Acute White-Matter Abnormalities in Sports-Related Concussion: A Diffusion Tensor Imaging Study from the NCAA-DoD CARE Consortium

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Abstract

Sports-related concussion (SRC) is an important public health issue. Although standardized assessment tools are useful in the clinical management of acute concussion, the underlying pathophysiology of SRC and the time course of physiological recovery after injury remain unclear. In this study, we used diffusion tensor imaging (DTI) to detect white matter alterations in football players within 48 h after SRC. As part of the NCAA-DoD CARE Consortium study of SRC, 30 American football players diagnosed with acute concussion and 28 matched controls received clinical assessments and underwent advanced magnetic resonance imaging scans. To avoid selection bias and partial volume effects, whole-brain skeletonized white matter was examined by tract-based spatial statistics to investigate between-group differences in DTI metrics and their associations with clinical outcome measures. Mean diffusivity was significantly higher in brain white matter of concussed athletes, particularly in frontal and subfrontal long white matter tracts. In the concussed group, axial diffusivity was significantly correlated with the Brief Symptom Inventory and there was a similar trend with the symptom severity score of the Sport Concussion Assessment Tool. In addition, concussed athletes with higher fractional anisotropy performed better on the cognitive component of the Standardized Assessment of Concussion. Overall, the results of this study are consistent with the hypothesis that SRC is associated with changes in white matter tracts shortly after injury, and these differences are correlated clinically with acute symptoms and functional impairments.

Keywords: acute; CARE; diffusion tensor imaging; sports-related concussion; tract-based spatial statistics; white matters

Introduction

SPORT-RELATED CONCUSSION (SRC) is an important public health issue. Based on the estimates of the Centers for Disease Control and Prevention, approximately 1.6–3.8 million SRC occurs among high school and collegiate athletes annually.^{1,2} Athletes

sustaining concussion may have a wide spectrum of clinical signs and symptoms, including psychological distress, cognitive impairment, somatic symptoms, and neurological disorders. To aid in return-to-play decision making, clinical assessment tools are used to evaluate SRC-specific signs and symptoms.³ Tools recognized by the NINDS TBI Common Data Elements (CDE) include the

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Sport Concussion Assessment Tool (SCAT),⁴ Brief Symptom Inventory (BSI),⁵ Standardized Assessment of Concussion (SAC),⁶ and Balance Error Scoring System (BESS).⁷ Although these clinical assessment tools are particularly useful in the evaluation and management of acute injury, the pathophysiology of SRC and the time course of neurobiological recovery after injury remain unclear.⁴ Further, unlike more severe forms of brain injury, individuals sustaining SRC usually show no abnormal findings in conventional clinical neuroimages (e.g., computed tomography, T1-weighted or T2-weighted magnetic resonance imaging [MRI]). Thus, objective and sensitive neuroimaging biomarkers to characterize concussion and monitor its recovery are of primary research interest.

Because an initial pathophysiological response after concussion is believed to involve diffuse axonal injury in the brain white matter,^{8–15} diffusion tensor imaging (DTI), an MRI technique focusing on white matter,^{16,17} is recommended^{18–21} and has been found to have adequate diagnostic sensitivity to changes in brain structure after SRC.²² Specifically, DTI produces two summary metrics, fractional anisotropy (FA) and mean diffusivity (MD), and two orthogonal metrics, axial diffusivity (AD) and radial diffusivity (RD). FA, the variance of AD and RD, indicates how directional the diffusion is and reflects the coherence of underlying tissue or fiber organization. MD, the mean of AD and RD, describes the general freedom of diffusion in the tissue regardless of the directionality. FA and MD have been a main focus in DTI studies of mild traumatic brain injury (TBI).²³ FA in particular has been used as an indicator of white matter “integrity,” though the word “integrity” is somewhat pathologically obscure. Although less discussed, AD and RD may provide a higher level of biological specificity than FA and MD. In a mouse model of experimental autoimmune encephalomyelitis, AD correlated with staining for neurofilaments indicating axonal injury in quantitative histology maps.²⁴ Further, in a Shiver mouse model with mutant myelin basic protein, RD decreased significantly with unchanged AD.²⁵ Theoretically and experimentally,²⁶ FA could increase in cases of two totally different underlying pathologies: 1) with increased AD and unchanged RD or 2) with unchanged AD and decreased RD. FA could remain constant if both AD and RD increase or decrease proportionally. Therefore, it may be prudent to include all four metrics to interpret DTI results and to better characterize microstructural alterations in SRC.

Since 2002, DTI has been used widely in neuroimaging studies of TBI,²⁷ resulting in more than 100 published studies.^{18,22,23,28,29} Of these studies, approximately 15 have focused on SRC. Although one study on pediatric sports injury reported no significant cross-sectional or longitudinal results,³⁰ across the majority of previous published studies, DTI has demonstrated significant sensitivity to SRC. However, the nature and direction of DTI changes after SRC are not uniform across studies. Such heterogeneous findings may be attributed to age differences between studied populations, limited sample sizes in most studies ($n < 20$), absence of previous exposure/concussion history, differences in DTI techniques, or image data processing.^{22,28}

Although anatomical locations of significant white matter findings also differ among studies, they have a common feature (i.e., belonging to long fiber tracts). White matter abnormalities in fibers running in a dorsal-ventral orientation have been most commonly noted in the internal capsule (anterior and posterior limbs) and corona radiata (anterior, superior, and posterior).^{31–37} These areas consist of fibers connecting cortical gray matter to the spinal cord or deep brain gray matter and include the corticobulbar, corticospinal,

corticofugal, and thalamocortical tracts. Abnormalities have also been reported in the corpus callosum,^{31,33,37,38} and the longitudinal fasciculus.^{32,34,36,37,39}

In this study, we used DTI to detect acute white matter alterations in football players after SRC, using imaging data collected within the part of the NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium study protocol.⁴⁰ DTI metrics were also correlated with clinical outcome measures to assess the relationship between white matter microstructure findings and clinical outcomes. To avoid potential bias from targeting particular white matter areas, whole-brain white matter was included in voxel-wise statistical analyses. Skeletonized whole-brain white matter was chosen to minimize partial volume effects from surrounding gray matter or cerebrospinal fluid (CSF) and to increase reliability of diffusion tensor estimation in white matter.⁴¹

Methods

Participants

The present multi-site study was conducted through the NCAA-DoD CARE Consortium Advanced Research Core (ARC). Sponsored by the National Collegiate Athletic Association (NCAA) and U.S. Department of Defense (DoD), CARE is a large, national study of the natural history of concussion and post-injury recovery in military service academy (MSA) cadets and NCAA student-athletes.⁴⁰ Participants for the DTI study were recruited from three ARC sites where multi-modal MRI studies were performed. The three sites include University of North Carolina (UNC), University of California Los Angeles (UCLA), and Virginia Tech (VT). Participating athletes account for approximately 48–75% of eligible football players at the three ARC sites. Among the participating football players, 30 sustained acute concussion and were recruited for the imaging study. Contact-sport controls ($n = 28$) were matched to concussed athletes on variables of age, sex, education, number of previous concussion, and estimated pre-morbid level of verbal intellectual functioning (i.e., Wechsler Test of Adult Reading [WTAR⁴²]). All participants provided informed consent approved by the guidelines of the institutional review board at the three ARC sites. The detailed characteristics of the concussed and control groups are listed in Table 1.

Clinical assessments

Clinical assessments followed the CARE Consortium study protocol and included a comprehensive battery of clinical outcome measures. The tests were performed on all enrolled athletes at baseline (pre-season), and for athletes diagnosed with concussion, the measures were repeated 24–48 h post-injury. The matched contact-sport controls received the same clinical assessments at similar time points. Clinical assessment measures included the SCAT⁴ to assess symptom severity, BSI⁵ to assess psychological distress, the SAC⁶ to assess cognition, and the BESS⁷ to assess postural stability. The BSI instrument can be further divided into three subcategories: BSI-soma for physical symptoms, BSI-anxiety, and BSI-depression to evaluate mood disorders. Thus, a total of eight clinical measures were compared between the concussed group and contact-sport control group, and were correlated with the DTI metrics.

Imaging protocol

The concussed athletes and their matched teammates underwent MRI scans within 24–48 h post-injury. The DTI scans were

TABLE 1. SUBJECT DEMOGRAPHICS AND PRE-SEASON CLINICAL MEASURES AS THE BASELINE

Demographic/measure	Contact control (n=28)	Concussed (n=30)	p value ^a
	Mean $\pm$ SD	Mean $\pm$ SD	
Demographics			
Age (years)	19.52 $\pm$ 1.44	19.17 $\pm$ 1.02	0.287
Education (years)	9.68 $\pm$ 1.02	9.84 $\pm$ 0.87	0.503
WTAR standard score	107.21 $\pm$ 14.63	106.92 $\pm$ 12.86	0.932
Clinical assessments			
Brief Symptom Inventory (BSI)	0.54 $\pm$ 1.35	1.58 $\pm$ 2.53 ^b	0.062
BSI-Soma	0.21 $\pm$ 0.57	0.58 $\pm$ 1.03 ^b	0.111
BSI-Anxiety	0.21 $\pm$ 0.69	0.35 $\pm$ 0.80 ^b	0.517
BSI-Depression	0.11 $\pm$ 0.315	0.65 $\pm$ 1.60 ^b	0.082
Standardized Assessment of Concussion (SAC)	26.92 $\pm$ 2.17	27.07 $\pm$ 2.11 ^b	0.797
Sport Concussion Assessment Tool (SCAT)			
Symptom Score	0.65 $\pm$ 0.83	1.00 $\pm$ 0.88 ^c	0.597
Symptom Severity Score	0.78 $\pm$ 1.03	1.17 $\pm$ 1.10 ^c	0.174
Balance Error Scoring System (BESS)	14.88 $\pm$ 6.13	13.28 $\pm$ 6.69 ^b	0.359

Bold funds indicate significant different between the contact sport control and concussed group.

^aTwo-tailed Student's *t*-test.

^b*n* = 26.

^c*n* = 29.

WTAR, Wechsler Test of Adult Reading; SD, standard deviation.

acquired on Siemens MAGNETOM 3T Tim Trio (VT, UNC, and UCLA) or 3T Prisma (UNC and UCLA) scanners across the three ARC sites with a 12CH (VT) or 32CH (UNC and UCLA) receiver-only head coil. A single-shot echo planar imaging sequence with a twice-refocused spin echo was used. The diffusion-encoding scheme consisted of 30 directions at *b*-value of 1000 s/mm² and 8 *b*₀ (*b*-value = 0 s/mm²). One of the *b*₀ volumes was acquired with a reversed phase-encoding direction. Other MRI parameters were echo time/repetition time = 98/7900 ms, field of view = 243 mm, matrix size = 90 $\times$ 90, whole-brain coverage of 60 slices with slice thickness of 2.7 mm, and isotropic resolution of 2.7 mm. Care has been taken to ensure diffusion MRI signal's quality and stability. Phantom studies were performed for quality control and assurance with a FBRIN gel phantom, and for evaluation of reproducibility and reliability with two traveling human phantoms. In addition, we have examined the DTI metrics' stability on matched non-contact-sport controls (Supplementary Fig. S1) (see online supplementary material at <http://www.liebertpub.com>) and on categorized DTI results (Supplementary Fig. S2) (see online supplementary material at <http://www.liebertpub.com>). We observed no obvious outliers that require advanced data harmonization approaches other than controlling site and scanner differences in general linear regression models described below in the *Statistical analysis* subsection. A complete description of the MRI protocols and QA/QC procedures are available in a previous work⁴⁰ and in a submitted manuscript by Nencka and colleagues.⁸⁸

Image processing

Image processing included pre-processing followed by computation of DTI metrics. Diffusion-weighted images were first denoised using the local principal component analysis (LPCA) approach.⁴³ With a pair of reverse-phase-encoded *b*₀ images as reference, diffusion-weighted images were then corrected for motion, eddy current artifacts, and static-field geometric distortion using the *eddy_openmp* command provided in the FMRIB Software Library (FSL).⁴⁴ Using an in-house Matlab script, the transformation matrices output from the *eddy_openmp* command were used to

rotate the corresponding diffusion-weighting directions to match the rotation of the brain image during the motion-correction procedure. After image pre-processing, DTI metrics (FA, AD, RD, and MD) were computed voxelwise¹⁶ with a linear fitting algorithm using the FSL *dtifit* command (Fig. 1). Brain images of DTI metrics were transformed to the standard Montreal Neurological Institute (MNI) space using Advanced Neuroimaging Tools (ANTs) non-linear registration.⁴⁵

Tract-based spatial statistic analysis

To minimize partial volume effects arising from finite imaging resolution, in the standard MNI space, a common whole-brain white matter skeleton was extracted using the FSL toolbox, tract-based spatial statistics (TBSS).⁴⁶ The white matter skeleton included only voxels that are in the center of white-matter tracts and excluded edge voxels that may be contaminated with signals from nearby gray matter or CSF. Within the white matter skeleton, nonparametric permutation-based statistics used in TBSS (i.e., the *randomise* command) was used for voxelwise statistical analysis. A threshold-free cluster enhancement⁴⁷ and 5000 permutations⁴⁸ were used in this study. White matter voxels were deemed significant if *p* < 0.05 after being adjusted for multiple comparisons by controlling family-wise error rate (FWER) within the white matter voxels. The general regression models used in TBSS were adjusted for site and scanner differences. Using TBSS, we tested: 1) between-group differences in DTI metrics and 2) within-group correlations between DTI metrics and clinical outcome measures.

Post-hoc region-of-interest analysis

Each of the TBSS regression analyses produced significant white matter voxels. These voxels were collected as ROIs in which means of DTI metrics were computed for each subject. Rather than to determine significance, the purpose of the post-hoc ROI analysis is to produce aggregate results over the significant white matter voxels for illustration. For between-group differences, a box plot was used with subjects' means plotted according to their group

FIG. 1. Averaged maps of the DTI metrics for the 58 subjects in MNI standard space. The DTI metrics include fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). The gray scale is $0\text{--}3 \times 10^{-6} \text{ mm}^2/\text{s}$ for diffusivities and is 0–1 for FA. DTI, diffusion tensor imaging; MNI, Montreal Neurological Institute.

membership. For within-group correlations, a scatter plot was used with subjects' means plotted against their neuropsychological outcome measures. Further, post-hoc regression analyses allow us to retrieve correlation coefficients (ρ) at the ROI level. Anatomical interpretation of significant white matter was based on the Johns Hopkins University (JHU) white matter atlas provided in FSL⁴⁹ (Table 3; Supplementary Fig. S3) (see online supplementary material at <http://www.liebertpub.com>). In particular, TBSS-significant white matter was superimposed with the JHU 48 white matter labels, and the percentage of voxels counts was summarized in a color-coded matrix.

Statistical analysis

For between-group comparisons, clinical outcome measures were analyzed with a two-tailed Student's *t*-test using Statistical Package for the Social Sciences (SPSS; version 24; SPSS, Inc., Chicago, IL). A value of $p < 0.05$ was deemed significant. TBSS regression analyses used general linear models to test between-group differences in DTI metrics and correlations between the four DTI metrics and eight clinical measures. To adjust skewness in

distributions of some of the clinical scores, a logarithmic transformation was performed before correlating with DTI metrics. Tests involving clinical measures were adjusted for pre-season baseline scores, and tests involving DTI metrics were adjusted for site and MRI scanner differences.

Results

Baseline demographics and clinical assessments

At pre-season baseline, there were no differences between concussed and control groups on matching variables of age, years of education, and estimated pre-morbid level of intellectual function (i.e., WTAR; Table 1; $p > 0.05$).

Acute post-injury clinical assessments

At the post-injury assessment (24–48 h), the concussed group performed more poorly than the control group on all of the clinical outcome measures ($p < 0.05$), except the SAC, which had a borderline significant level of $p = 0.059$ (Table 2).

TABLE 2. CLINICAL MEASURES AT 24–48 H POST-CONCUSSION

Measure	Contact control (n = 28)	Concussed (n = 30)	p value ^a
	Mean $\pm$ SD	Mean $\pm$ SD	
Clinical assessments			
Brief Symptom Inventory (BSI)	0.79 $\pm$ 1.57	6.50 $\pm$ 7.61 ^b	0.002
BSI-Soma	0.46 $\pm$ 1.04	2.69 $\pm$ 2.57 ^b	0.0003
BSI-Anxiety	0.25 $\pm$ 0.70	1.92 $\pm$ 2.91 ^b	0.03
BSI-Depression	0.07 $\pm$ 0.262	1.88 $\pm$ 3.01 ^b	0.003
Standardized Assessment of Concussion (SAC)	27.71 $\pm$ 1.84	26.81 $\pm$ 2.54 ^b	0.059
Sport Concussion Assessment Tool (SCAT)			
Symptom Score	2.03 $\pm$ 3.26	9.34 $\pm$ 7.33 ^c	<10⁻⁴
Symptom Severity Score	2.86 $\pm$ 4.63	22.79 $\pm$ 25.57 ^c	<10⁻⁴
Balance Error Scoring System (BESS)	11.57 $\pm$ 6.56	16.14 $\pm$ 11.97 ^b	0.017

Bold funds indicate significant different between the contact sport control and concussed group.

^aTwo-tailed Student's *t*-test adjusted for pre-season baseline scores.

^bn = 26.

^cn = 29.

SD, standard deviation.

TABLE 3. JHU WHITE MATTER LABELS AND ACRONYMS

ACR	Anterior corona radiata	PCR	Posterior corona radiata
ALIC	Anterior limb of internal capsule	PCT	Pontine crossing tract
BCC	Body of corpus callosum	PLIC	Posterior limb of internal capsule
CGC	Cingulum (cingulate gyrus)	PTR	Posterior thalamic radiation
CGH	Cingulum (hippocampus)	RLIC	Retro-lenticular part of IC
CP	Cerebral peduncle	SCC	Splenium of corpus callosum
CST	Corticospinal tract	SCP	Superior cerebellar peduncle
EC	External capsule	SCR	Superior corona radiata
Fx	Fornix (body of fornix)	SFO	Superior fronto-occipital fasciculus
Fx-ST	Fornix/stria terminals	SLF	Superior longitudinal fasciculus
GCC	Genu of corpus callosum	SS	Sagittal stratum
ICP	Inferior cerebellar peduncle	TAP	Tapatum
MCP	Middle cerebellar peduncle	UNC	Uncinate fasciculus
ML	Medial lemniscus		

JHU, Johns Hopkins University white matter atlas provided in FSL [Oishi, 2008 #1545].

Post-injury between-group differences in the diffusion tensor imaging metrics

Averaged maps of FA, AD, RD, and MD for concussed athletes and contact-sport athlete controls are shown in Figure 1. High intensity in white matter of the FA map indicates high tissue coherence. AD and RD have reverse contrast especially in compact fiber tracts with a known uniform orientation, such as the corpus callo-

sum and internal capsule. Relatively modest contrast between gray and white matter in the MD map indicates similar averaged diffusivity/diffusion freedom in these two tissue types regardless of their directionalities.

Most of the DTI metrics did not differ significantly between groups, except MD. Significant group differences (adjusted $p < 0.05$) in MD were found in the TBSS analysis (Fig. 2A). Within the three clusters, post-hoc analyses showed that MD is higher in

FIG. 2. Results of between-group differences in MD. (A) Significant maps of tract-based spatial statistics (TBSS) using a general linear model. Green voxels denote the white-matter skeleton where the statistical test was performed. Yellow color denotes voxels having significant differences in MD between the concussed and contact-sport athlete control group at $p < 0.05$ adjusted for multiple comparisons using family-wise error rate (FWER). Dark red is background enhancement for illustration purposes. Three separated significant clusters can be appreciated on the maps. (B) Bar plots of the post-hoc ROI analyses on the means of MD in the three clusters. Black dots denote the mean MD for each subject. Consistently across the three clusters, the concussed group demonstrated significantly higher MD. (C) The table lists the size, minimum p value (as in P_{min}), and anatomical distribution of the three clusters. The anatomical labeling was performed by superimposing the clusters with the skeletonized JHU white-matter atlas in Supplementary Figure S3A (see online supplementary material at <http://www.liebertpub.com>). MD, mean diffusivity; JHU, Johns Hopkins University; ROI, region of interest.

concussed subjects than in their matched teammate controls (Fig. 2B). The relative increase in the concussed group was between 5% and 7%. The three clusters were identified by the JHU white matter atlas (Supplementary Fig. S3) (see online supplementary material at <http://www.liebertpub.com>) as being in the corpus callosum (body and splenium), corona radiata (anterior and posterior), and superior longitudinal fasciculus (Fig. 2C).

Within-group correlations between the diffusion tensor imaging metrics and the clinical outcome measures

To investigate the relationship between the four DTI metrics and eight clinical outcome measures, the 32 DTI-outcome pairs were tested separately in TBSS. Within the contact-sport control group, no significant correlation in any of the DTI-outcome pairs was detected. For the concussed group, AD had a significant linear association with BSI ($P < 0.05$; Figs. 3 and 6A) and a trend association with the SCAT symptom severity score ($0.05 < p < 0.1$; Supplementary Fig. S4) (see online supplementary material at <http://www.liebertpub.com>). BSI also had a significant linear association with another DTI metric, MD ($p < 0.05$; Figs. 4 and 6B). In addition, FA also exhibited a significant correlation with SAC ($p < 0.05$; Figs. 5 and 6C). RD was not associated with any clinical outcome measures. Post-hoc ROI analyses (Fig. 6) demonstrated positive correlations for the TBSS-significant DTI-outcome pairs: AD-BSI, MD-BSI, and FA-SAC. The correlation coefficients (i.e., ρ) were all larger than 0.83 (Fig. 6). Among the three sub-

categories of BSI, there was not a significant relationship between the assessments of mood or anxiety (i.e., BSI-anxiety and BSI-depression) and any DTI metric, whereas assessment of physical symptoms (i.e., BSI-soma, somatization) was positively correlated with AD and MD with a correlation coefficient larger than 0.85 (Fig. 6D, E).

Anatomical distributions of the significant correlations in AD-BSI, MD-BSI, and FA-SAC can be appreciated in Figures 3–5, and are also summarized in the occupancy matrixes in Figure 7A. The occupancy matrix describes the percentage of voxels in the JHU white matter labels (horizontal axis) that had significant correlation in the DTI-outcome pair (vertical axis). The skeletonized JHU atlas is mapped in Supplementary Figure S3A (see online supplementary material at <http://www.liebertpub.com>), and the acronyms are listed in Table 3 and Supplementary Figure S3B (see online supplementary material at <http://www.liebertpub.com>). White matter with significant correlations in AD-BSI and MD-BSI focused on the corpus callosum (genu and body), anterior corona radiata with a lesser extent to superior and posterior corona radiata, and superior fronto-occipital fasciculus (Fig. 7A). Instead of the total score of BSI, when focusing on BSI-soma (Fig. 7B), the involved white matter extended to a broader area, especially for MD and BSI-soma, but still within the scope of the corpus callosum, corona radiata, and superior longitudinal fasciculus. Unlike BSI, the significant correlation in FA-SAC exhibited wider spread and located in the mid to lower level of the brain at the internal capsule (posterior and retro-lenticular part) and midbrain, such as the pontine

FIG. 3. Significant correlation maps of the TBSS analysis on AD and BSI of the concussed athletes. Green voxels denote the white-matter skeleton where the statistical test was performed. Yellow color denotes voxels having significant positive correlations between AD and the BSI total score at $p < 0.05$ adjusted for multiple comparisons using family-wise error rate (FWER). Dark red is background enhancement for illustration purposes. Maps are defined in MNI standard space and the X, Y, and Z are the MNI space coordinates. The anatomical interpretation of the significant white-matter voxels is summarized in Figure 7A, top row. AD=axial diffusivity; BSI=Brief Symptom Inventory; MNI, Montreal Neurological Institute; TBSS, tract-based spatial statistics.

FIG. 4. Significant correlation maps of the TBSS analysis on MD and BSI of the concussed athletes. Green voxels denote the white-matter skeleton where the statistical test was performed. Yellow color denotes voxels having significant positive correlations between MD and the BSI total score at $p < 0.05$ adjusted for multiple comparisons using family-wise error rate (FWER). Dark red is background enhancement for illustration purposes. Maps are defined in MNI standard space and the X, Y, and Z are the MNI space coordinates. The anatomical interpretation of the significant white-matter voxels is summarized in Figure 7A, middle row. BSI=Brief Symptom Inventory; MD, mean diffusivity; MNI, Montreal Neurological Institute; TBSS, tract-based spatial statistics.

crossing tract, cortical spinal tract, medial lemniscus, and cerebellar peduncle (superior and inferior; Figs. 5 and 7A, bottom row).

Discussion

In this study of football players, DTI demonstrates significant sensitivity to white matter differences between athletes in the acute stage of concussion and contact-sport controls. To avoid selection bias, whole-brain skeletonized white matter was examined. Four DTI metrics were investigated in both voxel-wise and post-hoc ROI-based analyses. Sensitivity of DTI in acute SRC manifested in between-group differences and within-group correlations with the clinical outcome measures. Our results are consistent with the meta-analyses^{18,22,23,28} of previous DTI studies in mild TBI and SRC, but with extended findings on the correlation of diffusion imaging metrics with clinical outcomes.

The freedom of water diffusion inferred by MD was observed to be significantly higher in the brain white matter of the concussed athletes compared to their teammates, the contact-sport athlete controls. Similar findings were detected in previous studies on adult populations experienced mild TBI within 72 h using the same TBSS analyses on the whole-brain white matter.^{50–52} Although two of these studies also found decreased tissue coherence inferred by FA, FA did not differ significantly between the groups in this study. Because the diffusion tensor model does not specify sources of diffusion signals (e.g., intra- or extracellular), but uses a Gaussian distribution to summarize an ensemble water diffusion in various

tissue compartments within an imaging voxel, it may be challenging to implicate specific microstructural mechanisms.^{53–55} An increase in MD could arise from axonal swelling, extracellular edema, breakdown of cytoskeleton, demyelination, or decreased viscosity in plasma or extracellular matrix. In fact, increased MD is observed in different disease mechanisms, including axonal Wallerian degeneration,⁵⁶ multiple sclerosis,⁵⁷ vasogenic edema,⁵⁸ tumor infiltrated edema,⁵⁹ autism,⁶⁰ aging,⁶¹ and dysmyelination.⁶²

The trend of DTI findings have been inconsistent across previous studies because of various reasons, such as age differences between studied populations, limited sample sizes, unknown previous exposure/concussion, differences in DTI techniques or image data processing, and differences in injury to imaging intervals.^{22,28} Increased FA and/or decreased MD were reported in high school athletes after acute SRC^{34,37} and adolescents after acute mild TBI caused by auto-pedestrian accidents,^{63–65} whereas decreased FA and/or increased MD were reported in studies focusing on adults and collegiate athletes after acute mild TBI.^{50–52} In addition, ROI-based or voxel-based analyses^{33,39} had different results (i.e., increased FA) from the skeletonized white matter TBSS analyses.³⁶ Whereas the direction of changes in AD and RD is also inconsistent across studies, within a study, AD and RD tend to change in the same direction, both increased in one work³⁵ decreased in another,³⁷ or unchanged.^{33,34} Further, increased FA driven by decrease RD, a myelin related imaging marker, is reported in a previous work,³⁹ whereas decreased FA driven by increased RD is also found.³⁶

FIG. 5. Significant correlation maps of the TBSS analysis on FA and SAC of the concussed athletes. Green voxels denote the white-matter skeleton where the statistical test was performed. Yellow color denotes voxels having significant positive correlations between FA and the SAC total score at $p < 0.05$ adjusted for multiple comparisons using family-wise error rate (FWER). Dark red is background enhancement for illustration purposes. Maps are defined in MNI standard space and the X, Y, and Z are the MNI space coordinates. The anatomical interpretation of the significant white-matter voxels is summarized in Figure 7A, bottom row. FA, fractional anisotropy; MNI, Montreal Neurological Institute; SAC, Standard Assessment of Concussion; TBSS, tract-based spatial statistics.

FIG. 6. Results of post-hoc regression analyses between DTI metrics and clinical outcome measures for concussed athletes. Each black dot denotes one individual's clinical assessment scores and means of DTI measurements over the significant voxels in the TBSS analysis (see Figs. 3–5). ρ denotes correlation coefficient. (A) Brief Symptom Inventory (BSI) total score versus axial diffusivity (AD). BSI total score was logarithmically transformed to eliminate left skewness in the original distribution. (B) BSI total score versus mean diffusivity (MD). (C) Standardized Assessment of Concussion (SAC) versus fractional anisotropy (FA). (D) BSI-Soma (soma-tization) versus AD. Similarly, BSI-soma score was logarithmically transformed to eliminate left skewness in the original distribution. (E) BSI-Soma versus MD. AU, arbitrary units; DTI, diffusion tensor imaging; MNI, Montreal Neurological Institute.

FIG. 7. Occupancy matrices summarizing anatomical distributions of the significant correlations between the DTI metrics and clinical outcomes within the concussed group. The vertical axis denotes the DTI-outcome pairs that had significant results in the TBSS analyses. The horizontal axis denotes the JHU white-matter labels with the length of the interval reflecting its three-dimensional size (in cubic root) in the atlas. Warm colors denote the percentage (%) of voxels in the labeled white-matter tract having significant positive correlations. (A) The occupancy matrix for AD-BSI, MD-BSI, and FA-SAC pairs. AD denotes axial diffusivity, MD denotes mean diffusivity, FA denotes fractional anisotropy, BSI denotes Brief Symptom Inventory (total score), and SAC denotes Standardized Assessment of Concussion. The acronyms of the white-matter labels are listed in Table 3 or Supplementary Figure S3 (see online supplementary material at <http://www.liebertpub.com>). (B) The occupancy matrix for AD versus BSI-soma and MD versus BSI-soma. BSI-soma is one of the three subcategories of the BSI test and assesses the somatic symptoms (i.e., somatization) after concussion. DTI, diffusion tensor imaging; TBSS, tract-based spatial statistics.

In the concussed group, AD had a significant positive correlation with BSI, suggesting a link between the DTI metrics associated with concussion and clinical presentation. This result is supported by a weak positive correlation between AD and the symptom severity score of the SCAT, which describes athletes with higher axial diffusivity suffered more severe symptoms. As expected with stable RD, the change in MD was similar to and driven by AD with overlapping significant white matter because, loosely speaking, MD is the mean of AD and RD. Previously, in a mouse model of autoimmune encephalomyelitis,²⁴ AD has been correlated with staining for neurofilaments to indicate axonal injury/damage. Therefore, positive findings in AD in this study are consistent with the current theory of diffuse axonal injury in mild TBI and SRC. It should be noted, however, that the interpretation of AD (and RD) is only valid in compact white matter bundles, as in our case (Fig. 7A), where single-fiber orientation satisfies the cylindrical assumption in DTI.⁶⁶ Whereas increased diffusivities were associated with worse clinical outcomes, increased coherence of white matter fibers inferred by higher FA was associated with better clinical outcomes with higher SAC score.

Consistent with previous publications,^{18,22,23,28} we found that long-range fibers are more vulnerable in acute SRC and mild TBI. These white matter fibers include vertical fiber tracts connecting cortical gray matter to deep brain nuclei or spinal cord, inter-hemispheric fibers connecting left and right cortical gray matter, and longitudinal fibers connecting anterior frontal lobes to posterior occipital lobes. Interestingly, unlike AD and MD, a wider extent of white matter was involved in the FA-SAC association. Specifically, in addition to long fibers, significant correlations in FA-SAC were detected in white matter tracts at the midbrain level, including the corticospinal tracts, medial lemniscus, pontine crossing tract, and cerebellar peduncles.

Our results support previous brain deformation and finite element analyses, in which the midbrain is found to be one of the brain regions to sustain the most strain and displacement during a

TBI.^{67–69} Nevertheless, limited publications reported DTI findings in the midbrain.^{18,22,23,28} Possible reasons for the underestimation include coarse imaging resolution compared to a small physical size of the midbrain, and misalignments in image registration using linear approaches. As adopted in this study, nonlinear image registration (e.g., ANTs) was recently reported producing better delineation of brain anatomies in group-level analyses.^{45,70}

We have demonstrated the sensitivity of the DTI metrics in acute SRC and their association with clinical outcomes. Despite a high degree of sensitivity, the biological interpretation of changes in DTI metrics remains challenging. Such limitation stems from trying to use a simplified diffusion tensor model to describe an ensemble effect of water diffusion in complex biological tissues, such as crossing fibers^{66,71–74} or compartmentalization.^{53,55} Therefore, to overcome the insufficiency of the second order proximate (i.e., the diffusion tensor), spherical harmonic deconvolution,⁷⁵ q-ball imaging,⁷⁶ or Bayesian estimation⁷⁷ were proposed to estimate multiple crossing fibers. The finer granularity of diffusion compartments may be decomposed by diffusion modeling, such as the composite hindered and restricted model of diffusion,⁷⁸ neurite orientation dispersion and density imaging,⁷⁹ or diffusion kurtosis imaging.⁸⁰ In addition, these advanced diffusion imaging techniques, which will be pursued in follow-up analyses with a larger sample size, may help to address the inconsistent DTI findings in literature.

The aim of this study was to find common white matter regions that are susceptible to sports-related injury regardless of heterogeneity of the injury. As such, TBSS types of data analyses were used. However, to control for injury heterogeneity arising from impact directionality and magnitude of the forces, one may consider individualized analyses. Similar to group analyses, the individualized analyses (or subject-specific analyses) may be performed by ROI-based analyses^{81,82} or voxel-by-voxel-based analyses.⁸³ In either approach, a “normal” distribution of DTI metrics is first established from a group of control subjects. Then,

the significance of individual's (i.e., mild TBI subject) DTI metrics compared to the "normal" distribution may be extracted as individualized DTI results to inform subject-specific findings. Our future studies will focus on the subject-specific analyses using the data from CARE-ARC with a large sample size (~100 per group).

As described in the Methods section,⁴⁰ the ARC imaging sites were designed to perform multi-modal MRI studies. The DTI results reported here are just one aspect of the multi-modal neuroimaging program. Other included MRI studies are: volumetric study using T1-weighted and T2-weighted imaging; functional network connectivity study using resting-state MRI; perfusion study using arterial spin labeling; and cerebral micro hemorrhage and iron deposition using quantitative susceptibility mapping imaging. Moreover, the DTI directionality measurements (i.e., eigenvectors) could be used in white matter tractography to create structural connectivity between cerebral cortices. The network analyses of cortical to cortical connectivity may help to address higher-order questions about the white matter structural system in sports-related concussion. The network analyses may reflect intrinsic characteristics of the system's topology and communicability,⁸⁴ such as integration (efficiency of routing),⁸⁵ segregation (organization into communities or subnetworks),⁸⁶ and centrality (establishing a ranked relevance for nodes and edges).⁸⁷ In addition, by integrating all the modalities, unsupervised machine learning may be able to extract the best imaging predictors for the underlying pathophysiological changes in sports-related concussion.

Conclusions

These findings from the NCAA-DoD CARE Consortium provide additional evidence of acute changes in brain microstructures that correlate with clinically meaningful signs and symptoms after SRC. Future efforts will leverage the sensitivity and stability of DTI metrics during the acute post-injury phase to track the trajectory and time course of neurobiological recovery after SRC (i.e., how long does it take for the *brain* to recover after SRC?). This line of research is not only valuable to our understanding of the underlying pathophysiology of concussion, but also has the potential for major translational impact in informing evidence-based guidelines for injury management and return to play after SRC.

Acknowledgments

This publication was made possible, in part, with support from the Grand Alliance Concussion Assessment, Research, and Education (CARE) Consortium, funded, in part, by the National Collegiate Athletic Association (NCAA) and the Department of Defense (DOD). The U.S. Army Medical Research Acquisition Activity (820 Chandler Street, Fort Detrick, MD 21702-5014) is the awarding and administering acquisition office. This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Psychological Health and Traumatic Brain Injury Program under Award NO W81XWH-14-2-0151. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense (DHP funds). Other funding supports include National Institutes of Health grant R21 NS075791 (to Y.C.W. and T.W.M.), R01 AG053993 (to Y.C.W.), P30 AG010133 and R01 AG019771 (to A.J.S.), and a Project Development Team within the ICTSI NIH/NCRR Grant Number UL1TR001108 (to Y.C.W.).

The authors would also thank Jody Harland, Janetta Matesan, and Larry Riggen (Indiana University); Ashley Rettmann (University of Michigan); Melissa Koschnitzke (Medical College of

Wisconsin); Michael Jarrett, Vibeke Brinck, and Bianca Byrne (Quesgen); Thomas Dompier, Melissa Niceley Baker, and Sara Dalton (Datalys Center for Sports Injury Research and Prevention); and the research and medical staff at each of the participating sites.

Author Disclosure Statement

No competing financial interests exist.

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