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ORIGINAL RESEARCH

Framing potential for adverse effects of repetitive subconcussive impacts in soccer in the context of athlete and non-athlete controls

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Abstract
The benefits of athletic activity may be attenuated by sport-related head impacts, including soccer-related concussion and subconcussive events. The purpose of this study is to characterize the specific effects of soccer heading on white matter microstructure and cognitive function, independent of concussion, relative to non-athlete controls and relative to active athletes who are not involved in collision sports. 246 amateur soccer players, 72 non-contact/non-collision sports athletes and 110 healthy,non-athlete controls were included in the study, and underwent cognitive testing and 3T diffusion tensor imaging (DTI). Voxelwise linear regression, comparing soccer players and non-contact/non-collision sports athletes healthy,non-athlete controls, identified regions of abnormally low and high fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) in athlete participants. Generalized estimating equations were used to examine the effects of 2 week and 1 year heading exposure quartile on cognitive performance and on the volume of each high and each low DTI parameter. Athletes with no or lower exposure to repetitive heading exhibited greater expression of low RD, greater expression of high FA and better performance on tasks of attention, processing speed, verbal memory, and working memory compared to non-athletes. Soccer players with the highest exposure to repetitive head impacts, however, did not differ significantly from healthy, non-athletes on either micro-structural features or cognitive performance, findings not explained by concussion history or demographic factors. These results are consistent with the notion that beneficial effects of athletic conditioning or training on brain structure and function may be attenuated by exposure to repeated subconcussive head impacts.

Introduction

Athletic activity confers beneficial effects on brain health (Forbes et al. 2013; Hillman et al. 2008; Callisaya and Nosaka 2017), a factor to consider in the overall risk and benefit equation for sports entailing head injury and other risks. On the one hand, benefits of athletics may be attenuated by sport-related head impacts, including soccer-related concussion (mild head injury resulting in loss of consciousness less than 30 min, post-traumatic amnesia less than 24 h, and GCS 13–15) and subconcussive events (head injury that does not result in clinical diagnosis of concussion(Bailes et al. 2013), which pose risks for transient (Straume-Næsheim et al. 2009) and potentially persistent adverse effects on brain structure and function(Bunc et al. 2017; Stålnacke et al. 2004). On the other hand, the beneficial effects of athletics, known to enhance cardiovascular and overall health, may contribute to brain reserve that buffers the adverse effects of repetitive head impacts (RHI). Adverse effects of head impacts in collision sports like soccer may thus be underestimated when active athletes are compared to non-athlete controls.

Soccer, the most popular sport worldwide with 224 million currently active players across 204 countries (Bunc et al. 2017; Kunz 2007), is associated with adverse effects of head impacts from heading and from collisions. Higher levels of heading are related to persistent white matter microstructural changes and lower performance on tests of cognitive function (Levitch et al. 2018; Lipton et al. 2013). Moreover, unrecognized injury due to repetitive heading may account for the dominant share of adverse cognitive effects, rather than recognized concussion (Stewart et al. 2018). In addition to

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functional effects, few studies have identified effects of heading, independent of concussion, on white matter (Tarnutzer et al. 2016; Rubin et al. 2018). An important limitation of most previous studies is that they largely address the effects of heading within groups of soccer players, without comparison to a control group. As a consequence, the beneficial effects of athletic activity on the brain cannot be parsed from adverse effects of heading (Tarnutzer et al. 2016).

The purpose of this study is to characterize the specific effects of soccer heading on white matter microstructure and cognitive function, independent of recognized concussion: (1) relative to non-athlete controls and (2) relative to active athletes who have no exposure to collision sports (i.e., non-contact/non-collision sports athletes).

Methods

Overall design

We separately examined effects of heading over the two distinct timeframes on diffusion tensor imaging (DTI) and cognitive performance. Two-week and 12-month heading exposure were studied as two separate categorical variables. For each variable, individual participants (healthy, non-athlete; non-contact/non-collision sports athletes athlete or soccer) were assigned to one of 6 groups. Group 1 included healthy, non-athletes only, Group 2 included non-contact/non-collision sports athletes only and Groups 3–6 comprised soccer players stratified by level of heading. Second, we determined, in each non-contact/non-collision sports athleteathlete and in each soccer player, the brain regions where each differed significantly from the non-athletes. We summarized abnormalities, in each individual, as the total volume of white matter exhibiting abnormally low DTI parameters and, separately, the total volume of white matter exhibiting abnormally high DTI parameters. Both low and high abnormalities can coexist in the same individual at discrete brain locations. This step yielded two summary measures (high and low) for each of 4 DTI parameters (FA, RD, AD, MD) in each non-contact/non-collision sports athleteand in each soccer player. These measures as well as cognitive test scores served as outcome variables.

Subject enrollment

The Einstein Soccer study is an ongoing longitudinal study examining the impact of heading in a group of adult amateur soccer players; subjects undergo imaging and other assessments at the beginning and end of a two-year period. The study complied with the Health Insurance Portability and Accountability Act, was approved by the institutional review board, and all subjects provided written, informed consent. Amateur soccer players, ages 18–55, were recruited via local advertisement and social media. Inclusion criteria included English language fluency, soccer play for at least 5 years, and current active soccer play for at least 6 months per year.

Exclusion criteria included history of Bipolar Disorder, Schizophrenia, neurological disorder, contraindication to MRI or recreational drug use within previous thirty days.

Non-contact/non-collision sport athletes met the above inclusion and exclusion criteria (active play at least 6 months per year for at least 5 years) with respect to a non-collision sport. “Non-collision” sports included baseball, swimming, tennis, running/track, gymnastics, rowing/crew, cycling, dancing, figure skating. Sports specifically excluded were basketball, football, soccer, hockey, wrestling, lacrosse, volleyball, rugby, boxing and martial arts. Healthy non-athletes comprised healthy individuals aged 18–55 years. Exclusion criteria for non-athletes included history of head injury, psychiatric disease (Bipolar Disorder, Schizophrenia, Anxiety, Depression), neurological disease, diabetes, heart disease, hypertension, contraindication to MRI or recreational drug use within previous thirty days.

All participants completed a baseline study visit that included the same data collection protocol for MRI and cognitive assessment. The initial visit also included collection of demographic features. Some of the soccer players completed an additional identical visit two years after initial enrollment. Handedness was assessed at the first visit using the Edinburgh Handedness Inventory (Oldfield 1971), which generates a laterality index on a continuous scale. The laterality index ranges from + 1 (strongly right-handed) to -1 (strongly left-handed).

Heading assessment

Heading was assessed at the time of enrollment using “HeadCount,” a structured, web-based questionnaire, the details and validation of which have been previously described (Catenaccio et al. 2016; Lipton et al. 2018). In brief, HeadCount-12m estimates heading over the prior 12 months and HeadCount-2w estimates heading over the prior 2 weeks based on a structured questionnaire that assesses exposure during outdoor practice, outdoor games, indoor practice and indoor games (Catenaccio et al. 2016). Twelve-month and two-week heading estimates served as the exposure measures of interest in this study.

Image acquisition

Imaging was performed at time of enrollment (V0) and at two years (V24) using a 3.0T Philips Achieva TX scanner (Philips Medical Systems, Best, The Netherlands) with a 32-channel head coil. T1-weighted 3D magnetization-prepared rapid acquisition of gradient echo imaging was performed with TR/TE/TI = 9.9/4.6/900 ms, flip angle 8°, 1mm^3 isotropic resolution, 240 × 188 × 220 matrix. Diffusion tensor imaging was performed using 2D single-shot EPI with 32 diffusion encoding directions, b-value = 800 s/mm^2, TR = 10 s, TE = 65 ms, 2 mm^3 isotropic resolution, 128 × 120 matrix, 70 slices.

Image processing, analysis and imaging variable calculation

Image processing was performed using a high-performance computing system running the Community Enterprise Operating System (CentOS) Linux distribution and utilized the FSL software package (FSL v2.0.18, https://fsl.fmrib.ox.ac.uk/). In brief, the 32 diffusion-weighted image sets (32 b = 800 s/mm2 images) were corrected for head motion and eddy current effects by using an affine registration algorithm, with the b = 0 s/mm2 image as the target volume. Brain extraction was performed using Brain Extraction Tool (BET), and a white matter mask was generated with FAST, to limit subsequent analyses to white matter voxels only. Tensor fitting was performed at each voxel using the FMRIB Diffusion Toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT).

To minimize the impact of potential registration errors, subject-based registration (SURE-Quant) was used to define subject-specific abnormalities, as described previously (Suri et al. 2015). Eddy current correction and tensor fitting was performed using the FSL software package. Field map-based EPI distortion correction of each diffusion tensor MRI dataset was performed using FSL-FUGUE. The distortion-corrected EPI volume thus produced was then registered to the patient's T1W volume, using FLIRT to perform a rigid body transformation. Diffusion parameter images for each control participant were transformed, using the nonlinear procedure within the Automated Registration Toolbox (ART) package, to match each individual athlete participant (soccer player, non-contact/non-collision sport athlete) according to the methods described by Suri et al. (2015) Voxelwise linear regression analysis, incorporating age and sex as covariates, was performed, comparing each participant to the group of 110 healthy controls, to identify subject-specific abnormalities. Regions were considered significant where more than 100 contiguous voxels, each meeting a threshold of $P = 0.01$, formed a contiguous cluster.

The statistical images from each participant, comprising clusters where FA, AD, RD or MD differed from controls, were each divided into two separate maps: (1) all clusters exhibiting diffusion parameter values > 0 and (2) all clusters exhibiting diffusion parameter values < 0. Total volume (number of 1-mm3 voxels) of all clusters meeting criteria for significance (above) was then computed for each map, for each subject, to generate the following eight imaging variables of interest for each subject: volume of all clusters where FA, AD, RD or MD > 0 and volume of all clusters where FA, AD, RD or MD < 0.

Neuropsychological assessment

Cognitive testing was performed at both study visits using Cogstate® (Cogstate, Ltd., NY, USA), a valid and reliable computer-administered battery (Maruff et al. 2009). Neuropsychological domains tested included: verbal learning and memory, psychomotor speed, attention, and working memory. The International Shopping List—Immediate (ISL) and International Shopping List—Delayed Recall tasks (ISRL) measured verbal learning and memory abilities, respectively (score reflects number of correct responses). The Groton Maze Chase Test (GMCT) measured psychomotor speed (score reflects total number of correct moves per second). The identification (IDN) and One Back Test (ONB) measure attention (scores reflect reaction time and accuracy). The Two Back Test (TWOB) measured working memory (score reflects number of correct responses). In addition, the WRAT4 Reading subtest was administered as a measure of premorbid verbal IQ (Bright et al. 2002).

Statistical analysis

Statistical analyses were performed using IBM SPSS (Statistical Package for the Social Sciences, IBM SPSS, Inc, Chicago, IL: Versions 24 and 25). Because distributions of both two-week and 12-month heading totals were positively skewed, to mitigate the high leverage of subjects with extreme high heading counts in the regression, each heading exposure variable was transformed into ordinal-categorical variables of four approximately equal size quartiles, with the lowest exposure group (i.e., Q1) having de minimis heading exposure (see Table 1). Cognitive test scores were treated as a continuous measure utilizing raw scores from each of the domain-specific tasks. Higher score reflects better performance on all tasks except for the IDN, where the score reflects reaction time and higher score therefore indicates worse performance. Data were included from multiple visits per subject such that data collected during a single session was the unit of analysis, where each soccer player could contribute one or two units depending on whether they completed one or two study visits.

We leveraged repeated measures within subjects across multiple visits, applying generalized estimating equations (GEE) (Hanley et al. 2003; Hardin 2005), to examine the effects of heading exposure on cognitive performance and on the volume of each high and each low DTI parameter. We also tested the relationship of each low and high DTI parameter with cognitive performance. GEE explicitly account for repeated measures from the same subject and appropriately adjust the standard errors of the parameter estimates for the within-subject correlation in the data. Data from repeated visits were pooled in order to increase the power of the study to assess the association of soccer heading with white

Table 1 Exposure characteristics of the soccer player group

Longer-Term Heading Quartiles (HeadCount-12m)						
Total number of reports n = 357			Q1 n = 89	Q2 n = 90	Q3 n = 89	Q4 n = 89
Years of heading	12.1 (7.2)		12.4 (8.2)	12.8 (8.1)	12.0 (7.07)	12.0 (6.3)
Heading-12m	Min	0	0	169	586	1529
	Max	139561	165	574	1500	139561
	Mean	2661.82	57.93	357.2	951.11	6701.01
	Median	790.5	44	335	887	2737
Recent Heading Quartiles (HeadCount-2w)						
Total number of reports n = 357			Q1 n = 104	Q2 n = 87	Q3 n = 83	Q4 n = 83
Heading − 2w	Min	0	0	1	11	40
	Max	635	0	10	39	635
	Mean	37.89	0	5.71	21.43	135.54
	Median	9	0	6	20	97
Lifetime concussion history	0	163	59	54	62	67
	1	36	17	18	10	8
	2+	46	13	18	17	13
Days of soccer play	Outdoor Games	2.19	1.61	1.94	2.12	2.92
	Outdoor Practice	2.89	1.91	2.11	2.82	4.28
	Indoor Games	1.49	1.04	1.39	1.3	1.81
	Indoor Practice	1.38	0.88	0.98	1.15	2.03

matter microstructure and cognitive function. For each model, age, sex, years of education, concussion history (Y/N), and verbal IQ were assessed as potential covariates. Those covariates demonstrating significance at $p < 0.1$ were included in the final model. Given the large number of statistical tests performed, Bonferroni correction was employed to control the familywise false positive error rate for all analyses involving DTI metrics.

Table 2 Baseline demographic characteristics. Continuous variables are reported as mean (standard deviation). Categorical variables are reported as frequency (%)

	Soccer Players (N = 246)	Non-Collision Athletes (N = 72)	Non-Athletic Controls (N = 116)	P value
Variable (continuous)				
Age	25.48 (7.2)	22.76 (5.2)	28.96 (11.1)	P < 0.001
Education (years)	15.6 (2.2)	15.14 (1.9)	15.38 (3.6)	P = 0.369
IQ (WRAT Score)	104.61 (14.6)	107.6 (10.4)	106.1 (17.8)	P = 0.291
Handedness	0.787 (0.4)	0.850 (0.33)	0.702 (0.46)	p = 0.048
Years of Play at Similar Frequency	12.11 (7.2)			
Age started (years)	7.70 (4.1)			
Variable (categorical)				
Gender				P < 0.001
Male	174 (70.7)	30 (41.7)	63 (54.3)	
Female	72 (29.3)	42 (58.3)	53 (45.7)	
Concussion History				P < 0.001
Yes	163 (66.3)	6 (8.3)		
No	83 (33.7)	66 (91.7)		
Race				P = 0.005
White	154 (62.6)	50 (69.4)	54 (46.6)	
Non-White	66 (26.8)	14 (19.4)	50 (43.1)	

Table 3 Presence of abnormal DTI measures in soccer players and non-collision athletes relative to a group of healthy controls. Volume indicates mean volume of the specified abnormal parameter across all white matter voxels in the group. Percent indicates prevalence of abnormality within each group

	Soccer Players				Non-Collision Athletes			
	Supranormal		Subnormal		Supranormal		Subnormal	
	Volume (mean, mm^3)	Percent (N = 357)	Volume (mean, mm^3)	Percent (N = 357)	Volume (mean, mm^3)	Percent (N = 72)	Volume (mean, mm^3)	Percent (N = 72)
FA	858	76.5%	589	39.5%	1403	86.1%	2109	36.1%
AD	964	78.7%	379	42.6%	4524	69.4%	3096	59.7%
RD	740	63.0%	902	66.1%	10759	45.8%	1682	80.6%
MD	1127	66.9%	1208	63.9%	7552	54.2%	2105	83.3%

Results

Subject characteristics

246 amateur soccer players ("soccer" group) were included in the study; 111 returned for a two-year follow-up visit, for a total of 357 assessments included in the analyses. Among soccer players, total number of heads per year ranged from 0 to 139,561 (mean = 2661.82 heads/ year, median = 790.5 heads/year). Total number of heads per two-week time period ranged from 0 to 635 (mean = 37.9 heads/2 weeks, median = 9 heads/2 weeks). Participants enrolled in the study were adult amateur recreational soccer players participating in leagues that are active for most if not all of the year. Players' active play period was thus not restricted to a specific season or timeframe.

Table 1 shows heading characteristics by quartile for both the 12 month and 2 week heading assessments. At the outset, we did not necessarily expect consistency of heading quartile assignment defined by HeadCount-2w and HeadCount-12m, as the two heading estimates address two different timeframes. For example, a player with high heading activity over the prior year might be assessed at a time when they happened to not have played much during the prior two weeks. Notwithstanding these expectations, we in fact found a high degree of consistency for quartile assignment by HeadCount-2w and HeadCount-12m. In 44% of cases, quartile assignment was exactly matched. In 40%, quartile assignment differed by

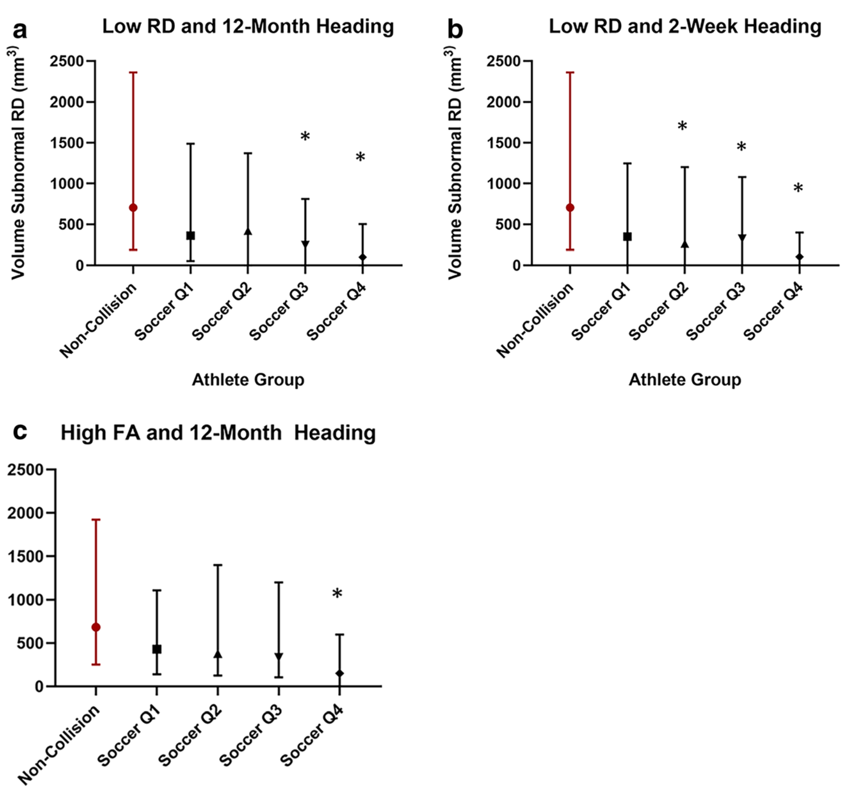

Fig. 1 DTI Parameters and Heading. Box and whisker plots show median and interquartile ranges for: **a** Low RD and long-term (12-month) heading quartiles. **b** Low RD and short-term (2-week) heading quartiles. **c** High FA and long-term (12-month) heading quartile. Red indicates reference group. * Indicates significant difference between the athlete quartile and the reference group

Table 4 Relationship of longer-term heading and DTI measures

Athlete Quartile (Longer Term Heading)	N	High AD	Low AD	High MD	Low MD	High RD	Low RD	High FA	Low FA (covariate: age)
Test of Model Effect raw p (adjusted p value)	-	0.204 (1.632)	0.214 (1.712)	0.216 (1.728)	0.012 (0.096)	0.477 3.816)	0.000000208 (0.0000016)	0.004 (0.032)	0.394 (3.152)
Q4 B(p)	89	-478.00 (0.40)	-764.63 (0.04)	-641.77 (0.49)	-1067.76 (0.00)	-1383.19 (0.28)	-1037.48 (0.00)	-886.73 (0.00)	-929.07 (0.61)
Q3 B(p)	91	-1.82 (0.99)	-714.28 (0.05)	-246.50 (0.79)	-717.18 (0.03)	1122.30 (0.38)	-560.23 (0.03)	-479.34 (0.09)	-1801.32 (0.23)
Q2 B(p)	88	-35.5 (0.43)	-594.7 (0.12)	-663.24 (0.47)	-342.94 (0.34)	-1393.72 (0.27)	-423.22 (0.10)	-456.34 (0.11)	-775.06 (0.6)
Q1 B(p)	89	-504.00 (0.35)	-529.63 (0.19)	-899.01 (0.32)	-93.15 (0.87)	-1435.64 (0.26)	-209.66 (0.58)	-356.38 (0.28)	-1614.34 (0.28)

only one rank, which is likely to occur due to slight variation of exposure that just crosses the quartile cutoff. 12% of cases showed higher quartile assignment of more than 1 rank for the 12 month measure compared to the 2 week measure. This is consistent with the scenario described above. Notably, only 4% of reports yielded a lower quartile assignment of more than 1 rank for the 12 month measure compared to the 2 week measure.

72 non-contact/non-collision sport athletes and 110 healthy, non-athletes were included in the analysis. Demographic characteristics of the soccer players, non-collision athletes, and non-athletes are shown in Table 2. There were no significant differences in years of education and WRAT score between the three groups, but there were a significant differences in other demographic characteristics between the three groups: age ($p < 0.001$; non-contact/non-collision sport athletes were younger than the soccer players and healthy, non-athlete controls, soccer players were younger than healthy, non-athletes), sex at birth ($p < 0.001$; there were significantly more males among the soccer players as compared to the non-contact/non-collision sport athletes and healthy, non-athletes), handedness ($p = 0.048$; there was a trend toward right-handedness among non-contact/non-collision athletes compared to healthy, non-athletes) and race ($p = 0.005$; there were significantly more 'Whites' among the non-contact/non-collision sport athletes and significantly more 'Non-Whites' among the healthy, non-athletes). Significantly more soccer players reported history of sports-related concussion, compared to non-contact/non-collision sport athlete ($p < 0.001$). Healthy, non-athletes had no history of concussion (this was an exclusion criterion for the healthy, non-athlete group).

Heading and DTI parameters

Voxelwise linear regression, adjusted for age and sex at birth, comparing soccer players and non-contact/non-collision sport athletes to healthy, non-athletes, identified regions of abnormally low and high FA, AD, RD and MD in most, but not all, athlete participants (Table 3).

12-Month Heading Expression of abnormally low RD did not differ between non-contact/non-collision sport athlete and soccer players with less exposure to heading (Q1-Q2), but soccer players with high levels of exposure to heading (Q3-Q4) showed a significantly greater expression of low RD as compared to non-contact/non-collision sport athletes (Fig. 1). Expression of high FA was similar among non-contact/non-collision sport athletes and soccer players with less exposure to heading (Q1-Q3) but soccer players with the highest level of exposure (Q4) showed significantly less expression of high

Table 5 Relationship of recent heading and DTI measures

Recent Heading	N	High AD	Low AD	High MD	Low MD (Covariate: WRAT)	High RD	Low RD (Covariate: Age)	High FA	Low FA
Test of Model Effect raw p (adjusted P)	-	0.773 (5.864)	0.163 (1.304)	0.442 (3.536)	0.097 (0.48)	0.291 (2.328)	0.002 (0.016)	0.036 (0.288)	0.090 (0.72)
Q4 B(p)	104	-361.57 (0.53)	-798.48 (0.03)	-474.03 (0.61)	-933.27 (0.01)	-1233.32 (0.33)	-972.66 (0.00)	-800.48 (0.00)	-197.55 (0.20)
Q3 B(p)	87	-311.91 (0.57)	-640.31 (0.09)	-352.98 (0.70)	-412.02 (0.23)	110.05 (0.37)	-672.91 (0.01)	-558.29 (0.04)	-1033.01 (0.56)
Q2 B(p)	83	-511.99 (0.35)	-718.50 (0.05)	-819.69 (0.36)	-36.28 (0.05)	1470.19 (0.25)	-672.56 (0.01)	-528.68 (0.05)	-2032.15 (0.18)
Q1 B(p)	83	-265.95 (0.63)	-494.72 (0.22)	-799.08 (0.38)	-186.61 (0.72)	1484.9 (0.24)	-346.14 (0.32)	-341.56 (0.29)	-1246.72 (0.45)

FA as compared to non-contact/non-collision sport athletes (Fig. 1). A similar trend was observed for the relationship of heading exposure with subnormal MD. No differences were observed among non-contact/non-collision sport athletes and Q1 and Q2 soccer heading groups on low RD or high FA. Volume of subnormal FA, subnormal AD or high RD, MD or AD were not significantly different among participant groups. None of the covariates were significant predictors of the imaging measures and were therefore not included in the final models. Table 4 displays quartile-specific regression coefficient (β) and significance (p) for each participant group.

2-Week heading Expression of abnormally low RD did not differ between non-contact/non-collision sport athletes and soccer players with less exposure to heading (Q1-Q3); however, there was greater expression of abnormally low RD in soccer players with highest level of heading exposure (Q4) as compared to non-contact/non-collision sport athletes (Fig. 1). Volume of subnormal FA, MD or AD and high FA, RD, MD or AD were not significantly different among participant groups. None of the covariates were significant predictors of the imaging measures and were therefore not included in the final models. Table 5 displays quartile-specific regression coefficient (β) and significance (p) for each group.

Heading and cognitive performance

12-Month Heading Non-contact/non-collision sport athletes and soccer players with low levels of heading exposure performed significantly better than healthy, non-athletes on tasks of attention (IDN; Fig. 2), processing speed (GMCT; Fig. 2) and verbal memory (ISRL; Fig. 2), whereas soccer players with higher levels of heading exposure did not differ from non-contact/non-collision sport athletes in performance on these tasks. No differences were observed between groups for performance on verbal learning (ISL), working memory (TWOB), or attention (ONB). None of the covariates were significant predictors of cognitive performance and were therefore not included in the final models. Table 6 shows quartile-specific regression coefficient (β) and significance (p) for each group.

2-Week Heading Non-contact/non-collision sport athletes and soccer players with low levels of heading exposure performed significantly better than healthy, non-athletes on tasks of attention (IDN; Fig. 2b), processing speed (GMCT; Fig. 2d), verbal memory (ISRL; Fig. 2f), and working memory

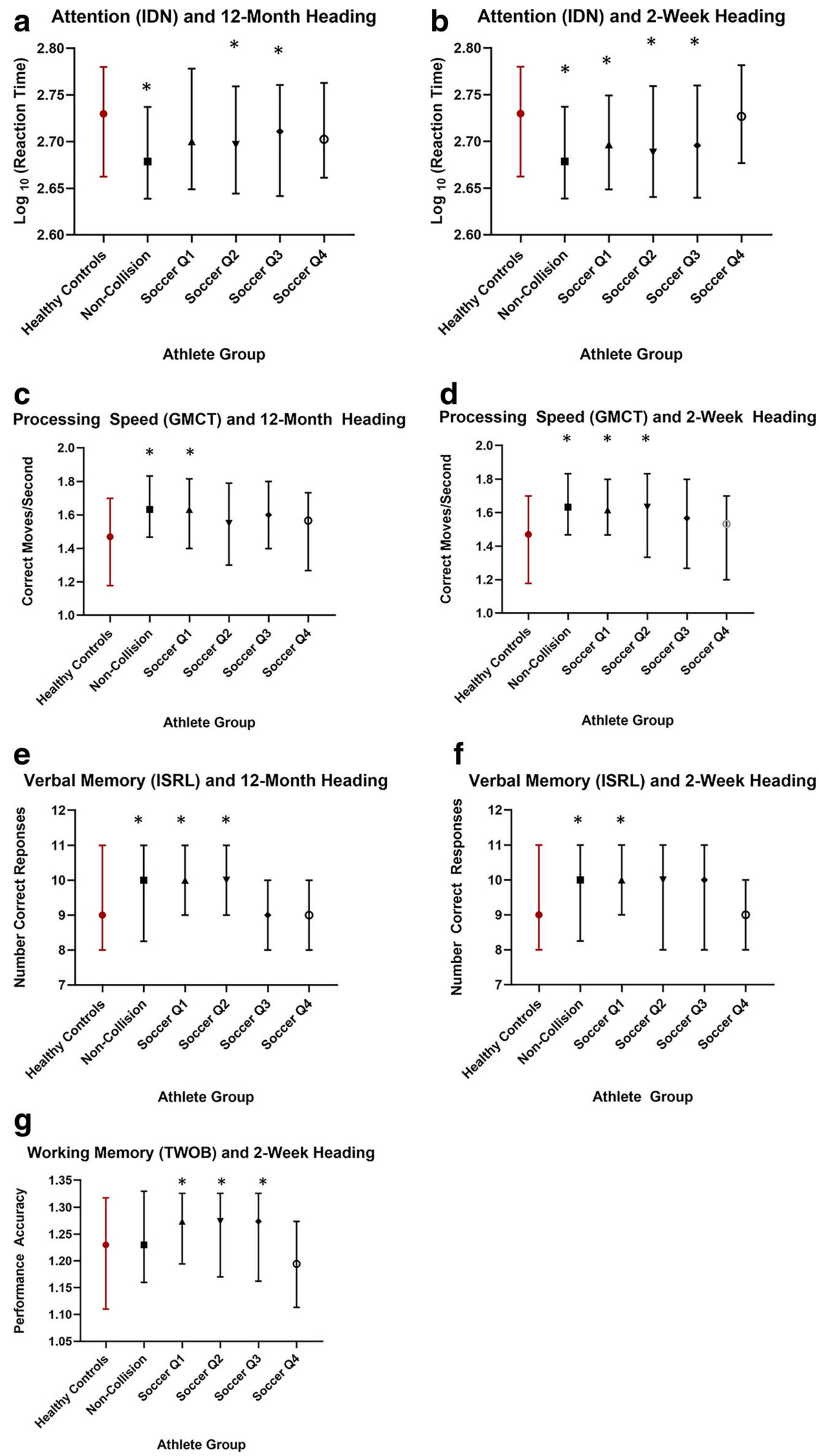

Fig. 2 Cognitive Function and heading. **a** Attention (IDN) and long-term (12-month) heading quartiles **b** Attention (IDN) and short-term (2-week) heading quartiles. **c** Processing Speed (GMCT) and long-term (12-month) heading quartiles. **d** Processing Speed (GMCT) and short-term (2-week) heading quartiles. **e** Verbal Memory (ISRL) and long-term (12-month) heading quartiles and **f** Verbal Memory (ISRL) and short-term (2-week) heading quartiles. **g** Working memory (TWOB) and short-term (2-week) heading quartiles. Box and whisker plots show median and interquartile ranges. Red indicates reference group. * Indicates significant difference between the athlete quartile and the reference group

(TWOB; Fig. 2g). No differences were observed among groups for verbal learning (ISL) or attention (ONB). None of the covariates were significant predictors of cognitive performance and were therefore not included in the final models. Table 7 displays quartile-specific regression coefficient (β) and significance (p) for each group.

Relationship of DTI parameters with cognition

There were significant associations between volume of low and high DTI measures and cognition. Greater volume of low AD was significantly related to better verbal memory performance (ISRL) (raw $p = 0.0004$, adjusted p value $= 0.02$), and

Table 6 Relationship of longer-term heading and cognitive performance

Task	Attention (IDN)	Procesing Speed (GMCT) (covariate: age)	Verbal Learning (ISL) (covariate: gender, education, WRAT)	Verbal Memory (ISRL)	Attention (ONB) (covariate: WRAT)	Working Memory (TWOB) (covariate: age, WRAT)
Test of Model Effect	0.003	0.01	0.068	0.019	0.795	0.070
Q4 B (p value)	-0.048 (0.142)	0.031 (0.610)	-0.584 (0.320)	0.012 (0.964)	0.002 (0.938)	0.063 (0.106)
Q3 B (p value)	-0.026 (0.030)	0.085 (0.188)	-0.489 (0.357)	-0.021 (0.934)	-0.006 (0.814)	0.048 (0.205)
Q2 B (p value)	-0.141 (0.020)	0.093 (0.098)	0.595 (0.282)	0.640 (0.008)	-0.002 (0.957)	0.070 (0.100)
Q1 B (p value)	-0.077 (0.082)	0.127 (0.045)	0.707 (0.211)	0.552 (0.028)	0.046 (0.188)	0.120 (0.002)
Athlete	-0.038 (0.001)	0.172 (0.001)	0.758 (0.192)	0.532 (0.033)	0.010 (0.695)	0.067 (0.103)

greater volume of low MD was associated with better processing speed (GMCT) (raw $p = 0.0003$, adjusted p value $= 0.01$) and attention performance (ONB) (raw $p = 0.001$, adjusted p value $= 0.048$). Greater volume of low RD was associated with better processing speed (GMCT) (raw $p = 0.006$, adjusted p value $= 0.288$) and attention performance (ONB) (raw $p = 0.041$, adjusted p value $= 1$). There were no significant associations of low FA or high FA, AD, RD or MD with cognitive performance. Table 8 shows raw and adjusted p values for the linear regression analyses.

Discussion

Our comparison of healthy non-athletes and non-contact/non-collision sport athletes with soccer players reveals an interesting divergence of microstructural features and cognitive performance. Athletes with no or lower exposure to repetitive heading exhibited both a higher degree of white matter anisotropy and better cognitive performance compared to non-athletes. Soccer players with the highest exposure to repetitive head impacts, however, did not differ significantly from non-athletes on either micro-structural features or cognitive performance. Statistically significant differences were not explained by concussion history or demographic factors. These results lead us to hypothesize that beneficial effects of athletic conditioning or training on brain structure and function might be attenuated by exposure to repeated subconcussive head impacts, a proposition that can motivate future investigation.

It is known that physical activity, and organized sports participation in particular, reduce all-cause mortality, as well as diabetes, cardiovascular disease, depression, dementia, breast cancer, and colon cancer (Khan et al. 2012); the observed benefit has been specifically linked to sports-related exercise (Sabia et al. 2012). It is postulated that beneficial effects of exercise are mediated through processes such as angiogenesis, neurogenesis, synaptogenesis, release of neurotrophins (Hötting and Röder 2013), and myelination (Kim and Sung 2017). In contrast to prior studies showing reduced mortality in American football players as compared to general United States population (Nguyen et al. 2019), Nguyen, et al. demonstrated elevated mortality among National Football League (NFL) players compared with Major League Baseball (MLB) players. The authors attribute this apparent discrepancy in findings to the choice of controls (Nguyen et al. 2019). If we had only compared soccer players to healthy non-athletes, potential beneficial effects of participation in athletics or training effects related to soccer might have masked these potentially adverse structural and functional effects of heading. We therefore compared soccer players to a similarly active group of non-contact/non-collision sport athletes in order to begin to disentangle potential opposing

Table 7 Relationship of recent heading and cognitive performance

	Attention (IDN)	Processing Speed (GMCT) (covariate: age)	Verbal Learning (ISL) (covariate: gender, education, WRAT)	Verbal Memory (ISRL)	Attention (ONB) (covariate: WRAT)	Working Memory (TWOB) (covariate: Age)
Test of Model Effect	0.003	0.00003	0.122	0.030	0.133	0.018
Q4 B (p value)	-0.061 (0.197)	-0.043 (0.500)	-0.407 (0.465)	-0.087 (0.750)	-0.054 (0.125)	0.006 (0.898)
Q3 B (p value)	-0.124 (0.030)	0.040 (0.544)	-0.511 (0.386)	0.178 (0.477)	0.012 (0.699)	0.089 (0.022)
Q2 B (p value)	-0.091 (0.044)	0.140 (0.021)	0.313 (0.579)	0.384 (0.144)	0.027 (0.420)	0.089 (0.020)
Q1 B (p value)	-0.027 (0.019)	0.178 (0.001)	0.643 (0.225)	0.607 (0.008)	0.045 (0.076)	0.105 (0.006)
Athlete	-0.038 (0.001)	0.176 (0.001)	0.762 (0.190)	0.535 (0.032)	0.011 (0.684)	0.069 (0.091)

effects of athletics/training vs. RHI on brain structure and function.

The potential adverse consequences of subconcussive impacts must also be considered in context of other sources of impact, such as recognized concussion. We have consistently found that prior concussion does not explain symptoms (Stewart et al. 2017), imaging abnormalities (Lipton et al. 2013; Koerte et al. 2012) or cognitive performance (Stewart et al. 2018), in adult amateur soccer players, whereas heading does (Lipton et al. 2013; Stewart et al. 2017, 2018; Koerte et al. 2012). Moreover, worse cognitive performance in soccer players is predicted by higher levels of heading, but not by subconcussive unintended impacts, such as collisions (Stewart et al. 2017). Many studies addressing subconcussive impact effects explicitly exclude subjects with history of concussion (Koerte et al. 2012; Davenport et al. 2016; McAllister and McCrea 2017; Miller et al. 2007). While this approach yields a potentially more homogeneous sample, it limits power and opens the door to selection bias. Players who experience concussion might exhibit patterns of play and heading behaviors that differ from concussion-naïve individuals. We therefore include players in the current study regardless of concussion history and characterize the role of concussion as a covariate in our models.

We examined associations of both shorter-term (two-week) and intermediate-term (one-year) exposure to heading with microstructure (DTI) measures. Greater heading over both timeframes was associated with lesser expression of low RD, a parameter shown to reflect myelin integrity (Winklewski et al. 2018), but only 12-month heading was associated with corresponding lesser expression of high anisotropy (FA). This pattern suggests that longer-term exposure to heading may be more robustly associated with adverse effects on microstructure, a pattern consistent with accumulating pathology in response to ongoing exposure to repeated head impacts. The pattern of findings is also concordant with Bartnik-Olson et al. (2014) who found that soccer players without cognitive impairment following concussion expressed lower RD and higher FA in the posterior limb of the internal capsule compared to controls, whereas those with cognitive impairment did not. Similarly, Bahrami et al. (2016) found lesser increase of FA in subjects with greater cumulative head impact exposure over a single season of American football compared to those with less exposure to head Koerte et al. (2012) reported *higher* RD in concussion-naive soccer players as compared to swimmers; this might be consistent with our findings that non-collision athletes express more low RD as compared to soccer players with high exposure to heading.

Several studies have reported an adverse association of heading with cognitive performance, most commonly affecting memory, attention and executive function (Straume-Næsheim et al. 2009; Levitch et al. 2018; Lipton et al. 2013;

Table 8 Relationship of volume DTI parameter abnormality and cognitive performance

Cognitive Measure	Imaging Measure	Raw P-value	Adjusted P-value
ISL	hFA	0.554	26.592
ISRL	hFA	0.820	39.36
ONB	hFA	0.477	22.896
TWOB	hFA	0.772	37.056
IDN	hFA	0.059	2.832
GMCT	hFA	0.674	32.352
ISL	lFA	0.078	3.744
ISRL	lFA	0.320	15.36
ONB	lFA	0.369	17.712
TWOB	lFA	0.610	29.28
IDN	lFA	0.230	11.04
GMCT	lFA	0.526	25.248
ISL	hRD	0.142	6.816
ISRL	hRD	0.00001577445690	0.000757
ONB	hRD	0.324	15.552
TWOB	hRD	0.852	40.896
IDN	hRD	0.666	31.968
GMCT	hRD	0.923	44.304
ISL	lRD	0.947	45.456
ISRL	lRD	0.904	43.392
ONB	lRD	0.041	1.968
TWOB	lRD	0.472	22.656
IDN	lRD	0.068	3.264
GMCT	lRD	0.006	0.288
ISL	hMD	0.883	42.384
ISRL	hMD	0.131	6.288
ONB	hMD	0.191	9.168
TWOB	hMD	0.425	20.4
IDN	hMD	0.547	26.256
GMCT	hMD	0.526	25.248
ISL	lMD	0.582	27.936
ISRL	lMD	0.640	30.72
ONB	lMD	0.001	0.048
TWOB	lMD	0.052	2.496
IDN	lMD	0.072	3.456
GMCT	lMD	0.000309	0.014832
ISL	hAD	0.959	46.032
ISRL	hAD	0.088	4.224
ONB	hAD	0.139	6.672
TWOB	hAD	0.291	13.968
IDN	hAD	0.451	21.648
GMCT	hAD	0.460	22.08
ISL	lAD	0.240	11.52
ISRL	lAD	0.00041803350800000	0.020066
ONB	lAD	0.137	6.576
TWOB	lAD	0.142	6.816
IDN	lAD	0.189	9.072
GMCT	lAD	0.039	1.872

Downs and Abwender 2002; Forbes et al. 2016; Janda et al. 2002; Kontos et al. 2011; Matser et al. 2001; Rutherford et al. 2005; Salinas et al. 2009; Stephens et al. 2010; Jones et al. 2013). However, many relied on non-validated self-report measures of exposure to heading (Tarnutzer et al. 2016), a limitation addressed in this study by using a validated, structured heading exposure assessment tool. Our findings in this large sample of amateur soccer players and non-athletes, whom we compare to non-collision athletes, not only reproduce the adverse associations of heading with cognitive performance that we previously reported in a smaller independent sample of players (Levitch et al. 2018), but further illustrates that this adverse effect may represent an attenuation of expected beneficial effects of athletic participation. Findings of Koerte et al. (2017) where adolescent non-contact sport athletes demonstrated improvement of cognitive performance over the course of a training season, whereas soccer players did not, are also consistent with the attenuation of an exercise- or training-related brain benefit among soccer players with high levels of heading exposure that we suggest based on our findings. We found recent heading was associated with working memory, but one-year heading was not. This suggests that effects of heading on working memory may be transient, similar to previous findings by Levitch et al. (2018).

The preliminary findings related to the association between volume of abnormal DTI parameters and cognitive function suggest that microstructural alterations reflected by DTI may index pathologic changes underpinning adverse functional effects. The significant association between greater volume of subnormal MD and improved performance on tasks of executive function is consistent with McAllister et al. (2014). We detected a trend association of more subnormal RD with better performance on tasks of executive function (GMCT), a task on which players with greater exposure to heading performed worse as compared to non-contact/non-collision athletes. These intriguing preliminary findings should motivate further investigation into potential mediating roles of imaging measures in the relationship of RHI with cognitive performance.

Our findings should be considered in context of several limitations. We did not explicitly test for a beneficial effect of athletics on brain function, but indirectly infer that such an effect might explain the relationships we describe. Thus, the notion that RHI attenuates the beneficial effect of sport participation represents a hypothesis that derives from our findings but remains to be definitively addressed by explicit testing. We cannot completely exclude the possibility that the non-athlete controls participated in athletics in the past. In any case, this would represent an unlikely source of bias because these same individuals serve as the reference group for both the non-collision athletes and soccer players. The cross-sectional analysis we report is limited in its ability to support causal relationships and to differentiate between shorter- versus longer-term heading exposure. For instance, it is plausible that individuals with poor brain health or lower baseline cognitive function are more inclined towards extreme levels of heading. We did not exclude soccer athletes who played other collision sports. If injury occurred while engaged in another sport, that contribution could not be disentangled from the effects of heading. For subjects with history of prior concussion, we did not have access to reliable data on time of concussion and tested the presence/absence of concussion history as a covariate. The potential role of recent concussion cannot therefore be addressed. The higher number of head impacts reported by soccer athletes included in the sample compared to some prior reports in the literature may reflect the generally fewer restrictions on adult recreational play and the fact that the players in our sample were not restricted to play during a circumscribed active season of play as well as other factors. However, these differences may also make our sample more representative of the more than 256 million players worldwide, compared to participants in professional, elite and educational settings." Finally, reporting bias and reverse causation cannot be absolutely excluded, but are unlikely explanations of our findings, which converge across distinct timeframes, exposures and outcomes.

In conclusion, our findings add to existing knowledge that athletic participation confers beneficial effects on brain structure and function and raises the possibility that these effects may be attenuated by exposure to high levels of subconcussive soccer heading over the shorter- and longer-terms. Further study is warranted to further characterize risk of repetitive subconcussive impacts in sports toward developing approaches for its mitigation.

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Compliance with ethical standards

Conflict of Interest Sara B. Strauss declares that she has no conflict of interest.

Roman Fleysher declares that he has no conflict of interest.

Chloe Ifrah declares that she has no conflict of interest.

Liane Hunter declares that she has no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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