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Research Report

The brains of elite soccer players are subject to experience-dependent alterations in white matter connectivity

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ABSTRACT

Soccer is the only major sport with voluntary unprotected head-to-ball contact. It is crucial to determine if head impact through long-term soccer training is manifested in brain structure and connectivity, and whether such alterations are due to sustained training per se. Using diffusion tensor imaging, we documented a comprehensive view of soccer players' brains in a sample of twenty-five right-handed male elite soccer players aged from 18 to 22 years and twenty-five non-athletic controls aged 19–24 years. Importantly, none had recalled a history of concussion. We performed a whole-brain tract-based spatial statistical analysis, and a tract-specific probabilistic tractography method to measure the differences of white matter properties between groups. Whole-brain integrity analysis showed stronger microstructural integrity within the corpus callosum tract in soccer players compared to controls. Further, tract-specific probabilistic tractography revealed that the anterior part of corpus callosum may be the brain structure most relevant to training experience, which may put into perspective prior evidence showing corpus callosum alteration in retired or concussed athletes practicing contact sports. Intriguingly,

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Brain injury
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experience-related alterations showed left hemispheric lateralization of potential early signs of concussion-like effects. In sum, we concluded that the observed gains and losses may be due to a consequence of engagement in protracted soccer training that incurs prognostic hallmarks associated with minor injury-induced neural inflammation.

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1. Introduction

Soccer is one of the most popular sports in the world, drawing interest from large audiences in both the outcomes of matches and other related aspects such as the fitness and injury status of the players. Sports injuries are inevitable, which underscores the importance of understanding the neural impact of long-term participation in sports with a risk of collision or contact, such as soccer, the only major sport with voluntary unprotected head-to-ball contact (Carman et al., 2015; Giza, Prins, & Hovda, 2017). For example, brain imaging techniques such as diffusion tensor imaging (DTI) (Alexander, Lee, Lazar, & Field, 2007; Mori & Zhang, 2006) have enabled the examination of white matter (WM) microstructural changes associated with brain injury in concussed athletes. In soccer, review studies on concussed athletes showed that repeated head-to-ball impacts were associated with traumatic brain injury (Allen & Karceski, 2017; Rodrigues, Lasmar, & Caramelli, 2016), including effects seen in DTI studies (Lipton et al., 2013). Specifically, these findings suggest that repeated soccer ball heading is associated with lower microstructural integrity in the temporo-occipital white matter. Furthermore, a systematic review of DTI studies of concussed athletes revealed that some critical regions (i.e., the corpus callosum tract (CCT), internal capsule, and longitudinal fasciculus) exhibited higher rates of concussion damage than others, suggesting that these brain structures are particularly vulnerable to diffuse axonal injury in contact/collision sport-related concussion (Gardner et al., 2012). Collectively, these studies seem to support sport-induced alterations in WM structure, possibly in the centrally localized junction of merging and/or crossing fiber tracts. These anatomical structures may be specifically susceptible to injury from the translational and rotational forces acting in sports-related concussion. However, the available evidence remains scarce and inconclusive, possibly because of the discrepancy regarding experimental protocols, especially with respect to the period of time between injury and scanning. Therefore, it is crucial to determine if such head impact through long-term soccer training would manifest itself at a brain structure level; and if so, whether such impact would result from neuronal inflammation or from the mere protracted exposure to intensive sports practice.

In this study, we focused specifically on CCT, a structure that has been consistently reported as a brain area particularly sensitive to sport-training-induced WM alterations (Gardner et al., 2012). Within a large sample of collegiate contact sports athletes, McAllister et al. (2014) examined whether practicing contact sports over a single season would affect white matter diffusion measures. Their results showed damage in membrane density within the CCT in athletes who did not wear a helmet over the training course (McAllister et al., 2014), which is in line with studies that have reported abnormalities in the CCT in athletes with a history of concussion practicing other collisions/contact sports (Chamard, Lefebvre, Lassonde, & Theoret, 2016; Stamm et al., 2015; Tremblay et al., 2014). Despite this, the underlying mechanisms relating WM alterations to CCT as a result of a specific training or neuronal inflammation remains unclear, particularly given that previous studies involved athletes who were either retired or diagnosed with a concussion, and importantly, lacked healthy subjects for comparison.

To address this issue, we employed DTI combined with whole-brain tract-based analysis and tract-specific probabilistic tractography to probe the underlying differences in whole-brain integrity and tract-specific connectivity between soccer players without a history of clinical concussion and matched non-athlete controls. We hypothesized that group differences of whole brain analysis between soccer players and healthy controls will be observed in the CCT, internal capsule, and longitudinal fasciculus. Furthermore, we examined whether the nature of such observed structural differences in soccer players could be attributed to sports training or to neural inflammation as manifested in other diffusion measures. Based on the tract-specific analysis of 27 WM tracts, we aimed to refine our understanding of the normality and abnormality in healthy soccer players' brains compared with their healthy peers. Specifically, given the abnormality of CCT commonly seen in retired and concussed soccer players (Chamard et al., 2016; Stamm et al., 2015; Tremblay et al., 2014), we postulated that WM microstructural differences in the CCT would be sensitive to contact/collision sports-specific training experience in our sample of healthy athletes. This was expected to offer insight into the potential for adverse neural changes even in the absence of concussion events.

2. Materials & methods

We report how we determined our sample size, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. *Participants*

Thirty-one male elite soccer players were recruited to take part in the present experiment. For safety purpose, four players who reported having metals embedded in their body were excluded. In addition, one player failed to complete the entire DTI session and another soccer player subject to motion-

related signal dropout and distortion were excluded from further analysis. Aa a consequence, twenty-five soccer players (m/sd: 20.2 ± 1.0 years) were eligible and completed all procedures. All players were competing at the highest level in national events at the time of the study, and represented Taiwan in international competitions. Specifically, none reported a history of brain injury or concussion-like symptoms such as headaches, dizziness, and nausea, persisting for months during the time of the study. A sample of twenty-five non-athletic controls (m/sd: 21.76 ± 1.4 years) matched for health and gender were recruited from the general university student population. None of these reported prior professional training in any sports. All participants were right-handed based on a self-reported questionnaire (Chapman & Chapman, 1987), and all had normal vision or corrected-to-normal vision, no major medical or psychological conditions, psychiatric disorders, neurological history, head injury, and were not taking medication at the time of the study. Before participating in the study, all participants gave written informed consent in accordance with the Declaration of Helsinki. The Research Ethics Committee of National Cheng Kung University (NCKU) approved the protocol. No part of the study procedures was pre-registered prior to the research being conducted.

2.1.1. *Demographic information*

Prior to scanning, all participants were asked to fill out a demographic questionnaire (height, weight, body mass index (BMI), years of soccer practice). The average duration of soccer training was 11.3 ± 1.95 years for the soccer players. Demographic information of soccer players and controls is summarized in Table 1. No significant difference was found in body height (t (48) = −.48, p = .633, Cohen's d = −.136), weight (t (48) = −.326, p = .746, Cohen's d = −.092), or BMI (t (48) = .036, p = .971, Cohen's d = .01). Independent Student's t-tests were performed for demographic variables using JASP software (version 0.8.6.0), with a significance level of α = .05.

2.2. *Magnetic resonance imaging data acquisition*

MRI images were collected on a GE MR750 3T scanner (GE Healthcare, Waukesha, WI, USA) in the Mind Research and Imaging Center of NCKU with a 32-channel brain array coil. All participants were scanned using the same MR scanner.

Table 1 – Demographics, anthropic, and sports training experience details for soccer players and control participants.

Group	Soccer players (N = 25)	Control (N = 25)	p-value
Height (cm)	173 (±5.6)	174 (±6.6)	.633
Weight (kg)	66.8 (±5.9)	67.5 (±8.9)	.746
BMI (kg/m^2)	22.3 (±2)	22.2 (±2.6)	.971
Training experience (years)	11.3 (±1.95)	N/A	N/A

Values in each cell are the mean ± standard deviation. cm = centimeter, kg = kilogram, kg/m2 = kilograms per square meter.

Diffusion-weighted spin-echo echo-planar imaging sequence images were obtained with a measured spatial resolution of 2.5 × 2.5 × 2.5 mm (acquisition matrix 100 × 100 pixels, 50 slices) and a reconstructed resolution of 1.56 × 1.56 × 2.0 mm (reconstructed matrix 100 × 100 pixels, 50 slices). The sequence parameters were repetition time (TR) = 5500 ms, echo time (TE) = 62–64 ms, 50 non-linear diffusion directions with b = 1000s/mm2, field of view (FOV) = 250 × 250 mm^2, number of excitations (NEX) = 3, and slice thickness = 2.5 mm. Reverse DTI was also acquired for top-up correction in the DTI preprocessing. The acquisition parameters for the reverse DTI were identical to the DTI except for that only six directions were obtained due to the time constraints. The total acquisition time was 15 min 24 s.

Three-dimensional high-resolution brain structural images were also acquired using a T1-weighted fast spoiled gradient-echo dual-echo (FSPGR) sequence for each participant to allow for spatial normalization and visualization. The sequence parameters were TR = 2900 ms; TE = 7.6 ms; matrix size 224 × 224; flip angle = 12°; 1 mm slice thickness; FOV = 22.4/1 (cm/Phase); receiver bandwidth (BW) = ±31.25 kHz, and 170 sagittal slices covering the whole brain were collected. The total acquisition time was 3 min 38 s. For each participant, all the diffusion and anatomical images were acquired in the same session.

2.3. *Diffusion MRI processing*

No part of the study analyses was pre-registered prior to the research being conducted. The FMRIB Software Library 5.0 (FSL, https://fsl.fmrib.ox.ac.uk/fsl) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) on a Linux platform was used to process imaging data. Firstly, all raw images were converted from DICOM to NIfIT format using "dcm2niix" (Li, Morgan, Ashburner, Smith, & Rorden, 2016). A preprocessing procedure recommended by FSL (Smith et al., 2007) were used that include: correcting for motion artifact and eddy currents with the "eddy" (Jesper L.R. Andersson & Sotiropoulos, 2016) and "topup" (Jesper L.R. Andersson, Skare, & Ashburner, 2003) toolboxes, removing skull and nonbrain tissue from the image using the Brain Extraction toolbox (BET) (Jesper L.R. Andersson et al., 2003) on one of the no diffusion weighting (b = 0) images, and voxel-by-voxel calculation of the diffusion tensors, using the B0 non-diffusion data as a reference volume. All imaging quality of each participant was checked by "eddyqc" using QUAD for quality control (Bastiani et al., 2019). Imaging quality past the screening criteria in which their max head motion did not exceed 2.5 mm, nor did their mean framewise displacement (FD) exceeds .25 (Baum et al., 2018). We also visually inspected all brain images after normalization and coregistration steps to confirm that there was no bad warping. The John Hopkins University (JHU)-ICBM-DTI-81 White Matter Atlas was used to label tracts that showed significant group differences.

2.3.1. *WM integrity (whole-brain tract-based spatial statistics)*

Diffusion tensors were calculated using the DTIFIT tool within FDT (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007) for whole-brain volumes to create several DTI parametric maps, including fractional anisotropy (FA), mean diffusivity (MD),

axial diffusivity (AD), and radial diffusivity (RD). FA and MD are commonly derived variables that describe the directional coherence and magnitude of water molecule diffusion, respectively (Alexander et al., 2007). Water molecules tend to diffuse with greater directional coherence and lower magnitude when constrained by tightly packed fibers (such as well-myelinated axons) and by cell membranes, microtubules, and other structures. Thus, group differences in FA and MD in WM reflect meaningful differences in underlying microstructure, borne out by comparison with post-mortem WM work (Miller et al., 2011). AD reflects water diffusivity parallel to axonal fibers (i.e., axonal density) for assessing axonal injury, whereas RD reflects diffusion perpendicular to myelinated fibers (i.e., myelin sheath integrity) for assessing myelin injury (Winklewski et al., 2018).

Tract-based spatial statistics (TBSS, unbiased whole-brain analysis of white matter tracts) (Smith et al., 2007), implemented in FSL, was used to perform voxel-wise statistical analysis of the FA data. First, FA images were created by fitting a tensor model to the raw diffusion data using FDT (Behrens et al., 2007), and then using BET (Jesper L.R. Andersson et al., 2003). All subjects' FA data were then aligned to the $1 \times 1 \times 1$ mm^3 standard Montreal Neurological Institute (MNI152) space via the FMRIB58_FA template using the FMRIB Nonlinear Registration Tool (FNIRT) (J L R Andersson, Jenkinson, & Smith, 2007). Next, mean FA images were created and thinned to generate a mean FA skeleton that represents the centers of all tracts common to the group. A threshold of .2 for the mean FA map was used to generate a WM-tract skeleton that represented the center of the tracts common to all subjects. Each subject's aligned FA data were then projected onto the skeleton (all_FA_skeletonise) and the resulting data fed into voxel-wise statistical comparison. FA maps were scaled between 0 (fully isotropic diffusion) and 1 (fully anisotropic diffusion). Even though our hypothesis relates only to differences in FA, we nonetheless analyzed RD, MD, and AD in order to aid the interpretation of potential significant FA findings. The "tbss_non_FA" script was then used to obtain different maps of diffusion scalars (RD, MD, and AD) for each study participant, and voxel-wise cross-subject statistical analysis of FA, MD, AD and RD were further performed within the skeleton-space. For illustrative purposes, the FSL program TBSS_fill was used to highlight significant clusters. This creates a darker expanded outline around the cluster images. We set the statistical threshold at .05 using the threshold-free cluster enhancement (TFCE) for the correction for multiple comparisons (Smith & Nichols, 2009). Final tract maps were binarized and back-transformed from MNI into subjects' native space using inverse linear transformation and were used as subject-specific masks for extraction of FA using the FSL functions "fslstats" and "fslmaths".

2.3.2. *White matter connectivity (tract-specific probabilistic tractography)*

Within-voxel multi-fiber tract orientation structure was modeled using BEDPOSTx (Behrens et al., 2007) (Bayesian Estimation of Diffusion Parameters obtained using sampling techniques) followed by probabilistic tractography (with crossing fiber modeling) using PROBTRACKx implanted in FSL (Jbabdi, Sotiropoulos, Savio, Graña, & Behrens, 2012; Smith et al., 2007). These tracts have been identified as major WM bundles in the human brain (Hua et al., 2008). Prior to the estimation of diffusion parameters for probabilistic tracking, the subject's DTI images were first motion and eddy current corrected using a rigid body registration, followed by BET (Jesper L.R. Andersson et al., 2003) implemented in FSL. Automatic mapping of the 27 major white matter tracts (see Fig. 2a) was conducted in standard space of each participant using start/stop region-of-interest masks (implemented using the AutoPtx plugin for FSL) (De Groot et al., 2013) to derive tract-averaged measures of FA for the following tracts of interest: middle cerebellar peduncle (MCP), forceps major (FMaj), forceps minor (FMin) and bilateral medial lemnisci, corticospinal tract (CSTs), acoustic, anterior thalamic, posterior thalamic, superior thalamic radiation (STRs), superior, inferior longitudinal and inferior frontal-occipital fasciculi, uncinate fasciculus, and both the cingulate gyrus and parahippocampal portions of the cingulum bundle. Maps of FA, registered with the AutoPtx tract masks, allowed the calculation of tract-averaged values for each parameter across all voxels pertaining to each tract of interest. This produces an estimate of the probability and strength of the most likely location of a pathway (Behrens et al., 2007). Connection strength was determined from the number of sample streamlines from each seed brain region that successfully reached the target mask. This count how many such samples of streamlines succeed from the predefined seed region to the predefined target region. Subsequently, statistically normalized tracts were set at a threshold of .05 incorporating only those voxels where at least 5% of the total number of streamlines passed. For each participant and pair of seed and target regions, connectivity strength was computed and was determined from the number of sample streamlines from each seed that reached the target (Eickhoff et al., 2010). Within-tract probabilistic values were then normalized at the individual level by dividing the number of streamlines passing through each voxel by the total number of obtained streamlines ("waytotal") (Scholz, Tomassini, & Johansen-Berg, 2013a). We then took the output of tractography (i.e., waytotal and number of streamlines) transforms to the same anatomical space using fslmaths and fslstats to obtain tract-averaged measures of FA maps. Above we recreated known white matter tracts by guiding the streamlines using masks. Here we aimed to estimate the connectivity between brain matter regions by counting the number of streamlines connecting them (https://fsl.fmrib.ox.ac.uk/fslcourse/lectures/practicals/fdt2/index.html#connectivity). Connectivity strength is a measure of successful connectivity between the seed and the target. Training-induced white matter tract differentiation was initially explored by visualizing whether the strength of cross-tract associations altered between groups for FA for all tracts.

2.3.3. *Statistical analyses*

Voxel-wise statistics of the DTI parameters (FA, MD, AD, RD) for group differences (see Fig. 1) (controls *vs* soccer players) were tested in the general linear model (GLM) framework with two sample unpaired *t*-tests adjusted for covariates (i.e., age), using the FSL randomise tool with nonparametric permutation testing (10,000 permutations) (Winkler, Ridgway,

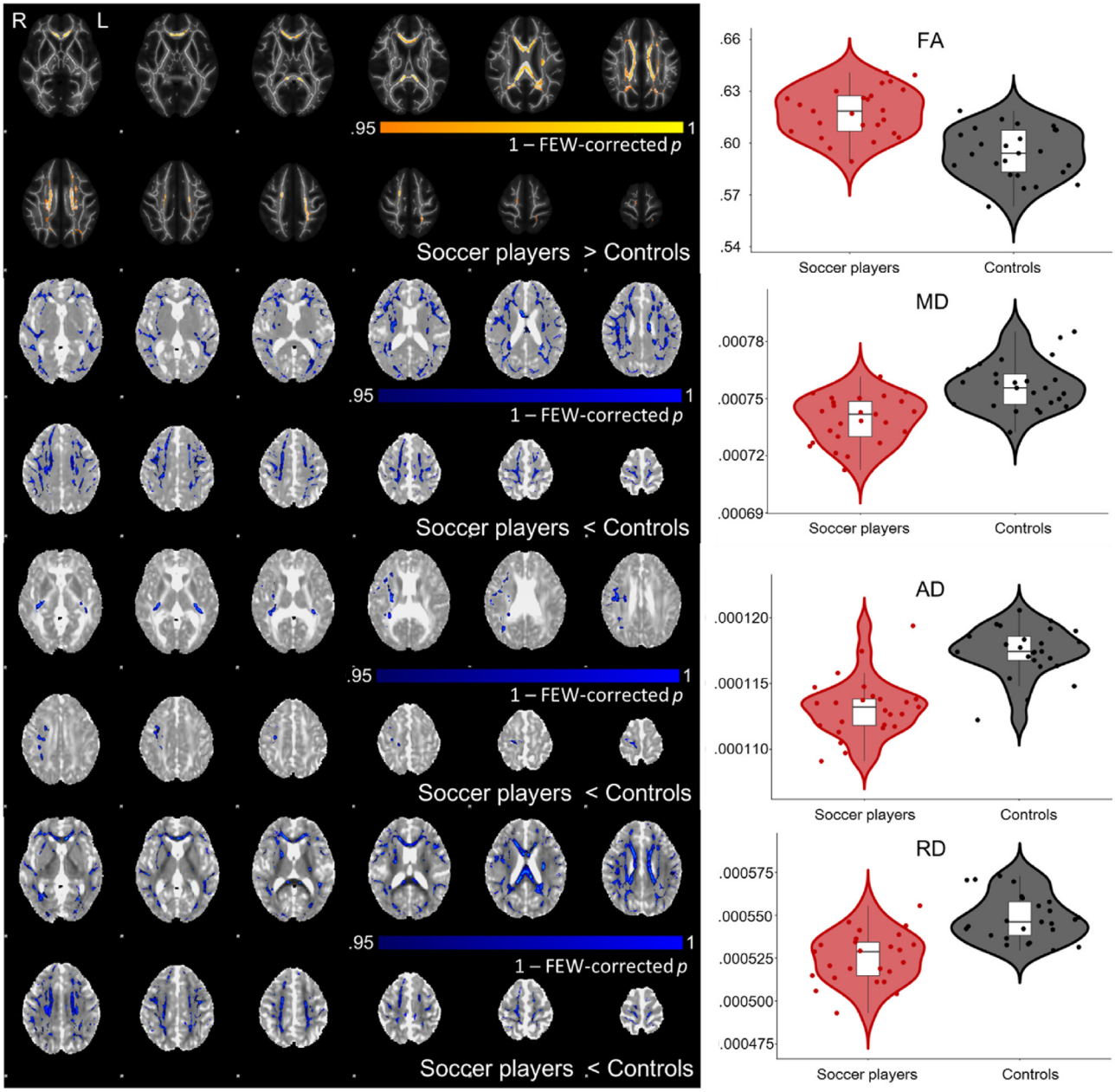

Fig. 1 – Group comparisons of diffusion measures between the soccer (N = 25) and control groups (N = 25). FWE-corrected p < .05. FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; AD = axial diffusivity.

Webster, Smith, & Nichols, 2014). Statistical maps were obtained with family-wise error (FWE) corrected *p*-values less than .05. Pearson's correlation analyses between DTI indices and years of training were performed to investigate the relationships between years of training experience and diffusion MRI-derived indices in the players. Based on the tracts showing significant group-level differences in the previous TBSS analysis, we examined the pre-defined white matter fiber bundle tracts of interest derived from a previous study conducted in large samples (e.g., UK biobank) (Cox et al., 2016). To extract the DTI indices, these targeted masks were transformed back to each subject's original images, and the mean DTI indices values of each tract were extracted from each soccer player to test association with sports experience. It was also of interest to explore whether the connection strength of each tract correlated with years of training experience. To examine this, the tracts were extracted based on the masks showing evident group-level differences in the previous probabilistic tractography analysis. The mean connection strength of each tract was then extracted from each soccer player and correlated with years of training experience.

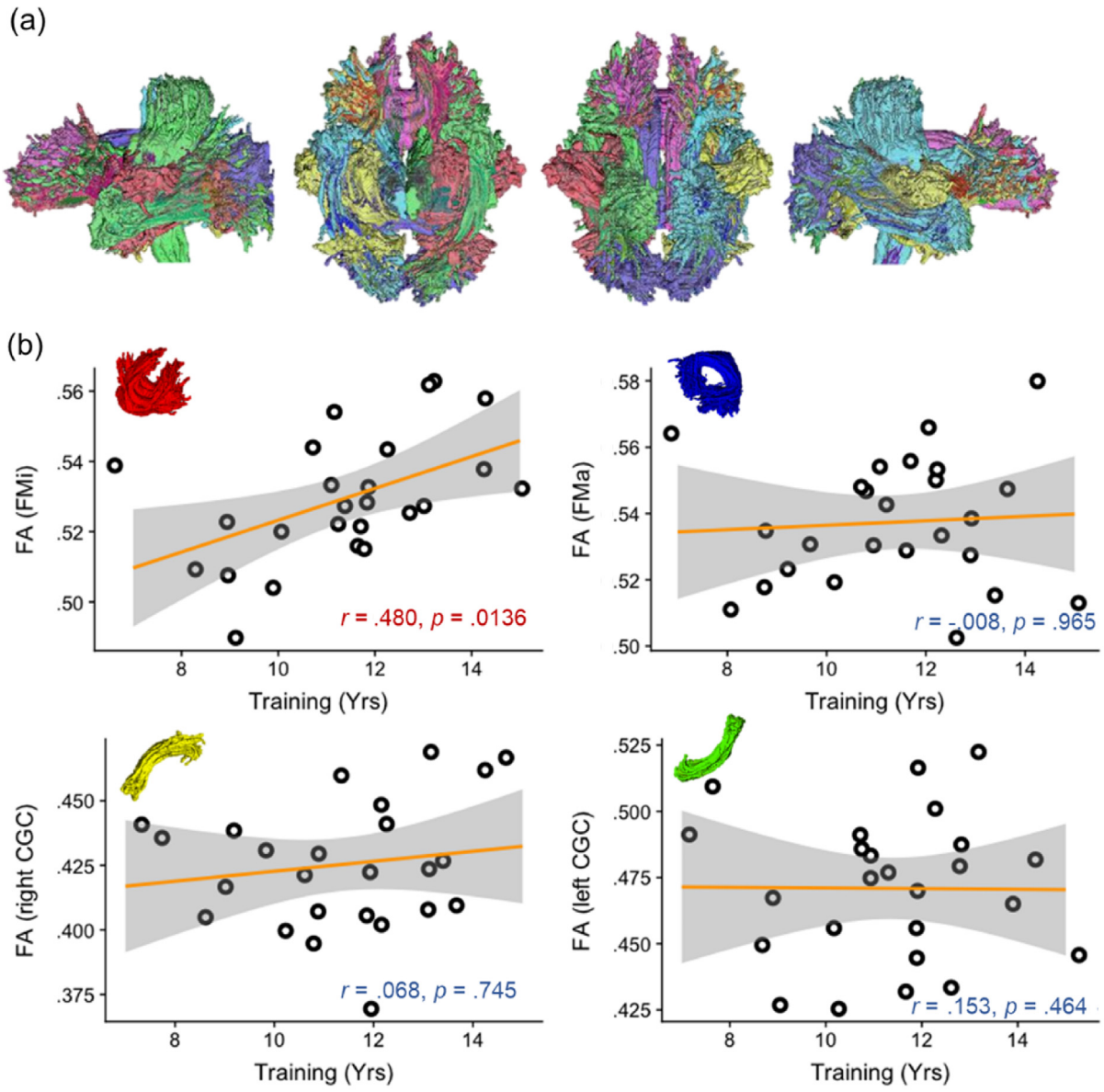

Fig. 2 – a. White matter tracts of interest. Four individual fiber tracts identified as part of the corpus collosum. b. Association between callosal fibers and years of training. Fractional anisotropy (FA) in tracts correlates with soccer training experience (years). p = probability value; r = Pearson correlation coefficient. FMi = forceps minor; FMa = forceps major; Right CGC = right cingulum; Left CGC = left cingulum.

3. Results

3.1. *WM integrity (whole-brain tract-based spatial statistics)*

Tract-averaged values for MR diffusion parameters FA, MD, AD and RD in each white matter-tract skeleton are plotted in Fig. 1. We found that soccer players showed higher coherence of directional diffusion (FA; t (48) = −5.921, p = 3×10^{-7}, Cohen's d = −1.675) than non-athlete controls, while a higher magnitude of water diffusion (MD; t (48) = 5.039, p = 7×10^{-6}, Cohen's d = 1.425) was found in non-athlete controls. Moreover, other diffusion scalars from TBSS results revealed significant group differences in radial diffusion (RD; t (48) = 5.808, p = 5×10^{-7}, Cohen's d = 1.643) and axial diffusion (AD; t (48) = 7.202, p = 3×10^{-9}, Cohen's d = 2.037) between athletes and non-athlete controls. No significant correlation between whole-brain FA value and years of training experience in soccer players was found (r = .274, p = .186).

The percentages indicate the average probability of a voxel being a member of the different labeled tracts within the atlas. Specifically, soccer players exhibited extensive brain regions with significantly higher FA in the genu (13.6%), body (29.4%), and splenium (15.8%) of the CCT, anterior (3.2%), superior (10.2%), and posterior (4.8%) bilateral corona radiate, posterior thalamic radiation (.02%), bilateral cingulum (cingulate gyrus) (.03%), and left tapetum (.06%). Non-athlete controls showed higher MD in genu (.06%), body (2.6%), and splenium (.02%) of

CCT, anterior (.6%) and posterior (.4%) bilateral limb of internal capsule, bilateral retrolenticular part of internal capsule (1.5%), anterior (5.7%), posterior (1.9%), and superior (5.2%) corona radiate, posterior thalamic radiation (1.6%), bilateral sagittal stratum (1.2%), bilateral external capsule (1.4%), bilateral cingulum (.09%), bilateral superior longitudinal fasciculus (5.2%), bilateral superior (.11%) fronto-occipital fasciculus, bilateral uncinate fasciculus (.01%) and bilateral tapetum (.06%).

Other common diffusion measures include AD and RD, which are thought to measure axonal and myelin pathology, respectively. Group comparisons showed that soccer players exhibited significantly lower RD ($t(48) = 5.8078$, $p = 4.922 \times 10^{-7}$, Cohen's $d = 1.6427$) in the genu (4.1%), body (9.0%), and splenium (4.0%) of the CC tract, the anterior (1.2%), and posterior limb of the internal capsule (.2%), the bilateral retrolenticular part of internal capsule (.07%), the anterior (5.5%), posterior (2.2%), superior (5.7%) and bilateral corona radiate, posterior (1.5%) thalamic radiation, bilateral sagittal stratum (.6%), bilateral external capsule (1.6%), left cingulum (.3%), bilateral superior longitudinal fasciculus (3.5%), bilateral superior fronto-occipital fasciculus (.1%), bilateral uncinate fasciculus (.11%), and right tapetum (.06%), and in AD ($t(48) = 7.2021$, $p = 3.6 \times 10^{-9}$, Cohen's $d = 2.037$) in the body of the CCT (.02%), right anterior limb of internal capsule (.0004%), bilateral posterior limb of internal capsule (1.05%), bilateral retrolenticular part of internal capsule (15.8%), right anterior (.9%), superior (6.9%), posterior (1.8%) corona radiata, and bilateral posterior thalamic radiation (1.7%), right sagittal stratum (3.3%), bilateral external capsule (2.7%), bilateral superior longitudinal fasciculus (11.6%), and right tapetum (.3%) than controls.

3.2. *WM connectivity (tract-specific probabilistic tractography)*

To formally test whether stronger WM connectivity in the CCT of soccer players was associated with sports training, we derived the tract-averaged values for MR diffusion parameters (i.e., FA) in each WM callosal fiber tract of interest. Although the CCT is a single large fiber bundle connecting the two hemispheres, a number of individual callosal fiber tracts can be identified. Two callosal fiber tracts of interest are the forceps minor (FMi), which connects the lateral and medial surfaces of the frontal lobes and crosses the midline via the genu of the corpus callosum, and the forceps major (FMa), which connects the occipital lobes and crosses the midline via the splenium of the corpus callosum (see Fig. 2b). The corpus callosum and cingulum are the WM tracts that run along the midline of the brain. Along its course, the cingulum collects prominent projections from the cingulate gyrus, it is evident that the cingulum contains some fibers from the corpus callosum (Wakana, Jiang, Nagae-Poetscher, Van Zijl, & Mori, 2004). A confirmatory analysis showed that FA in the FMi, but not in other tracts, was strongly correlated with sports experience (testing training-induced brain microstructural changes) (see Fig. 2b; FMi, $r = .486$, $p = .013$).

To examine whether soccer players had stronger connectivity across 27 major white matter tracts, we quantified the connection strength for each individual participant by means of a connectivity index for each tract. A significant difference of connection strength was found in seven tracts including the left acoustic radiation tract ($t(48) = -2.524$, $p = .015$, Cohen's $d = -.714$), the right acoustic radiation tract ($t(48) = -2.384$, $p = .021$, Cohen's $d = -.674$), the right corticospinal tract ($t(48) = 2.097$, $p = .041$, Cohen's $d = .593$), the right posterior thalamic radiation tract ($t(48) = 2.185$, $p = .034$, Cohen's $d = .618$), the right superior longitudinal fasciculus ($t(48) = 2.050$, $p = .046$, Cohen's $d = .58$), the right superior thalamic radiation tract ($t(48) = -2.591$, $p = .013$, Cohen's $d = -.733$), and the left superior thalamic radiation tract ($t(48) = -2.678$, $p = .01$, Cohen's $d = -.758$). Specifically, soccer players had stronger connectivity in two tracts: bilateral acoustic radiation and bilateral superior thalamic radiation tract, whereas weaker connectivity was observed in the right superior longitudinal fasciculus, corticospinal, and posterior thalamic radiation tract. Among these tracts, a strong positive correlation between connection strength and years of training in the left acoustic radiation tract ($r = .415$, $p = .039$) was found, together with a robust negative correlation between connection strength and years of training in the right corticospinal tract ($r = -.423$, $p = .035$) (see Fig. 3). The diffusion data was reconstructed and rendered in DSI Studio (Yeh & Tseng, 2011).

4. Discussion

Consistent with our initial hypothesis, we provide the first evidence for a clear association between years of training experience and neuroanatomical structural integrity in elite soccer players. Specifically, effects were seen in the anterior parts of CCT (i.e., forceps minor, connecting the surfaces of the left and right frontal lobes), possibly explaining the abnormality of CCT commonly seen in retired and concussed soccer players (Chamard et al., 2016; Stamm et al., 2015; Tremblay et al., 2014). Tract-specific connectivity analysis further showed that soccer players had stronger connectivity in the bilateral acoustic radiation and bilateral superior thalamic radiation tracts, whereas they exhibited weaker structural connectivity in the right superior longitudinal fasciculus, corticospinal, and posterior thalamic radiation tracts, suggesting structural lateralization toward the left hemisphere. A positive association between connection strength and years of training was found in the left acoustic radiation tract, while such a relationship was found to be negative in the right corticospinal tract, which has shown to be particularly vulnerable to concussion (Gardner et al., 2012). Together, these findings seemingly indicate a possible soccer training-induced sign of motor cortex neuron changes (i.e., gain or loss), even in the absence of concussion diagnoses.

Previous studies have reported either no difference (Chamard et al., 2016; Multani et al., 2016; Strain et al., 2017) or lower FA values (Lipton et al., 2013; Stamm et al., 2015; Tremblay et al., 2014) in concussed or retired contact sport athletes as compared to healthy controls who are either non-concussed healthy athletes or retired athletes without diagnosis of concussion. However, our findings not only showed greater FA within the CCT in soccer players compared to controls but also a robust positive correlation between microstructural integrity in the anterior forceps within the

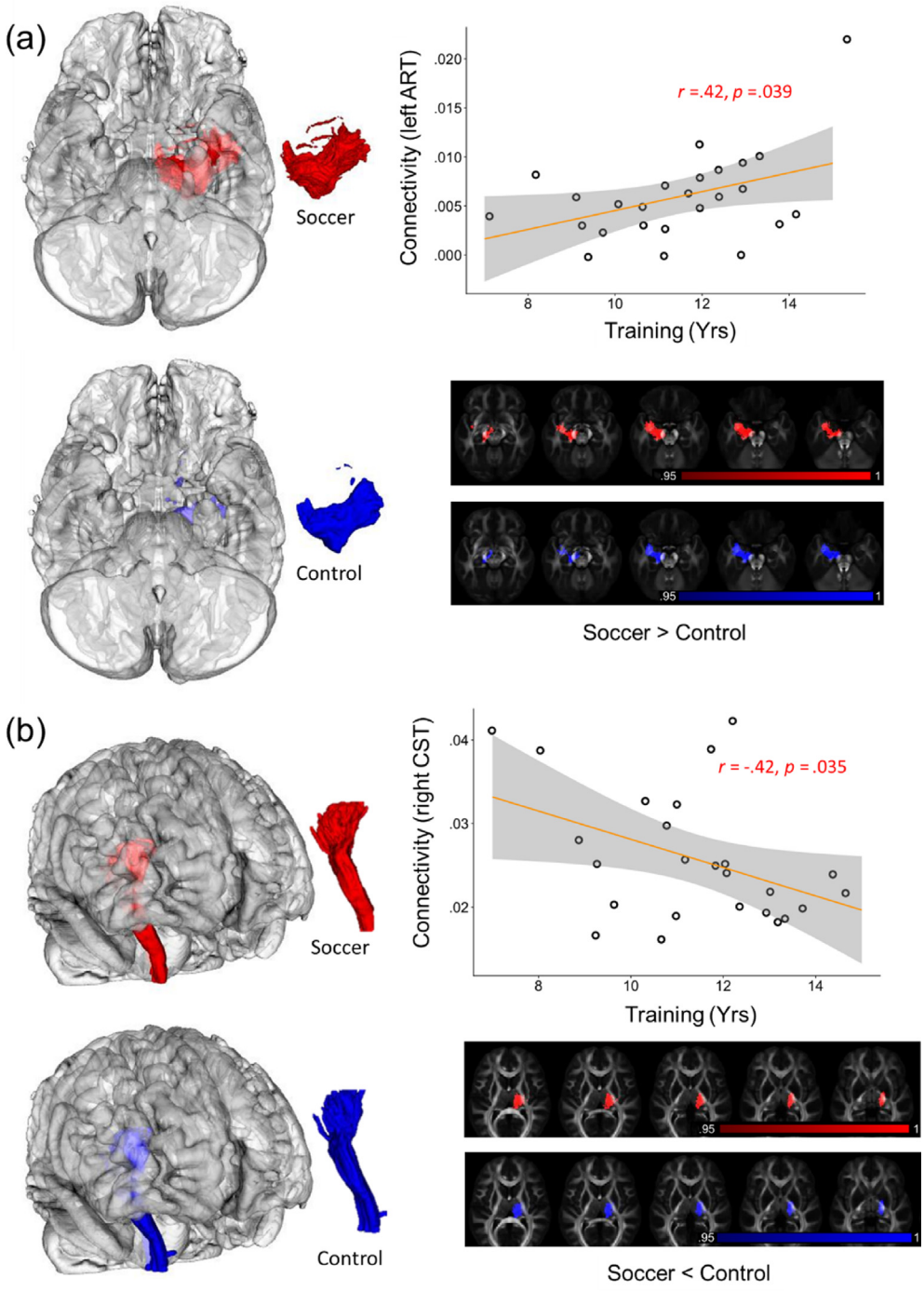

Fig. 3 – a. Correlation between structural connections and the left acoustic radiation tract; b. Correlation between structural connections and the right corticospinal tract. Red = mean connection strength in left acoustic radiation tract in soccer players (N = 25); Blue = mean connection strength in right corticospinal tract in control individuals (N = 25). FWE-corrected p < .05.

CCT (i.e., forceps minor) and years of training experience, possibly implying that the stronger CCT connectivity seen here may be linked to soccer training experience. In white matter, the level of FA is believed to be associated with microstructural features of fiber tracts, including the relative alignment of individual axons, how tightly they are packed, and myelin content (Paus, 2016). Thus, the greater integrity seen in soccer players may indicate the presence of more brain voxels containing water molecules that move predominantly along a preferred direction within the CCT. In addition, we also reported the results of cortical integrity that could provide supporting information of the observation of CCT. According to the voxel-based morphometry (VBM) results of whole-brain cortical integrity (see Supplementary material),

greater cortical integrity was seen in soccer players relative to controls (see Supplementary material Fig. 1a). Specifically, we observed that anterior parahippocampal gyrus is the major brain structure contributing to the group difference (see Supplementary material Fig. 1b). The possible reason may be that anterior parahippocampal gyrus projects fibers to the CCT, which could be attributed to its anatomical locations behind and below the splenium of the corpus callosum (Jones, Christiansen, Chapman, & Aggleton, 2013; Mark, Daniels, Naidich, & Borne, 1993).

To date, only two studies have investigated the brains of contact sports players without a concussion diagnosis (Koerte, Ertl-Wagner, Reiser, Zafonte, & Shenton, 2012; McAllister et al., 2014). Their findings demonstrated white matter alterations in contact sports players, which is in line with findings observed in patients with mild TBI (Sharp & Ham, 2011; Wilde et al., 2008), and suggests the possible attributes to training-related head impact exposure. However, the lack of health-matched non-athletic controls may diminish the conclusions of these studies. For example, it is possible that the effects they reported may be a result of structural changes associated with sport-specific training experience rather than due to the impact of concussion. Our findings thus extend current knowledge by raising the possibility that the previously reported findings (Koerte et al., 2012; McAllister et al., 2014) may result from structural changes associated with sport-specific training experience. Future work will need to further examine this speculation.

The observed differences in diffusion between groups could have several interpretations. For instance, increased myelination may cause diffusion to be hindered perpendicular to the axon orientation that may have resulted in increases in FA. Increased axon coherence may also lead to the increased FA via facilitating diffusion along the axons. Alternatively, it is also likely that neural inflammation may modulate synaptic maps resulting in inefficient axonal pruning (Cohen-Cory, 2002). Deficits in axonal pruning may lead to redundant networks which may result in decreased efficiency in information transmission, manifested by increased FA (Alba-Ferrara & de Erausquin, 2013). In line with this, it has been considered that forming and maintaining the brain's axonal wiring incurs a metabolic cost (Laughlin & Sejnowski, 2003), since it is assumed that the brain attempts to minimize wiring costs. Thus, the increased FA perhaps reflects poor cost-efficiency (Alba-Ferrara & de Erausquin, 2013). Although it is yet to be determined whether such a simple interpretation could be generalized to healthy populations (Scholz, Tomassini, & Johansen-Berg, 2013b), it may be helpful to consider multiple levels of diffusion measures, such as mean diffusivity, as well as perpendicular and parallel diffusivity, in addition to FA.

According to the previous discussion, there is no one-to-one relationship between a given anatomical feature and a particular diffusion MR measure. Further, it is worth noting that higher FA might not always be associated with better integrity, especially for crossing-fiber areas (Douaud et al., 2011). Hence, it is necessary to provide other diffusion measures to further elucidate the subtle changes associated with a particular tissue characteristic of interest (Soares, Marques, Alves, & Sousa, 2013). In this regard, it is assumed that other DTI-derived metrics, such as MD, may be able to improve tissue characterization (Winklewski et al., 2018). In some patients with acute mild TBI, an increase in FA along with a decrease in mean diffusivity occurs, which can be attributed to the effect of acute edema compressing white matter pathways (Sharp & Ham, 2011; Wilde et al., 2008). In this study, we observed that MD was lower in soccer players compared to controls, suggesting a possible progressive injury within the brain tissues of the soccer group. By analyzing other DTI-derived metrics (e.g., AD and RD), we obtained detailed map of structural properties, and the results showed lower AD and RD values in soccer players. Typically, AD captures diffusion along the neuronal axons (i.e., a measure of axonal integrity/diameter), while RD reflects the degree of myelination (i.e., a measure of myelin development) (Winklewski et al., 2018). Previous animal research has shown higher AD to be associated with axonal damage, whereas decreased AD was associated with progressive resolution of edema/inflammation (Budde, Xie, Cross, & Song, 2009; Sun et al., 2006). On the other hand, increased RD reflects the severity of demyelination and increased cellularity, whereas decreased RD reflects the progression of remyelination (Song et al., 2005). Indeed, inflammation and remyelination can occur after injury (Freund, Orjalo, Desprez, & Campisi, 2010; Ruffini, Kennedy, & Antel, 2004; Winklewski et al., 2018). Accordingly, our observation of significantly lower AD and RD values in soccer players possibly suggests that training experience may incur minor injury that may have induced inflammation and which the healthy athletes managed to recover from as indicated by their remyelination.

Additionally, our results showed that soccer players exhibited stronger structural connections in left acoustic and left superior thalamic radiation tracts, but weaker connections in right superior longitudinal fasciculus, right corticospinal, and right posterior thalamic radiation tracts than controls group. These findings may suggest a left-hemispheric specialization in soccer players. More interestingly, we found that soccer training experience was positively associated with the strength of the left acoustic radiation tract, whereas there was a negative association for the right corticospinal tract, which provides supportive evidence for the argument that soccer training experience may be associated with structural lateralization toward the left hemisphere. A well-documented finding is that the human brain has a dominant hemisphere for handedness (i.e., the left hemisphere controls right-handedness, while the right hemisphere controls dominant left-handedness) (Corballis, 2014; Sainburg, 2014). In this study, all participants were right-handed; hence, a dominant hemisphere for handedness could be countervailed. As a result, it is plausible that the group difference in the left-hemispheric specialization might be driven by soccer training experience.

Regarding the WM bundles difference associated with soccer training experience, the acoustic radiation tract is a primary sensory pathway known to help gate auditory information and facilitate language comprehension (Berman, Lanza, Blaskey, Edgar, & Roberts, 2013). One prior study reported lower MD in concussed athletes within this tract (Cubon, Putukian, Boyer, & Dettwiler, 2011), while other studies examining concussed contact/collision sports athletes reported lower membrane density in this tract (Cubon et al.,

2011; Gardner et al., 2012). In line with these findings, we observed that WM connection strength in the acoustic radiation tract was associated with soccer training experience, implying that the alterations in the auditory tract may be in part attributable to long-term participation in contact/collision sports.

Moreover, a negative association between right corticospinal tract and years of training experience was seen, indicating that practicing soccer training may be related to the reduction of this fiber bundle. As mentioned previously, CST has been reported as a fragile structure for sport-related concussion in retired and concussed athletes (Gardner et al., 2012). Although this corticospinal tract is a WM motor pathway, controlling limbs and trunk movements (Martin, 2005), the connections of CST to the somatosensory cortex suggest that these pyramidal tracts are also responsible for modulating sensory information from the body. A recent study demonstrated that patients with spinal cord injury showed improved arm and hand functions after applying transcranial direct-current stimulation over the CST followed by 1 h of robot-assisted arm training (Yozbatiran et al., 2017). Specifically, their diffusion imaging results revealed increased FA values among these patients. Based on these findings, we speculate that the weaker connection strengths within the CST in the soccer players may be an early sign of mild traumatic brain injury associated with long-term soccer training. Additional studies with long-term follow-up are needed to further assess this possibility.

It is important to note the limitations of this study. First, the relatively small sample size may limit the generalizability of any findings to other contact sports. Second, the current experimental design was cross-sectional, thus limiting causal interpretation from the observed findings, and hindering our ability to assess the predictive power of DTI with respect to long-term WM alterations. Moreover, despite the demographic homogeneity seen between the two groups, some possible idiosyncratic differences may potentially bias the effects of interest. For example, it has been claimed that any observed group differences associated with sports expertise may not be a definite consequence of the nature of sports expertise but rather a reflection of idiosyncratic differences (e.g., personality) (Wang, Yang, Moreau, & Muggleton, 2017). These concerns could be overcome with a longitudinal design to systematically investigate whether sustained participation in soccer training actually induces changes in specific microstructures of the brain. On the other hand, although we did not report any cognitive outcomes potentially linking to the neural inflammation seen here, healthy athletic populations might not necessarily show impairments at the behavioral level. For example, there is increasing evidence demonstrating superior executive functions in elite soccer players relative to their sub-elite peers or general populations (Vestberg, Gustafson, Maurex, Ingvar, & Petrovic, 2012), which may be presumably due to the fact that long-term participation in motor skill or coordinative training (like soccer) could lead to significant cognitive gains (Ludyga, Gerber, Pühse, Looser, & Kamijo, 2020; Wang, 2020). Indeed, it remains to be determined whether purposeful heading may significantly impact overt behavioral outcomes in healthy athletes (Kaminski, Wikstrom, Gutierrez, & Glutting, 2007; Stewart et al., 2018). To alleviate this concern, we provided a psychological variable that may be pertained to cognitive outcomes, namely cognitive style, a self-reported measure of thinking style, and found no significant differences across groups (see Supplementary material Table 3). Cognitive style has been recently reported to be associated with individual differences in flanker task performance (Hsieh, Yu, Chen, Yang, & Wang, 2020), which allows the investigation of selective attention and executive control in athletes (Wang, Liang, & Moreau, 2020; Wylie et al., 2018). Thus, we conjecture that any long-term training-induced neural inflammation may occur even in the absence of visible behavioral impairments. Nevertheless, future research should investigate whether the neural inflammation reported in this study could be associated with certain cognitive impairments. Finally, although this study demonstrates the potential impact of long-term training experience on brain integrity, such effects may not specifically be attributed to heading events. Future research should examine whether heading experience in recent games may mediate the relationship between training experience and structural brain alterations using more specific measures (e.g., the Einstein Heading Questionnaire). Despite these limitations, our findings provide important insights into individual differences concerning sport-related concussion, and into factors that may predict neurocognitive performance outcomes, and, arguably, into the mechanisms underlying resiliency to neurological damage. For example, characterizing the dose–response curve linking sport-specific measures and risks of concussion might facilitate safety guidelines, which in turn could allow minimizing the risk of adverse effects in the brains of athletes.

5. Conclusion

Overall, we provide the first evidence of microstructural differences in the WM between soccer players without a history of concussion and their non-athletic peers, with further evidence showing the link between soccer training experience and the potential changes in DTI measures. Crucially, the evidence presented here gives important insight into soccer training experience and its potential consequence for structural brain alterations, particularly in the anterior part of the corpus callosum tract (i.e., forceps minor). Together with the connectivity analysis, the results offer the possibility that individual differences in CCT for concussed and retired soccer players reported in the prior literature might be a consequence of protracted soccer training that incurs minor injury-induced neural inflammation. Our study emphasizes the need to examine the potential adverse effect of long-term soccer training on brain structures. We propose that the nature of the interaction between WM microstructural changes and years of training involves a latent microstructural injury that leaves the brain more vulnerable to the deleterious effects of practice, even after training ceases.

Credit author statement

CHW, DM, ZFY, and CTY conceived and designed the experiments. CTY, CHW, and SH performed the experiments. ZFY, IGS, NM and KRR analyzed the data. CTY, CHW, and SH

contributed materials/experimental tools. ZFY, IGS, DM, and CHW wrote the manuscript. KRR and NM edited/commented on the manuscript. All authors reviewed and approved the final version of manuscript.

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Data accessibility statement

The datasets collected, and codes analyzed that supporting this study are available on https://datadryad.org/stash/dataset/doi:10.5061/dryad.905qftthx.

Open Practices

The study in this article earned an Open Data badge for transparent practices. Materials and data for the study are available at https://github.com/zfyao/diffusion_soccer.git.

Declaration of competing interest

The authors confirm that there are no known conflicts of interest associated with this publication.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2020.07.016.

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