

# Longitudinal white-matter abnormalities in sports-related concussion

## A diffusion MRI study

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## Abstract

### Objective

To study longitudinal recovery trajectories of white matter after sports-related concussion (SRC) by performing diffusion tensor imaging (DTI) on collegiate athletes who sustained SRC.

### Methods

Collegiate athletes (n = 219, 82 concussed athletes, 68 contact-sport controls, and 69 non-contact-sport controls) were included from the Concussion Assessment, Research and Education Consortium. The participants completed clinical assessments and DTI at 4 time points: 24 to 48 hours after injury, asymptomatic state, 7 days after return-to-play, and 6 months after injury. Tract-based spatial statistics was used to investigate group differences in DTI metrics and to identify white-matter areas with persistent abnormalities. Generalized linear mixed models were used to study longitudinal changes and associations between outcome measures and DTI metrics. Cox proportional hazards model was used to study effects of white-matter abnormalities on recovery time.

### Results

In the white matter of concussed athletes, DTI-derived mean diffusivity was significantly higher than in the controls at 24 to 48 hours after injury and beyond the point when the concussed athletes became asymptomatic. While the extent of affected white matter decreased over time, part of the corpus callosum had persistent group differences across all the time points. Furthermore, greater elevation of mean diffusivity at acute concussion was associated with worse clinical outcome measures (i.e., Brief Symptom Inventory scores and symptom severity scores) and prolonged recovery time. No significant differences in DTI metrics were observed between the contact-sport and non-contact-sport controls.

### Conclusions

Changes in white matter were evident after SRC at 6 months after injury but were not observed in contact-sport exposure. Furthermore, the persistent white-matter abnormalities were associated with clinical outcomes and delayed recovery time.

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## Glossary

**AD** = axial diffusivity; **ARC** = Advanced Research Core; **BESS** = Balance Error Scoring System; **BSI** = Brief Symptom Inventory; **CARE** = Concussion Assessment, Research and Education; **DoD** = Department of Defense; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FSL** = FMRIB Software Library; **MD** = mean diffusivity; **NCAA** = National Collegiate Athletic Association; **RD** = radial diffusivity; **ROI** = region-of-interest; **SRC** = sports-related concussion; **TBSS** = tract-based spatial statistical; **UCLA** = University of California Los Angeles; **UNC** = University of North Carolina; **VT** = Virginia Tech.

Sports-related concussion (SRC) is a serious public health issue. According to estimates by the Centers for Disease Control, each year, 1.6 to 3.8 million concussions occur in sport- and recreation-related injuries among high school and collegiate athletes.<sup>1,2</sup> While standardized assessment tools are useful in the clinical management of SRC,<sup>3</sup> the natural history of SRC and the time course of pathophysiologic recovery remain unclear.<sup>4,5</sup>

MRI, a safe and noninvasive imaging technique, is especially suitable for detecting pathophysiologic changes after SRC and monitoring progression. While conventional clinical MRI methods have difficulty detecting changes in white matter after SRC, diffusion tensor imaging (DTI), a method for probing white-matter microarchitecture, has demonstrated adequate diagnostic sensitivity to acute changes of the brain after SRC.<sup>6</sup> Similarly, we have previously shown that mean diffusivity (MD), a DTI metric describing averaged water diffusion in tissue, was higher in concussed athletes and associated with clinical symptoms at acute concussion.<sup>7</sup>

Historically, large prospective longitudinal studies on SRC have been difficult due to low incidence rates (<1 per 1,000 athlete exposures)<sup>2</sup> and challenges in proper identification of concussion. There are only a few studies on longitudinal changes in DTI metrics after SRC.<sup>5,8–12</sup> In the present study, we investigated longitudinal white-matter alterations using DTI and clinical data from a large national multicenter study, the Concussion Assessment, Research and Education (CARE) Consortium. We hypothesized that white-matter abnormalities as in elevated DTI-derived MD persist beyond the point when athletes became clinically asymptomatic (i.e., cleared to begin their return-to-play protocol) and that white-matter abnormalities would be associated with clinical outcomes and recovery time.

## Methods

### Study cohorts

The participants were recruited in a multisite study of the natural history of concussion conducted through the National Collegiate Athletic Association (NCAA)–Department of Defense (DoD) CARE Consortium Advanced Research Core (ARC).<sup>13</sup> Study sites included in this analysis are the University of North Carolina (UNC), the University of California Los Angeles (UCLA), and Virginia Tech (VT). A total of 219 collegiate athletes who completed the CARE protocol by July 2018

were included in this study. There were 3 cohorts: 82 athletes diagnosed with concussion, 68 matched contact-sport controls, and 69 matched non-contact-sport controls. The concussed and contact-sport athletes were from the football, soccer, and lacrosse teams. The non-contact-sport controls were from the baseball, softball, basketball, track and field, and cross-country teams. Contact-sport and non-contact-sport controls were matched to concussed athletes on the variables of age, sex, education, and estimated premorbid level of verbal intellectual functioning (i.e., Wechsler Test of Adult Reading<sup>14</sup>). For contact-sport controls, additional matching variables included the number of prior concussions, types of sport, and position.

### Standard protocol approvals, registrations, and patient consents

All participants provided informed consent approved by the Medical College of Wisconsin Institutional Review Board and the Human Research Protection Office. The Institutional Review Board protocol number is PRO23196.

### Longitudinal study design

All participants received baseline clinical assessments when recruited into the CARE-ARC study. Concussed athletes received clinical assessments<sup>13</sup> and multimodal MRI scans<sup>15</sup> at 4 time points: (1) 24 to 48 hours after injury, (2) the point at which the concussed athletes became asymptomatic (cleared for return-to-play progression), (3) 7 days after unrestricted return to play, and (4) 6 months after injury. When the concussed athletes became asymptomatic, they started a stepwise exercise progression protocol of 5 rehabilitation stages that had to be completed before unrestricted return to play. The return-to-play progression protocol followed the recommendations outlined in the Berlin consensus statement.<sup>16</sup> For simplicity, hereafter we label the 4 time points as time points 1, 2, 3, and 4. In addition to clinical assessments, the interval from injury to asymptomatic state (i.e., time to asymptomatic) and the interval from injury to unrestricted return to play (i.e., time to return to play) were used as indicators of recovery trajectory. The 2 matched control groups received the same clinical assessments and MRI scans at similar time intervals. All participants underwent MRI scans on the same day as clinical assessments.

### Clinical assessments

Clinical assessments followed the CARE Consortium study protocol.<sup>13</sup> The comprehensive battery of clinical outcome measures included the Standardized Assessment of Concussion<sup>17</sup> to assess cognition, the Sports Concussion Assessment Tool<sup>4</sup> to assess symptom and symptom severity, the Balance

Error Scoring System (BESS)<sup>18</sup> to assess postural stability, and the Brief Symptom Inventory (BSI)<sup>19</sup> to assess psychological health. The BSI can be further divided into 3 subcategories: BSI-soma for somatic symptoms and BSI-anxiety and BSI-depression for evaluating affective symptoms. Thus, a total of 8 clinical measures were studied for longitudinal clinical recoveries, associations with white-matter abnormalities, and predictions of persistent postinjury white-matter changes.

### Diffusion imaging protocol

Diffusion MRI was performed on the participants on Siemens MAGNETOM 3T Tim Trio (VT, UNC, and UCLA; Siemens, Munich, Germany) or 3T Prisma (UNC and UCLA) scanners across 3 ARC sites with a 12-channel (VT) or 32-channel (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 a b value of 1,000 s/mm<sup>2</sup> and 8 b<sub>0</sub> (b value = 0 s/mm<sup>2</sup>). One of the b<sub>0</sub> volumes was acquired with a reversed phase-encoding direction.

Care has been taken to ensure the quality and stability of the longitudinal diffusion MRI signal. Three quality assurance/quality control-related studies were performed before this study to ensure the MRI quality and to evaluate cross-site DTI signal stability. These studies included physical phantom scans, traveling human phantom scans, and analyses of non-contact-sport controls across sites.<sup>7,15,20</sup> For physical phantom scans, each imaging site performs the phantom study periodically and before and after the scanner upgrade. For diffusion MRI, the phantom study used a Function Biomedical Informatics Research Network gel phantom to detect the geometric distortion, eddy current distortion, and k-space spike artifacts. For traveling human phantom scans, to evaluate cross-site reproducibility and reliability, 2 traveling human phantoms visited each site, where they received repeated scans for test-retest evaluation.<sup>15</sup> In analyses of non-contact-sport controls, coefficients of variation of DTI metrics in non-contact-sport controls were evaluated.

### Image processing

We used the same diffusion image processing pipelines as that used in a previous study.<sup>7</sup> All the raw and motion-corrected diffusion-weighted images were inspected by a single trained researcher (S.M.M.). Two datasets (UCLA\_FB\_2016 and UCLA\_FB\_2017) (of 721) that had severe motion artifacts beyond correction were excluded. Diffusion image processing included preprocessing followed by computation of DTI metrics. The diffusion-weighted images were first denoised with the local principal component analysis approach.<sup>21</sup> Unlike conventional denoising methods by smoothing the image, the local principal component analysis denoising approach does not sacrifice the image spatial resolution. With a pair of reverse-phase-encoded b<sub>0</sub> images as reference, the diffusion-weighted images were then corrected for motion, eddy current artifacts, and static-field geometric distortion with the eddy\_openmp command provided in the FMRIB Software Library (FSL).<sup>22</sup>

The FSL eddy command detects outliers slice by slice with gaussian process predictions. After the image preprocessing, DTI metrics were computed voxel-wise with a linear fitting algorithm using the FSL dtifit command. Maps of DTI metrics were transformed to the standard Montreal Neurological Institute space with the use of Advanced Neuroimaging Tools nonlinear registration.<sup>23</sup>

### Interpretation of DTI metrics

Four DTI metrics were included in this study (figure e-1, data available from Dryad, doi:10.5061/dryad.sn02v6x13): MD describing the speed of water movement (i.e., diffusion) in the brain tissue regardless of the directionality, radial diffusivity (RD) describing diffusion perpendicular to the axonal axis, axial diffusivity (AD) describing diffusion parallel to axons, and fractional anisotropy (FA) describing the variance among the eigenvalues of the diffusion tensor. An abnormal increase in MD may indicate destruction of the tissue microarchitectures such as axonal beading, cellular swelling, demyelination, or brain edema. An abnormal increase in RD indicates structural destruction perpendicular to the axons such as demyelination, while an abnormal increase in AD indicates structural destruction parallel to the axons such as destruction of cytoskeletons. An abnormal decrease in FA may indicate disorganization of axons or demyelination (table e-1, data available from Dryad).

### Tract-based spatial statistical analyses

Tract-based spatial statistical (TBSS) was used to test for between-group differences in the DTI metrics at each time point. In the standard Montreal Neurological Institute space, a common whole-brain white-matter skeleton was extracted with the FSL toolbox.<sup>24</sup> Within the white-matter skeleton, nonparametric permutation-based statistics used in TBSS (i.e., the randomise command) was used for voxel-wise statistical analysis. A threshold-free cluster enhancement<sup>25</sup> and 5,000 permutations<sup>26</sup> were used in this study. White-matter voxels were deemed significant if  $p < 0.05$  after adjustment for multiple comparisons by controlling the family-wise error rate. The general regression models used in TBSS were adjusted for age, sex, site, scanner, and receiver-coil differences.

### Region-of-interest analyses

Region-of-interest (ROI) analyses were used to study longitudinal changes in the DTI metrics across the time points and associations of the diffusion metrics with clinical outcomes. Each of the TBSS regression analyses produced white-matter voxels that had significant differences in the DTI metrics between study cohorts. These voxels were collected and intersected across time points to generate a white-matter ROI in which DTI metrics had persistent between-group differences from acute concussion to 6 months after injury. Means of the DTI metrics in the persistent white-matter ROI were computed for each participant to study (1) longitudinal white-matter changes, (2) correlations with outcome assessment scores at the same time points, (3) associations with outcome assessment at different time points using a prediction model

(see Statistical Analyses section), and (4) associations with recovery rates measured by time to asymptomatic state and time to return to play.

## Statistical analyses

The following statistical analyses were conducted with R-3.5.1 software (r-project.org, R Foundation for Statistical Computing, Vienna, Austria). Analysis of variance was used to test group differences of continuous variables in demographic and clinical outcome measures (table 1). If the analysis of variance test was significant, post hoc pair-wise tests were performed with Tukey adjustments for multiple comparisons. For categorical variables,  $\chi^2$  tests were used to assess the differences in sex compositions between groups. To analyze longitudinal changes in outcome measures (figure 1) and diffusion metrics (figure 3, B–D), generalized linear mixed models were used. In particular, the longitudinal trajectories were modeled as a function of group (i.e., concussed, contact-sport control, and non-contact-sport control groups) and time point, as well as their interaction. Contrasts between the groups at each time point (figure 1) and contrasts between time points within a group (figure 3) were estimated with a compound symmetry correlation structure. A value of  $p < 0.05$  was deemed significant after adjustment by the Tukey method for multiple comparisons of groups and time points. Similarly, generalized linear mixed models were used to study associations between the DTI metrics in persistent white-matter and outcome measures at individual time points (figure 4) and across-time-points associations (table 2). The latter was to infer which outcome measure at the acute time point can best predict white-matter changes in later time points. The clinical recovery times (i.e., time to asymptomatic state and time to return to play) in the concussed athletes were first studied with Kaplan-Meier analyses (figure e-2, data available from Dryad, doi:10.5061/dryad.sn02v6x13). The dependence of recovery time on the DTI metrics was analyzed with the Cox proportional hazards model. DTI metrics were considered to have significant associations with recovery time if their coefficient  $p$  values in the model were  $<0.05$ .

## Data availability

The MRI data and clinical data were collected through the CARE Consortium funded by the NCAA-DoD Grand Alliance. Deidentified data will be made available following the existing data-sharing plans outlined in the CARE Consortium and the Federal Interagency Traumatic Brain Injury Research platform.

## Results

The characteristics of the concussed and control groups are listed in table 1. The 82 concussed athletes were football ( $n = 49$ ), soccer ( $n = 25$ ), and lacrosse ( $n = 8$ ) players. The 68 contact-sport controls were teammates of the concussed athletes and consisted 39 football, 23 soccer, and 6 lacrosse players. The sport types of the non-contact-sport controls

included baseball ( $n = 32$ ), softball ( $n = 7$ ), basketball ( $n = 3$ ), track and field ( $n = 2$ ), and cross-country ( $n = 25$ ).

## Baseline demographics and clinical assessments

There were no group differences in age, sex compositions, years of participation in primary sport types, and premorbid level of intellectual function measured by the Wechsler Testing of Adult Reading test (table 1). Compared to the other 2 groups, the non-contact-sport controls had slightly more years of education (0.43–0.57 years more;  $p < 0.03$ , table 1). Similar to our previously published results of modest sample sizes,<sup>7</sup> at the preseason baseline, there were no differences between the concussed and control groups in clinical assessment scores.

## Sample sizes

Similar to many longitudinal studies, not all the baseline participants received clinical assessments and MRI scans at all time points despite our best efforts. Therefore, the sample sizes varied across time points. Table e-2 (data available from Dryad, doi:10.5061/dryad.sn02v6x13) lists the numbers of participants who had both available clinical assessment scores and usable MRI data for each study group at each time point. These sample sizes were used in the statistical analyses for the following results.

## Acute postinjury clinical assessments

At the acute time point (i.e., time point 1), the concussed group performed more poorly than the 2 control groups on all of the clinical outcome measures ( $p < 0.01$ , table 1 and figure 1), as expected. The 2 control groups did not differ significantly in the acute assessments ( $p > 0.30$ , table 1 and figure 1).

## Recovery time

After concussion, the average time until an athlete was cleared to begin the return-to-play protocol (i.e., time to asymptomatic state) was 9.34 days ( $n = 65$ , median = 7.60 days; quartiles 1,3 = 5.60, 11.90 days; table 1). As demonstrated in the survival curves (figure e-2, available from Dryad, doi:10.5061/dryad.sn02v6x13), it took  $\approx 7.6$  days for 50% of the concussed athletes to become asymptomatic and to initiate the return-to-play progression procedures. On average, the concussed athletes took 16.23 days ( $n = 58$ , median = 14.00 days; quartiles 1,3 = 9.26, 18.00 days; table 1) from injury to finish stepwise rehabilitation and to return to unrestricted play. The survival analyses demonstrated that 50% of the concussed athletes returned to unrestricted play between days 13 and 15, and 100% returned to play by day 27 (figure e-2, available from Dryad).

## Longitudinal changes in clinical assessments

For clinical outcome measures, differences were observed only between the concussed athletes and the controls (figure 1). No significant differences were observed between the 2 control groups (i.e., contact-sport and non-contact-sport controls). The between-group differences in clinical outcome measures were largest at acute concussion (time point 1), and most of them decreased to a nonsignificant level at time point

**Table 1** Subject demographics and clinical measures at acute concussion (i.e., 24–48 hours after injury)

	Concussed, mean (SD)	Contact control, mean (SD)	Noncontact, mean (SD)	ANOVA <sup>a</sup>	Tukey post-hoc <i>t</i> test		
				<i>p</i> Value	<i>p</i> Value <sup>b</sup>	<i>p</i> Value <sup>c</sup>	<i>p</i> Value <sup>d</sup>
<b>Demographics at baseline, n</b>	n = 82	n = 68	n = 69				
<b>Age, y</b>	18.87 (0.93)	18.82 (1.26)	19.20 (1.22)	0.10	—	—	—
<b>Sex, M:F, n<sup>e</sup></b>	69:13	54:14	55:14	0.70	—	—	—
<b>Education, y</b>	12.52 (0.75)	12.66 (1.04)	13.09 (1.10)	<10 <sup>-2i</sup>	0.67	<10 <sup>-2i</sup>	0.03 <sup>i</sup>
<b>WTAR standard score</b>	106.04 (13.98)	106.30 (13.96)	110.53 (9.49)	0.12	—	—	—
<b>Years of participation in primary sports</b>	10.28 (3.63)	10.62 (3.82)	11.18 (3.69)	0.34	—	—	—
<b>Clinical assessments at acute concussion<sup>f</sup></b>	n = 68	n = 64	n = 63				
<b>SAC</b>	26.15 (2.59)	27.69 (2.06)	27.60 (1.85)	<10 <sup>-4i</sup>	<10 <sup>-4i</sup>	<10 <sup>-3i</sup>	0.99
<b>SCAT</b>							
<b>Symptom score</b>	10.70 (6.59)	2.36 (3.81)	2.16 (2.76)	<10 <sup>-19i</sup>	<10 <sup>-22i</sup>	<10 <sup>-2i2</sup>	0.97
<b>Symptom severity score</b>	26.09 (21.83)	3.47 (5.59)	3.19 (4.84)	<10 <sup>-22i</sup>	<10 <sup>-22i</sup>	<10 <sup>-22i</sup>	0.99
<b>BESS score</b>	16.11 (10.67)	10.41 (5.41)	12.11 (5.93)	<10 <sup>-2i</sup>	<10 <sup>-2i</sup>	0.01 <sup>i</sup>	0.30
<b>BSI score</b>	6.22 (7.29)	1.17 (2.29)	0.94 (1.90)	<10 <sup>-12i</sup>	<10 <sup>-9i</sup>	<10 <sup>-10i</sup>	0.87
<b>BSI-somatization score</b>	2.72 (3.19)	0.38 (0.81)	0.27 (0.68)	<10 <sup>-16i</sup>	<10 <sup>-12i</sup>	<10 <sup>-13i</sup>	0.79
<b>BSI-anxiety score</b>	1.61 (2.52)	0.36 (0.86)	0.40 (1.06)	<10 <sup>-4i</sup>	<10 <sup>-3</sup>	<10 <sup>-3i</sup>	0.99
<b>BSI-depression score</b>	1.89 (2.76)	0.44 (1.42)	0.27 (1.02)	<10 <sup>-7i</sup>	<10 <sup>-5i</sup>	<10 <sup>-6i</sup>	0.84
<b>Clinical recovery times, d</b>							
<b>Time to asymptomatic state<sup>g</sup></b>	9.34 (6.60)	NA	NA	—	—	—	—
<b>Time to unrestricted return to play<sup>h</sup></b>	16.23 (11.77)	NA	NA	—	—	—	—

Abbreviations: ANOVA = analysis of variance; BESS = Balance Error Scoring System; BSI = Brief Symptom Inventory; n = sample size; NA = not applicable; SAC = Standardized Assessment of Concussion; SCAT = Sport Concussion Assessment Tool; WTAR = Wechsler Test of Adult Reading.

<sup>a</sup> One-way ANOVA test was used for the continuous variables except sex.

<sup>b</sup> *p* Values for comparisons between the concussed athletes and contact-sport controls.

<sup>c</sup> *p* Values for comparisons between the concussed athletes and non-contact-sport controls.

<sup>d</sup> *p* Values for comparisons between the contact-sport and non-contact-sport controls.

<sup>e</sup> The  $\chi^2$  test was used for sex.

<sup>f</sup> Assessment scores were logarithmically transformed to adjust skewness.

<sup>g</sup> n = 65.

<sup>h</sup> n = 58.

<sup>i</sup> Significant, *p* < 0.05.

2 (figure 1). The only measures that had lasting effects at time point 2 were BSI total score and its subcategories BSI-soma and BSI-depression. The clinical assessment scores did not differ between the 3 groups for time points 3 and 4.

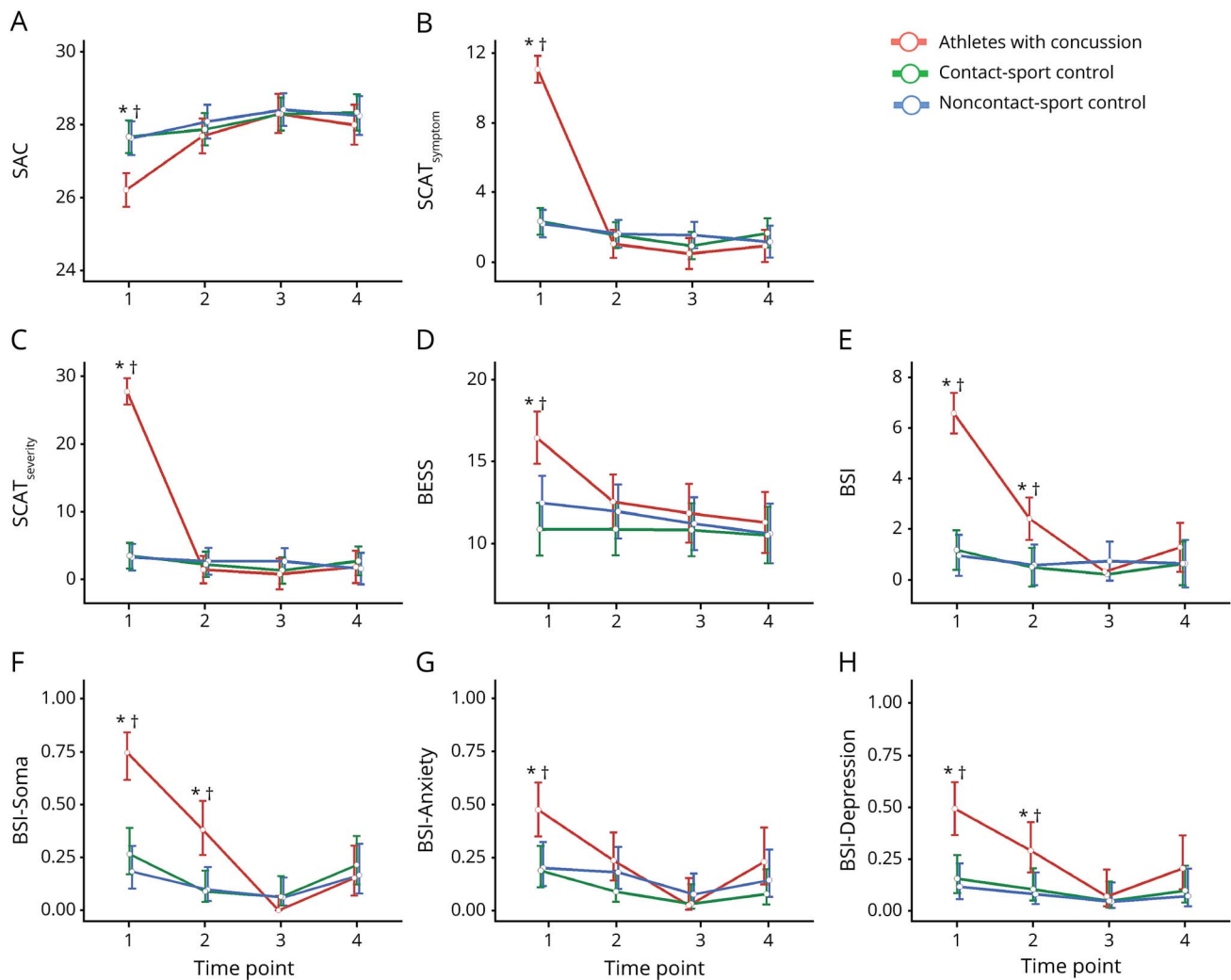
### Longitudinal changes in DTI metrics

The TBSS analyses demonstrated significantly increased MD in the concussed athletes (compared to the 2 control groups) at each time point (*p* < 0.05 after controlling for family-wise error rate). White-matter voxels that had significant MD findings between the concussed athletes and contact-sport controls are shown in figure 2A. The extent of the significant between-group white-matter changes decreased over time from 4,834 voxels at time point 1 to 1,763 voxels at time point 4 (figure 2B). RD was also higher in the concussed athletes but reached significance only at acute concussion (time point 1). AD and

FA did not differ between groups at any time points. Results (not shown) between the concussed athletes and non-contact-sport controls were similar. No between-group differences in DTI metrics were observed at each time point between the contact and noncontact control groups.

By intersecting the significant voxels across time points in figure 2A (i.e., concussed athletes vs contact controls), a white-matter area of 512 voxels was found to have persistently elevated MD in the concussed athletes (figure 3A). This white-matter area was located in the genu and body of the corpus callosum (based on the Johns Hopkins University white-matter atlas provided in FSL<sup>27</sup>). In this region, MD in the concussed athletes was highest at acute concussion ( $\approx 40$  mm<sup>2</sup>/s or 5% more compared to the controls) and decreased significantly between time points 1 and 2 (*p* < 0.05, asterisk in figure 3B). It reached

**Figure 1** Longitudinal changes in clinical assessments



(A) Standard Assessment of Concussion (SAC) scores for the concussed athletes (red), contact-sport controls (green), and non-contact-sport controls (blue) across the 4 time points. Higher SAC scores indicate better performance in the test of cognitive function. (B) Symptom scores in the Sports Concussion Assessment Tool (SCAT) across time points. (C) Symptom severity scores in SCAT. (D) Posture stability scores in the Balance Error Scoring System (BESS). (E) Total psychological distress score in the Brief Symptom Inventory (BSI). (F) BSI subcategory to measure somatization (BSI-soma). (G) BSI subcategory to measure anxiety (BSI-anxiety). (H) BSI subcategory to measure depression (BSI-depression). For SCAT, BESS, and BSI, higher scores indicate worse symptoms. Means and 95% confidence intervals of the means were plotted for the primary clinical measures (subplots A–E). Mean proportions estimated by the generalized linear mixed model and their respective 95% confidence intervals were plotted for the BSI subcategories (subplots F–H) because for more than half of the participants, these measures were close to the floor (i.e., zero) at some of the time points. \*Significant differences ( $p < 0.05$ ) between the concussed athletes and contact-sport controls at the situated time point. †Significant differences ( $p < 0.05$ ) between the concussed athletes and non-contact-sport controls at the situated time point. There were no significant differences detected between the 2 control groups.

a plateau at time point 2 and beyond, at which point no significant temporal differences were found (figure 3B). Similar results were shown for RD in figure 3C. In the persistently affected white matter, there were no significant temporal changes in the longitudinal trajectories of AD and FA (figure 3, D and E, respectively).

In the persistently affected white matter, both MD and RD were significantly higher in the concussed athletes than in the 2 control groups. The percentages of differences in MD between the concussed athletes and contact-sport controls were 5.6% at time point 1, 2.8% at time point 2, 1.8% at time point 3, and 1.8% at time point 4. The percentages were calculated by subtracting

the mean MD of the contact-sport control group from the mean MD of the concussed group and then dividing by the mean MD of the contact-sport control group:  $(MD_{\text{concussed}} - MD_{\text{contact-sport control}}) / MD_{\text{contact-sport control}} \times 100\%$ . Similarly, the percentages of differences in RD between the concussed athletes and contact-sport controls were 6.7% at time point 1, 4.0% at time point 2, 2.4% at time point 3, and 2.4% at time point 4.

### Associations between the clinical outcome measures and DTI metrics

#### At the same time point

Within the concussed athletes, higher psychological symptoms (BSI total score and BSI-soma subscale) and concussion

**Table 2** Effects of acute clinical assessment scores on later white-matter changes measured by MD and RD

Clinical assessments	Association <i>p</i> values					
	MD <sub>tp2</sub>	RD <sub>tp2</sub>	MD <sub>tp3</sub>	RD <sub>tp3</sub>	MD <sub>tp4</sub>	RD <sub>tp4</sub>
SAC <sub>tp1</sub>	0.16	0.28	0.85	0.23	0.97	0.78
<b>SCAT</b>						
Symptom score <sub>tp1</sub>	0.78	0.39	0.09 <sup>a</sup> (+)	0.32	0.87	0.36
Symptom severity <sub>tp1</sub>	0.82	0.64	0.27	0.98	0.71	0.19
BESS <sub>tp1</sub>	0.66	0.24	0.07 <sup>a</sup> (+)	0.52	0.07 <sup>a</sup> (+)	0.63
<b>BSI total score<sub>tp1</sub></b>						
BSI-somatization <sub>tp1</sub>	0.48	0.69	0.60	0.10	0.04 <sup>b</sup> (-)	0.95
BSI-anxiety <sub>tp1</sub>	0.42	0.86	0.15	0.40	0.29	0.84
BSI-depression <sub>tp1</sub>	0.75	0.88	0.54	0.09 <sup>a</sup> (-)	0.56	0.92

Abbreviations: BESS = Balance Error Scoring System; BSI = Brief Symptom Inventory; DTI = diffusion tensor imaging; MD = mean diffusivity; RD = radial diffusivity; SAC = Standard Assessment of Concussion; SCAT = Sports Concussion Assessment Tool; - = negative association; + = positive association.

Generalized linear mixed models were used to test associations of clinical outcome measures at acute concussion (time point 1 as in subscript <sub>tp1</sub>) with MD and RD at later time points 2, 3, and 4 (as in subscripts <sub>tp2</sub>, <sub>tp3</sub>, and <sub>tp4</sub>). The model used MD and RD as response variables and the clinical outcome measures as predictors (i.e., independent variables). Primary clinical measures (SAC<sub>tp1</sub>, SCAT, BESS<sub>tp1</sub>, BSI total score<sub>tp1</sub>) were tested in a single model that automatically adjusted for multiple comparisons across clinical measures and time points. The BSI subcategories were tested separately; thus, their *p* values were adjusted only within the subcategories and time points.

<sup>a</sup> Marginal significance with  $0.05 < p < 0.1$ .

<sup>b</sup> Significance with  $p < 0.05$ .

symptom severity were associated with higher MD and RD values in the persistently affected white matter at acute concussion ( $p < 0.01$  and  $r^2 > 0.49$ , figure 4). There were no associations between the clinical assessment scores at time points 2, 3, and 4 and the respective DTI metrics at each time point.

### Prediction across time points

The clinical assessment scores at acute concussion were also associated with MD and RD in the persistent white matter at later time points (table 2). The associations were strengthened over time with no significant findings at time point 2 ( $p > 0.16$ , table 2), some marginal significances at time point 3 ( $0.05 < p < 0.1$ ), and significant findings at time point 4 ( $p < 0.05$ ). In particular, the best clinical outcome predictor for long-term white-matter changes was BSI-soma subscale ( $p = 0.04$ , table 2, last column) in which higher scores were associated with lower MD. Multiple comparisons were adjusted across clinical measures and time points, but not MD and RD. The primary clinical measures (i.e., Standardized Assessment of Concussion, Sports Concussion Assessment Tool, BESS, and BSI total score) were included and tested in a single model that automatically adjusted for multiple comparisons among the clinical measures and time points (i.e.,  $5 \times 3$ ). Because of strong correlations between the BSI total score and its subcategories, the subcategories (i.e., BSI-soma, BSI-anxiety, and BSI-depression) were tested separately; thus, their *p* values were adjusted only within the subcategories and time points (i.e.,  $3 \times 3$ ).

### Effects of the DTI metrics on recovery time

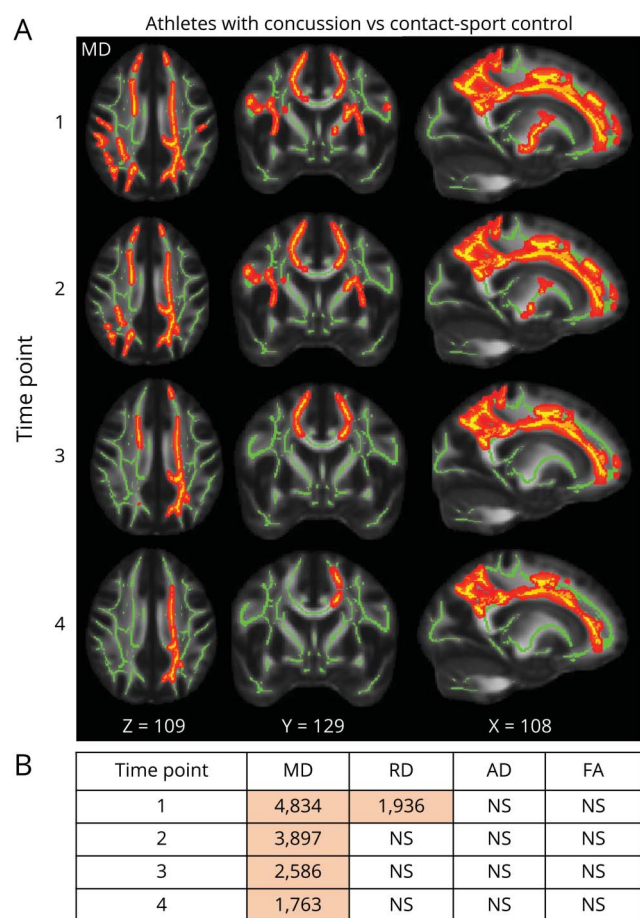
Among the DTI metrics, MD and RD at the acute time point were significantly associated with recovery time (hazard ratio  $p$

$< 0.05$ ). As MD increased, the Kaplan-Meier curves for recovery time shifted to the right (figure 5). In particular, as MD increased from 660 to 780  $\text{mm}^2/\text{s}$ , the time required for 50% of the concussed athletes to reach asymptomatic state increased from 3 to 12 days (figure 5A). Under extreme conditions, e.g., MD  $> 780 \text{mm}^2/\text{s}$ , the model extrapolated a chance of at least 7% that the concussed athletes will never achieve asymptomatic state (figure 5A, blue and pink curves). Note that in this study, the concussed athletes had a mean MD of 750  $\text{mm}^2/\text{s}$ , whereas the control groups had a mean MD of  $\approx 710 \text{mm}^2/\text{s}$  at acute concussion (figure 3B). Similarly, for time to return to play, as MD increased from 660 to 780  $\text{mm}^2/\text{s}$ , the interval from injury to unrestricted return to play for 50% of the concussed athletes increased from 8 to 17 days (figure 5B).

## Discussion

In this study, we demonstrated that white-matter differences persist beyond the point when the concussed athletes were cleared to return to play (time point 3). While clinical assessment scores in the concussed athletes recovered to a level similar to that of the controls at the asymptomatic state (time point 2) by design, the white matter of the concussed athletes had elevated MD at the asymptomatic point and out to 6 months after injury. The extent of affected white matter, however, decreased over time, suggesting partial recovery or at least restoration of the white-matter microstructure. Nevertheless, we observed a small, but statistically significant, white-matter area in the corpus callosum, where MD was persistently higher in the concussed athletes across all the time points.

**Figure 2** Results of group differences in the DTI metrics between the concussed athletes and contact-sport controls



(A) Maps of white-matter voxels (yellow) in which the concussed athletes had significantly elevated mean diffusivity (MD) compared to the contact-sport controls. Tract-based spatial statistics (TBSS) were used with a general linear model;  $p < 0.05$  adjusted for multiple comparisons with the family-wise error rate was deemed significant. Green voxels denote the white-matter skeleton, where the statistical test was performed. Dark red is background enhancement for illustration purposes. (B) Voxels counts of significant TBSS voxels that had significant group differences (e.g., yellow voxels in A) for DTI metrics, including MD, radial diffusivity (RD), axial diffusivity (AD), and fractional anisotropy (FA). NS = not significant.

The location of the persistently affected white matter (genu and body of the corpus callosum) is consistent with previous publications on acute and chronic SRC.<sup>8–10,28,29</sup> The corpus callosum contains long-range fibers connecting the left and right hemispheres of the brain. It is unclear whether the physical and biological properties of long fibers make them vulnerable<sup>30–32</sup> or their anatomic locations (near the center of mass) make them susceptible to biomechanical forces.<sup>33–35</sup> Combining finite element analysis, white-matter tractography, and fiber streamline properties may provide further insights.

Our results were consistent with previous studies of modest sample sizes ( $n < 30$ )<sup>8–12</sup> that changes in white matter measured by DTI were detectable even when clinical assessments

returned to normal levels. Among these longitudinal studies, the direction of changes in DTI metrics, however, is not consistent.<sup>5,8–12</sup> Higher MDs were reported in widespread white-matter areas of concussed female athletes ( $n = 10$ ) at long-term time points ( $>7$  months).<sup>8</sup> On the other hand, decreased MD was reported in the corticospinal tract of concussed athletes ( $n = 16$ )<sup>9</sup> and widespread white-matter areas of high school football players ( $n = 17$ ) at 6 months after injury.<sup>10</sup> The remaining studies with no significant findings in MD also reported inconsistent results in FA and RD.<sup>11,12</sup> While DTI metrics are quantitative measures, the discrepancy between studies may stem from differences between studied populations, limited sample sizes, unknown previous exposure/concussion history, differences in DTI acquisition techniques, or image data processing pipelines.

MD of DTI describes an ensemble water diffusion within an imaging voxel, which is of great complexity at the microscopic level and could consist of various tissue compartments. Thus, MD is sensitive to several pathophysiologic factors, including axonal swelling, extracellular edema, a breakdown of cytoskeleton, demyelination, or decreased viscosity in plasma or extracellular matrix. Increased MD has been observed in different disease mechanisms such as axonal wallerian degeneration,<sup>36</sup> multiple sclerosis,<sup>37</sup> vasogenic edema,<sup>38</sup> tumor-infiltrated edema,<sup>39</sup> autism,<sup>40</sup> aging,<sup>41</sup> and dysmyelination.<sup>42</sup> Despite only a 5.6% higher mean value of MD for the concussed individuals, the significant associations of MD with clinical outcomes and recovery time suggest that such a change in MD is clinically meaningful.

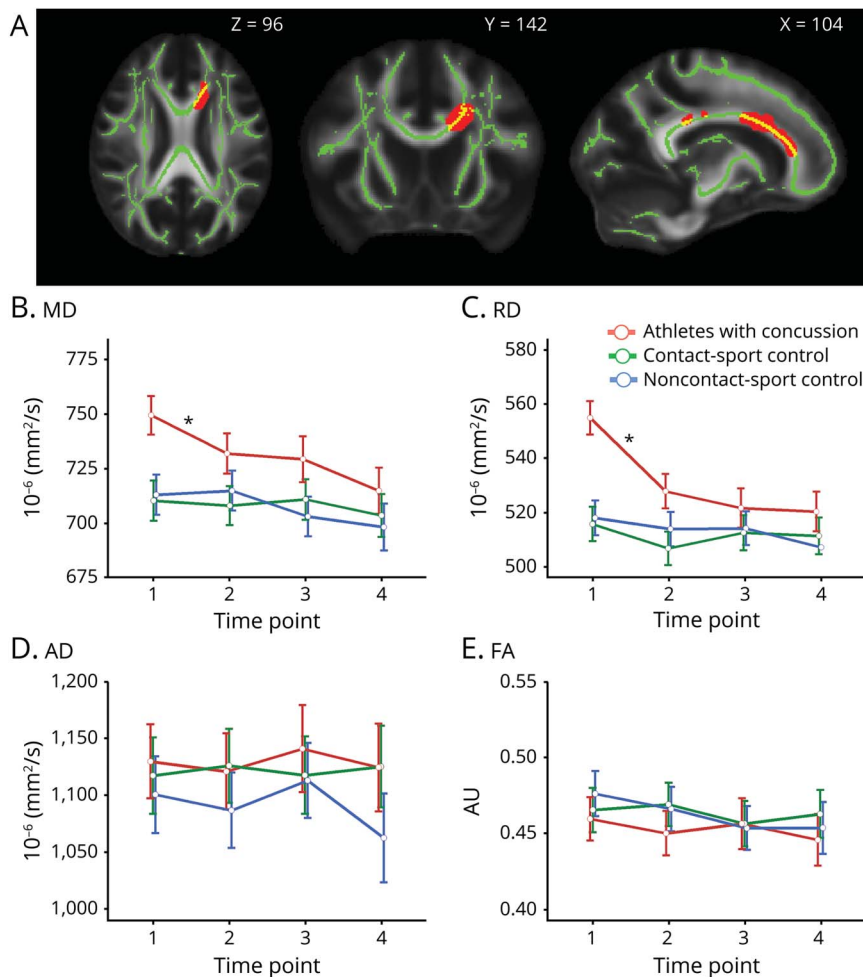
Although RD was not statistically significant in the TBSS whole-brain analyses except at time point 1, the average RD in the persistent white matter (defined by persistently elevated MD) was significantly higher across all time points in the concussed athletes in the post-hoc Student  $t$  test. Inferring from previous animal studies in which RD was associated with myelin integrity,<sup>43,44</sup> we suggest that the underlying pathophysiology changes after SRC may involve myelin deterioration. This observation is supported by a prospective cohort study in collegiate hockey players using myelin water fraction MRI in which transient myelin disruption was detected after SRC.<sup>45</sup>

In the persistently affected white matter, if the concussed athletes had higher MD or RD at acute concussion, they tended to have worse symptom severity and psychological symptoms. This result is consistent with the previous publication of modest sample size focusing on acute concussion.<sup>7</sup> Higher MD and RD at acute concussion were also associated with longer recovery time. Given the minimal previous studies of the impact of white-matter abnormalities on recovery time, the present results may be of particular importance for future considerations regarding SRC management.

Although no associations were observed between the clinical assessments and DTI metrics other than acute concussion, the



**Figure 3** Longitudinal changes of the DTI metrics in the persistently affected white matter



(A) Maps of the persistently affected white matter. Yellow voxels were selected by intersecting the significant voxels across time points in figure 2A. Dark red voxels are background enhancement for illustration purposes. (B) Longitudinal changes of mean diffusivity (MD) in the persistent white matter for the concussed athletes (red), contact-sport controls (green), and non-contact-sport controls (blue) across the 4 time points. (C) Longitudinal changes in radial diffusivity (RD). (D) Longitudinal changes in axial diffusivity (AD). (E) Longitudinal changes in fractional anisotropy (FA). Means (circle markers) and 95% confidence intervals (error bars) of the means were plotted. \*Significant differences ( $p < 0.05$ ) in the diffusion tensor imaging (DTI) metrics between the time points within a group.

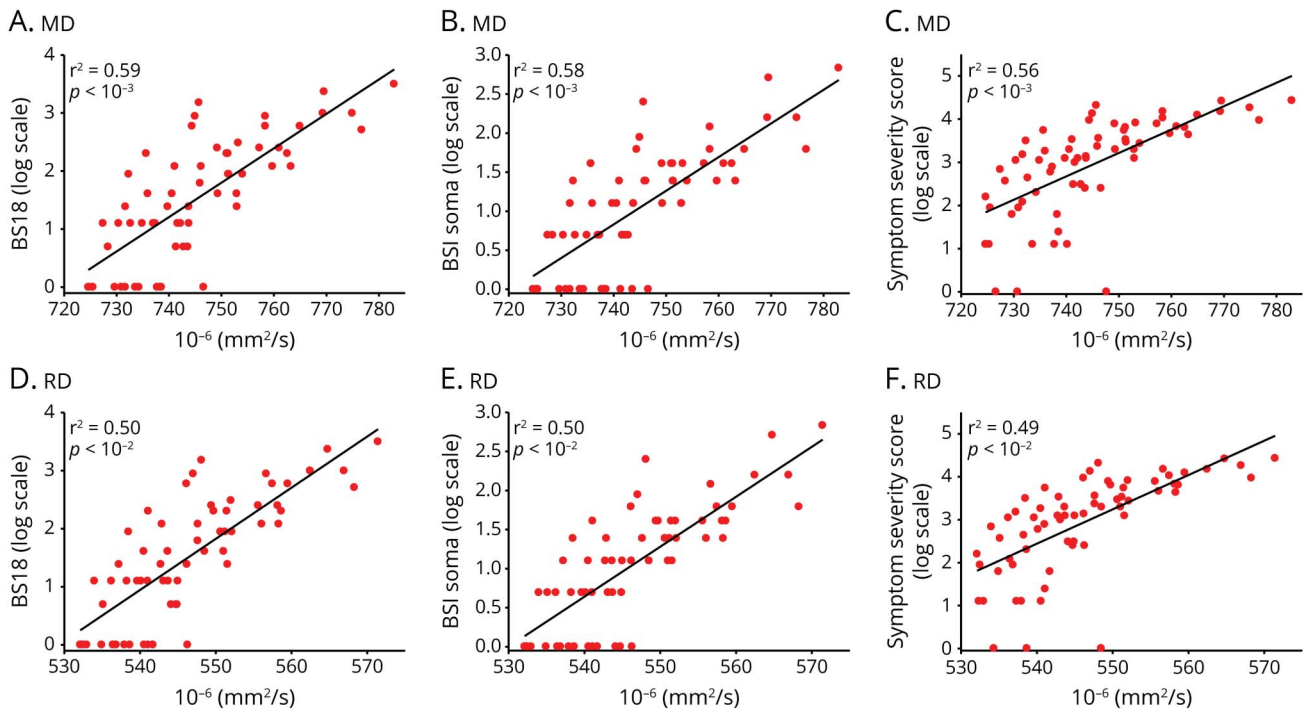
clinical outcome measures acutely after concussion were associated with chronic white-matter changes. This across-time-point prediction has not been studied or reported before in the literature. Here, we found that the prediction power of the acute clinical measures was enhanced along the course of SRC; the associations progressed from not significant at the asymptomatic state to marginally significant at 7 days after return to play to significant at 6 months after injury. The direction of prediction had mixed results: worse performance on BSI-soma was associated with later low MD, but worse concussion symptom (i.e., high symptom score) and postural stability (i.e., high BESS score) seemed to be associated with later high MD.

BSI-soma and BSI-depression values in the concussed individuals were higher than in controls at the second time point, asymptomatic. In the CARE project and postinjury management,<sup>13</sup> the asymptomatic time point indicates the time when the concussed athletes are cleared to start a graduated step-wise rehabilitation, called the return-to-play progression program.<sup>4</sup> The decision about this time point is made by team physicians and medical staff and is based on the SRC

assessment battery, clinical evaluations, and neuropsychological tests. While BSI measures are part of the CARE research protocol, they are not commonly used by clinicians in determining an athlete's recovery of postconcussion symptoms and deficits. Thus, some of the concussed athletes may still have higher scores than controls at this time point.

Exposure to contact sports and head impacts has been associated with chronic traumatic encephalopathy,<sup>46</sup> a neurodegenerative condition that does not yet have validated antemortem diagnostic criteria.<sup>47</sup> In this study, we did not find significant exposure effects on the white-matter microstructures measured by DTI in a group of athletes with acute and chronic exposure to contact sports. The 2 control groups (i.e., contact-sport controls and non-contact-sport controls) had similar DTI metrics over time, except there was a trend of elevated AD in the contact-sport controls from the ROI analyses. A recent study suggested that younger age of exposure in participants with chronic traumatic encephalopathy was associated with earlier neurobehavioral symptom onset.<sup>48</sup> Thus, future research effort will focus on effects of age at first exposure to contact sport on DTI metrics and interaction

**Figure 4** Regression analyses between the DTI metrics and clinical outcome measures within concussed athletes



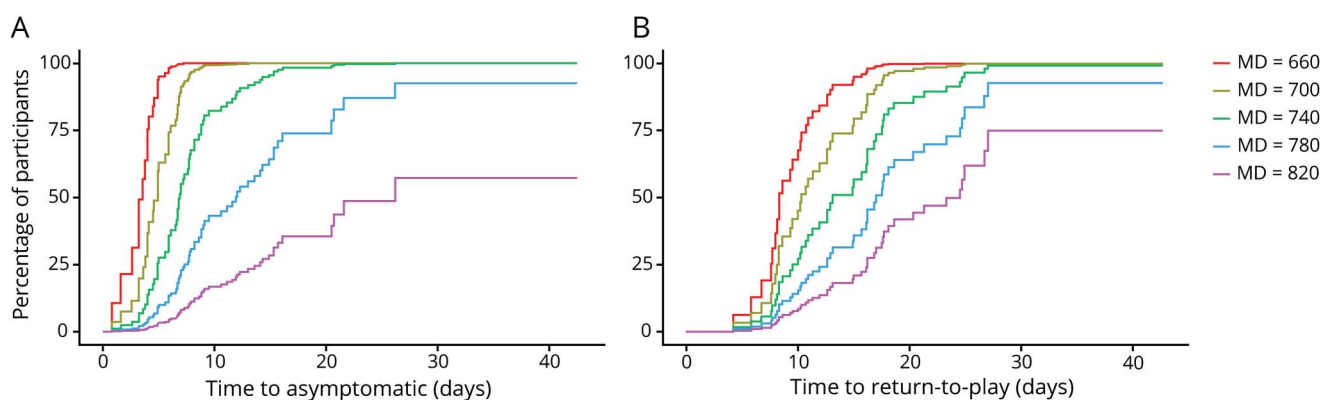
Each red dot denotes 1 individual's clinical assessment scores and means of diffusion tensor imaging (DTI) measurements in the persistently affected white matter (figure 3A). The  $r^2$  denotes the coefficient of determination, and  $p$  denotes the significance of the regression coefficients. Only significant associations ( $p < 0.05$ ) are presented. (A) Brief Symptom Inventory (BSI) total score vs mean diffusivity (MD). BSI total score was logarithmically transformed to eliminate left skewness in the original distribution. (B) Subcategory BSI-somatization vs MD. (C) Symptom severity score in the Sports Concussion Assessment Tool (SCAT) vs MD. (D) BSI total vs radial diffusivity (RD). (E) BSI-somatization vs RD. (F) SCAT symptom severity vs RD.

effects of exposure on associations between the DTI metrics and neurobehavioral outcomes.

Similar to many longitudinal studies, despite our best efforts, there were intermittent missing data across time points. Nevertheless, the missing data (assuming missing at random) were addressed by the generalized linear mixed models that adjusted

missingness automatically.<sup>49</sup> Classic DTI may also limit the study with a gaussian distribution model that makes the interpretation of specific underlying microstructural mechanisms challenging. Furthermore, the directionality of DTI in the white matter was not fully evaluated in this study. Structural connectivity and network analyses may address higher-order questions such as intrinsic characteristics of the topology and communicability of

**Figure 5** Dependence of recovery time on MD



(A) Effect of mean diffusivity (MD) on the survival curves for time to asymptomatic state. (B) Effect of MD on Kaplan-Meier curves for time to unrestricted return to play. Line colors denote different levels of MD with a unit of  $10^{-6} \text{ mm}^2\text{/s}$ . Survival curves to estimate the time to event were modeled with a Cox proportional hazards model with MD as a risk factor.

the system.<sup>50</sup> In addition, history of concussion was not included but will be incorporated into future research.

In this prospective study, we demonstrated that SRC has effects on white matter beyond the point when concussed athletes become asymptomatic. There was evidence of normalization, but some area of the white matter had persistent abnormalities up to 6 months after injury. The acute white-matter abnormalities were associated with acute postinjury clinical outcomes and prolonged recovery time.

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## Disclosure

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<b>Y.C. Wu, MD, PhD, DABMP</b>	Indiana University School of Medicine	Study concept and design, interpretation of data and results, drafting manuscript for intellectual content, and critical revision of the manuscript for important intellectual content

## Appendix (continued)

Name	Location	Contribution
<b>J. Harezlak, PhD</b>	Indiana University	Study concept and design, statistical analyses, interpretation of data, and critical revision of the manuscript for important intellectual content
<b>S.M. Mustafi, PhD</b>	Indiana University School of Medicine	Data analyses, statistical analyses, and manuscript preparation
<b>N.M.H. Elsaid, MS</b>	Indiana University School of Medicine	Data analyses and interpretation of data
<b>Z. Lin, PhD</b>	Indiana University School of Medicine	Statistical analyses and manuscript preparation
<b>Q. Wen, PhD</b>	Indiana University School of Medicine	Statistical analyses, interpretation of data, and manuscript preparation
<b>L.D. Rikken, MS</b>	Indiana University School of Medicine	Data analyses
<b>K.M. Koch, PhD</b>	Medical College of Wisconsin	Study concept and design, data acquisition, and critical revision of the manuscript for important intellectual content
<b>A.S. Nencka, PhD</b>	Medical College of Wisconsin	Data acquisition and critical revision of the manuscript for important intellectual content
<b>T.B. Meier, PhD</b>	Medical College of Wisconsin	Study concept, interpretation of data, and critical revision of the manuscript for important intellectual content
<b>A.R. Mayer, PhD</b>	The Mind Research Network	Study concept, interpretation of data, and critical revision of the manuscript for important intellectual content
<b>Y. Wang, MD, PhD</b>	Medical College of Wisconsin	Critical revision of the manuscript for important intellectual content
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<b>S.M. LaConte, PhD</b>	Virginia Tech	Data acquisition and critical revision of the manuscript for important intellectual content
<b>S.M. Duma, PhD</b>	Virginia Tech	Data acquisition and critical revision of the manuscript for important intellectual content
<b>S.P. Broglio, PhD, ATC</b>	University of Michigan	Study concept and design, interpretation of data, and critical revision of the manuscript for important intellectual content

Continued

## Appendix (continued)

Name	Location	Contribution
<b>A.J. Saykin, PsyD, ABCN</b>	Indiana University School of Medicine	Study concept and design, interpretation of data, and critical revision of the manuscript for important intellectual content
<b>M. McCrea, PhD, ABPP</b>	Medical College of Wisconsin	Study concept and design, interpretation of data, and critical revision of the manuscript for important intellectual content
<b>T.W. McAllister, MD</b>	Indiana University School of Medicine	Study concept and design, interpretation of data, and critical revision of the manuscript for important intellectual content

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