Advanced mapping of the human white matter microstructure better separates elite sports participation

Bradley Caron, Daniel Bullock, Lindsey Kitchell, Brent McPherson, Derek Kellar, Hu Cheng, Sharlene Newman, Nicholas Port, and Franco Pestilli

Abstract

Collision-sport athletes, especially football players, are exposed to a higher number of repetitive head impacts. Little is known, however, regarding the effects of long-term exposure to repetitive head impacts on brain tissue structure and the locations (i.e. superficial or deep tissue structures) affected. On top of this, little is known about the effects of highly competitive, strenuous, long-term athletics on brain tissue structure. We investigated this relationship using advanced microstructural mapping techniques. Specifically, we examined the baseline differences in collegiate athletic participants by using two models of the diffusion-weighted magnetic resonance imaging signal (the Diffusion Tensor and NODDI model). DTI and NODDI parameters were mapped in both cortical and subcortical structures, as well as in the major white matter tracts. Three groups of young adults participated in our study; IU football players, cross country runners, and non-athlete students. For both models, athletes were found to have consistently higher measures of microstructure than controls. The NODDI model parameters showed stronger results indicating that it might be more sensitive to capturing differences in brain white matter tissue microstructure than the DTI model. This was the first investigation into the effects of repetitive head impacts to use an open-source data processing platform *brainlife.io*. Data and analyses for this study are available at <https://doi.org/10.25663/brainlife.pub.14>.

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Introduction

Elite athletes are highly motivated individuals with physical and psychological characteristics that make them uniquely fit to compete in a sport (**Figure 1a**). In order to get to the elite level of competition within a given sport, athletes must often go through intensive and extensive physical conditioning and exercise, including cardiovascular endurance training and weight lifting. This conditioning is in addition to the physically-demanding aspects of their respective sports. This training has been shown to have a great deal of both beneficial and potentially harmful effects on all 79 organ systems of the body. As of today, a great deal of research is invested in identifying the potentially harmful effects of elite athletics, especially contact and collision-sports athletes, on the brain tissue of athletes. However, little is known regarding the inherent differences in brain tissue structure between elite sports athletes compared to the normal population (**Figure 1b**). In this paper, we investigated the baseline differences in white matter microstructure in two groups of collegiate athletes (football players, cross country runners) and group matched controls (**Figure 1a**).

The potential risks to the brain tissue from participation in impact-prone sports are of major interest to society (Montenigro et al., 2017). In Division 1 NCAA Collegiate football, a starting player may receive up to 1,400 head impacts in a single season, and the average starting player receives 200-400 impacts per season, with peak linear and rotational acceleration of around 20g and 1400 rad/s², respectively (Broglio et al., 2010; Crisco et al., 2011, 2010; Gysland et al., 2012; Myer et al., 2016b). For perspective, automobile accidents have been shown to have peak linear and rotational accelerations ranging from 29g to 120g and 2100-9400 rad/s², respectively (Zhang et al., 2006). Among elite athletes, American football players have received increasing attention due to the high rate of the body and head collisions in the sport and the higher prevalence of symptoms related to neurodegenerative disorders in retired athletes as compared to the general population (Gavett et al., 2011; McKee et al., 2009; Mez et al., 2017; Saulle and Greenwald, 2012). The potential for brain tissue damage is greater in these athletes than

those that participate for example, in non-collision sports, such as cross country. Historically, the concern regarding the effects of head impacts in collision sport athletes has been focused on concussion and traumatic brain injury (TBI). However, only a small proportion of head impacts in American football result in a concussion diagnosis, as the estimated rate of concussions is less than 1.5 concussions across both practice and game sessions (Kerr et al., 2017). The concern among some scientists is that repetitive head impacts may be more detrimental to athletes than concussions, as they have been associated with a higher risk of developing neurodegenerative disorders, most-notably Chronic Traumatic Encephalopathy (Critchley, 1957; Gavett et al., 2011; McKee et al., 2009; Roberts, 1969).

Figure 1. Multiple effects of head impact and sports participation on deep and superficial brain tissue. **a.** Example of collision (left) and non-collision (middle) sports and non-athlete (right) participants investigated in this study. Athletics participation has been found to have a variety of psychological and physiological effects on the body, including the brain. However, little is known regarding the exact effects of elite sports participation on brain tissue structure. *Note. Final images will be added to panel a, after acceptance to the journal.* **b.** The effects of elite sports participation on white matter tissue structure is much less investigated than the detrimental effects of impact-prone sports, as indicated by the number of PubMed citations obtained. Searches conducted December 2019, see **Methods** for more details. **c.** Illustration of the potential effects of collisions on brain tissue. Inertial forces (blue arrows) generated from the linear or rotational accelerations of the impact and contact affect primarily deep and long-range neuronal fibers and white matter. Dispersive forces (red arrows) generated by a single point head impact. Inertial forces (blue) travel along the major axis of head motion during head rotation – we suggest that these forces are most likely to affect long-range neuronal fibers and deep white matter tissue. Contact forces (red) are local and disperse in multiple, fanning, directions – we speculate that these forces are more likely to affect superficial brain structures and superficial white matter. **d.** The effects of sports participation and repetitive head impacts can have differential impacts on neuronal tissue. Healthy neuronal fibers (i.e. top) can be highly oriented, and densely packed. Neuronal fibers (i.e. middle) undergoing repetitive sub-concussive hits may become damaged, less cohesively oriented, less packed, or even swollen due to neuroinflammatory processes. (Image modified from [Wikipedia, CC BY license](#), original by P.J. Lynch). However, the same changes in orientation of neurites can be observed via neuroplasticity and generation of new neuritic processes from sports participation (bottom). **e.** Example demonstrating the inability of the fractional anisotropy (FA) measure from the Diffusion Tensor Model (DTI) to identify differences in the neuroinflammatory condition, especially with microglial infiltration, and will show minor differences in neuroplastic situations shown in **d**, but orientation dispersion index (ODI) from the Neurite Orientation Dispersion Density Imaging (NODDI) model is able to

distinguish between the two and will be able to identify neuroinflammatory processes such as microglial infiltration (Yi et al., 2019).

Different types of forces affect the brain following an impact to the head or body. These forces are generally subdivided into contact and inertial (McAllister, 2011; Meaney and Smith, 2011) (**Figure 1c**). Immediately following an impact, the acceleration due to the contact forces is loaded onto the surface of the brain, potentially imposing superficial brain tissue compression and dispersion (**Figure 1c** red). Inertial forces follow thereafter translating the impact onto the deep brain tissue, affecting also long-range brain structures (**Figure 1c** blue). Contact and inertial forces have been shown to lead to a plethora of alterations to brain tissue structure such as neuronal membrane permeability and axonal swelling (Geddes et al., 2003a, 2003b; LaPlaca et al., 2005), neuronal response alterations (Kao et al., 2004; Lamb et al., 1997; Zhang et al., 1996), axonal beading (Gaetz, 2004; Kilinc et al., 2009, 2008; Maxwell and Graham, 1997), shearing of the long-range neuronal fibers (Adams et al., 1989, 1982; Gennarelli et al., 1982; Johnson et al., 2013; Nevin, 1967; Povlishock et al., 1983; Povlishock and Becker, 1985; Povlishock and Katz, 2005), inflammatory cascades (Giza and Hovda, 2014; Israelsson et al., 2008; Shultz et al., 2012) all the way to Wallerian degeneration and axotomy (Armstrong et al., 2016; Frati et al., 2017; Maxwell et al., 2015; Pierpaoli et al., 2001; Rotshenker, 2007; Yoshimine et al., 2018). Athletes are exposed to increased risks of musculoskeletal injury, increased stress and anxiety, with increased risk for chronic inflammation (Gleeson, 2007; Hootman et al., 2007; Rice et al., 2019). These alterations and biological cascades from repetitive head impacts are in addition to increased risks of musculoskeletal injury, increased stress, and anxiety, with increased chronic inflammation (Gleeson, 2007; Hootman et al., 2007; Rice et al., 2019) and increased exposure to reactive oxygen species from elite sports participation (Hadžović-Džuvo et al., 2014; Powers et al., 2020) and the athletic conditioning required. This increased inflammation may potentially impact brain tissue microstructure and lead to neuroinflammatory processes (Huang et al., 2018; Kempuraj et al., 2017) including microglial infiltration and mitochondrial dysfunction (**Figure 1d**). Thus, in order to fully understand the full effects of repetitive head impacts and the potential determinants seen in some former impact-prone athletes, it is important to fully clarify the baseline differences (i.e. non-contact related) between elite sports athletes and the general population.

The positive benefits of physical exercise and activity generally are well-documented. Beneficial effects of physical activity range from improved cognition (Hillman et al., 2008; Voss et al., 2011), overall better wellbeing (Penedo and Dahn, 2005), longer lifespan (Reimers et al., 2012), and even increased integrity of brain tissue structure (Bracht et al., 2016; Chaddock-Heyman et al., 2018, 2014; Esteban-Cornejo et al., 2019; Hayes et al., 2015; Ruotsalainen et al., 2020; Saraulli et al., 2017; Voss et al., 2013) (**Figure 1d**). Physical exercise has even been documented to lead to increased synaptogenesis and dendritic spine density (El-Sayes et al., 2019; Hötting and Röder, 2013). Long-term physical exercise has also been shown to moderate the effects of the brain to reactive oxidative species (Brunetta et al., 2020; Radak et al., 2013) and inflammatory processes in healthy and elderly populations (Seo et al., 2019). Despite this evidence of benefits of physical activity and exercise, the full effect of elite sports participation on brain tissue structure is not well understood. Specifically, the potential effect of sport participation on the brain white matter has not been fully characterized. For example, some investigations into white matter tissue structure of elite athletes find increases in measures of structural integrity (Hänggi et al., 2015), while others show decreases in those measures (Deng et al., 2018; Hänggi et al., 2010; Jäncke et al., 2009). This lack of consensus in the literature highlights the need for a more thorough characterization of the effects of elite sports participation on the brain tissue structure of athletes. This is especially important for understanding the potentially harmful effects of a specific class of sports, impact-prone sports.

Diffusion-weighted magnetic resonance imaging (dMRI) and tractography allow measuring white matter tissue in the living human brain. The method provides a unique opportunity to clarify the positive and negative effects of sports participation. The method allows measuring the macro- and microstructural composition of the brain white matter tissue *in vivo* (Basser et al., 1994a; Basser and Jones, 2002). Recent advancements in diffusion MRI acquisition parameters, including the use of multi-shell acquisitions to exploit multi-parameter models to derive brain microstructural tissue properties such as neurite orientation dispersion and density (Zhang et al., 2012), show increased promise for improving discrimination of brain tissue changes in a variety of human disease relative to more traditional single-shell acquisition parameters and models (Pestilli, 2018; Rokem et al., 2017; Thomason and Thompson, 2011; Wandell, 2016). Such models can also be used to provide neurite composition information for both deep (Jelescu and Budde, 2017; Sato et al., 2017; Schilling et al., 2018) and cortical white matter (Fukutomi et al., 2018) structures, for instance.

Advanced diffusion methods, including multi-shell acquisition and higher order diffusion signal models, have been previously used to examine brain tissue structure across multiple large tissue structures. For example, these methods have been previously used to examine brain tissue structural differences in deep white matter structures (Rokem et al., 2017) (hereafter referred to as major white matter tracts), superficial white matter (Fukutomi et al., 2018) (i.e., white matter mixed with neuronal cell bodies, such as white matter in the cortex; hereafter referred to as cortical white matter) and subcortical (i.e. amygdala, hippocampus, basal ganglia) white matter. These methods have been used to measure the putative effects of concussion, concussion history, and repetitive head impacts, including disorientation of myelinated structures, disruption of myelin properties, axonal swelling and *tau*-accumulation (Churchill et al., 2018, 2017a; Mayer et al., 2017). A great deal of previous work has studied structural differences in a single tissue-type or combination of tissue types, including major (Bahrami et al., 2016; Bazarian et al., 2014; Churchill et al., 2017a, 2017b; Davenport et al., 2016a, 2016b; Koerte et al., 2012; Kuzminski et al., 2018; Lefebvre et al., 2020; Mayinger et al., 2018; McAllister et al., 2014; Merchant-Borna et al., 2016; Saghafi et al., 2018; Sollmann et al., 2018; Stamm et al., 2015; Strauss et al., 2020; Yuan et al., 2018), cortical and subcortical (Gong et al., 2018; Mayer et al., 2017; Meier et al., 2016) white matter between collision sport participants and controls (i.e., non-athletes, non-collision sports athletes, within-subject longitudinal). However, few studies (Lefebvre et al., 2020; Mayer et al., 2017) have looked at all three tissue-types to fully characterize the effects of sports participation across the entirety of the human brain.

To fully characterize the structural properties of the groups of subjects in our study, we compared the microstructural properties of major white matter tracts, cortical, and subcortical white matter using two of the dominant models (**Figure 1e**). We compared results using the original Diffusion Tensor model (DTI; (Basser et al., 1994b; Pierpaoli et al., 1996)) and the relatively more recent, Neurite Orientation Dispersion Density Imaging (NODDI; (Zhang et al., 2012)) model. More specifically, we compared the performance of DTI and NODDI in identifying differences between the groups. We used a state-of-the-art, anatomically informed approach to measuring white matter tracts (Mori et al., 2005; Pestilli et al., 2014; Yeatman et al., 2012), cortical white matter (Destrieux et al., 2010; Fukutomi et al., 2018), and subcortical white matter structures (Bruce Fischl et al., 2002). Microstructural measurements demonstrated widespread differences in tissue microstructure across a majority of major structures (cortical and deep white matter structures) between athletes and non-athletes, with collision-sports athletes demonstrating the greatest differences from non-athletes. We performed additional tests to rule out effects due to a series of alternative nuisance drivers such as brain tissue size and volume.

Methods

Open cloud computing services and brainlife.io. We investigated how the microstructural tissue properties in major white matter tracts differed among the three groups: football players, cross country runners, and non-athlete collegiate students. To do so, we developed a reproducible data processing workflow using the cloud computing platform brainlife.io (Avesani et al., 2019). Our workflow consisted of 17 brainlife.io Apps (see also **Table 1**). Specifically, sixty one major white-matter tracts (Mori et al., 2005; Pestilli, 2018; Rokem et al., 2017; Yeatman et al., 2012) were identified using the Anatomically-constrained tractography (ACT; brainlife.app.297) app to perform tractography (Smith et al., 2012; Takemura et al., 2016) and the White Matter Anatomy Segmentation (brainlife.app.188) app for the segmentation (Bullock et al., 2019) of these 61 major white matter tracts (**Figure 3a**; see also **Methods: White matter microstructure modelling (Tractography) and White matter microstructure modelling (Segmentation)**). We used the NODDI (brainlife.app.365) and DTI (brainlife.app.292) apps to estimate the microstructural properties of the previously segmented major white matter tissue using parameters derived with the NODDI model (Daducci et al., 2015; Zhang et al., 2012) and the DTI model (Basser et al., 1994a, 1994b). These maps were combined with the Tract Analysis Profiles (brainlife.app.361) app to map the microstructural parameters on to the anatomy of each tract of interest (Yeatman et al., 2012). See also **Methods: White matter microstructure modelling: Tract profile generation**. We used an empirically-documented categorization scheme that grouped major white matter tracts that have been historically associated with a variety of functional domains and behaviors (Schmahmann and Pandya, 2006) (**Figure 3a**). The NODDI model estimates brain microstructural properties such as neurite orientation dispersion (i.e., *ODI*), neurite density (i.e., *NDI*), and CSF volume fraction (i.e., *ISOVF*). See **Methods: White matter microstructure modelling: Neurite Orientation Dispersion and Density Imaging (NODDI)** for details on the microstructural modelling and interpretation. The DTI model estimates brain microstructural properties such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). See **Methods: White matter microstructure modelling (DTI)** for details on the microstructural modelling.

We also investigated how the microstructural properties of the cortical and subcortical white matter might differ among football players, cross country runners, and non-athletes. We used the Freesurfer app ([brainlife.app.0](https://brainlife.io/app/0)) to segment cortical and subcortical white matter parcels (Fischl, 2012) (**Figure 5a**; see also **Methods: Anatomical data (T1w) processing**). We used an empirically-documented parcellation scheme that grouped cortical white matter parcels into eight regions that have been historically associated with a variety of functional domains and behaviors (Chayer and Freedman, 2001; Ebbesen and Brecht, 2017; Gerard et al., 1933; Gogolla, 2017; Irimia et al., 2012; Kanwisher, 2010; Rajmohan and Mohandas, 2007; Scott et al., 2000; Singh-Curry and Husain, 2009; Tootell et al., 1998) (**Figure 5a**). We used the NODDI ([brainlife.app.365](https://brainlife.io/app/365)), DTI ([brainlife.app.292](https://brainlife.io/app/292)), and Cortex Tissue Mapping ([brainlife.app.379](https://brainlife.io/app/379)) apps to map microstructural tissue properties derived using the NODDI model and DTI model in the cortical white matter parcels (Fukutomi et al., 2018). Using Freesurfer, we also segmented subcortical structures and mapped the average microstructural tissue properties derived using NODDI and DTI in the subcortical white matter. See **Methods: Anatomical data (T1w) processing** and **Cortical and subcortical white matter mapping** for more details on the mapping and segmentation

Availability of data and open services for the reproducibility of the data analyses. Deidentified data are shared minimally processed and are published using brainlife.io. The brainlife.io platform allows publishing processed data and associated analyses step (Apps) integrated into a single record referenced by a digital-object-identifier (DOI; (Avesani et al., 2019)). Apps and data produced as part of the present project are published on brainlife.io interlinked and each dataset is preserved with associated provenance information to allow other investigators to download the analyses or reuse the App on the cloud platform. Data and Apps associated with the present project are published and preserved at <https://doi.org/10.25663/brainlife.pub.14>.

The data processing pipeline (**Table 1**) outlined in the **Methods** section of this paper can be accessed as computable applications via open services hosted at brainlife.io (Avesani et al., 2019; Stewart et al., 2015; Towns et al., 2014), or as static code available on <https://github.com/brainlife>. The services allow the processing of data in the same fashion outlined below. The services can be viewed here <https://doi.org/10.25663/brainlife.pub.14> and links to public GitHub repositories with their source code are included for each step described below and in **Table 1**. Code (MATLAB, python) for the analyses performed in this paper is freely available at <https://github.com/bacaron/athlete-brain-study>.

Application	Github repository	Open Service DOI	GitHub Branch
FSL Anat	https://github.com/brainlife/app-fsl-anat	10.25663/brainlife.app.273	v1.0
Freesurfer Cortical and Subcortical Segmentation	https://github.com/brain-life/app-freesurfer	10.25663/bl.app.0	1.11
Tissue-Type Segmentation	https://github.com/brainlife/app-mrtrix3-5tt	10.25663/brainlife.app.239	binarize-v1.0
Multi-Atlas Transfer Tool (MaTT)	https://github.com/faskowit/app-multiAtlasTT	10.25663/bl.app.23	0.0.5
FSL Topup & Eddy - CUDA	https://github.com/brainlife/app-FSLTopupEddy	10.25663/brainlife.app.287	cuda-v1.0
Mrtrix3 preproc	https://github.com/brain-life/app-mrtrix3-preproc	10.25663/bl.app.68	1.6
SNR Calculation	https://github.com/davhunt/app-snr_in_cc/tree/plot	10.25663/bl.app.120	plot
FSL BET	https://github.com/brain-life/app-FSLBET	10.25663/brainlife.app.163	dwi
NODDI Fit via Amico	https://github.com/brain-life/app-noddi-amico	10.25663/brainlife.app.365	1.3
FSL DTIFIT	https://github.com/brainlife/app-fslDTIFIT	10.25663/brainlife.app.292	v1.0
Cortex Tissue Mapping	https://github.com/brainlife/app-cortex-tissue-mapping	10.25663/brainlife.app.379	v1.1
Fit Constrained Spherical Deconvolution Model For Tracking	https://github.com/bacaron/app-mrtrix3-act	10.25663/brainlife.app.238	csd_generation-v1.0
Anatomically Constrained Tractography using precomputed 5tt & CSD	https://github.com/bacaron/app-mrtrix3-act	10.25663/brainlife.app.297	1.3
merge2TCKs	https://github.com/bacaron/app-mergeTCK	10.25663/brainlife.app.305	two-tck
White Matter Anatomy Segmentation	https://github.com/brainlife/app-wmaSeg	10.25663/brainlife.app.188	3.7
Remove Tract Outliers	https://github.com/brainlife/app-removeTractOutliers	10.25663/brainlife.app.195	1.3
Tract Analysis Profiles	https://github.com/brain-life/app-tractanalysisprofiles	10.25663/brainlife.app.361	1.8
Tractography Quality	https://github.com/brainlife/app-tractographyQualityCheck	10.25663/brainlife.app.189	1.2

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Table 1. Description, weblinks, and DOI for the open cloud services used to process the data.

Data sources for the analyses of the scientific articles. Data utilized for **Figure 1c** were collected by performing customized searches on the NIH PubMed portal. Search results were generated using the format:

Search query for “Impact/TBI/CTE.”

```
(((((sports[Text Word]) OR (sports participation[Text Word])) OR (elite[Text Word])) OR (world class[Text Word])) OR (professional athlete/s[Text Word])) OR (athlete[Text Word])) AND (white matter[Text Word])) NOT (chess[Text Word])) NOT (music[Text Word]))
```

Search query for “Sports & white matter.”

```
NOT (Concussion[Text Word])) NOT (concussion[Text Word])) NOT (head trauma[Text Word])) NOT (brain trauma[Text Word])) NOT (brain injury[Text Word])) NOT (TBI[Text Word])) NOT (brain damage[Text Word])) NOT (concussions[Text Word])) NOT (repetitive head impacts[Text Word])) NOT (RHI[Text Word])) NOT (head impact[Text Word])) NOT (CTE[Text Word])) NOT (injury[Text Word])).
```

Literature searches were conducted on December 20, 2019.

Neuroimaging data sources. Data were collected at the Indiana University Imaging Research Facility (IRF, <https://www.indiana.edu/~irf/home>).

Study participants. A total of fifty-one male participants participated in the study. Twenty-one participants were 4th- and 5th-year varsity Indiana University (IU) football “starters” (age 21.1 ± 1.5 years). This number accounts for approximately 60% of the total IU football team active players matching our criteria. Potential participants were excluded if they reported a diagnosed concussion within 6 months of the beginning of the study. One football player did not complete the study, and three football players did not complete the diffusion MRI (dMRI) scans. This left 17 usable datasets from the football group. Following scanning, football players received a socioeconomic status survey gathering information regarding estimated family income and the area in which they were raised (i.e. urban, small town, suburbs). Nineteen members of the IU cross country running team (age 20.2 ± 2.5 years) were included as a non-collision sports group and were matched to the football players based on age and experience level. Three of the players' anatomical (T1w) images were unusable due to aliasing and motion artifacts and thus their data was not included. This left us with 16 eligible members. Our access to the socioeconomic status of non-athlete undergraduates was limited to Psychology and Neuroscience undergraduates who had filled out the socioeconomic survey in an IRB approved subject pool. Eleven controls (non-athletes) participants were selected from the limited pool matched to the football players (age 19.9 ± 3). Two of the participants' diffusion data contained strong distortions artifacts that were beyond correction with our processing protocol and thus their data were not included, leaving nine usable datasets. Overall, the released dataset contains usable data from 17 football players, 16 cross country runners, and 9 non-athletes for analysis ($N = 42$). In regards to concussion history, two football players had been diagnosed with a concussion approximately 3 years before the study and one player had been diagnosed approximately 2 years before the study. There was no history of concussion in the cross country runners while they were at IU. No information was collected regarding the concussion history of the participants before their arrival at IU, however. Although we did not have this information available, we can estimate around 7.25% of football players to have been diagnosed with a concussion prior to college given estimates from the literature (Dompier et al., 2015). Participants gave informed written consent that was approved by the Indiana University Institutional Review Board. All participants were recruited through flyers handed out by the athletic trainers of each team or posted around campus. Participants were compensated for participation with a cash payment.

Neuroimaging parameters. Participants were imaged using a 3-Tesla TIM Trio scanner located in the Imaging Research Facility at Indiana University. A 12-channel head coil was used as the 32-channel coil did not fit the heads of our larger subjects. Diffusion-weighted magnetic resonance imaging (dMRI) data were collected with two phase-encoding schemes, i.e anterior-posterior (AP) and posterior-anterior (PA). The following parameters were used for the dMRI pulse sequence: TR/TE = 4930/99.6 ms, iPAT acceleration factor = 2; voxel size = $2 \times 2 \times 2$ mm isotropic, 143 diffusion-weighting directions, including sixty-four directions with $b = 1000$ s/mm² and sixty-four directions with $b = 2000$ s/mm². Fifteen non-weighted images were also acquired ($b = 0$). One T1-weighted (T1w) anatomical image was acquired for each participant using the following sequence: TR/TE = 1800/2.67 ms, TI = 900 ms, flip angle = 9° , bandwidth = 150 Hz/pixel, 160 sagittal slices, FOV = 256 mm, matrix =

256x256, slice thickness = 1 mm, resulting in 1 mm isotropic voxels. The total acquisition time for T1w was 7 minutes and 42s.

Anatomical data (T1w) processing. Raw anatomical (T1w) images were preprocessed using the *fsl_anat* functionality provided by the FMRIB Software Library (FSL) (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). In brief, the raw anatomical (T1w) images were cropped and reoriented to match the orientation of the MNI152 template. Then, the cropped and reoriented images were *linearly* and *non-linearly* aligned to the MNI152 0.8mm template using *flirt* and *fnirt* functionality respectively (Greve and Fischl, 2009; Jenkinson et al., 2002; Jenkinson and Smith, 2001). The *linearly* aligned images will hereafter be referred to as the ‘acpc aligned’ anatomical (T1w) images. The warps generated from the *non-linear* alignment were subsequently used for mapping diffusion metrics to the cortex (Fukutomi et al., 2018). Following alignment, the ‘acpc aligned’ anatomical (T1w) images were processed via *Freesurfer’s recon-all* function to generate pial (i.e. cortical) and white matter surfaces and to parcellate the brain into known anatomical atlases (Dale et al., 1999; Dale and Sereno, 1993; Desikan et al., 2006; B. Fischl et al., 2002; Fischl et al., 2004a, 2004b, 2001, 1999a, 1999b; Fischl and Dale, 2000; Han et al., 2006; Jovicich et al., 2006; Kuperberg et al., 2003; Reuter et al., 2012, 2010; Reuter and Fischl, 2011; Rosas et al., 2002; Salat et al., 2004; Segonne et al., 2007, 2004). The Destrieux (aparc.a2009s) atlas was used for subsequent white matter tract segmentation and for mapping of diffusion metrics to the cortical surface. Finally, the ‘acpc aligned’ anatomical (T1w) image was segmented into different tissue-types using *MrTrix3.0’s 5ttgen* functionality (Segonne et al., 2007; Tournier et al., 2019). The gray- and white-matter interface mask was subsequently used as a seed mask for white matter tractography (Smith et al., 2012).

Diffusion data (dMRI) processing. Raw dMRI images were first reoriented to match the orientation of the MNI152 template using the *fsorient2std* command provided by FSL. Images containing opposite-facing distortions due to the phase encoding direction (i.e. PA and AP) were then combined into a single corrected image in a method similar to the one described in Andersson and colleagues (2003) (Andersson et al., 2003; Smith et al., 2004) (i.e. *topup* command) as provided by FSL (Jenkinson et al., 2012; Woolrich et al., 2009). Eddy-current and motion correction was then applied via the *eddy_cuda8.0* with replacement of outlier slices (i.e. *repol*) command provided by FSL (Andersson et al., 2018, 2017, 2016; Andersson and Sotiropoulos, 2016). *MRTrx3’s dwigradcheck* functionality was used to check and correct for potential misaligned gradient vectors following top-up and eddy (Jeurissen et al., 2014a). Following this, dMRI images were debiased using ANT’s *n4* functionality (Tustison et al., 2014) and the background noise was cleaned using *MrTrix3.0’s dwidenoise* functionality (Veraart et al., 2016). Finally, the preprocessed dMRI images were registered to the ‘acpc aligned’ anatomical (T1w) image using FSL’s *epi_reg* functionality (Greve and Fischl, 2009; Jenkinson et al., 2002; Jenkinson and Smith, 2001) and resliced to 1mm isotropic voxels. A brainmask of the preprocessed, acpc-aligned dMRI images were then used for subsequent modelling and tractography using FSL’s *bet2* functionality (Smith, 2002). Masks from three participants were manually-edited in order to remove excess non-brain material.

White matter microstructure modelling (DTI). In order to investigate advanced microstructural properties of white matter, the diffusion tensor (DTI) model was fit to the preprocessed, acpc-aligned dMRI data using FSL’s *dtifit* functionality. For white matter tract profiles, the default parameters of *dtifit* were used and the $b = 1000$ shell was chosen for fitting. However, for mapping of the DTI measures to the cortex, both the $b = 1000$ and $b = 2000$ shells were used, kurtosis was calculated, and the sum of squared errors was outputted following the parameters used in (Fukutomi et al., 2018).

White matter microstructure modelling: Neurite Orientation Dispersion and Density Imaging (NODDI). In order to investigate advanced microstructural properties of white matter, the Neurite Orientation Dispersion and Density Imaging (NODDI) (Zhang et al., 2012) model was fit to the multi-shell (i.e. $b = 1000, 2000 \text{ s/mm}^2$) dMRI data via the Accelerated Microstructure Imaging via Convex Optimization (AMICO; <https://github.com/daducci/AMICO>) toolbox (Daducci et al., 2015). The NODDI model represents the diffusion of water in a given location based on biophysical decay patterns of different tissues (i.e. axons, glial cells, extra-axonal space) based on the following function:

$A = (1 - IsoVF)(ICVF A_{ic} + (1 - ICVF) A_{ec}) + IsoVF A_{iso}$, where A_{ic} and A_{ec} are the normalized signal of the intracellular and extra-cellular components, respectively. Metrics obtained from the NODDI model include intra-cellular volume fraction (ICVF), which is a measure of neurite density (NDI), orientation dispersion (ODI), a measure of spread or fanning of neurites, and isotropic volume fraction (IsoVF), a measure of CSF water volume fraction. The AMICO toolbox was used in order to significantly speed-up the time necessary to fit the NODDI model by reformulating the NODDI model as a linear system, without sacrificing accuracy (Daducci et al., 2015).

Before model fitting, the multi-shell dMRI image was linearly aligned to the single-shell, anatomically-aligned dMRI image using the *flirt* command provided by FSL. For major white matter tract analysis, the isotropic diffusivity parameter (d_{iso}) was set to $3.0 \times 10^{-3} \text{ m}^2/\text{s}$ (the rate of unhindered diffusion of water) while the intrinsic free diffusivity parameter ($d_{||}$) was set to $1.7 \times 10^{-3} \text{ mm}^2/\text{s}$. For cortical white matter parcel analyses, the isotropic diffusivity parameter was also set to $3.0 \times 10^{-3} \text{ mm}^2/\text{s}$ while the intrinsic free diffusivity parameter was set to $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$, which is the optimal value of diffusivity found by Fukutomi & colleagues (Fukutomi et al., 2018).

White matter microstructure modelling (CSD). The CSD model was fit to the preprocessed multi-shell data utilizing MrTrix3 *dwi2fod* function across 4 maximum spherical harmonic orders (i.e. L_{max}) parameters (2,4,6,8) (Jeurissen et al., 2014a, 2014b; Tournier et al., 2004). L_{max} 's 6 and 8 were chosen for subsequent white matter tractography.

White matter microstructure modelling (Tractography). Anatomically-constrained probabilistic tractography (ACT) (Smith et al., 2012) implemented in MrTrix3 (Tournier et al., 2010) was used to generate tractograms on preprocessed multi-shell dMRI data for each participant. A total of 1.5 million was tracked over both L_{max} 6 and 8. The two tractograms were then combined to create a single tractogram of 3 million streamlines. The step-size was set to 0.2mm for both L_{max} 6 and 8. The minimum length of streamlines was set to 25mm, and the maximum length was set to 250mm. A maximum angle of curvature of 35° was set. The merged tractogram of 3 million streamlines was then used for subsequent white matter tract segmentation and network generation.

White matter microstructure modelling (Segmentation). Sixty one human white matter tracts were segmented using a custom method analogous to white matter query language (Bullock et al., 2019; Wassermann et al., 2016). These tracts include the following: L/R arcuate, frontal aslant, corticospinal tract (CST), contralateral anterior frontal cerebellar tracts, contralateral motor cerebellar tracts, inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), middle longitudinal fasciculus-angular gyrus (MDLF-ang) and- superior parietal lobule (MDLF-spl) components, motor cerebellar tracts, occipital cerebellar tracts, superior longitudinal fasciculus components 1&2 and 3 (SLF-1&2, SLF-3), temporo-parietal connection, thalamic cerebellar tracts, uncinate, vertical occipital fasciculus (VOF), Baum's and Meyers' loops, cingulum, frontal thalamic tracts, motor thalamic tracts, parietal arcuate (pArc), parietal thalamic tracts, spinothalamic tracts, and temporal thalamic tracts. The callosal tracts, including anterior frontal, forceps major, forceps minor, middle frontal, and parietal corpus callosum, are also included. We used an empirically-documented categorization scheme that grouped major white matter tracts that have been historically associated with a variety of functional domains and behaviors (Schmahmann and Pandya, 2006) (**Results: Figure 3a**). Specifically, tracts with terminations that connected multiple regions of cortex were classified as associative. Tracts with terminations in cortex and in subcortical structures were classified as projection. Finally, tracts that crossed hemispheres, including the callosal tracts, were classified as commissural.

White matter microstructure modelling: Tract profile generation. Tract profiles (Yeatman et al., 2012) for each NODDI (i.e. *NDI*, *ODI*, *ISOVF*) and DTI (i.e. FA, MD, AD, RD) parameter estimate were generated by estimating the "core" representation of each tract, resampling and partitioning each streamline into 200 equally-spaced nodes, applying a gaussian weight to each streamline based on the distance away from the "core", and then obtaining the weighted average metric at each node. This was performed using MATLAB code utilizing the *dtiFiberGroupPropertyWeightedAverage* command provided by VISTASOFT developed into a brainlife.io app ([brainlife.app.361](https://brainlife.io/app/361)). In order to avoid partial-voluming effects and to cleanly separate tracts from neighboring gray matter, we removed the first and last 10 nodes from the tract profiles for our white matter tract analyses. Averages were then computed for each tract, along the remaining 180 nodes, averaged over each group, and were displayed as group averaged Tract Profiles (Yeatman et al., 2012) for group comparisons (**Results: Fig. 2**).

White matter microstructure modelling: Tract statistics: length and volume. The mean length and volume of each tract were computed using MatLab code designed to quantify a number of tract properties, which has been developed into a brainlife.io app ([brainlife.app.189](https://brainlife.io/app/189)). In order to compute the average streamline length for a given tract, we first iteratively computed the length of each individual streamline composing the given tract. Because streamlines are represented by an ordered sequence of nodes placed in three dimensional space, this was achieved by computing the Euclidean distance (across all three dimensions) between each adjacent pair of nodes, and then summing, to give the three-dimensional distance between all adjacent nodes in a specific streamline. This streamline-specific vector of internode distances was then summed (for each individual streamline), resulting in the total length of the given streamline. The resultant vector of streamline lengths (for the tract in question) was

then averaged, resulting in the average streamline length of the tract. Volume was computed as the binarized sum of the number of 1 mm³ voxels containing at least one node from a given tract's streamlines.

Cortical and subcortical white matter mapping. DTI and NODDI measures were mapped to each participant's cortical white matter parcels following methods found in Fukutomi and colleagues (Fukutomi et al., 2018) using functions provided by Workbench Command. First, mid-thickness surfaces between the cortical pial surface and white matter surface provided by the Freesurfer segmentation were computed using the `wb_command -surface-cortex-layer` function provided by Workbench command. A Gaussian smoothing kernel (FWHM = ~4mm, $\sigma = 5/3\text{mm}$) was applied along the axis normal to the surface, and DTI and NODDI measures were mapped using the `wb_command -volume-to-surface-mapping` function. Freesurfer was used to map the average NODDI parameter estimates to subcortical white matter parcels. NODDI parameter estimates for each segmented cortical and subcortical white matter parcel were extracted and averages for each parcel were computed for each participant. Group average and standard errors (SE) for each parcel were computed.

Signal-to-noise ratio (SNR) calculation. Signal-to-noise ratio (SNR) was calculated on the normalized preprocessed dMRI image using *DIPY*'s workflow for calculating SNR (Descoteaux et al., 2011; Garyfallidis et al., 2014; Jones et al., 2013). First, a mask of the corpus callosum was generated from the dMRI image. The mean signal in each direction (i.e. X, Y, Z) and the dwi images without a diffusion gradient (i.e. b0 images) were then calculated inside the corpus callosum mask. Next, the standard deviation of the signal in the background of the image outside of the brain was calculated. The ratio between the mean signal in the corpus callosum mask for each direction and the standard deviation of the noise was computed for each subject and used for statistical analyses (see **Methods: Statistical analyses**). We reported the value found in the b0 image, representing the best possible SNR of the data.

Statistical analyses. *Non-parametric statistical tests of the difference between the means and estimation of the confidence intervals.* We performed a bootstrap test of the difference between two means (see (Pestilli et al., 2011)). We will describe one example test for a single NODDI measure, NDI, and the white matter tracts. The same approach applies to all other measures for NODDI and DTI and for cortical and subcortical parcels as well as for all other group comparisons (football - cross country, football - non-athlete, and cross country - non-athlete). First, we assumed that H_0 is true (i.e. no differences between groups) to test for a significant difference in NDI measures between groups. To do so, the averaged NDI for each white matter tract, for each group was collected ($n = 61$ tracts). This produced two distributions of NDI one for the first and one for the second group of subjects, G_1 and G_2 both of size n . We then assumed H_0 true by combining the two groups into a union vector: $G_{H_0} = G_1 \cup G_2$. After that, we resampled with replacement two samples 10,000 times from G_{H_0} , randomly assigned one sample to a G_1 and the other to G_2 and repeated this process so to build an $n \times 10,000$ set for G'_1 and an $n \times 10,000$ set for G'_2 . The difference between G'_1 and G'_2 was computed for the 10,000 samples. This process generated a distribution of differences D_{H_0} with mean 0, implementing the null hypothesis. The empirical difference obtained $D_e = G_1 - G_2$ was then compared with D_{H_0} by computing the two-tailed percentiles that D_e represented in D_{H_0} , after transforming the percentile to probability by dividing by 100, we reported this value in all our tests. If the value was less than 0.05 or less when corrected for multiple comparisons a difference between two samples was deemed statistically significant. A strict Bonferroni correction was applied for most of our tests so that p used for significance was effectively 0.0023 ($0.05 / (7 \text{ measures (DTI + NODDI)} * 3 \text{ group comparisons})$). Confidence intervals and effect sizes were also computed via bootstrap. The subject's in each group were resampled with replacement 10,000 times. An individual participant's NODDI or DTI data for each structure within a tissue type were organized into a vector, and the average difference across all structures and participant group comparisons were recorded. The confidence interval around the difference was identified as the 2.5 and 97.5 percentile group difference values. Effect sizes were calculated as the average participant group difference in each DTI or NODDI measure divided by the pooled variance of the two groups across all structures within a tissue-type. The average effect sizes across NODDI or DTI measures was then computed and used to rank the structures in **Results: Figures 3(a,b), 5(a,b), and 7(a,b)** and are reported in **Supplementary Tables 1, 3, and 4**.

Demographics, brain size, body size. We performed multiple one-way ANOVAS between our groups utilizing the python repository *statsmodels*' `ols` function to test for differences in the following: age, body weight, SNR, average gray-matter cortical thickness, total brain volume, gray-matter cortical volume and white matter volume. Bonferroni multiple comparisons correction was performed, and all reported p-values were significantly below a corrected $p < 0.0083$ ($0.05 / 6 \text{ measures}$).

Structure size versus NODDI parameter estimate. We computed the regression between group average NODDI and DTI parameter estimates and various macro-measures of segmented structures, including log-volume and thickness for cortical white matter parcels, and log-volume and length for major white matter tracts. The log-transformed data was used to account for the large range in parameters values across segmented structures. Significant effects of macro-structure on microstructure were tested utilizing MATLAB's *aocool*.

Results

Microstructural estimates in the human major white matter tracts.

Figure 2. Example tract profiles of one major-white matter tract. a. Sixty one white-matter tracts, such as the Right Uncinate depicted, were segmented in each participant (orange: football players, pink: cross country runners, blue: non-athlete students) using a cloud computing white matter segmentation application publicly available at [brainlife.io \(bl.app.188\)](http://brainlife.io/bl.app.188). b. Tract profiles for the Right Uncinate illustrating average group values for orientation dispersion (ODI, *top*), neurite density (NDI, *middle*), and isotropic volume fraction (ISOVF, *bottom*; [bl.app.361](http://brainlife.io/bl.app.361)). Profiles were averaged within each group (i.e. orange: football players, pink: cross country runners, blue: non-athletes). Error bars ± 1 SE. c. Tract profiles for the Right Uncinate illustrating average group values for fractional anisotropy (FA, *top*), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD; *bottom*). Profiles were averaged within each group (i.e. orange: football players, pink: cross country runners, blue: non-athletes). Error bars ± 1 SE. d. Group average tract ODI and FA computed from tract profiles in b,c. Error bar ± 1 SE.

Figure 2a shows one example white matter tract, the Right Uncinate, segmented in one representative individual from each group. The tract profiles reporting the NODDI parameters (ODI, NDI, and ISOVF) and DTI parameters (FA, MD, AD, RD) for the parietal corpus callosum example were averaged across participants in each group and are shown in **Figure 3b,c**. Group averages and SE for ODI and FA across the entire track were computed from the tract profiles in **Figure 3b,c**, and are shown in **Figure 3d**.

Collegiate athletes were found to have higher NODDI parameter estimates across the majority of the parietal corpus callosum (**Figure 2b**). Across the majority of the segmented tracts there was an orderly arrangement of NODDI parameters with football players having larger values, cross country runners being in the middle, and non-athletes having smaller values (**Figure 3b**). Via bootstrapping analyses (**Figure 4**), football players were found to have significantly higher NDI (difference: 0.048; p-value: 0.0001; CI: 0.023-0.073) values than cross country runners. Football players were also found to have significantly higher ODI (difference: 0.020; p-value: 0.0019; CI: 0.014-0.026), NDI (difference: 0.068; p-value: 0.0000; CI: 0.045-0.091), and ISOVF (difference: 0.046; p-value: 0.0000; CI: 0.036-0.056) than non-athletes. Cross country runners were found to have significantly higher ISOVF (average difference: 0.028; p-value: 0.0007; CI: 0.019-0.036) than non-athletes.

DTI parameter estimates proved to be less orderly in the differences between groups across the segmented tracks (**Figure 3c**). No DTI measures were identified as significantly significant in bootstrapping analyses (**Figure 4**), after Bonferroni correction.

Figure 3. Major white-matter tract microstructure between participant groups. **a.** *Top Left:* ODI overlayed on a representation of the Right Uncinate core fiber in one participant. *Top Right and Bottom:* Tract segmentations were categorized by functional domains (i.e. Associative - red, Projection - blue, Callosal - green; See **Supplemental Table 1** for the explanation of domains). **b.** Average group NODDI white matter estimates (ODI, NDI, and ISOVF) values for all major white matter tracts (orange: football players, pink: cross country runners, blue: non-athletes). Error bars ± 1 SE. Tracts were then arranged in order of average effect size across all comparisons (football - cross country, football-non-athletes, cross country - non-athletes) and NODDI measures. The tracts with the largest average effect size for NODDI measures are listed (*right*). **c.** Average group DTI white matter estimates (FA, MD, AD, and RD) values for all major white matter tracts (orange: football players, pink: cross country runners, blue: non-athletes). Error bars ± 1 SE. Tracts were arranged in order of average effect size across all comparisons (football - cross country, football-non-athletes, cross country - non-athletes) and DTI measures.

Figure 4. Major white-matter tracts show microstructure differences between participant groups. a. Average group differences between participant groups across all tracts for ODI (top), NDI (middle), and ISOVF (bottom). b. Average group differences between participant groups across all tracts for FA (top), MD, AD, and RD (bottom). Histograms were computed over the estimates across 61 white matter tracts and smoothed using a kernel density estimate (KDE) computed with *seaborn's distplot* function (Waskom and Others, 2020).

Microstructural estimates of cortical white matter.

Collegiate athletes were found to have higher NODDI parameter estimates across a majority of cortical regions (**Figure 5b**). In a similar fashion to the white matter tract analysis, football players have larger NODDI parameter estimates, cross country runners are in the middle, and non-athletes have small NODDI parameters across the 8 cortical regions. Via bootstrapping analyses (**Figure 6**), football players were found to have significantly higher ODI (difference: 0.016; p-value: 0.0001; CI: 0.004-0.027), and NDI (difference: 0.030; p-value: 0.0000; CI: 0.015-0.043) values than cross country runners. Football players were also found to have significantly higher ODI (difference: 0.029; p-value: 0.0000; CI: 0.015-0.043), NDI (difference: 0.028; p-value: 0.0000; CI: -0.022-0.020), and ISOVF (difference: 0.036; p-value: 0.0000; CI: 0.014-0.058) than non-athletes. Cross country runners were found to have significantly higher ODI (difference: 0.013; p-value: 0.0006; CI: 0.001-0.026), and ISOVF (difference: 0.028; p-value: 0.0004; CI: 0.007-0.050) than non-athletes.

DTI parameter estimates proved to be less orderly in the differences between groups across the segmented cortical regions (**Figure 5c**). Via bootstrapping analyses (**Figure 6**), football players were found to have significantly lower FA (difference: -0.013; p-value: 0.0000; CI: -0.026 - -0.001) than non-athletes. Cross country runners were found to have significantly lower FA (difference: -0.016; p-value: 0.0000; CI: -0.028 - -0.005), and higher RD (difference: 0.044; p-value: 0.0008; CI: 0.016-0.072) than non-athletes. No other DTI measures identified statistically significant group differences after Bonferroni correction.

Figure 5. Comparing cortical white-matter microstructure between participant groups. **a.** Top. Cortical white matter ODI and FA surface maps in one representative subject (Fukutomi et al., 2018) generated using [brainlife.app.0](#) and [brainlife.app.379](#). Bottom. Cortical regions-of-interest (ROIs) used for the analyses. **b.** Average group NODDI white matter microstructure estimates (ODI, NDI, and ISOVF) for the ROIs in **a**. Domains were arranged in order of average effect size across all comparisons (football - cross country, football-non-athletes, cross country - non-athletes) and NODDI measures. The domains with the largest average effect size for NODDI measures are listed (right). Legend: football players (orange), cross country runners (pink), non-athletes (blue); error bars show ± 1 SE. **c.** Average group DTI white matter microstructure estimates (FA, MD, AD, RD) for the ROIs in **a**. Domains were arranged in order of average effect size across all comparisons (football - cross country, football-non-athletes, cross country - non-athletes) and DTI measures. Legend: football players (orange), cross country runners (pink), non-athletes (blue); error bars show ± 1 SE. **Supplemental Table 2** reports the mapping between the Freesurfer parcels and ROIs in **a**.

Figure 6. Cortical white matter parcels show microstructural differences between participant groups. **a.** Average group differences between across all cortical parcels for ODI (*top*), NDI (*middle*), and ISOVF (*bottom*). **b.** Average group differences between participant groups across all cortical parcels for FA (*top*), MD, AD, and RD (*bottom*). Histograms were computed over the estimates across 148 cortical structures and smoothed using a kernel density estimate (KDE) computed with *seaborn's distplot* function (Waskom and Others, 2020).

Microstructural estimates of subcortical white matter.

Only minor differences were found in subcortical white matter tracts with collegiate athletes having non-significant higher NODDI parameter estimates across a majority of cortical regions (**Figure 7b**). A bootstrapping analysis (**Figure 8**) demonstrated no group differences in any of the NODDI or DTI measures after Bonferroni correction.

Figure 7. Comparing subcortical white-matter microstructure between participant groups. **a.** Subcortical white matter parcels used for the analyses in one representative subject. **b.** Average group NODDI white matter microstructure estimates (ODI, NDI, and ISOVF) for the ROIs in **a**. Legend: football players (orange), cross country runners (pink), non-athletes (blue); error bars show ± 1 SE. Subcortical parcels were arranged in order of average effect size across all comparisons (football - cross country, football-non-athletes, cross country - non-athletes) and NODDI measures. The parcels with the largest average effect size for NODDI measures are listed (*right*). **c.** Average group DTI white matter microstructure estimates (FA, MD, AD, RD) for the ROIs in **a**. Legend: football players (orange), cross country runners (pink), non-athletes (blue); error bars show ± 1 SE. Subcortical parcels were arranged in order of average effect size across all comparisons (football - cross country, football-non-athletes, cross country - non-athletes) and DTI measures.

Figure 8. Subcortical white matter parcels show little microstructural differences between participant groups. **a.** Average group differences between participant groups across all subcortical parcels for ODI (top), NDI (middle), and ISOVF (bottom) **b.** Average group differences between participant groups across all subcortical parcels for FA (top), MD, AD, and RD (bottom). Lines represent the kernel density estimate (KDE) computed with *seaborn's distplot* function. Histograms were computed over the estimates across 19 subcortical structures and smoothed using a kernel density estimate (KDE) computed with *seaborn's distplot* function (Waskom and Others, 2020).

Brain volume does not explain white matter microstructural property differences despite differences in body mass.

Football players, on average, have a different body composition and size as compared to cross country runners and non-athlete students ($F(2,39)$, $p < 0.0001$; **Figure 9e**). Because of this, we tested whether the differences in microstructural tissue properties may be due to differences in overall brain size. To test this, we obtained the brain volume, cortical volume, white matter volume, and cortical thickness measures from each participant using Freesurfer (**Methods: Anatomical data (T1w) processing**) and computed one-way ANOVAs between our groups for each measure (Bonferroni corrected $p < 0.01$). We found no significant difference between our groups in terms of either brain volume (**Figure 9a**), cortical volume (**Figure 9b**), white-matter volume (**Figure 9c**), or cortical thickness (**Figure 9d**).

Figure 9. Total brain volume, gray-matter cortical volume, white matter volume, and average gray-matter cortical thickness show no differences between groups despite differences in body mass. Group distributions of total brain volume (a), cortical volume (b), white matter volume (c), and average cortical thickness (d). One-way ANOVAs showed no significant differences between the groups in these measures. A significant difference was observed between the mass (e) of football players and the two other groups ($p < 0.005$ Bonferroni corrected).

Discussion

This study characterized group differences among football, cross country athletes, and matched non-athlete controls. Measurements were obtained in cortical and deep white matter as well as in several subcortical structures. The results demonstrated widespread differences in white matter microstructure in cortical white matter and major white matter tracts between collegiate football players, cross country runners and non-athletes.

Microstructural differences were better identified using the NODDI model as opposed to the DTI model, with a majority of the measures from NODDI being able to identify significant differences between our three groups while only FA and RD were able to identify any differences. This result is consistent with previous investigations into the discriminative power of DTI and NODDI across a wide range of populations (By et al., 2017; Churchill et al., 2018; Colgan et al., 2016; Mitchell et al., 2019; Schneider et al., 2017). This study extended previous studies by investigating alterations across the entirety of the brain in athletes and non-athletes using both the standard DTI model and a more advanced NODDI model. The observed differences between athletes and non-athletes in white matter microstructural properties, including increased NDI, ODI, and ISOVF, may be due to a number of potential biological or biomechanical factors. An increase in NDI could be related to exercise-associated increases in synaptogenesis and dendritic spine density (Hötting and Röder, 2013), or, alternatively, alterations in ionic and metabolic balance leading to axonal swelling associated with neuroinflammatory mechanisms (Pettus et al., 1994; Skinner et al., 2015; Z. Wang et al., 2019), including mitochondrial clearance dysfunction (Errea et al., 2015; Lee et al., 2020; Powers et al., 2020). Increased ODI may also reflect increased neuroplastic alterations as well as increased proliferation of microglia and other neuroinflammatory-related cellular structures (Yi et al., 2019). Increased ISOVF is typically associated with mechanisms elevating free water, including neuroinflammation (Fick et al., 2017; Suzuki et al., 2017). Overall, the corresponding increases in NDI, ODI, and ISOVF may be reflective of neuroinflammatory mechanisms related to differences in stress-levels and peripheral inflammation between athletes and non-athletes. This hypothesis is further supported by the lack of reliable differences identified with the DTI model, which is not as effective at identifying tissue alterations due to neuroinflammatory mechanisms (Yi et al., 2019). However, to fully understand the underlying pathology of the observed differences requires histological investigations that are beyond the scope of this investigation.

Identifying direct interpretations of the white matter microstructural properties derived from diffusion MRI models, however, is challenging (Rokem et al., 2017; Wandell, 2016). The most widely used model, diffusion tensor imaging model or DTI, has limitations, most notably the inability to accurately model regions with crossing fibers ((Jeurissen et al., 2013). More recent models attempt to provide parameters that also characterize the tissue in the presence of crossing fibers. Another issue of the DTI model is its proven inability to identify alterations in glial cell infiltration and activity (Yi et al., 2019). Measuring signals indirectly related to glial cells infiltration is critical in order to identify and characterize the potential effects of chronic stress and inflammation from elite athletics (**Figure 1e**). NODDI addresses these issues by exploiting multishell dMRI data (Frank, 2002) to characterize both axonal and dendritic (i.e. neurite) density and orientation by separately modeling the anisotropic component (hindered and restricted diffusion provided by myelin and neurites) and isotropic component (free-moving water). These separate models can then provide information regarding the density and orientation of neurites in tissue, and potentially the infiltration of glial and inflammatory processes. NODDI parameter estimates provide measures with different degrees of sensitivity to the various components of the white matter tissue microstructure. For example, differences in ODI can be attributed to a variety of biophysical or biomechanical factors including the formation of new spines, alterations to axonal diameter (Alexander et al., 2010; Zhang et al., 2011), myelin density (N. Wang et al., 2019), microglial density (Yi et al., 2019), alterations to the patterns of crossing fibers (Sato et al., 2017; Schilling et al., 2018), and gross alterations to the orientation of neurites that could arise from repetitive head impacts (**Figure 1e**). Changes in NDI can be interpreted as changes in the density of myelinated neurites (Zhang et al., 2012) but have also been associated with hyper-phosphorylated tau-deposition in the cortex (Colgan et al., 2016), axonal beading (Skinner et al., 2015), and alterations in ionic balance (Z. Wang et al., 2019), mitochondrial density and shape (Errea et al., 2015; Lee et al., 2020), and myelin density (Luo et al., 2018; Sepehrband et al., 2015; N. Wang et al., 2019). Finally, ISOVF relates to changes in intra-voxel fluid content (Zhang et al., 2012) and can be potentially related to changes in microscopic fluid content for example due to inflammatory processes (Fick et al., 2017; Suzuki et al., 2017) such as those observed following head impacts. In sum, the NODDI model allows us to evaluate various microstructural parameters with different biological interpretations. To date, it is agreed that it is difficult to uniquely interpret the differences in any of the parameters as a reduction or increase in brain tissue quality. Nonetheless, the parameters can be used for predictions or

correlated with phenotypic characteristics of the study participants to clarify the putative effects –beneficial or detrimental– of sports participation on the brain white matter tissue.

Relation to previous investigations. A variety of previous investigations into the effects of sports participation, repetitive head impacts, and white matter tissue properties of athletes have used the diffusion tensor (DTI) model (Bahrami et al., 2016; Basser et al., 1994a; Bazarian et al., 2014; Burzynska et al., 2016; Chang et al., 2015; Chun et al., 2015; Churchill et al., 2017a, 2017b; Davenport et al., 2016a, 2016b, 2014; Deng et al., 2018; Duru and Balcioglu, 2018; Gajawelli et al., 2013; Gong et al., 2018; Hänggi et al., 2015, 2010; Jäncke et al., 2009; Koerte et al., 2012; Kuzminski et al., 2018; Lao et al., 2015; Lefebvre et al., 2020; Marchi et al., 2013; Mayinger et al., 2018; McAllister et al., 2014; Merchant-Borna et al., 2016; Myer et al., 2018, 2016a, 2016b; Park et al., 2015; Rubin et al., 2018; Saghafi et al., 2018; Schlaffke et al., 2014; Schranz et al., 2018; Slobounov et al., 2017; Sollmann et al., 2018; Stamm et al., 2015; Strauss et al., 2020; Yuan et al., 2018). The studies investigating the effects of elite sports participation, especially collision-prone sports, commonly report lower fractional anisotropy (FA) and higher mean diffusivity (MD) between athletes and non-athletes (Bahrami et al., 2016; Bazarian et al., 2014; Chang et al., 2015; Chappell et al., 2006; Deng et al., 2018; Gong et al., 2018; Hänggi et al., 2010; Kuzminski et al., 2018; Lefebvre et al., 2020; Mayer et al., 2017; Rubin et al., 2018). However, this trend is not reported in all investigations, with some finding the exact opposite trend (Churchill et al., 2017b; Gajawelli et al., 2013; Hänggi et al., 2015; Mayinger et al., 2018). Of these studies investigating these effects, results commonly differ. These differing results depend on a number of factors, including sport and competition-level of the athletes studied, the inclusion criteria for non-athlete controls, time points at which athletes were scanned, and methodology employed (Schneider et al., 2019). Of the investigations investigating white matter tissue differences between collision, non-collision, and non-athletes, Lefebvre et al (Lefebvre et al., 2020) employed the most similar study design to this using only the DTI model, however key differences are important to note. They reported higher FA in non-contact sports athletes as compared to both contact and non-athletes in segments of the corpus callosum (CC) and the corticospinal tract (CST). However, they used different athlete groups for their collision and non-collision sports types, and the athletes included were not competing at a D-I level. These results are in contrast to the direction of differences observed in this study, with non-athletes tending to have higher FA than both athlete groups. The inconsistency in results using DTI further speaks to the need for advanced microstructural biomarkers such as the neurite orientation dispersion density imaging model – NODDI (Zhang et al., 2012).

To the authors' best knowledge, there is only one previous investigation into the effects of repetitive head impact exposure and microstructural properties derived using the NODDI model (Mayer et al., 2017). Mayer and colleagues (Mayer et al., 2017), investigated the effects of repetitive head impact exposure in a group of mixed-martial arts athletes and compared NODDI-derived microstructural properties to those of non-contact physically-active athlete controls. The authors did not use tract-profiles nor cortical and subcortical white matter mapping as done in the current study. They used a voxel-wise approach and reported that NDI, ODI, and ISOVF were all higher in mixed-martial arts participants in a variety of brain structures, including the corpus callosum, internal and external capsule, and the SLF. These results are consistent with our findings. The correspondence in the results of these two studies provides evidence that NODDI may be useful in differentiating the effects of elite sports participation and RHI on white matter tissue structure. This differentiation is vital for future biomarker investigations into the potentially detrimental effects of RHI on brain tissue structure.

A secondary observation in our study regards the brain volumes observed across our three groups. Specifically, no significant differences between our three groups were observed in total brain matter volume, white matter volume, gray matter volume, or gray matter cortical thickness despite an observed difference in body mass (**Figure 9**). This is of particular interest as previous investigations into the effects of sports participation, collision-sports participation, and repetitive head impacts have reported differences in brain volumes between groups of interest and controls (Koerte et al., 2015; Tremblay et al., 2018), and the relation between body weight and brain volume (Gunstad et al., 2008). The lack of observed differences in brain volume between groups may be reflective of the effect of timing of observation, as a number of investigations into this link focus on former athletes while we observed athletes while they were still competing. However, this investigation was not designed to fully investigate this link. Future investigations are needed to fully understand the relationship between sports participation, collision-sports participation, and gross brain structure.

Several limitations to the current study exist and will need to be addressed by future research. First, due to the difficulty in collecting participants, our study had a relatively small number of participants and sports. The lack of

participants reduces the interpretative power and generalization to other sports. For this reason, we openly share all the data, results, and analyses in the hope to contribute to the larger community in repetitive head impact research. Second, we report differences in signal to noise (SNR) across groups (see **Supplementary Figure 9k**). These differences can in principle affect the reliability of the NODDI model estimates (Daducci et al., 2015), yet, the SNR variation across groups (higher in cross country runners and indistinguishable between controls and football players) disagree with the direction of the effects in microstructural differences we found. Third, our study was limited to male football players in all three groups. This is an important limitation that will need to be addressed by future research to clarify the potential role of sex differences in sports participation, repetitive head impacts, and concussion. Finally, both the DTI and NODDI models have been found to provide biased measurements in gray matter (Fukutomi et al., 2019; Kaden et al., 2016; Lampinen et al., 2017; Novikov et al., 2018). These biases impact the interpretative power of the structural differences between our groups. However, since these biases are common across all of our participants, the differences between groups should still be reliable.

The present study contributes to the larger societal needs to identify the effects of sports participation on the brain tissue by combining anatomically guided methods for brain tissue microstructural mapping (Alexander et al., 2007; Fukutomi et al., 2018; Pedregosa et al., 2011; Pestilli et al., 2014; Rokem et al., 2017; Smith et al., 2012; Takemura et al., 2016; Wandell, 2016; Zhang et al., 2012) across multiple tissue types (deep white matter tracts, cortical white matter, and subcortical white matter) in collision-prone, non-collision-prone, and non-athletes. More specifically, we measured the biological properties of human brain tissue in two elite athlete groups and a control group. We measured athletes from collision (football players) and non-collision sports (cross country runners) and compared them to non-athlete students. We focused our analyses on the microstructural properties of the myelinated brain tissue (i.e. white matter) for two reasons. First, the alterations in myelinated tissue can be used to identify both beneficial and detrimental effects of long-term sports participation, including neuroinflammation and neuroplasticity. Second, diffuse axonal injury and atrophy of myelinated tissue are consistent features found in the brains of those diagnosed with CTE at autopsy (Chappell et al., 2006; Graham et al., 2014; Smith, 2016), and are thought to be precursors to the *tau* build-up (McKee et al., 2015).

Advancing scientific understanding of elite sports participation and repetitive head impact exposure using open science methods and data sharing. In addition to advancing the scientific understanding both the effects of participation in elite collegiate athletics and repetitive head impact exposure, we embraced an open science approach and use the recently developed cloud-computing platform brainlife.io to share the full research assets developed for the study – data and reproducible analyses methods (Avesani et al., 2019; Bullock et al., 2019; Pestilli, 2018; Stewart et al., 2015; Towns et al., 2014). This investigation is the first in the field of sports participation, including collision and non-collision sports, examining white matter tissue structure to use a fully-automated open science data processing platform. The brainlife.io platform allows other researchers to reuse the data, derivatives, and analyses methods to replicate or build upon our findings. Due to the difficulties associated with the collection and analysis of data related to sports, including RHI and TBI, we believe that promoting open sharing of data and methods will become paramount for the success of the scientific enterprise. All of our data, data derivatives, and analyses can be found associated with a single digital record, referenced by <https://doi.org/10.25663/brainlife.pub.14>. We hope this effort will accelerate the development of understanding regarding the effects of elite sports participation on brain tissue.

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