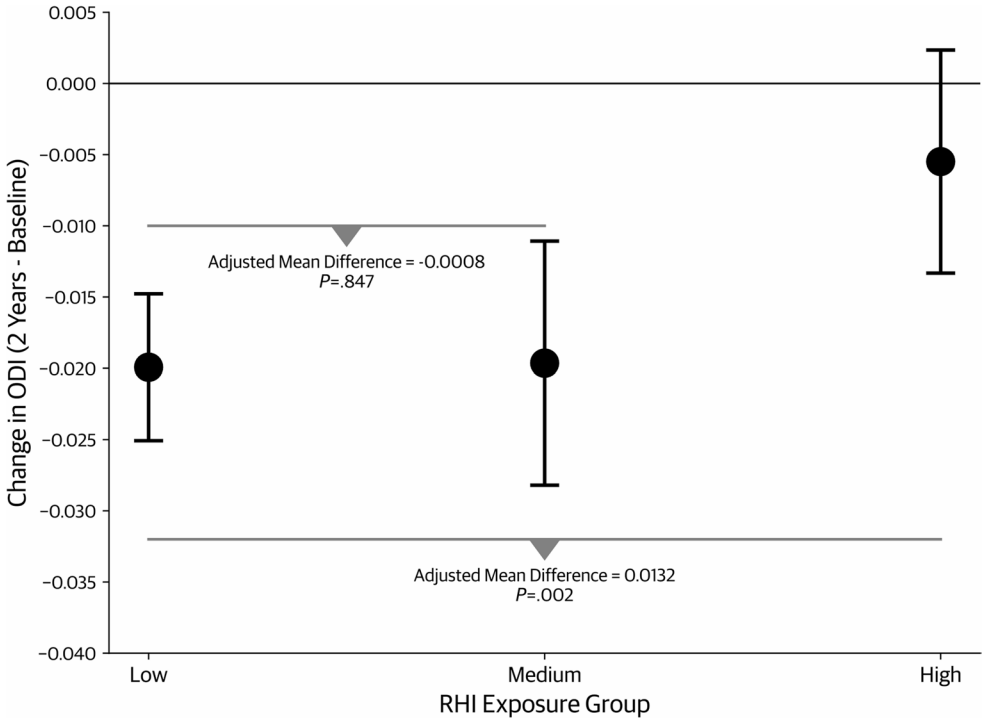

Fig. 1 Two-Year Change in Orientation Dispersion Index in the Right Middle Fronto-orbital White Matter by Repetitive Head Impact Exposure Level. Mean 2-year change in orientation dispersion index (ODI) from baseline to 24-month follow-up in the right middle fronto-orbital white matter region among soccer players stratified by repetitive head impact (RHI) exposure level. Error bars indicate 95% CIs. The adjusted mean differences and P values are from linear regression models comparing medium vs. low and high vs. low exposure groups, adjusted for baseline ODI value, age, sex, and concussion history. The high RHI exposure group showed a significantly smaller decrease in ODI compared with the low exposure group, while the medium vs. low comparison was not statistically significant

Fronto-orbital white matter integrity predicts cognitive performance

Following preplanned analyses, we examined whether the significant microstructural changes predicted cognitive performance changes. Increases in right middle fronto-orbital white matter ODI were significantly associated with worsening performance on a working memory task (TWOB; β = -1.35; 95% CI, -2.45 to -0.24; P = .018) (Fig. 2). No significant associations were found between these ODI changes and verbal learning (ISL), verbal memory (ISRL), attention (ONB, IDN), or processing speed (GMCT).

Assessment for potential bias due to selective attrition

Study participants who completed the two study visits compared with those who only completed the baseline visit were marginally older at the time of the baseline visit (median [IQR], 26.39 [22.76–30.02] vs. 25.03 [21.27–28.80] years; difference, 1.36 years; P = .01) and had a lower proportion of female participants (34 of 140 [24.3%] vs. 74 of 211 [35.1%]; difference, −10.8%; P = .043). The follow-up completion group had a lower proportion of participants reporting prior concussions compared to the group who only completed the baseline visit (39 of 140 [27.9%] vs. 89 of 211 [42.2%]; difference, −14.3%; P = .023), despite both groups having identical median values (median [IQR], 0 [0–1] for both groups). Educational attainment was similar between the two groups, with the follow-up completion group having a median of 15.83 [IQR, 14.69–16.97] years of education compared to 15.55 [14.45–16.66] years for the group who only completed the baseline visit (P = .21). Baseline heading exposure also did not differ significantly between the groups, with the follow-up completion group having a median of 660 [IQR, 0-1394] headers compared to 695 [0-1607] for the group who only completed the baseline visit (P = .67).

Discussion

Our two-year longitudinal investigation is the first to examine microstructural effects from soccer RHI using advanced dMRI techniques over an extended follow-up period. We detected measurable white matter microstructural change over two years in young, active players. The findings may represent early markers of cumulative RHI effects While cognitive performance did not significantly decline over two years, the white matter changes could precede cognitive decline, consistent with other environmental exposures where tissue pathology precedes clinical effects (Jack et al., 2010; Sotiropoulos et al., 2011). These findings thus warrant further confirmation and follow-up. Our failure to detect cognitive effects may also reflect limited statistical power, as the study was only powered to detect effect sizes of Cohen d=0.55 or larger for group comparisons in the cognitive cohort. No significant cognitive effects were observed in two previous longitudinal studies that examined soccer RHI effects in 16 adolescents (Koerte et al., 2017) and in

Table 2 Association of Cognitive Changes Over Time with RHI Exposure Group

Contrast	Cognitive Test	Unstandardized β (95% CI)	Cohen d (95% CI)	*P* Value[a]
Group (Medium vs. Low)	Verbal Learning (ISL)	-0.571 (-1.877 to 0.734)	-0.17 (-0.55 to 0.21)	0.39
Group (High vs. Low)		-1.210 (-2.550 to 0.130)	-0.35 (-0.73 to 0.03)	0.08
Group (Medium vs. Low)	Verbal Memory (ISRL)	-0.090 (-0.709 to 0.529)	-0.06 (-0.44 to 0.33)	0.77
Group (High vs. Low)		-0.601 (-1.228 to 0.025)	-0.37 (-0.75 to 0.01)	0.06
Group (Medium vs. Low)	Attention (IDN)	0.001 (-0.025 to 0.028)	0.01 (-0.37 to 0.40)	0.94
Group (High vs. Low)		0.025 (-0.003 to 0.052)	0.35 (-0.03 to 0.73)	0.08
Group (Medium vs. Low)	Attention (ONB)	-0.029 (-0.063 to 0.004)	-0.35 (-0.73 to 0.04)	0.08
Group (High vs. Low)		0.014 (-0.019 to 0.046)	0.16 (-0.22 to 0.54)	0.41
Group (Medium vs. Low)	Working Memory (TWOB)	-0.010 (-0.069 to 0.049)	-0.07 (-0.45 to 0.32)	0.74
Group (High vs. Low)		-0.065 (-0.125 to -0.006)	-0.42 (-0.81 to -0.04)	0.03
Group (Medium vs. Low)	Processing Speed (GMCT)	0.021 (-0.088 to 0.129)	0.07 (-0.31 to 0.46)	0.71
Group (High vs. Low)		-0.124 (-0.238 to -0.010)	-0.42 (-0.80 to -0.04)	0.03

Abbreviations: ISL, International Shopping List; ISRL, International Shopping List Delayed Recall; IDN, Identification; ONB, One Back Test; TWOB, Two Back Test; GMCT, Groton Maze Chase Test.Exposure group contrasts were derived from linear regression adjusted for baseline cognitive test performance, age, sex, and concussion history.[a] No significant group differences in longitudinal performance remained after FDR correction for multiple comparisons

24 professional players (Steven Kemp et al. 2016a, b). Our investigation addresses key limitations of these studies by implementing a sensitive dMRI approach, examining both male and female adult recreational players, and employing longer follow up over a two-year period.

In contrast to previous cross-sectional studies in contact athletes (Brett et al., 2024; Churchill et al., 2017; Mayer et al., 2017), our investigation is the first to longitudinally track microstructure alterations in soccer players with NODDI, revealing subtle microstructural change that may represent early marker of cumulative RHI effects. NODDI leverages multi-shell acquisition to model diffusion across three tissue compartments: free water, extracellular water, and intracellular water characterized as the parameters: ODI (reflecting the angular variation of neurites), ICVF (representing neurite density), and ISO (measuring the proportion of unrestricted diffusion, typically associated with cerebrospinal fluid and edema), respectively. Importantly, NODDI disentangles coherence of fiber orientation from fiber density, properties that are combined in the FA parameter in DTI. In our analysis, only ODI showed significant between-group differences after FDR correction, while ICVF and ISO did not differ significantly between exposure groups. The preservation of ICVF suggests that despite RHI, there was no detectable reduction in axonal density or neuronal loss during this two-year timeframe. This may indicate that alterations in fiber organization (indexed by ODI) occurs before frank neurodegeneration, though alternatively, concurrent neuroinflammatory processes could potentially mask axonal or myelin loss. Similarly, the absence of ISO differences does not indicate an association of RHI with measurable edema in the examined ROIs.

Our study identified one white matter region with significant heading-related ODI changes after FDR correction for 70 tests (7 diffusion metrics × 10 white matter ROIs). In the right middle fronto-orbital white matter, the Low RHI group exhibited significant ODI decrease over two years, consistent with expected developmental maturation, whereas the High RHI group showed no significant ODI change. This pattern, attenuated decrease rather than absolute increase, indicates that the effect of higher overall exposure level is attenuation of the expected developmental decrease. The fronto-orbital cortex is associated with decision-making and flexible behavior (Klein-Flügge et al., 2022), and disruption of its white matter connectivity could have functional implications. The attenuated ODI decrease observed in high-exposure players in the fronto-orbital region represents absence of the expected developmental reduction seen in low-exposure players. During early adulthood, ODI typically decreases as axonal organization becomes more coherent. The absence of this expected decrease in high-exposure players could reflect disrupted developmental processes, or alternatively, pathological effects that override expected developmental changes. Given that multiple cellular processes occur in parallel within each voxel, the observed net effect likely represents a combination of concurrent mechanisms (Yi et al., 2019, 2020).

Regional specificity suggests fronto-orbital white matter vulnerability to heading exposure, likely reflecting biomechanics where rotational forces transmit through the brain, with frontal regions experiencing greater strain due to their position relative to the neck rotation axis (Perkins et al., 2022). Previous mTBI studies have similarly demonstrated preferential frontal white matter involvement (DeMessie et al., 2025; Eierud et al., 2014). Soccer training's mechanical and physiological demands may modulate region-specific vulnerabilities through impact frequency, angular acceleration, and playing style.

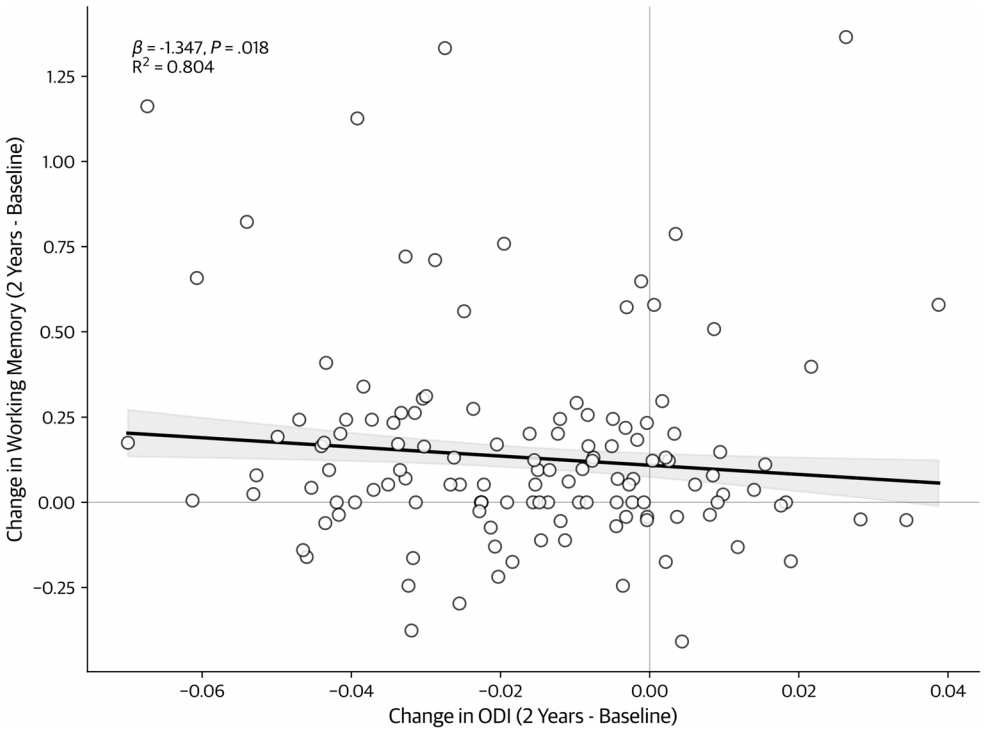

Fig. 2 Two-Year Changes in Fronto-orbital White Matter Microstructure Predict Working Memory Performance in Soccer Players. Increases in orientation dispersion index (ODI) in the right middle fronto-orbital white matter were associated with worsening Two-Back working memory performance over 2 years in amateur soccer players. Each circle represents 1 participant. The black line indicates the fitted regression line from a multivariable linear model adjusted for baseline TWOB performance, age, sex, and concussion history. The gray shaded area represents the 95% CI for the regression line. The R2 value reflects the full multivariate model adjusting for baseline ODI, age, sex, and concussion history. The scatter in the displayed data reflects the unadjusted marginal relationship; the adjusted model accounts for additional variance explained by covariates

The significant finding was localized to the right hemisphere. Hemispheric asymmetry in white matter microstructure is a fundamental organizing principle of the nervous system that enables functional specialization. NODDI studies in children have demonstrated hemispheric asymmetries in ODI across white matter tracts (Parekh et al., 2023). This rightward asymmetry is established in early childhood and remains stable across development, suggesting it reflects an intrinsic feature of white matter organization rather than maturational differences (Dimond et al., 2020). Large-scale lifespan studies spanning infancy to late adulthood have confirmed that such asymmetries are ubiquitous across major white matter pathways, though the direction and magnitude of lateralization are feature-dependent and pathway-specific (Kanakaraj et al., 2025). The corresponding left hemisphere regions showed similar directions of effect but did not survive correction for multiple comparisons. We therefore cannot exclude the possibility that the observed lateralization reflects differential detection sensitivity rather than a true biological asymmetry in vulnerability to RHI. Notably, the temporal dynamics of lateralized white matter changes following head impact may be complex. A recent prospective study of soccer heading found that acute changes evolved toward left-hemisphere predominance over subsequent months, suggesting that the hemisphere showing greater effects may depend on the timeframe of assessment (McCloskey et al., 2025). Future studies with larger samples and multiple assessment timepoints are needed to determine whether right-hemisphere predominance in ODI changes is a reproducible finding in longitudinal RHI research.

The significant sex × RHI interaction observed for the fronto-orbital white matter suggests potential sex differences in susceptibility to RHI effects. While the association between heading exposure and ODI change was evident among male participants, no significant association was observed among females. Prior cross-sectional research has suggested sex differences in RHI outcomes (Rubin et al., 2018), potentially related to hormonal influences, neck strength, or structural brain differences. Exploratory analysis of heading trajectory characteristics revealed that exposure variability (coefficient of variation) was not associated with ODI change beyond cumulative exposure. Interestingly, non-linearity in heading trajectories, reflecting spikes or dips at the 12-month assessment, was significantly associated with ODI change but in the opposite direction from cumulative exposure effects. This suggests that intermittent or variable exposure patterns may not produce the same sustained microstructural effects as overall exposure levels. These findings support our use of cumulative exposure as the primary exposure metric.

We found no significant RHI effect on FA change, the most widely reported dMRI metric in sport-related head impacts (Koerte et al., 2023). FA represents the overall directional coherence of diffusion within a voxel but lacks compartmental specificity, potentially conflating changes occurring in different tissue microenvironments (Soares et

al., 2013). ODI specifically quantifies extracellular neurites angular variation, making it more sensitive to cellular disorganization. Competing microstructural alterations may oppositely affect FA while consistently increasing ODI. Additionally, FA can normalize despite persistent damage (Edlow et al., 2016), potentially masking cumulative RHI effects detectable through ODI.

Longitudinal normative NODDI data in healthy adults remain scarce. Cross-sectional lifespan studies report age-related ODI increases in white matter, with effects modest before age 50 (Billiet et al., 2015; Chang et al., 2015; Kodiweera et al., 2016). Lehmann et al. (2021) reported high test-retest reproducibility for ODI (ICC > 0.8), indicating measurement stability. Our cohort (mean age 26 years) falls within the early adult period where minimal age-related ODI change is expected. The within-group findings provide interpretive context for the between-group differences. The Low RHI group's significant ODI decrease is consistent with ongoing myelination and axonal organization characteristic of early adulthood, a normative developmental pattern. The High exposure group's fronto-orbital ODI showed no significant change from zero, while the Low group showed significant decrease. Analysis of the minimally exposed subgroup (≤100 headings) showed no evidence that age-related variation confounds the exposure group comparisons. The consistency of trajectories among minimally-exposed participants supports their utility as an internal normative reference.

Cognitive performance typically improves through practice effects (Salthouse, 2010), observed in our cohort. Based on prior cross-sectional findings (Levitch et al., 2018; M. L. Lipton et al., 2013), we explored whether high RHI exposure would be associated with attenuated cognitive improvement compared to low exposure. No significant associations between heading exposure and cognitive change were observed after multiple comparison correction, possibly reflecting limited statistical power, measurement error in neuropsychological assessment (Duff, 2012), or the possibility that microstructural changes precede detectable cognitive effects in this young adult population. Alternative explanations warrant consideration. First, cognitive reserve may mask overt effects of underlying neuropathological changes (Stern et al., 2019). Athletes may develop robust cognitive reserve through years of sport-specific cognitive demands. Physical fitness provides additional cognitive enhancement and neuroprotection (Singh et al., 2025; Tari et al., 2025), potentially explaining why structural abnormalities may not immediately manifest as performance deficits (Barulli & Stern, 2013). Second, our assessment timepoints at baseline, 12 months, and 24 months may not align with RHI-related cognitive change evolution. Third, cognitive deficits may require cumulative RHI exposure thresholds not reached during our two-year study period. However, microstructural changes identified before cognitive decline emerges could represent early markers of emerging injury and open a critical window for prevention of irreversible dysfunction. Early detection could be particularly valuable if brain changes are reversible during this preclinical phase. These are important areas for future investigation. Our cognitive tests may not have optimally targeted regions showing greatest imaging changes. Though not statistical significant after multiple comparison correction, high RHI exposure players showed trends toward reduced working memory performance and processing speed (Table 2).

Significant associations between increased right middle fronto-orbital ODI and decreased working memory performance contextualize the potential functional significance of microstructural alterations. Following our a priori analysis plan, white matter changes may disrupt neural networks critical for information processing and working memory (Kinnunen et al., 2011). The orbitofrontal region contains prefrontal-subcortical projection fibers involved in multiple cognitive processes (Rolls, 2019); injury to these fibers could impair network efficiency (Blennow et al., 2016). While group-level cognitive change was not significant after correction, association of structural and cognitive change among athletes with high RHI exposure suggest structural alterations may predict subsequent cognitive changes consistent with a subclinical injury model where microstructural changes precede functional effects (Hellstrøm et al., 2017; Jack et al., 2010). The ODI-performance association provides a pathway explaining previously reported cross-sectional heading-cognition relationships (Levitch et al., 2018; M. L. Lipton et al., 2013). Future studies with larger samples and longer follow-up may better detect downstream cognitive consequences suggested by these emergent structure-function relationships. As a sensitivity analysis, we applied trimmed *k*-means clustering to identify data-driven exposure groups; this approach yielded similar findings to the quartile-based analysis (see eResults), supporting the robustness of our results across different exposure categorization methods. Future multi-site studies could evaluate whether specific heading thresholds predict clinically meaningful outcomes.

Limitations

The primary exposure metric, estimated number of headers, was assessed using HeadCount-12 m. Although this instrument has demonstrated validity in previous research (Catenaccio et al., 2016), its self-report nature introduces potential recall bias. However, this bias is likely

to attenuate significant effects rather than create false systematic effects, and the instrument has shown stable quartile assignment across repeated assessments and consistent performance across multiple independent cohorts (Catenaccio et al., 2016; Lipton et al., 2018). Estimated number of headers was positively skewed, so we categorized RHI, rather than treat it as a continuous variable. However, sensitivity analyses treating RHI as a continuous variable yielded similar results (eTable 2). Even the Low exposure group is not entirely unexposed, and a true non-heading control group would strengthen interpretation. However, the consistency of ODI trajectories within the Low group, including the 21 participants with ≤100 headings, and the absence of age effects supports its utility as an internal reference. Future longitudinal studies with dedicated non-athlete control groups would provide more definitive normative benchmarks. The two-year follow-up period is likely insufficient to fully characterize the long-term consequences of RHI exposure in soccer. Participant attrition occurred during the study period, potentially introducing bias if those who dropped out differed systematically from those who remained. For example, women were less likely to complete follow-up. However, we found no evidence of differential attrition across other characteristics examined. This differential attrition by sex suggests that our findings might underestimate the true effect magnitude, particularly for women, if those who experienced more adverse effects were more likely to drop out. Separately, the exclusion of poor-quality neuroimaging data further reduced the sample size but strengthened the validity of our findings by ensuring high-quality data for analysis. The a priori ROI approach to image quantification may have reduced sensitivity to spatially heterogeneous microstructural changes across individuals. The study population comprised adult amateur soccer players from the northeastern United States, potentially limiting the generalizability of our findings to other demographic groups, geographic regions, or levels of play. Nonetheless, our cohort's characteristics have been described as comparable to those of adult amateur soccer players in general (Lingsma & Maas, 2017). This study was exploratory, without a pre-specified primary imaging endpoint. While we applied FDR correction across 70 tests, future confirmatory studies with pre-registered hypotheses targeting specific metrics and regions are needed to validate these findings. Whether the observed sex difference in associations reflects true biological differences in susceptibility to RHI or insufficient statistical power among female participants cannot be determined from these data. Future studies should prioritize recruitment of female athletes from heading-intensive positions.

Conclusion

Greater RHI over two years was associated with attenuated ODI decrease in right middle fronto-orbital white matter, suggesting RHI from soccer heading may disrupt normative white matter maturation among adult amateur players. Considering adverse associations of dMRI change with cognitive performance change, further investigation is needed to characterize the longer-term impact of RHI on brain health.

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Data availability Deidentified participant data are available in the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System (National Institutes of Health, Center for Information Technology) at [https://fitbir.nih.gov/study_profile/220] (https:/fitbir.nih.gov/study_profile/220) . Qualified researchers can request access to data stored in FITBIR for research purposes only (not commercial) with the intention to enhance knowledge for the benefit of human health. Individuals requesting access must have a medical or scientific degree or position relevant for the request and must be affiliated with a research, industry, or non-profit institution. All data access requests must be signed by an individual legally authorized to sign on behalf of the institution. To gain access to shared data, an investigator must obtain data access privileges from the Data Access and Quality Committee established to oversee access to the FITBIR shared data.

Code Availability Not applicable.

Declarations

Ethics approval The study and procedures were approved by the Institutional Review Boards of Albert Einstein College of Medicine and Columbia University Irving Medical Center. The study adhered to ethical standards for research involving human participants in accordance with the Declaration of Helsinki.

Consent for publication Not applicable.

Consent to participate Written informed consent was obtained from all participants before study enrollment.

Competing interests R.B. Lipton discloses the following: U01 AT011005 (Investigator), 1R01 AG075758 (Investigator), 1R01 AG077639 (Investigator), 1RO1A1011875 (Investigator), 1RM1DA0055437 (Investigator), RO1AG080635 (Investigator), SG24988292 (Investigator), U19AGO76581 (Investigator), 1RO1NS123374 (Investigator), R61NS125153 (Investigator), and K23 NS107643 (Mentor); he receives support from the Migraine Research Foundation and the National Headache Foundation and research grants from TEVA, Satsuma, and Amgen; he serves on the editorial board of Neurology®, is a senior advisor to Headache, and is an associate editor to Cephalalgia; he has reviewed for the NIA and National Institute of Neurological Disorders and Stroke; he holds stock and stock options in Biohaven Holdings, CoolTech, and NuVieBio; he serves as a consultant and an advisory board member, or has received honoraria from Abbvie (Allergan), the American Academy of Neurology, the American Headache Society, Amgen, Axsome, Biohaven, Eli Lilly, GlaxoSmithKline, Grifols, Lundbeck (Alder), Manistee, Merck, Pernix, Pfizer, Satsuma, Supernus, Teva, Vector, and Vedanta. He receives royalties from Wolff's Headache 7th and 8th Edition, Oxford Press University, 2009, Wiley and Informa. All other authors report no disclosures relevant to the manuscript.

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