Hockey Concussion Education Project, Part 3. White matter microstructure in ice hockey players with a history of concussion: a diffusion tensor imaging study

Clinical article

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Object. The aim of this study was to examine the brain’s white matter microstructure by using MR diffusion tensor imaging (DTI) in ice hockey players with a history of clinically symptomatic concussion compared with players without a history of concussion.

Methods. Sixteen players with a history of concussion (concussed group; mean age 21.7 ± 1.5 years; 6 female) and 18 players without a history of concussion (nonconcussed group; mean age 21.3 ± 1.8 years, 10 female) underwent 3-T DTI at the end of the 2011–2012 Canadian Interuniversity Sports ice hockey season. Tract-based spatial statistics (TBSS) was used to test for group differences in fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and the measure “trace,” or mean diffusivity. Cognitive evaluation was performed using the Immediate Postconcussion Assessment and Cognitive Test (ImPACT) and the Sport Concussion Assessment Tool–2 (SCAT2).

Results. TBSS revealed a significant increase in FA and AD, and a significant decrease in RD and trace in several brain regions in the concussed group, compared with the nonconcussed group (p < 0.05). The regions with increased FA and decreased RD and trace included the right posterior limb of the internal capsule, the right corona radiata, and the right temporal lobe. Increased AD was observed in a small area in the left corona radiata. The DTI measures correlated with neither the ImPACT nor the SCAT2 scores.

Conclusions. The results of the current study indicate that a history of concussion may result in alterations of the brain’s white matter microstructure in ice hockey players. Increased FA based on decreased RD may reflect neuroinflammatory or neuroplastic processes of the brain responding to brain trauma. Future studies are needed that include a longitudinal analysis of the brain’s structure and function following a concussion to elucidate further the complex time course of DTI changes and their clinical meaning.

Key Words • concussion • mild traumatic brain injury • diffusion tensor imaging • ice hockey • fractional anisotropy • white matter

Abbreviations used in this paper: AD = axial diffusivity; CIS = Canadian Interuniversity Sports; DTI = diffusion tensor imaging; FA = fractional anisotropy; HCEP = Hockey Concussion Education Project; ImPACT = Immediate Postconcussion Assessment and Cognitive Test; mTBI = mild traumatic brain injury; RD = radial diffusivity; SCAT2 = Sport Concussion Assessment Tool–2; SHB = subconcussive head blow; TBSS = tract-based spatial statistics.

* Drs. Echlin and Koerte share senior authorship of this work.

Sports-related concussion is an important public health problem given the annual incidence of approximately 300,000 sports-related concussions in the US alone.12,49 Concussion, a subset of mild traumatic brain injury (mTBI),19 is caused by high-speed acceler-
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ation-deceleration head motions, leading to complex pathophysiological processes affecting the brain’s function and structure. Common symptoms of concussion include confusion, dizziness, headache, nausea, and balance problems. These symptoms resolve in the majority (80%–90%) of individuals within the first 10 days. However, in some individuals a concussion may result in symptoms lasting for more than 3 months, also known as prolonged postconcussive syndrome. Moreover, repeated concussions have been associated with the development of chronic traumatic encephalopathy.

To date, diagnosis and management of concussion are largely based on clinically observed or self-reported symptoms. However, this approach is both incomplete and inaccurate because symptoms may either not be reported by the athlete or not be associated with a concussion. In addition, conventional neuroimaging such as CT and MRI fail to detect traumatic axonal injury, the underlying mechanism of mTBI.

Diffusion tensor imaging (DTI) is sensitive for detecting traumatic axonal injury and is therefore expected to improve the diagnosis of mTBI by providing objective parameters to quantify and to localize white matter alterations (see review by Shenton et al.). DTI measures the movement of water in the brain. In white matter, water molecules move more in directions parallel to the fiber tracts than perpendicular to them. This characteristic, which is referred to as anisotropic diffusion, is most commonly measured by fractional anisotropy (FA), a measure derived from DTI that reflects the coherent microstructural organization of white matter. In addition to FA, the measure “trace,” or mean diffusivity, denotes the overall average of diffusion. Axial diffusivity (AD) and radial diffusivity (RD) denote the extent of diffusion parallel and perpendicular to the direction of maximal diffusivity, respectively; AD is purported to be sensitive to axonal damage, whereas RD is purported to be sensitive to myelin degeneration.

Reports on alterations of diffusivity following TBI vary in the literature: FA has been shown to either decrease or increase after head trauma. Moreover, regions with increased and those with decreased FA have been reported within the same individual following mTBI. It has been suggested that these diffusivity changes are determined by the severity and/or chronicity of the injury.

Ice hockey is a high-speed collision sport for which a high incidence rate of concussions is known. A recent study by Echlin et al. reported the number of concussions per 1000 athlete exposures to be as high as 11.67. To date, DTI studies have been performed in players of other contact sports such as American football and soccer, with only a small number of studies including ice hockey players. However, evaluating the effects of sports-related concussion on the brain’s microstructure among ice hockey players will probably contribute to earlier and more accurate diagnosis, which in turn may lead to improved and more specific therapeutic management and a more informed decision about when an athlete should return to play.

The aim of this study was to examine the brain’s white matter microstructure using DTI in ice hockey players with a history of a clinically symptomatic concussion compared with players without a history of concussion.

Methods

Participants and Clinical Information

All participants were part of the Hockey Concussion Education Project (HCEP), a cohort study performed during a Canadian Interuniversity Sports (CIS) ice hockey season (2011–2012). Thirty-nine players underwent imaging at the end of the season. None of the included participants had a history of any neurological or psychiatric disorder other than concussion. Players with gross structural MRI abnormalities were excluded. The study protocol was approved by the ethics committees within the universities at which the CIS teams were based. All participants provided written informed consent prior to the beginning of the study.

Five players were excluded for the following reasons: severe motion artifacts (3 players); a large arachnoidal cyst (1 player); or an age more than 8 SDs from the mean (1 player). Therefore, 34 players (18 male and 16 female) were included in the statistical analyses.

A self-report of concussion history was obtained from the players prior to the beginning of the season by using a questionnaire. At the time the data were collected, concussion was defined according to the Zürich consensus statement on concussion from the 3rd International Conference on Concussion in Sport, which took place in 2009. However, the definition used here also meets the concussion criteria from the 4th International Conference on Concussion in Sport, which took place in 2012.

Prior to the current season, team members received physical examinations by the team physician (not study related). Thirteen of the 34 players reported that they had suffered at least 1 concussion prior to the start of the study (mean number of concussions 1.46 ± 0.88 [mean ± SD], range 1–4). Additionally, 8 of the 34 players experienced at least 1 clinically symptomatic concussion during the season. Concussions occurring during the season were directly observed and diagnosed by the independent designated specialist physician who attended the game. The average concussion-to-scan interval was 95 ± 45 days (range 42–161 days) for those who suffered from concussion during the study. For those who sustained a concussion prior to the study, the concussion-to-scan interval was by definition more than 6 months. In total, 16 players had concussion(s) either prior to the study (n = 8), during the study (n = 3), or both (n = 5) (concussed group; mean age 21.7 ± 1.5 years), and 18 players reported no history of concussion (nonconcussed group; mean age 21.3 ± 1.8 years) (Fig. 1).

Cognitive Examination

At the end of the CIS season, cognitive testing was performed using the Immediate Postconcussion Assessment and Cognitive Test (ImPACT) examination (ImPACT Applications, Inc.) and the Sport Concussion Assessment Tool–2 (SCAT2). The ImPACT is a computer-based test battery consisting of a concussion symptom inventory.
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Fig. 1. The schematic illustration of grouping: nonconcussed (n = 18) and concussed (n = 16) groups. Within the concussed group, 8 players had a concussion during the season, and 13 players had a concussion prior to the start of the study. Five players had a concussion both during the season and prior to the start of the study.

and 6 modules measuring neurocognitive function. It is the most widely used system for evaluating sports-related concussion; however, to date it has not been independently evaluated. These modules were used to generate 4 composite scores: verbal memory, visual memory, visual motor speed, and reaction time. The SCAT2 is a test battery for the evaluation of concussion that consists of 8 component scores. These are designed to assess concussion symptoms, cognition, balance, Glasgow Coma Scale score, and other neurological symptoms.14

Protocol for MRI and Data Acquisition

Data were acquired using a 3-T MRI scanner (Achieva, Philips Medical Systems) with an 8-channel head coil array. A DTI sequence with 2 averages and the following parameters was performed: 60 noncollinear diffusion directions, TR 7015 msec, TE 60 msec, b = 0 and 700 sec/mm², and 70 slices. Data were acquired using a 2.2 mm isotropic voxel size and a 100 x 100 matrix reconstructed into a 112 x 112 matrix with a resolution of 2 x 2 x 2.2 mm³.

Processing of DTI

Postprocessing and statistical analyses were performed by the first author (T.S.), who was not blinded to the groups. Blindness to group membership was not an issue, because the postprocessing measures are automated. The MRI data sets were examined for image quality. To remove intrascan misalignments due to eddy currents and head motion, an affine registration of the diffusion-weighted images to the baseline image was performed for each participant (FSL version 4.1, Functional MRI of the Brain [FMRIB] Software Library [FSL]). Gradient directions were adjusted using the rotational component of the affine transformations. Nonbrain tissue and background noise were then removed from the b0 image with the aid of 3D Slicer version 3.6.2 (Surgical Planning Laboratory, Brigham and Women’s Hospital). The diffusion tensor for each voxel was estimated using a multivariate linear fitting algorithm, and the 3 pairs of eigenvalues and eigenvectors were obtained. From these tensor volumes, scalar measures including FA, AD, RD, and trace for each voxel were calculated as follows:

\[
FA = \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}
\]

\[
AD = \lambda_1
\]

\[
RD = \frac{(\lambda_2 + \lambda_3)}{2}
\]

\[
\text{trace} = \lambda_1 + \lambda_2 + \lambda_3,
\]

where \(\lambda_1\), \(\lambda_2\), and \(\lambda_3\) are the largest to smallest eigenvalues.

To avoid any bias due to head motion in the scanner, we computed a relative motion index. This parameter was then compared between groups by using a t-test. In addition, we included this index as a covariate in the statistical analysis (see below).

White Matter Analysis

Whole-brain tract-based spatial statistics (TBSS) version 1.2,47 a voxel-based standard-space group statistical analysis (FSL version 4.1, Functional MRI of the Brain [FMRIB] Software Library [FSL]), was used for the investigation of white matter. The TBSS procedure is described in detail by Smith et al.47 In short, FA images from all subjects were coregistered into a template and then linearly aligned into Montreal Neurological Institute 152 space. These aligned FA images were then averaged to generate a cross-participant mean FA image. The mean FA image was then thinned to create a mean FA skeleton, which represents the center of all white matter fiber tracts common to the group. The mean FA skeleton was thresholded to contain only voxels with FA > 0.3 to exclude peripheral voxels with significant intersubject variability and/or partial volume effects with gray matter. Each participant’s aligned FA data were then projected onto the skeleton by searching the local maxima along the perpendicular direction from the skeleton to create a skeletonized FA map. Thus, without prior perfect coregistration, the central course of each subject’s fiber tract is represented on the skeleton. To analyze group differences in the other scalar measures (AD, RD, and trace), we applied the nonlinear warps obtained from the FA registration, as well as the skeleton projection of the FA data, to the other diffusion scalar volumes.

Statistical Analyses

Group comparisons for each voxel on the skeleton were performed by a nonparametric permutations-based test (Randomise, Functional MRI of the Brain [FMRIB] Software Library [FSL]). Threshold-free cluster enhancement was used to avoid choosing an arbitrary initial cluster-forming threshold. The data were tested against an empirical null distribution generated by 5000 permutations for each contrast, thus providing statistical maps fully cor-
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corrected for multiple comparisons across space. A corrected value of $p < 0.05$ was considered significant. The test was linearly adjusted for age, handedness, sex, and motion, even though there was no significant difference in these variables between the groups (Table 1). Statistical maps plotting the corrected $p$ values were visualized using FSL (TBSS_fill and FSLView). The Pearson linear analysis was used to assess the correlation between DTI parameters and measures of cognitive function. The Spearman rank correlation was used when normal distribution was not given. A $p$ value $< 0.05$ was considered statistically significant.

Results

Demographic Characteristics and Neuropsychological Examination

Concussed and nonconcussed groups did not differ significantly with respect to age, sex, handedness, or head motion. There was also no significant difference in ImPACT score between the concussed and nonconcussed group (Table 1). For 1 player in the concussed group there were no ImPACT test results available. There was no significant difference between the groups for the SCAT2 score. For 4 players in the concussed group there were no SCAT2 results available.

Analyses Within the Concussed Group

The 8 subjects that suffered a concussion during the season did not differ within the group when a comparison was made regarding the number of concussions sustained, ImPACT scores, or SCAT2 scores (Table 2). A group comparison using TBSS did not show a significant difference (data not shown).

White Matter Analysis

The TBSS analysis revealed a significant increase in FA and AD and a significant decrease in RD and trace for the concussed group compared with the nonconcussed group ($p < 0.05$).

For FA, the concussed group showed significantly higher values in the bilateral corona radiata, the bilateral posterior limb of the internal capsule, the bilateral superior frontal white matter, and the right superior temporal white matter (Fig. 2A). For AD, the concussed group showed significantly higher values in the left corona radiata (Fig. 2B). For RD, the concussed group showed significantly lower values in the genu of the corpus callosum, bilateral corona radiata, bilateral posterior limb of the internal capsule, right anterior limb of the internal capsule, right cerebral peduncle, bilateral superior frontal and orbitofrontal white matter, right superior and inferior temporal white matter, and right external capsule (Fig. 2C). For trace, the concussed group showed significantly lower values in the right corona radiata, the right anterior and posterior limbs of the internal capsule, the right superior frontal white matter, and the right inferior temporal white matter (Fig. 2D). Diffusivity measures of the clusters with significant group differences are displayed in the respective scatterplots in Fig. 3. For those clusters, median value and interquartile range (median [interquartile range]) for the nonconcussed and concussed group were as follows: FA (0.547 [0.017] and 0.582 [0.022], respectively); AD (0.0013 [0.000037] and 0.0014 [0.000091] mm²/second, respectively); RD (0.000560 [0.000037] and 0.000518 [0.000018] mm²/second, respectively); and trace (0.00247 [0.00013] and 0.00235 [0.000049] mm²/second, respectively).

There were no areas of significant decrease in FA or AD, nor were there any areas of significant increase in RD or trace. The DTI measures did not correlate with SCAT2 scores or with any of the composite scores of ImPACT (Table 3).

| TABLE 1: Demographic characteristics and neuropsychological tests in 34 ice hockey players with and without concussion* |
|------------------|------------------|------------------|------------------|
| Characteristic   | Nonconcussed Group | Concussed Group | Statistical Test, $p$ Value |
| no. of players   | 18               | 16               | $t_{32} = 1.22$, $p = 0.23$ |
| mean age in yrs  | $21.25 \pm 1.84$ | $21.68 \pm 1.54$ | $t_{31} = 0.78$, $p = 0.44$ |
| no. of females (%)| 10 (56)          | 6 (38)           | $\chi^2 = 1.11$, $p = 0.29$ |
| handedness (no. rt/either/lt) | 15/1/2            | 13/0/3           | Fisher exact test, $p = 0.82$ |
| mean head motion in mm | $0.78 \pm 0.09$ | $0.79 \pm 0.12$ | $t_{12} = -0.368$, $p = 0.716$ |
| mean ImPACT score†| verbal memory | 92.3 ± 5.94 | 90.3 ± 9.26 | $t_{11} = 0.78$, $p = 0.44$ |
|                   | visual memory | 79.7 ± 11.1 | 80.9 ± 13.5 | $t_{11} = 0.28$, $p = 0.87$ |
|                   | visual motor speed | 45.7 ± 5.34 | 45.0 ± 6.95 | $t_{11} = 0.33$, $p = 0.74$ |
|                   | reaction time | 0.53 ± 0.06 | 0.54 ± 0.07 | $t_{11} = 0.41$, $p = 0.68$ |
|                   | symptom scale | 3.4 ± 4.7 | 5.3 ± 13.2 | $U = 114.0$, $p = 0.43$ |
| mean SCAT2 score‡| total         | 94.4 ± 3.40 | 95.5 ± 1.62 | $t_{16} = -1.05$, $p = 0.30$ |

* The mean values are expressed ± SD.
† One subject’s data in the concussed group were not available.
‡ Four subjects’ data in the concussed group were not available.
TABLE 2: Analysis within the concussed group of 16 ice hockey players

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Concussed During (Season) Period of Study</th>
<th>Concussed Only Prior to (Season) Period of Study</th>
<th>Statistical Test, p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of players</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>mean age in yrs</td>
<td>21.56 ± 1.5</td>
<td>22.16 ± 1.6</td>
<td>( t_{14} = 0.76, p = 0.46 )</td>
</tr>
<tr>
<td>no. of females (%)</td>
<td>5 (63)</td>
<td>1 (13)</td>
<td>Fisher exact test, ( p = 0.12 )</td>
</tr>
<tr>
<td>handedness (rt/lt)</td>
<td>7/1</td>
<td>6/2</td>
<td>Fisher exact test, ( p = 1.00 )</td>
</tr>
<tr>
<td>mean no. w/ concussion</td>
<td>2.13 ± 1.4</td>
<td>1.25 ± 0.46</td>
<td>( U = 18.0, p = 0.11 )</td>
</tr>
<tr>
<td>mean ImPACT score*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>verbal memory</td>
<td>89.9 ± 9.9</td>
<td>90.7 ± 9.2</td>
<td>( t_{13} = 0.17, p = 0.87 )</td>
</tr>
<tr>
<td>visual memory</td>
<td>78.5 ± 16.3</td>
<td>83.7 ± 9.9</td>
<td>( t_{13} = 0.73, p = 0.48 )</td>
</tr>
<tr>
<td>visual motor</td>
<td>44.8 ± 7.8</td>
<td>45.2 ± 6.5</td>
<td>( t_{13} = 0.1, p = 0.92 )</td>
</tr>
<tr>
<td>reaction time</td>
<td>0.56 ± 0.08</td>
<td>0.51 ± 0.04</td>
<td>( t_{13} = 1.4, p = 0.20 )</td>
</tr>
<tr>
<td>total symptom</td>
<td>8.00 ± 18.0</td>
<td>2.39 ± 3.1</td>
<td>( U = 23.0, p = 0.56 )</td>
</tr>
<tr>
<td>mean SCAT2 score†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>96.4 ± 1.82</td>
<td>94.9 ± 1.22</td>
<td>( t_{10} = 1.78, p = 0.11 )</td>
</tr>
</tbody>
</table>

* One subject’s data were not available.
† Four subjects’ data were not available.

Fig. 2. Results of the TBSS analysis showing the clusters of significantly increased FA (A) and AD (B) (red to yellow), and decreased RD (C) and trace (D) (blue to light blue) for concussed players compared with nonconcussed players (\( p < 0.05 \)). Voxels are thickened into local tracts (TBSS_fi12 implemented in FSL) on the FA skeleton (green) and a T1-weighted template image. The left side in each image corresponds to the right hemisphere.
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Discussion

This study examined varsity-level ice hockey players and found a significant difference in DTI measures between the players with and without a history of concussion. We found a widespread increase in FA that overlapped with decreased trace and RD in the white matter of the brain in ice hockey players who had a history of concussion compared with players who did not report a history of concussion. These areas included the right corona radiata, the right posterior limb of the internal capsule, the right superior frontal white matter, and the right superior temporal white matter. Additionally, TBSS revealed a small cluster in the left corona radiata with increased FA and AD, but no changes in RD or trace. These results suggest possible alterations in white matter microstructure due to concussion. The lack of difference in the ImPACT and SCAT2 scores between the 2 groups suggests that DTI is highly sensitive for detecting brain alterations following a concussion, even in the absence of clinical symptoms, as evaluated using the ImPACT and SCAT2.

Other studies in which DTI was used to investigate the brain have reported either a decrease or an increase in FA following TBI.3,28 Decreases in FA have been associated with demyelination and axonal degeneration disrupting the microstructural coherence.4 As Wilde et al.50 pointed out, the studies reporting decreased FA generally included patients with more severe cases (for example, with hemorrhages) and/or cases with a rather long interval between injury and MRI scan. On the other hand, most of the studies reporting an increase in FA have included patients in the acute and subacute phase following an mTBI.18,33,50 In this context, an increase in FA has been explained in relation to the presence of an intracellular edema with consecutive restriction of diffusion in the extracellular space perpendicular to the main axis.18,25,28 However, increases in FA have been observed in the chronic phase following mTBI.18,25,30,33,34 This is in line with the results of the present study, which revealed increased FA in large parts of the brain in participants who had a history of concussion. Mayer et al.33 reported that increased FA persisted 3–5 months in some brain areas including the genu of the corpus callosum and the left internal capsule (left corona radiata) in patients with mTBI. Henry et al.18 found increased FA in the corticospinal tracts and the corpus callosum of concussed athletes in

<p>| TABLE 3: Correlation analysis between DTI measures and cognitive tests in 34 ice hockey players* |</p>
<table>
<thead>
<tr>
<th>DTI Measure</th>
<th>ImPACT Score</th>
<th>Verbal</th>
<th>Visual</th>
<th>Visual Motor</th>
<th>Reaction</th>
<th>Symptom</th>
<th>Total SCAT2 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>correlation coefficient</td>
<td>−0.10</td>
<td>−0.11</td>
<td>0.02</td>
<td>0.02</td>
<td>0.026</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.58</td>
<td>0.53</td>
<td>0.93</td>
<td>0.91</td>
<td>0.89</td>
<td>0.98</td>
</tr>
<tr>
<td>AD</td>
<td>correlation coefficient</td>
<td>0.16</td>
<td>−0.03</td>
<td>0.08</td>
<td>0.11</td>
<td>−0.052</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.36</td>
<td>0.88</td>
<td>0.65</td>
<td>0.55</td>
<td>0.77</td>
<td>0.31</td>
</tr>
<tr>
<td>RA</td>
<td>correlation coefficient</td>
<td>0.13</td>
<td>0.00</td>
<td>0.09</td>
<td>0.00</td>
<td>−0.043</td>
<td>−0.03</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.45</td>
<td>0.98</td>
<td>0.64</td>
<td>0.99</td>
<td>0.81</td>
<td>0.86</td>
</tr>
<tr>
<td>trace</td>
<td>correlation coefficient</td>
<td>0.08</td>
<td>−0.05</td>
<td>0.12</td>
<td>0.00</td>
<td>−0.057</td>
<td>−0.12</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.66</td>
<td>0.77</td>
<td>0.50</td>
<td>0.99</td>
<td>0.75</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* Correlation coefficients represent the Pearson r value, except for the symptom subscore of the ImPACT scale, where it is the Spearman rho value.
the acute (1–6 days) and chronic (6 months) phases. Lo et al.\textsuperscript{30} reported increased FA in the posterior limb of the internal capsule more than 2 years after the head trauma, although there were also areas with decreased FA. Additionally, Lipton et al.\textsuperscript{28} reported areas with increased or decreased FA in the brains of individuals following an mTBI. The number of voxels with high FA initially increased between 2 weeks and 3 months, followed by a decrease in the number of voxels with high FA at 6 months.

Although the time course of FA changes following an mTBI is not fully understood, the existing literature and our current results suggest that increased FA may persist for months or even years following an mTBI. The underlying mechanism of increased FA is, however, not clear. Nonetheless, it is noteworthy that both the increase in FA and the decrease in trace are mathematically linked to the decrease in RD, which is probably due to restriction of diffusion in the extracellular space perpendicular to the main axis. This could either be caused by axonal swelling or it could be due to more glial cells taking up the extracellular space. Histological studies have reported long-lasting neuroinflammation with persistent microglial activation in the white matter tissue of patients with a history of TBI.\textsuperscript{13,20} Increased FA has also been interpreted as neuroplastic processes of the brain responding to head trauma.\textsuperscript{28} However, the evidence for such changes remains tenuous due to the lack of direct, quantitative comparisons between DTI results and histological preparations. Finally, in the current study there was a small area localized in the left corona radiata in which we found increased FA based on an increase in AD, indicating increased diffusivity parallel to the axon. This finding is not easy to explain in the context of a history of concussion. It may reflect axonal swelling due to acute and/or subacute neuroplastic processes.

Subconcussive head blows (SHBs) may have an additional effect on our results. Koerte et al.,\textsuperscript{22} for example, found differences in white matter microstructure in soccer players without a history of concussion compared with swimmers. Additionally, Lipton et al.\textsuperscript{29} reported an association between exposure to soccer heading and both abnormal white matter microstructure and impaired memory. Furthermore, comparing pre- and postseason head scans of football and ice hockey players, Bazarian et al.\textsuperscript{3} reported increased FA and decreased mean diffusivity for the players who had SHBs in the absence of a clinically diagnosed concussion. The presence of SHBs was positively correlated with the degree of change in diffusivity, suggesting an association between white matter alterations and SHBs.\textsuperscript{3} All athletes included in this study, both concussed and nonconcussed, probably experienced frequent SHBs during the ice hockey season in the months before the MRI scan. Players with a previous concussion may be more vulnerable to the additional effect of SHBs. The increase in FA and AD may therefore not only reflect the effects of concussions in the past, but also those of recently sustained SHBs resulting in ongoing repair mechanisms.

The lack of differences in cognition evaluated using ImPACT and SCAT2 measures between the groups indicates that there might be no clinically evident symptoms, despite alterations in white matter microstructure, or that these tests are not sufficiently sensitive to detect subtle differences in cognitive performance. The latter hypothesis is supported by a study by Mayer et al.\textsuperscript{33} in which patients with a history of mTBI showed differences in DTI parameters but showed no differences in neuropsychological measures, compared with a control group. Further studies are nonetheless needed to determine whether changes in the microarchitecture of white matter in the brain in concussed players might precede symptoms and cognitive changes, or if other measures of cognitive and clinical function might be more sensitive and therefore more likely to be correlated to the observed DTI changes.

Limitations of this study include the small sample size and the lack of a control group consisting of athletes taking part in noncontact sports. A further limitation of the study is that information regarding the history of concussion before the season is based on the athlete’s self-report. Self-reports of sports-related concussion may not be reliable.\textsuperscript{21} Future studies should also include information on the frequency of SHBs. Furthermore, groupwise analysis by TBSS may not be sensitive to variable spatial location of abnormal DTI measures in heterogeneous conditions such as mTBI. Thus, future studies should include analysis of subject-specific changes such as tractography. Additionally, future studies should also include free-water corrected DTI measures. The free-water method as used by Pasternak et al. (Part 2 in this series\textsuperscript{43}) estimates the extracellular portion of diffusion. Accordingly, free-water–corrected DTI parameters provide more specific information about the brain’s tissue. Finally, subjects included in this study also underwent imaging before the start of the season. However, a gradient coil change occurred during the season and a possible bias could not be entirely ruled out, and so we refrained from comparing pre- and postseason scans in this sample.

Conclusions

The results of the current study indicate that a history of concussion may result in alterations of the brain’s white matter microstructure in ice hockey players. The increase in FA due to a decrease in RD may reflect neuroinflammatory or neuroplastic processes of the brain responding to brain trauma. Future studies are needed that include longitudinal analyses of the brain’s structure and function following a concussion, to elucidate the complex time course of DTI changes and their clinical meaning.

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