Acute White Matter Changes following Sport-Related Concussion: A Serial Diffusion Tensor and Diffusion Kurtosis Tensor Imaging Study

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Abstract: Recent neuroimaging studies have suggested that following sport-related concussion (SRC) physiological brain alterations may persist after an athlete has shown full symptom recovery. Diffusion MRI is a versatile technique to study white matter injury following SRC, yet serial follow-up studies in the very acute stages following SRC utilizing a comprehensive set of diffusion metrics are lacking. The aim of the current study was to characterize white matter changes within 24 hours of concussion in a group of high school and collegiate athletes, using Diffusion Tensor and Diffusion Kurtosis Tensor metrics. Participants were reassessed a week later. At 24 hours post-injury, the concussed group reported significantly more concussion symptoms than a well-matched control group and demonstrated poorer performance on a cognitive screening measure, yet these differences were nonsignificant at the 8-day follow-up. Similarly, within 24-hours after injury, the concussed group exhibited a widespread decrease in mean diffusivity, increased axial kurtosis and, to a lesser extent, decreased axial and radial diffusivities compared with control subjects. At 8 days post injury, the differences in these diffusion metrics were even more widespread in the injured athletes, despite improvement of symptoms and cognitive performance. These MRI findings suggest that the athletes might not have reached full physiological recovery a week after the injury. These findings have significant implications for the management of SRC because allowing an athlete to return to play before the brain has fully recovered from injury may have negative consequences. *Hum Brain Mapp* 37:3821–3834, 2016. © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

Athletes who engage in contact sports are at a heightened risk of sustaining a sport-related concussion (SRC), a form of mild traumatic brain injury induced by biomechanical forces. It is well documented that SRC results in the rapid onset of a specific constellation of physical, cognitive, and emotional sequelae [Giza and Hovda, 2014; McCrory et al., 2013]. Despite the disruptive nature of these symptoms, no abnormalities are typically seen with conventional neuroimaging protocols. Furthermore, several studies suggest that most athletes report resolution of symptoms and show a return to their baseline level of functioning on standardized cognitive measures within as little as 7 days of injury [Belanger and Vanderploeg, 2005; McCrea et al., 2003]. As a result, SRC has historically been viewed as a minor injury without long-term consequences, and athletes are often allowed to return to play soon after symptom resolution.

More recently, advanced neuroimaging techniques have allowed for detailed investigation of changes in brain structure and function following SRC. These techniques, which include measures of brain metabolism, glucose utilization, and cerebral blood flow, suggest that functional brain alterations may persist beyond an athlete's report of symptom recovery [Dimou and Lagopoulos, 2014; Gardner et al., 2014; Gosselin et al., 2010; Meier et al., 2015; Pulsipher et al., 2011]. There is also evidence that white matter (WM) structural changes persist past the point when an athlete is symptom free [Dimou and Lagopoulos, 2014; Gardner et al., 2012]. These findings are suggestive of a *window of cerebral vulnerability*, during which the brain has not fully recovered physiologically and the athlete may be at a heightened risk of re-injury if prematurely returned to contact sports. Novel approaches based on this theoretical construct may be critical in informing concussion management strategies and return-to-play guidelines.

Diffusion tensor imaging (DTI) may be a useful method for studying the nature of the WM changes that occur following SRC. DTI quantifies water diffusion patterns in relation to brain structures, and various parametric maps are derived from DTI measurements. Four of those parametric maps are commonly used to describe white matter microstructure: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (Drad), and axial diffusivity (Dax). While FA and MD are measures of overall diffusion disruption, Dax and Drad, which are measures of diffusion direction, may provide additional information about the specific nature of white matter injury in SRC. White matter pathology resulting from demyelination, axonal

damage, or Wallerian degeneration is believed to manifest itself in different patterns of relative Dax or Drad change [Song et al., 2002, 2003]. Despite its potential utility, only a few DTI studies have investigated these diffusion metrics following SRC. Furthermore, methodology has been variable in these studies, with the time interval between injury and DTI scan ranging from days to years [Bazarian et al., 2012; Borich et al., 2013; Chamard et al., 2013; Cubon et al., 2011; Henry et al., 2011; Murugavel et al., 2014; Tremblay et al., 2014; Zhang et al., 2010].

In order to fully understand the longitudinal course of white matter changes following SRC, the immediate effects of injury must be captured. A few studies have applied DTI to measure white matter changes in the acute phase of SRC with mixed results. Murugavel et al. [2014] demonstrated that male contact sport athletes who received DTI scanning within 2 days of SRC had increased Drad in a cluster identified during within-group analyses; however, they did not find significant group differences in their initial whole-brain analyses after correction for multiple comparisons. Henry et al. [2011] found increased FA and decreased MD in the corpus callosum and bilateral corticospinal tract as well as increased Dax in the right corticospinal tract in concussed college football players within 6 days of injury compared with non-injured control athletes. Conversely, Maugans et al. [2012] did not find any DTI changes in adolescent athletes within 3 days of SRC in their investigation of the corpus callosum and internal capsule. DTI studies of individuals with general mild traumatic brain injury have also reported mixed findings within the first week of injury [Arfanakis et al., 2002; Chu et al., 2010; Narayana et al., 2015; Toth et al., 2013; Veeramuthu et al., 2015; Wilde et al., 2012; Wu et al., 2010; Zhu et al., 2014]. However, as highlighted by Murugavel et al., SRC represents the mildest form of mTBI, and general mTBI studies may include individuals with injuries of greater magnitude. It is therefore important to study individuals with SRC separately from other mTBI cases in order to best understand and generalize findings to injured athlete populations. Furthermore, no known DTI studies of SRC have scanned concussed athletes within 24 hours of injury.

While DTI is a useful tool for understanding white matter changes following SRC, one potential limitation is that it is based on the premise that diffusion of water molecules follows a Gaussian distribution. In reality, the brain is a complex intracellular and extracellular environment that causes the diffusion of water molecules to deviate from this pattern [Steven et al., 2014]. Furthermore, water diffusion patterns would be further altered following a

brain injury, which leads to a complex cascade of neurochemical and neurophysiological changes [Cervos-Navarro and Lafuente, 1991]. Diffusion Kurtosis Tensor Imaging (DKTI) is an advanced diffusion MRI technique that helps estimate deviations from Gaussian diffusion. Therefore, it might be sensitive to complex tissue changes following mTBI that might not be captured by DTI [Steven et al., 2014]. A few studies have demonstrated that DKI is sensitive to changes in the subacute and chronic phases of mTBI [Grossman et al., 2012, 2013; Stokum et al., 2015]. Stokum et al. [2015] investigated DTI and DKI measures in the corpus callosum, internal capsule, and thalamus in individuals diagnosed with mTBI at 10 days, 1 month, and 6 months following injury. Decreased mean kurtosis (MK) and radial kurtosis (Krad) were found in the anterior internal capsule at all three visits, and decreased MK was evident in the posterior internal capsule after 10 days only. On the other hand, no DTI differences were found between the groups. While this study indicates that DKI is a promising marker of traumatic brain injury, no known studies have investigated DKI changes in an SRC sample or in the acute phase following injury.

The current study utilized DTI and DKTI analyses to investigate whole-brain white matter changes in the acute and sub-acute phases of SRC (24 hours and 8 days post-injury) in a carefully controlled sample of high school and collegiate athletes. Concussed athletes were re-evaluated 1 week after their initial assessment given our previous findings that 90% of athletes followed closely after SRC had returned to their baseline performance on measures of cognition, balance, and self-reported symptoms within 7 days [McCrea et al., 2003]. This 8-day time point, therefore, allowed us to investigate whether white matter changes in injured athletes may exceed symptom resolution in athletes who would typically be allowed to resume activity. It was hypothesized that DTI and DKTI would be sensitive to acute post-injury white matter changes and physiological recovery over the course of 1 week, with DKTI a more sensitive biomarker of brain injury following SRC.

MATERIALS AND METHODS

Participants

Participants were recruited from Project Head to Head, a prospective study of clinical recovery from SRC funded by the U.S. Department of Defense that enrolled contact and collision sport athletes from nine high schools and four colleges in southeastern Wisconsin between August 2012 and November 2014 [see LaRoche et al., 2015; Nelson et al., 2015]. From this larger sample, 27 male football players who sustained concussions during the fall 2014 season (concussed group) underwent neuroimaging as part of the concurrent GE-NFL Head Health Challenge-I research effort in addition to the parent project's standard

clinical post-injury protocol. One subject received an incorrect diffusion encoding prescription, resulting in 26 injured athletes in the current study. Twenty-six non-injured control athletes were selected to match injured athletes based on age, gender, sport, estimated premorbid level of verbal intellectual functioning, and grade point average (control group). Group characteristics can be found in Table I.

In keeping with the requirements of the study sponsor, SRC was defined in the current study using the U.S. Department of Defense's definition for mild traumatic brain injury: "an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering, and/or difficulty concentrating" [Helmick et al., 2006]. Concussed athletes were first identified by their team athletic trainers based on sideline assessment of symptoms, cognition, and balance. Athletic trainers then contacted the study team, who determined if the player was appropriate for study enrollment based on the study definition of SRC and inclusion/exclusion criteria. Participants were excluded from the parent study if their additional injuries precluded participation in study procedure or if they reported their injuries outside the 24-hour window, had a current diagnosis of psychotic disorder, were using prescribed narcotics prior to injury, or had a history of moderate or severe TBI or other medical conditions known to cause cognitive dysfunction (e.g., epilepsy, stroke). Participants were also excluded from the current study if they were unable to complete an MRI scan (e.g., claustrophobia, metal implant).

Written informed consent was obtained from all adult athletes and parents of minor athletes prior to their first evaluation; minor participants completed assent. Participants were financially compensated for completing pre-season baseline assessments, each follow-up clinical assessment, and each MRI session. All testing procedures were approved by the Institutional Review Board at the Medical College of Wisconsin.

Baseline and Post-Injury Clinical Assessments

To establish a baseline, demographic information was collected and a detailed, self-reported health history was obtained from all potential participants who enrolled in the study. These participants then completed an assessment protocol that included the Wechsler Test of Adult Reading (WTAR), Sport Concussion Assessment Tool-3 (SCAT-3) symptom checklist [McCrory et al., 2013], Standardized Assessment of Concussion [SAC; McCrea et al., 1997], and Balance Error Scoring System [BESS; Riemann and Guskiewicz, 2000] before the football season started.

TABLE I. Participant characteristics

	Concussed <i>n</i> = 26 <i>M</i> (<i>SD</i>)	Control <i>n</i> = 26 <i>M</i> (<i>SD</i>)	<i>P</i>	Effect size
Demographics				
Age (yr)	17.6 (1.5)	18.0 (1.5)	0.452	0.267
Education (yr)	12.4 (1.4)	12.9 (1.3)	0.202	0.370
WTAR standard score	96.3 (15.7)	95.9 (15.2)	0.922	0.026
Race (<i>N</i> , %)				
White	20 (76.9%)	20 (76.9%)		
Black	5 (19.2%)	5 (19.2%)		
Other/unknown	1 (0.0%)	1 (0.0%)		
Height (in.) ⁺	71.6 (3.3)	71.7 (2.5)	0.871	0.034
Weight (lbs.) ⁺	216.6 (56.9)	199.3 (35.0)	0.195	0.366
ADHD diagnosis (<i>N</i> , %) ⁺	2 (8.0%)	2 (7.7%)	0.967	0.006
Learning disability (<i>N</i> , %) ⁺	2 (8.0%)	2 (7.7%)	0.967	0.006
Previous diagnosed concussions ⁺	0.6 (0.6)	0.3 (0.5)	0.118	0.444
Acute injury characteristics				
LOC	2 (7.7%)	–		
PTA	5 (19.2%)	–		
RGA	4 (15.4%)	–		

Note: + denotes one concussed subject had missing data. Effect sizes are Cohen's *d* unless otherwise noted; ^ denotes Cramer's *V*. WTAR, Wechsler Test of Adult Reading; ADHD, Attention Deficit Hyperactivity Disorder; LOC, loss of consciousness; PTA, posttraumatic amnesia; RGA, retrograde amnesia.

Then, during the season, injured athletes and their matched controls completed an identical protocol within 24 hours of injury ($M = 19.69$ hours, range 14–24 hours) and again at 8 days post-injury ($M = 8.38$ days, range 7–11 days) with the exception that WTAR scores and health history information were not re-obtained. Alternate forms of the SAC were used at each testing session.

SCAT-3 symptom severity score, SAC total score and the BESS total score were used to assess injury symptoms and severity. The SCAT-3 symptom checklist is a 22-item scale that evaluates somatic, cognitive, and emotional post-concussive symptoms. It has a score range of 0–132, with high scores indicating more severe symptom burden. The SAC is a brief cognitive screening tool that assesses orientation, concentration, and immediate and delayed memory. Scores range from 0 to 30, with higher scores indicating better performance. The BESS is a brief clinical measure of postural stability. Scores range from 0 to 60, with higher scores indicating more balance difficulties.

MRI Acquisition

Participants underwent MRI scanning at the Center for Imaging Research at the Medical College of Wisconsin as part of their 24-hour and 8-day post-injury assessment. Participants were scanned on a General Electric (GE) Discovery MR750 whole body 3-Tesla MRI scanner with a receive-only 32 channel head coil. Diffusion weighted images (DWI) were acquired using a single-shot SE-EPI sequence with 3 mm isotropic voxels. The DWI data set consisted of four non-diffusion-weighted reference images

and 60 diffusion-weighted images with $b = 1,000$ s/mm² and 2,000 s/mm² (30 diffusion directions for each shell). Acquisition time for the DWI data set was approximately 5 minutes and 30 seconds. An additional non-diffusion-weighted scan was acquired with the phase encode polarity reversed. This additional scan was used to correct distortions due to tissue magnetic susceptibility variations using post-processing algorithms.

Processing of the Diffusion MRI Data and Estimation of Diffusion Tensor and Kurtosis Tensor Parameters

Prior to any data processing and analysis, each subject's DWI data set was visually inspected to verify that the images were free from major artifacts (e.g., head motion). Susceptibility induced distortions were corrected using the TOPUP function of the FSL software (version 5.0.7, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), and motion and eddy current related distortions were corrected using the EDDY function of FSL (Andersson et al., 2003; Smith et al., 2004).

DTI and DKI tensors were estimated using software developed in-house. The core of this software is based on the algorithm published by Jensen et al. [2005]. The kurtosis and diffusion tensors were estimated via unconstrained singular value decomposition.

From the diffusion kurtosis tensor estimates at each voxel, mean kurtosis (MK), radial kurtosis (Krad), and axial kurtosis (Kax) maps were calculated. Similarly, mean, axial, and radial diffusivity maps (MD, Dax, and

Drad) and fractional anisotropy (FA) maps were calculated from the diffusion tensors. Then, each of these parametric maps was processed using Tract-Based Spatial Statistics [TBSS; Smith et al., 2006] in FSL. TBSS creates a mean white matter skeleton and then projects each parametric map onto this skeleton. As part of the standard TBSS analysis pipeline, all images were aligned to the FMRIB58 standard image in cubic 1 mm standard space. First, the FA images from each subject were registered to the FMRIB58 standard image and skeletonized. This process generated a group FA skeleton data set for analysis. For the remaining DTI/DKI parametric maps, the values were mapped to the white matter skeleton in a similar manner.

Statistical Analysis

Diffusion imaging data

Voxel-wise statistical analyses were carried out using the Randomize function in FSL [Winkler et al., 2014]. This is a non-parametric, permutation-based approach to perform voxel-wise statistical analysis on brain image data. Four thousand permutations were tested for this study and each statistical test was corrected for multiple comparisons using a family-wise error rate of $P = 0.05$. Threshold-Free Cluster Enhancement (TFCE) was included when running the Randomize program [Smith and Nichols, 2009]. Separate between-subjects ANCOVAs with age as a covariate were performed for the 24-hour and 8-day time periods to measure group differences between the concussed and control groups. The analyses were conducted for each DTI (FA, MD, Dax and Drad) and DKI (MK, Kax, Krad) parametric map. A within-subjects design was used to investigate changes in each group from 24 hours to 8 days post-injury. Within the General Linear Model (GLM) framework, we generated a contrast vector to compare differential changes from day 1 to day 8 in the concussed group with respect to the variance in the repeated scans from the control group. This helped reduce any potential sources of bias between the two scans. The variance between the two longitudinal scans from the control group accounts for various sources of systematic bias or variance between the two scan sessions. Age did not differ between groups in our sample, but it was included as a covariate of no interest in all analyses due to known effects of age on DTI and DKI measures [Coutu et al., 2014; Paydar et al., 2014; Pfefferbaum and Sullivan, 2003; Pfefferbaum et al., 2000]. Identification of affected WM fiber tracts was aided by co-registering the FA skeleton with the ICBM DTI-81 probabilistic white matter atlas [Mori et al., 2008].

The associations between diffusion metrics and clinical measures were also analyzed. For this purpose, the average value across the significant voxels for each parametric map was calculated for each subject such that each subject was assigned a set of single FA, MD, Dax, Drad, MK, Kax, and Krad values. These values were then used to calculate

correlations between clinical measures and DTI and DKI variables (see next section).

Demographic and clinical data

The Statistical Package for Social Sciences (SPSS, version 21.0) was used to assess differences in demographic and clinical measures (at each time point) between groups. To examine group differences between continuous variables, ANOVAs were employed, while χ^2 tests were used to examine group differences in categorical variables. Multiple comparisons were controlled using the false discovery rate (FDR) procedure [Benjamini and Hochberg, 1995]. Within-group, longitudinal changes in each DTI and DKI metric were assessed via repeated-measures t -tests performed in FSL. Partial correlations adjusted for age were computed in SPSS to examine relationships between average diffusion metrics in significant voxels and clinical measures. Correlations were corrected for multiple comparisons using an FDR correction.

RESULTS

Subject Characteristics

All participants were male. As expected based on our matching criteria, no differences existed between concussed and control athletes in age, race, years of education, height, or weight (Table I). Furthermore, the groups did not differ regarding number of individuals diagnosed with attention deficit hyperactivity disorder or a learning disability and were comparable on a measure of reading ability (WTAR). Although not statistically significant, a trend existed for a higher number of prior sport-related concussions in the concussed group ($P = 0.070$). The groups did not differ on number of non-sport-related concussions.

Clinical Injury Measures

Between-group differences

At preseason baseline, there were no differences between the concussed group and controls on the SCAT-3 symptom checklist, SAC, or BESS (Table II). At 24-hours post-injury, the concussed group reported significantly more concussion symptoms on the SCAT-3 than the control group ($P < 0.001$) and demonstrated poorer cognitive performance on the SAC ($P = 0.010$). The groups did not differ on balance testing assessed via the BESS at 24 hours. At day 8 follow-up, no significant differences existed between groups (Fig. 1). Significant differences survived correction for multiple comparisons using FDR.

Within-group change

The concussed group reported significantly more SCAT-3 symptoms at 24 hours post-injury than at baseline ($P < 0.001$). At 8 days post-injury, however, reported

TABLE II. Clinical assessment of participants

	SRC (<i>n</i> = 26) <i>M</i> (<i>SD</i>)	Control (<i>n</i> = 26) <i>M</i> (<i>SD</i>)	<i>P</i>	Effect size
SCAT-3 Symptom Severity				
Baseline ⁺	4.7 (4.6)	4.7 (5.0)	0.998	< 0.001
24 hours	27.6 (17.1)	2.8 (2.8)	< 0.001	2.024
8 days	5.4 (8.3)	2.1 (3.4)	0.066	0.520
SAC Total Score				
Baseline ⁺	26.6 (2.1)	26.8 (1.8)	0.776	0.102
24 hours	24.5 (2.4)	26.1 (1.9)	0.010	0.739
8 days	26.8 (2.4)	27.6 (1.6)	0.140	0.392
BESS Total Score				
Baseline ⁺	14.0 (5.3)	11.8 (4.8)	0.130	0.435
24 hours	13.5 (4.6)	11.8 (3.8)	0.172	0.403
8 days	12.0 (4.6)	10.2 (4.5)	0.154	0.396

Note: + denotes 3 concussed participants had missing data. *P*-values in bold and italics survived false discovery rate correction for multiple comparisons. Effect sizes are Cohen's *d*. SCAT-3, Sport Concussion Assessment Tool, 3rd Edition; SAC, Standardized Assessment of Concussion; BESS, Balance Error Scoring System.

symptoms in the concussed group did not significantly differ from baseline at the $P < 0.05$ significance level. The concussed group also performed significantly worse on the SAC at 24 hours compared with baseline ($P < 0.001$), but day 8 SAC scores did not differ from baseline. BESS scores in the concussed group did not differ between time points. Of 23 concussed athletes with baseline data, 14 (61%) reported SCAT-3 symptom severity scores at day 8 that were equal to or lower than their baseline score. The control group reported slightly lower symptom burden than baseline on the SCAT-3 at 24 hours ($P = 0.039$) and 8 days ($P = 0.013$). Twenty-three of twenty-six controls (89%) reported SCAT-3 scores at or below their baseline report at day 8. Additionally, their SAC or BESS scores did not differ from baseline at either additional time point.

While unexpected, the slight drop in SCAT-3 scores at 24 hours with respect to baseline could be due to the subjectivity of symptom reporting. These small variations seen in the controls do not have any clinical significance. Furthermore, the time period during which these assessments were taken should also be considered. The baseline was taken before the football season started and the scores are slightly higher. On the other hand, the two following evaluations were done during season and they were not significantly different.

Acute DTI Changes

Between-group differences

At 24 hours post-injury, the concussed group demonstrated widespread decreased MD compared with controls bilaterally in regions including the genu and splenium of the corpus callosum, cingulum, internal capsule, superior longitudinal fasciculus, inferior longitudinal fasciculus,

and inferior fronto-occipital fasciculus as well as portions of the right external capsule (Fig. 2; FWE corrected $P < 0.05$). At 8 days post-injury, widespread decreases in MD in the concussed group remained and also included bilateral cerebral peduncle and right thalamic white matter (FWE corrected $P < 0.05$).

At 24 hours post-injury, the concussed group showed decreased Dax compared with controls mostly on the left hemisphere in the inferior longitudinal fasciculus and cerebral peduncle (corticospinal tract) as well as smaller portions of the posterior cingulum, posterior limb of the internal capsule, and superior longitudinal fasciculus (Fig. 3; FWE corrected $P < 0.05$). At this time point, Drad was also decreased in the concussed group relative to the control group, but mostly on the right hemisphere in the corticospinal tract, posterior limb of the internal capsule, and superior longitudinal fasciculus (Fig. 4; FWE corrected $P < 0.05$).

At 8 days post-injury, the concussed group showed more widespread areas of decreased Dax and Drad

Figure 1.

Longitudinal assessment of symptoms and cognitive performance. Note. SAC, standardized assessment of concussion; SCAT-3, sport concussion assessment tool, 3rd Edition. Error bars reflect 95% confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 2.

Results of Tract-Based Spatial Statistics analyses comparing mean diffusivity of concussed and control subjects at 24 hours and 8 days post-injury. The red-yellow voxels represent areas of significant differences corrected for family-wise error at $P < 0.05$. Significant voxels have been inflated using *tbss_fill* for viewing purposes

and are overlaid on the mean white matter skeleton (green). Results are displayed on the MNI152-T1-1mm standard image. MD, mean diffusivity. (Images are in radiological orientation.) [Color figure can be viewed at wileyonlinelibrary.com]

bilaterally compared with controls (Figs. 3 and 4; FWE corrected $P < 0.05$). Table III lists the total number of voxels that survived FWE correction ($P < 0.05$) in each analysis at 24 hours and 8 days. Substantial increases in spatial extent of the effects can be clearly seen in the voxel counts. The list of major white matter fiber tracts that were significantly different between the concussed group and controls are given in Table IV. No differences existed between groups in FA at either 24 hours or 8 days post-injury.

Supplemental analyses investigated the impact of history of previous sport-related concussions on between-group findings. Including number of previous SRCs as an additional covariate did not significantly alter any of the results reported above.

Within-group change

TBSS analysis did not reveal statistically significant changes from 24 hours to 8 days post-injury on any of the DTI metrics in the concussed or the control group.

DTI correlations with clinical measures

In the full sample, SCAT-3 symptom severity scores at 24 hours correlated with MD, Dax, and Drad measured at

24 hours such that higher symptom scores were related to decreased diffusion metric values (Table V). Furthermore, SCAT-3 symptom severity score at 24 hours correlated strongly with MD, Dax, and Drad at 8 days. Also, SCAT-3 scores at 8 days correlated with MD and Drad at 8 days. SAC and BESS scores did not correlate significantly with DTI variables, which may be attributable to our small sample and restricted range of scores on these measures. Additionally, when concussed participants alone were examined, there were no significant correlations between DTI and clinical measures. However, the magnitudes of the correlations in the concussed-only participants were greater than those for the total sample for MD and Drad, indicating that low power kept these correlations from reaching significance. Table III presents correlations for both the total sample and the concussed group alone.

Acute DKI Changes

Between-group differences

At 24 hours post-injury, the concussed group showed increased Kax compared with controls in the corpus callosum and predominantly on the right, the internal capsule, uncinate fasciculus, cerebral peduncle, corticospinal

Figure 3.

Results of Tract-Based Spatial Statistics analyses comparing axial diffusivity of concussed and control subjects at 24 hours and 8 days post injury. The pink-light pink voxels represent areas of significant differences corrected for family-wise error at $P < 0.05$. Significant voxels have been inflated using *tbss_fill* for

viewing purposes and are overlaid on the mean white matter skeleton (green). Results are displayed on the MNI152-T1-1mm standard image. Dax, axial diffusivity. (Images are in radiological orientation.) [Color figure can be viewed at wileyonlinelibrary.com]

tract, inferior fronto-occipital fasciculus, and the inferior longitudinal fasciculus (FWE corrected $P < 0.05$). Similar to DTI metrics, there were more widespread increases in Kax bilaterally 8 days after the injury (Fig. 5; FWE corrected $P < 0.05$). Including number of previous SRCs as an additional covariate did not significantly alter these findings. No group differences existed for MK or Krad.

Within-group change

Within group comparisons using TBSS did not reveal any statistically significant Kax changes for either group from 24 hours to 8 days post-injury.

DKTI correlations with clinical measures

In the total sample, Kax at 24 hours post-injury correlated positively with SCAT-3 symptom score at 24 hours such that higher kurtosis was associated with more symptoms (Table III). SCAT-3 symptom score at 24 hours also correlated with Kax at 8 days. Furthermore, SCAT-3 symptom score at 8 days correlated with Kax at 8 days. SAC and BESS scores did not correlate with Kax. No significant

associations between DKTI and clinical measures existed when only concussed participants were examined.

DISCUSSION

This study is the first in the literature to capture white matter changes within 24 hours of SRC and again after 1 week, demonstrating advancement of white matter disruption in the acute phase. In addition to the conventional DTI metrics that use a simplified model of a Gaussian diffusion distribution, this study also employed the diffusion kurtosis tensor model to investigate complex diffusion patterns in brain white matter after SRC.

Results of the current study indicate a pattern of evolving alterations in brain white matter in concussed athletes in the acute post-injury stage. On DTI, the concussed group demonstrated a widespread decrease in mean diffusivity and, to a lesser extent, decreases in axial and radial diffusivities compared with control subjects at 24 hours post injury. Areas of DTI differences between groups became more widespread at 8 days post injury. On DKTI, the concussed group showed increased axial kurtosis at 24

Figure 4.

Results of Tract-Based Spatial Statistics analyses comparing radial diffusivity of concussed and control subjects at 24 hours and 8 days post injury. The light blue-magenta voxels represent areas of significant differences corrected for family-wise error at $P < 0.05$. Significant voxels have been inflated using `tbss_fill` for

viewing purposes and are overlaid on the mean white matter skeleton (green). Results are displayed on the MNI152-T1-1mm standard image. Drad, radial diffusivity. (Images are in radiological orientation.) [Color figure can be viewed at wileyonlinelibrary.com]

hours post injury relative to controls, with a larger area of significant differences after 8 days.

There were also notable associations between diffusion metrics and symptom severity measured by the SCAT-3, while performance on screening measures of cognition and balance did not correlate with white matter changes. The concussed group reported significantly more symptoms and performed more poorly on the SAC at 24 hours following injury. Higher SCAT-3 symptom severity scores correlated significantly with decreased mean, axial, and radial diffusion and increased axial kurtosis metrics obtained at 24 hours in the total sample. However, these correlations were not significant when the concussed group alone was studied. This finding is possibly due to range restriction on the SCAT-3; since the group studied here experienced a mild form concussion, this resulted in a relatively narrow range of SCAT-3 scores.

At the 8-day time point, no statistically significant group differences in symptoms, cognition, or balance existed. This indicated that the symptoms in the concussed group diminished, on average, within a week. Interestingly, day 8 SCAT-3 symptom severity scores still correlated with diffusion measures at day 8 in the total sample, with increased symptom burden related to reduced diffusion

and increased axial kurtosis. This finding might be expected because even though the injured athletes demonstrated substantial symptomatic recovery, there continued to be a notable, but non-significant, difference in symptoms between the two groups at day 8 (Table II). When only concussed athletes were studied using diffusion metrics and SCAT-3 at day 8, the correlations did not reach statistical significance. However, the magnitude of the correlations was greater for MD and Drad than those seen in the entire sample (Table III), indicating that low power due to small sample size might have affected the significance of these tests.

TABLE III. Number of significant voxels at each time point between concussed and control participants

	MD	Dax	Drad	Kax
24 hours	34,807	1,311	2,404	9,392
8 days	57,030	33,168	36,000	30,871

Note: Significant voxels survived family-wise error correction ($P < 0.05$). Voxel counts are taken from the skeletonized analysis results. Dax, axial diffusivity; Drad, radial diffusivity; Kax, axial kurtosis; MD, mean diffusivity.

TABLE IV. Major fiber tracts with significant differences between the concussed and control subjects at 24 hours and 8 days

	CST	SLF	ILF	IFO	ALIC/PLIC	ATR	UNC	BCC	GCC	SCC	CGC
MD	Dorsal segment bilateral	Left, partial	None	None	None	None	None	None	None	None	None
8 days	Whole tract, bilateral	Left, whole tract	None	None	Bilateral	Whole tract	Left, whole tract	None	Tract body	None	Right, ventral
Dax	Left, ventral	None	Left, partial	None	None	None	None	None	None	None	Left, posterior
8 days	Whole tract, bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Whole tract	Bilateral dominant on left	Tract body	Tract body	None	Left, posterior and anterior
Drad	Right, dorsal	Right, dorsal	None	None	Right, dorsal	None	None	None	None	None	None
8 days	Dorsal bilateral	Bilateral most of tract	Bilateral	Bilateral	Bilateral	None	None	None	Tract body	Tract body	None
Kax	Right, ventral	None	Right	None	Right, partial	None	Bilateral partial	None	Tract body	Partial	None
8 days	Bilateral whole tract	Bilateral	Bilateral	None	Bilateral most of tract	Bilateral	Bilateral dominant on left	None	Tract body	Tract body	None

CST, corticospinal tract; SLF, superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus; IFO, inferior fronto-occipital fasciculus; ALIC/PLIC, Anterior/posterior limb of internal capsule; ATR, anterior thalamic radiation; UNC, uncinatus; BCC, body of corpus callosum; GCC, genu of corpus callosum; SCC, splenium of corpus callosum; CGC: cingulum.

Another interesting finding was that SCAT-3 scores at 24 hours correlated significantly with diffusion metrics on day 8. More specifically, greater symptom severity on the SCAT-3 at 24 hours predicted lower diffusion and higher axial kurtosis at 8 days after injury. This is an indication that a more severe injury might result in physiological changes that persist longer than 1 week. Moreover, the correlations between day 8 diffusion metrics with 24-hour SCAT-3 scores were stronger than the correlations between 24-hour diffusion metrics and 24-hour SCAT-3 scores. It is possible that the relatively slow progression of injury processes post-injury could account for this finding and that diffusion imaging techniques could monitor the trajectory of such changes.

Overall, our findings demonstrate that, while acute clinical symptoms of SRC approached baseline over the course of 1 week following injury, increased diffusion restriction and complexity were evident beyond the point of apparent clinical recovery. In other words, as concussion symptoms diminished, microstructural white matter changes appear to have persisted. Furthermore, there is a notable increase in the spatial extent of the injury-related white matter changes on day 8, suggesting an evolving neuropathological process in concussed group. However, voxel-based analysis of these longitudinal changes did not reach a significance level of $P < 0.05$ (FWE corrected) in the concussed group. While unexpected, understanding the underpinnings of this statistical analysis may explain this finding. Hypothetically, consider a voxel that has a sizable difference in mean Drad values between the concussed and control groups at 24 hours, but this effect is just below the $P < 0.05$ (FWE) threshold. The difference between the two groups becomes slightly larger on day 8 and survives the $P < 0.05$ (FWE) threshold. Because the within-subjects analysis of changes between 24 hours and 8 days is a measurement of the difference between the two effect sizes, it is possible that that difference may not survive the $P < 0.05$ (FWE) threshold.

Current findings of decreased mean diffusivity in concussed athletes compared with controls are consistent with known pathophysiological processes occurring in the acute period following SRC. It is generally accepted that forces sustained during the injury lead to axonal stretching, which, as a result, disrupt neurofilaments and microtubules that extend down the axon and lead to axonal swelling [Blumbers et al., 1994]. This swelling results in decreased extracellular space and thus decreased ability for water to diffuse perpendicular to axons, which is reflected in decreased radial diffusion [Pasternak et al., 2014]. On the other hand, the ensuing neuroinflammatory response causes an increase in glial cells, which could change axonal fiber volume and uniformity, restricting parallel (axial) diffusion. The results presented here are in accord with earlier studies, which also reported decreased diffusion in the acute phase (within a week of injury) in concussed athletes [Henry et al., 2011; Pasternak et al.,

TABLE V. Associations between reported concussion symptom severity and average diffusion metrics in significant voxels

	24-hour SCAT-3 versus 24 hour DWIM				24 hour SCAT-3 versus Day 8 DWIM				Day 8 SCAT-3 versus Day 8 DWIM			
	Concussed + control		Concussed only		Concussed + control		Concussed only		Concussed + control		Concussed only	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
MD	−0.337	0.021	0.065	0.774	−0.417	0.004	−0.099	0.660	−0.282	0.048	−0.321	0.117
Dax	−0.347	0.017	0.314	0.155	−0.419	0.003	0.068	0.765	−0.169	0.240	−0.069	0.744
Drad	−0.364	0.012	0.116	0.608	−0.459	0.001	−0.166	0.460	−0.311	0.028	−0.386	0.056
Kax	0.478	0.001	0.040	0.859	0.478	0.001	−0.040	0.859	0.280	0.049	0.116	0.581

Note: Bold indicates significant at $P < 0.05$; italics indicates correlation survived false discovery rate correction for multiple comparisons. Four participants (3 concussed) had missing SCAT-3 data at 24 hours; 1 control participant had missing SCAT-3 data at 8 days. Dax, axial diffusivity; Drad, radial diffusivity; DWIM, diffusion weighted imaging metrics; Kax, axial kurtosis; MD, mean diffusivity; SCAT-3, Sport Concussion Assessment Tool-3rd Edition.

2014] and others with mild TBI [Bazarian et al., 2007; Chu et al., 2010; Wilde et al., 2008; Wu et al., 2010]. However, some groups have also reported increased diffusion in the acute phase of mild TBI [Croall et al., 2014; Henry et al., 2011; Ilvesmaki et al., 2014; Narayana et al., 2015; Toth et al., 2013; Veeramuthu et al., 2015], a pattern also seen in

subacute and chronic recovery phases [Chamard et al., 2013; Cubon et al., 2011; Grossman et al., 2013; Tremblay et al., 2014] when presumably initial inflammatory reactions have subsided and injured axons are in the process of degeneration [Buki and Povlishock, 2006; Johnson et al., 2013]. It is unclear if our results support the notion that

Figure 5.

Results of Tract-Based Spatial Statistics analyses comparing axial kurtosis of concussed and control subjects at 24 hours and 8 days post injury. The blue-light blue voxels represent areas of significant differences corrected for family-wise error at $P < 0.05$. Significant voxels have been inflated using `tbss_fill` for

viewing purposes and are overlaid on the mean white matter skeleton (green). Results are displayed on the MNI152-T1-1mm standard image. Kax, axial kurtosis. (Images are in radiological orientation.) [Color figure can be viewed at wileyonlinelibrary.com]

injury renders neurons temporarily dysfunctional or more permanently damaged.

The current study was the first to assess measures of diffusion kurtosis tensor analysis in the acute stage of SRC recovery and indicates that DKTI provides unique, complementary information in characterizing injury sequelae. Our findings are consistent with an animal model of mTBI in which K_{ax} was increased in the external capsule and corpus callosum within 2 hours after injury and remained after 7 days [Zhuo et al., 2012]. An increase in axial kurtosis is consistent with the proposed mechanism of axonal beading that occurs when axons are stretched. As a result, calcium invades the cell and disrupts axonal transport, causing proteins and membrane-bound organelles accumulate in “beads” at distinct locations along an axon’s diameter [Kilinc et al., 2008, 2009]. This change in axonal architecture is hypothesized to increase the complexity of molecular diffusion in the extracellular space parallel to the axons. Our DKTI findings are in contrast to some studies investigating sub-acute to chronic stage of mild TBI, which have reported decreased mean and radial kurtosis [Grossman et al., 2012, 2013; Stokum et al., 2015]. This is possibly due to eventual axonal degeneration secondary to axonal beading [Buki and Povlishock, 2006; Johnson et al., 2013]. Additional work is needed to determine the relationship between the SRC recovery curve and patterns of disrupted kurtosis.

A major strength of this first serial diffusion imaging study of very-acute SRC is its utilization of a well-controlled sample of contact sport athletes. Because the mechanism of injury in this sample was less heterogeneous than in studies of mTBI in the general population, findings will be useful in understanding the immediate neurophysiological consequences of SRC. However, there are some limitations that may hinder the generalizability of the current findings. More specifically, given that we focused on high school and collegiate football players, our sample was relatively young and completely male; the results will need replication in female athletes, other age groups, and other types of contact sport athletes. In addition, it must be noted that while at the group level all concussed athletes reported a decrease in symptoms after 8 days, not all had returned to their pre-injury baseline at this time, making interpretation at the individual level somewhat limited.

The findings reported here might have significant implications for proper management of SRC. Even though most injured athletes had reported symptom relief on day 8, neurophysiological differences not only existed at this time point but appeared to have worsened since an earlier assessment in our concussed sample. The current consensus is that an athlete may return to activity once asymptomatic [Echemendia et al., 2015]; however, long-term implications of return to play when imaging findings still suggest neurophysiological changes is unknown. The full trajectory of physiological recovery is not well understood

at this time, with some studies reporting changes in brain structure and function months to a year post-injury [for review see Dimou and Lagopoulos, 2014; Eierud et al., 2014; Gardner et al., 2012; Slobounov et al., 2012]. Considering that athletes are more susceptible to sustaining a second concussion within 10 days of their first injury and that a history of multiple concussions is associated with poorer recovery [Guskiewicz et al., 2003], there is some indication that lingering physiological alterations may be contributing to poor outcomes. Future studies must strive to better illuminate the full picture of SRC recovery in order to inform return-to-play decisions that are in the best interest of athletes.

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