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Hockey Concussion Education Project, Part 2. Microstructural white matter alterations in acutely concussed ice hockey players: a longitudinal free-water MRI study

Clinical article

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Object. Concussion is a common injury in ice hockey and a health problem for the general population. Traumatic axonal injury has been associated with concussions (also referred to as mild traumatic brain injuries), yet the pathological course that leads from injury to recovery or to long-term sequelae is still not known. This study investigated the longitudinal course of concussion by comparing diffusion MRI (dMRI) scans of the brains of ice hockey players before and after a concussion.

Methods. The 2011–2012 Hockey Concussion Education Project followed 45 university-level ice hockey players (both male and female) during a single Canadian Interuniversity Sports season. Of these, 38 players had usable dMRI scans obtained in the preseason. During the season, 11 players suffered a concussion, and 7 of these 11 players had usable dMRI scans that were taken within 72 hours of injury. To analyze the data, the authors performed free-water imaging, which reflects an increase in specificity over other dMRI analysis methods by identifying alterations that occur in the extracellular space compared with those that occur in proximity to cellular tissue in the white matter. They used an individualized approach to identify alterations that are spatially heterogeneous, as is expected in concussions.

Results. Paired comparison of the concussed players before and after injury revealed a statistically significant ($p < 0.05$) common pattern of reduced free-water volume and reduced axial and radial diffusivities following elimination of free-water. These free-water–corrected measures are less affected by partial volumes containing extracellular water and are therefore more specific to processes that occur within the brain tissue. Fractional anisotropy was significantly increased, but this change was no longer significant following the free-water elimination.

Conclusions. Concussion during ice hockey games results in microstructural alterations that are detectable using dMRI. The alterations that the authors found suggest decreased extracellular space and decreased diffusivities in white matter tissue. This finding might be explained by swelling and/or by increased cellularity of glia cells. Even though these findings in and of themselves cannot determine whether the observed microstructural alterations are related to long-term pathology or persistent symptoms, they are important nonetheless because they establish a clearer picture of how the brain responds to concussion.
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Key Words • **concussion** • **diffusion MRI** • **free-water** • **ice hockey** • **atlas** • **traumatic brain injury**

Abbreviations used in this paper: AD = axial diffusivity; ADt = axial diffusivity corrected for free-water; dMRI = diffusion MRI; DTI = diffusion tensor imaging; FA = fractional anisotropy; FAt = FA corrected for free-water; HCEP = Hockey Concussion Education Project; JHU-ICBM = Johns Hopkins University–International Consortium for Brain Mapping; RD = radial diffusivity; RDt = RD corrected for free-water; ROI = region of interest; TBI = traumatic brain injury; TBSS = tract-based spatial statistics.

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Concussion is a subset of traumatic brain injury (TBI),[7,23] sometimes referred to as mild TBI, and is reported in more than 1.4 million individuals in the US every year.[12] The incidence of concussion is likely much higher, as not all those who sustain a concussion

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

either recognize the injury or seek medical help.[11] Current treatment of concussion primarily involves physical and cognitive rest appropriate for resolution of concussion symptoms.[23] These symptoms include somatic (for example, headache), cognitive (for example, feeling like in a fog), and/or emotional (for example, lability) symptoms. They may also be accompanied by physical signs such as amnesia, behavioral changes (for example, irritability), cognitive impairment, and sleep disturbance.[7,23] Most concussed individuals recover within a few days or weeks, but for a minority (15%–30%) the symptoms persist.[23,33] Evidence suggests that traumatic axonal injury is the main short-term process that occurs following concussions, making white matter a primary area in the search for acute abnormalities.[35] Nevertheless, little is known about the pathophysiology that follows traumatic axonal injury.

Common causes of concussion are vehicle accidents, falls, assault, exposure to explosions, and sports-related injuries.[21] Some sports involve more physical contact and thus are associated with a higher risk of sustaining a concussion than is found in the general population. Ice hockey players are among those at the highest risk for sustaining concussion during a game or practice,[41] despite their use of protective devices such as helmets and mouth guards.

Identification of a possible sports-related concussion is based upon an observed or self-reported blow to the head or body and on immediate or delayed neurological signs and symptoms. For example, a player may be unstable, lack coordination, or be slow to return to play and may report headache, dizziness, or alteration of vision.[11] Current clinical concussion diagnosis and management protocols include a significant component that depends on the athlete's self-report of symptomatology.[13,23] Establishing the diagnosis of a sports-related concussion is complicated by the fact that athletes may not recognize, or may purposefully fail to admit to, concussion symptoms. Purposeful nonreporting occurs because the players are anxious to return to play and are fearful of being restricted from play during the recommended period of rest.[10]

The nonreported and medically nonevaluated possible concussions are probably not in the best interest of players, as recent evidence suggests that repeated concussions and even subconcussive blows, especially if in close temporal proximity to each other, may lead to longer-term disabilities such as chronic traumatic encephalopathy. The latter involves persistent, long-term neurodegeneration, similar to Alzheimer's disease, in addition to psychiatric problems.[24,42]

Imaging modalities could potentially provide more accurate diagnosis of concussion, which could lead to a better prognosis and to objective measures that might help physicians in deciding whether a player is fit to return to play or whether a concussed individual is fit to return to his or her daily routines. Of note here is that conventional imaging modalities such as CT and anatomical MRI often show no evidence of pathology in cases of mild TBI because the pathology appears to be subtle.[40] Recent advances in diffusion MRI (dMRI), an imaging modality that is sensitive to microstructural alterations, have, however, shown that white matter alterations can be detected following a concussion or a mild TBI.[35] The vast majority of the published dMRI studies tend to include subjects only after they have sustained an injury. Such studies are cross-sectional in nature, involving comparisons of injured individuals with healthy controls. In the current study, we take advantage of the fact that ice hockey players have a high likelihood of sustaining a concussion during an ice hockey season. Accordingly, we compared brain scans obtained before the beginning of the season to brain scans obtained within 72 hours of concussion. This study was performed as part of the 2011–2012 Hockey Concussion Education Project (HCEP), and the data sets presented here are a subset of the data acquired in this study.

We used dMRI to identify microstructural alterations that occur following concussion. To increase further the sensitivity of dMRI, we applied a recently developed free-water imaging method[29] that enhances the popular diffusion tensor imaging (DTI) method.[2,3] The DTI method summarizes all microstructural information that appears within an image voxel into a single diffusion tensor, deriving scalar parameters to quantify specific features that are related to the shape of the obtained tensor.[31] These include axial diffusivity (AD), which measures the diffusion along white matter fibers; radial diffusivity (RD), which measures the diffusion perpendicular to the white matter fibers; and fractional anisotropy (FA), which measures the variability of diffusion along all directions and is high when the tensor is elongated (that is, AD >> RD) and low when the tensor is round (that is, RD and AD are similar). Changes in these measures are associated with pathologies such as axonal degeneration, axonal swelling, and inflammation.[1,38] The free-water imaging model enhances DTI by adding a compartment that models freely diffusing water molecules that can be found in CSF or in large enough extracellular spaces in the brain tissue.[29,30] The advantage of using the free-water imaging model rather than DTI is that it provides a separate estimation of a free-water map, which is proportional to the extracellular volume. In addition, the method estimates free-water–corrected DTI measures that are affected by water molecules in proximity to cellular membranes and are therefore more specific to changes that occur in the tissue itself.[25,30]

In addition to the free-water imaging method, we also applied a recently proposed statistical analysis method that compares scans of individual subjects to an atlas.[9,18] This approach provides a way of quantifying similar alterations that occur within a group of subjects (for example, concussed players) without assuming that all alterations share the same location in the brain. This is important for studying concussion because we expect that alterations will depend on the location, direction, and strength of impact to the head,[32] which in ice hockey are likely different from individual to individual.

Methods

Subjects

The HCEP study included 45 ice hockey players (25 males and 20 females).[11] In the present report we included 38 of those players (21 males and 17 females) for whom usable dMRI scans were available. All 38 players were between 17 and 26 years of age. The clinical data for this

study have been described in detail in a previous publication.[11] The study protocol was approved by the ethics committees within the universities at which the Canadian Interuniversity Sports teams were based. All participants provided written informed consent prior to the beginning of the study. Participants underwent assessment shortly before the start of the Canadian Interuniversity Sports ice hockey season (2011–2012). The assessment included neuropsychological evaluation and an MRI session that included dMRI. The HCEP study followed the players throughout the season, and whenever one of the players experienced a concussion, he or she was evaluated and MRI was repeated within 72 hours of the injury.

Eleven HCEP players experienced a concussion during the Canadian Interuniversity Sports ice hockey season. Concussion was clinically diagnosed using an observed or self-reported mechanism. A full report of the diagnosed concussions was provided in a previous publication.[11] Of the 11 concussed players, 7 completed and had a usable dMRI scan within 72 hours of injury. The individuals included in this study were also evaluated and scanned again at a number of follow-up time points. However, a gradient coil change occurred during the season, and because a possible bias could not be entirely ruled out, we therefore chose to compare only scans that were taken before the gradient coil replacement—that is, the preseason scans and the 72-hour postconcussion scans. On average, the 7 concussed players suffered a concussion 63 days following the preseason assessment (range 19–137 days). This meant that there was a range of different times between the first and second assessments, and we used this value to check whether our findings depended on how much time had elapsed between evaluations.

Imaging

All individuals underwent imaging in the same 3-T MRI scanner (Achieva, Philips). An 8-channel head coil was used in an MRI protocol that included a dMRI scan with the following parameters: 60 noncolinear diffusion directions with b-value = 700 sec/mm^2 and one baseline image with b = 0, TR = 7015 msec, TE = 60 msec, and 70 slices with 2.2-mm slice thickness. The acquired matrix size was 100 × 100 reconstructed into 112 × 112 with 2 × 2–mm^2 in-plane resolution. The dMRI sequence was repeated twice and averaged.

Image Processing

The diffusion-weighted images were corrected for motion and artifacts using affine registration with the baseline volume (FLIRT; Functional MRI of the Brain [FMRIB] Software Library [FSL]). Diffusion gradients were compensated for rotations. A relative-motion parameter was estimated from the transformation matrices.[20] The images were masked to exclude non-brain areas by manually annotating a label map that was initialized using Otsu's method as implemented in the 3D Slicer software (www.slicer.org). The DTI model[3] was fitted using in-house software based on a linear least square, with an added procedure to correct tensors with negative eigenvalues.[9] Fractional anisotropy (Fig. 1) maps were calculated for each voxel using 3D Slicer.

Free-water maps and free-water–corrected DTI indices were calculated by fitting the free-water model in each voxel.[29,30] The model includes 2 compartments: a free-water compartment and a tissue compartment. The free-water compartment models isotropic diffusion with a diffusion coefficient fixed to diffusivity of water in body temperature (3×10^{-3} mm^2/sec). The estimated volume fraction of the free-water compartment is mapped to provide a free-water map (Fig. 1), which is proportional to the volume of the extracellular space.[30,43] The signal of the tissue compartment originates from all other water molecules, which include all of the intracellular molecules and some extracellular molecules that are in proximity to cellular restrictions. The tissue compartment was fitted to a diffusion tensor, and DTI indices were extracted (using 3D Slicer) to provide maps of FA corrected for free-water (FAt; see Fig. 1 for a comparison with FA), as well as RD corrected for free-water (RDt) and axial diffusivity corrected for free-water (ADt). These corrected measures are less affected by partial volume effects with CSF in the extracellular space and are therefore more specific than the DTI measures to processes that occur within the brain tissue.[25,30] The free-water imaging model was fitted using a regularized minimization process with a euclidean distance between tensors.[28,30]

In this study we restricted the analysis to the skeleton of the white matter, which was reconstructed from the FA maps of all players using tract-based spatial statistics (TBSS) software.[36] Following the construction of the skeleton, we projected all other diffusivity measures (that is, free-water, FAt, ADt, and RDt) onto the skeleton.

Statistical Analysis

Voxel-based group comparisons between the scans of each concussed player at baseline (preseason) and within 72 hours of sustaining a concussion were conducted using a nonparametric, permutations-based paired test[27] with threshold-free cluster enhancement[37] and 5000 permutations for each contrast; $p < 0.05$ (corrected for multiple comparisons) was considered statistically significant. The test was linearly adjusted for motion, age, and sex, all of which were included as covariates.

To perform region of interest (ROI)–based group comparisons, we used the JHU-ICBM (Johns Hopkins University–International Consortium for Brain Mapping) white matter labels,[26] which define 48 white matter anatomical ROIs in the same space as the white matter skeleton. For each ROI, we averaged all of the skeleton voxels that fall within that ROI. To compare the groups we used a paired t-test adjusted for motion and corrected using the false discovery rate[5] for multiple comparisons (across the number of ROIs). A similar test was run for the whole brain, where instead of the ROIs we used the average over the entire skeleton. The ROI-based tests were performed for each diffusivity measure (FA, free-water, FAt, ADt, and RDt) separately. A value of $p < 0.05$ (corrected for multiple comparisons) was considered statistically significant.

Since it is likely in concussions that the location of the abnormalities depends on the location, strength, and type of impact, which varies from person to person,[32] we also analyzed the data by individually comparing each

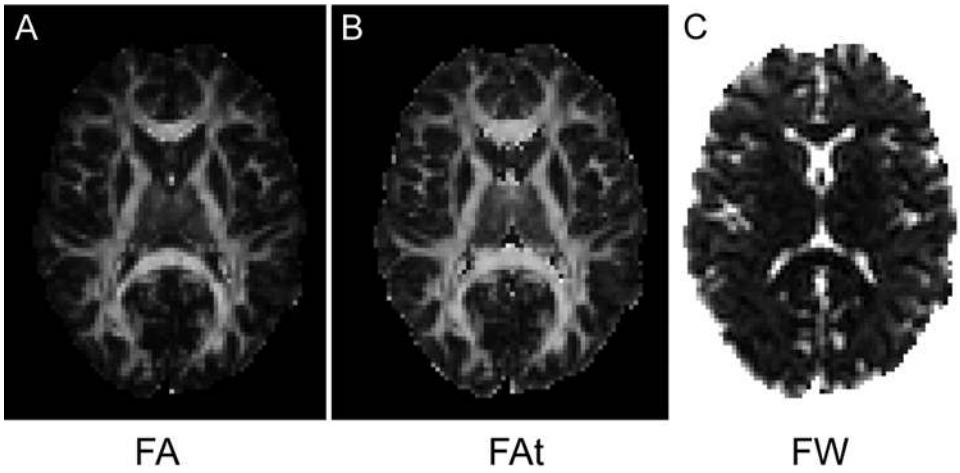

Fig. 1. Diffusion MRI contrasts. **A:** Fractional anisotropy is a contrast sensitive to elongated shapes, such as those found in myelinated axons. It provides a clear contrast between white matter and gray matter. **B:** Using the free-water imaging method provides an FAt map, which is an FA map that is corrected for CSF and free-water contaminations. The FAt map provides a similar contrast to the FA map, except that it is brighter in areas next to the ventricles and around the brain parenchyma, where partial volume with CSF occurs. **C:** The free-water measure (labeled as FW) provides a contrast that measures the fractional volume of free-water, which is expected to be high in CSF-filled spaces and low (but not necessarily 0) in areas of condensed white matter fibers.

scan of the concussed players (either preseason or postconcussion) with an atlas that represented the preseason scans of the remaining 31 players. To construct the atlas and to compare scans of individual concussed players to the altas, we used methods similar to those described by Bouix et al.[9] In short, the atlas captures the distribution of the dMRI indices (FA, free-water, FAt, ADt, and RDt), corrected for age, sex, and motion, across the 31 preseason scans. The distribution is represented by the sample mean and standard deviation over the population. A subject-specific profile for the concussed players, at preseason and postconcussion, was generated by calculating a z-score for each dMRI index against the corresponding normal distribution, as represented by the preseason atlas. Unlike the ROI-based atlas reported on by Bouix et al.,[9] here we were interested in the white matter skeleton. Therefore the atlas was defined on each voxel in the white matter skeleton (see above).

To quantify the deviation of a specific scan from the atlas, we defined an extent measure as the number of voxels that had z-score values more extreme than a given threshold.[9,18] We used Bonferroni correction to select a threshold of $z > 4.58$ (equivalent to $p < 0.05$ corrected for 3.5×10^{-4} voxels on the white matter skeleton).[9] As a result, we obtained a separate extent value for increased measures ($z > 4.58$) and for decreased measures ($z < 4.58$). To evaluate whether the concussed players as a group showed consistent brain alterations following concussion, we ran a paired t-test on the extent measures (both positive and negative) of the preseason scan versus the extent measure of the postconcussion scan. A value of $p < 0.05$ was considered statistically significant.

Results

Conventional Group Analysis

Voxel-based (TBSS), ROI-based (JHU-ICBM) and whole-brain paired group comparisons were performed for each diffusivity measure (FA, FAt, free-water, ADt, and RDt). None of the conventional group analysis methods yielded a statistically significant ($p < 0.05$ corrected for multiple comparisons) difference between the preseason scans and the postconcussion scans for any of the diffusivity measures.

Atlas-Based Analysis

The atlas-based analysis individually compared each concussed player (both before and after the concussion) with an atlas composed of the group of all players at preseason. The result is a distribution of z-scores for each player that can then be compared across the groups. Figure 2 shows the preseason and postconcussion average z-score distributions of the studied diffusion measures for the 7 concussed players. Visually inspecting these distributions shows that within the range of z-scores close to 0 (that is, where values are similar to the atlas) the average preseason z-score distribution (*blue line*, Fig. 2) is always higher than the average postconcussion z-score distribution (*red line*, Fig. 2). This means that, on average, the concussed players were more similar to the atlas before the beginning of the season than they were after sustaining a concussion. Complementing this, but visually harder to appreciate, the tail of most average postconcussion z-score distributions is heavier (has more voxels) than that of the average preseason z-score distribution, suggesting that there are more abnormal locations (relative to the atlas) following concussion.

To evaluate quantitatively the differences between the distributions, we performed a matched group comparison of the extent measures obtained for the 7 concussed players before (preseason) and after (within 72 hours of) the concussion. This comparison revealed the following statistically significant changes following concussion (Fig. 3): increased FA ($t = 2.57$; $p = 0.0213$), decreased free-water ($t = 2.70$; $p = 0.018$), decreased ADt ($t = 2.01$; $p =$

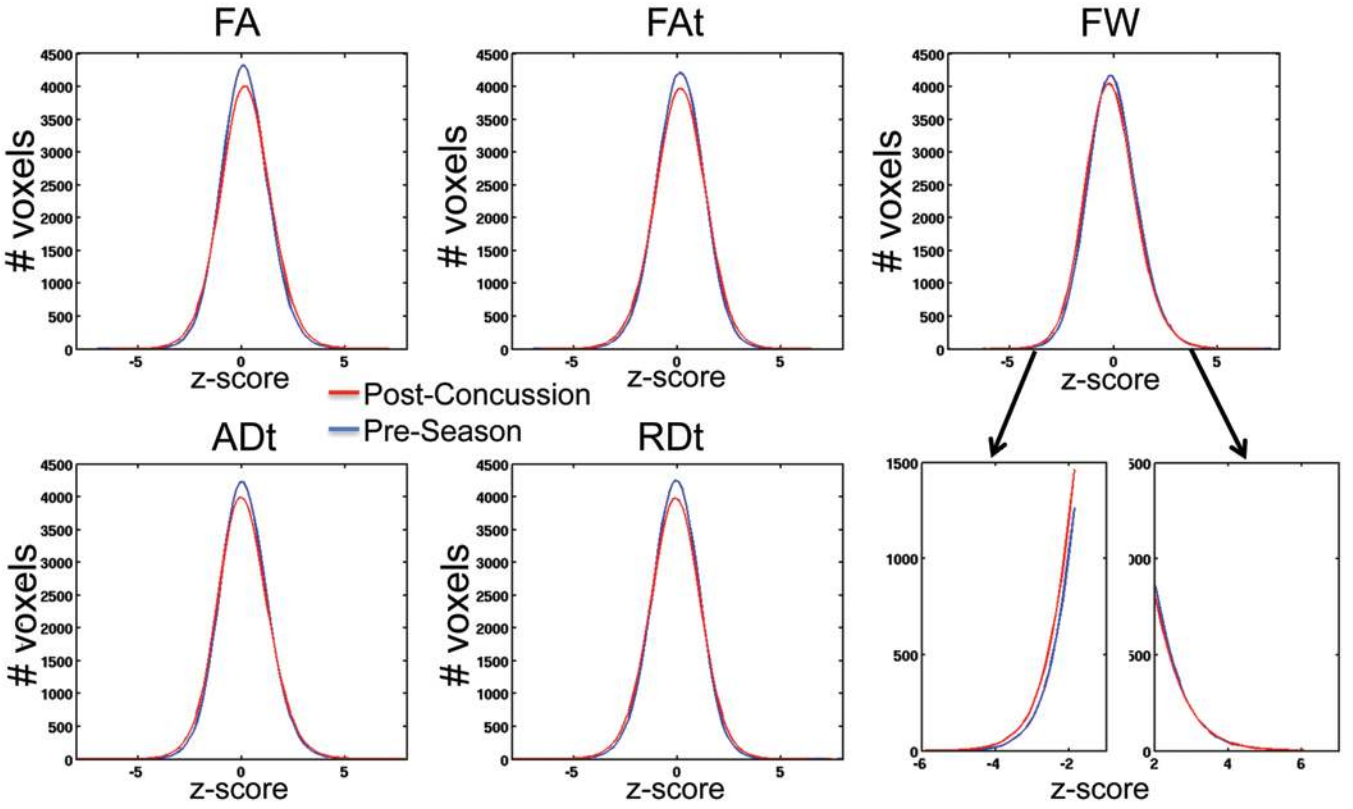

Fig. 2. Distribution of z-scores. Graphs show the average distribution of z-scores in 7 concussed players before the concussion (preseason, *blue*) and after the concussion *(red)*. Following the concussion, the distribution is lower around the 0 and has heavier tails (for example, see enlargements of the negative tail of the free-water z-score distribution), which means that the brains differ more from the atlas following a concussion.

0.046), and decreased RDt (t = 3.16; p = 0.009). Increases or decreases in FAt were not significant (t = 1.42, p = 0.102 [increased FAt]; t = 0.47, p = 0.327 [decreased FAt]). None of the extent measures correlated with the number of days between the first and second assessments.

Figure 4 presents the individual change in the extent measures of increased FA and increased FAt. The increased FA extent was much higher postconcussion than preseason, yet following the free-water correction most players did not show large changes in the extent of increased FAt following concussion. Figure 5 shows, for each individual, the changes in the extent measure of decreased ADt, decreased RDt, and decreased free-water—the 3 measures that had a significant change following concussion. These plots show that, for most of the players, the extent measure increased following a concussion. However, the amount of changes in the extent measure varied among players, with a small number of players

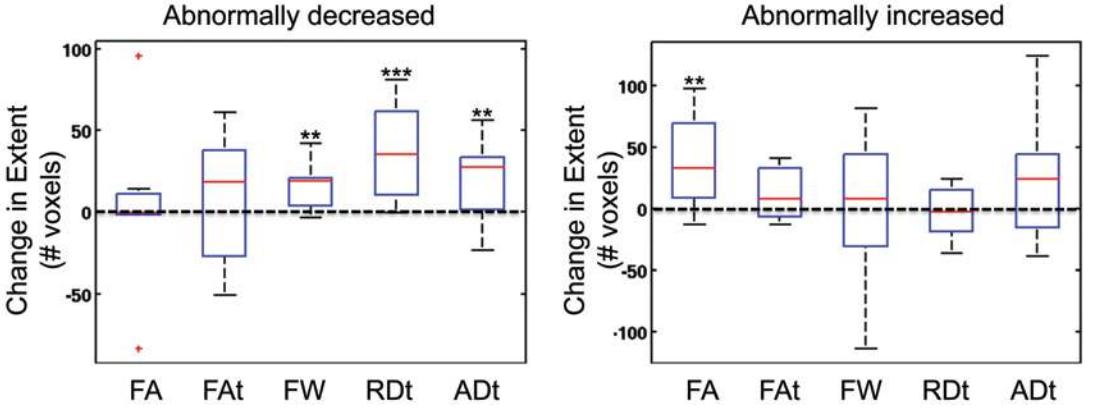

Fig. 3. Comparison of extent measures. Comparing the extent measure before and after a concussion shows that there were more abnormally decreased free-water, RDt, and ADt voxels after a concussion than before a concussion. In addition, there were more abnormally increased FA voxels following the concussion, although following a free-water correction the FAt measure was not significantly increased. **p < 0.05; ***p < 0.01.

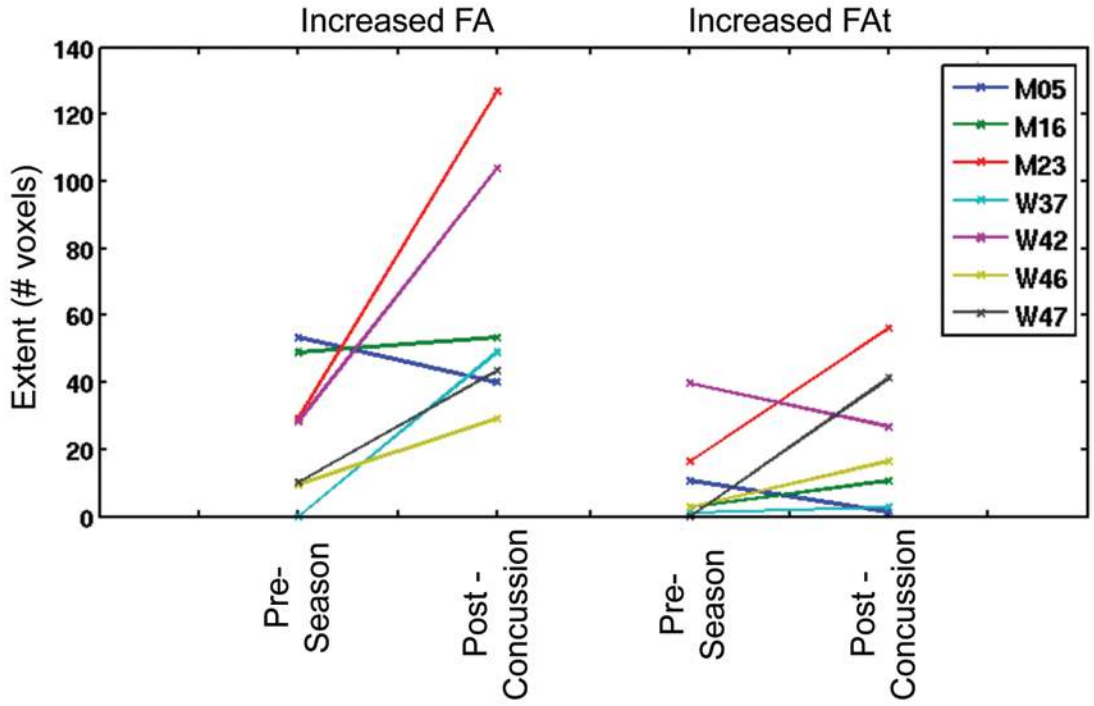

Fig. 4. Comparison of extent measures. Comparing the extent measure before and after a concussion shows that there were more voxels with abnormally decreased free-water measure, RDt, and ADt after a concussion than before a concussion. In addition, there were more voxels with abnormally increased FA following the concussion, although following a free-water correction the FAt measure was not significantly increased. Alphanumeric code represents each of the 7 players, where M is man and W is woman. **p < 0.05; ***p < 0.01.

who had a decrease in the extent measure following concussion.

Discussion

Of the 11 players who suffered a concussion during the study period, 7 had MRI scans that were appropriate for diffusion analysis at both baseline and within 72 hours postconcussion. Despite the loss of the other 4 players who suffered a concussion, we were still able to identify shared white matter microstructural alterations that occurred following a concussion. The alterations were not revealed in a standard, location-dependent group analysis, suggesting that there was not a common brain area that underwent similar changes across the players or that there was not sufficient statistical power to identify such an area. On the other hand, we found significant alterations when using an atlas-based approach, which compares distributions over

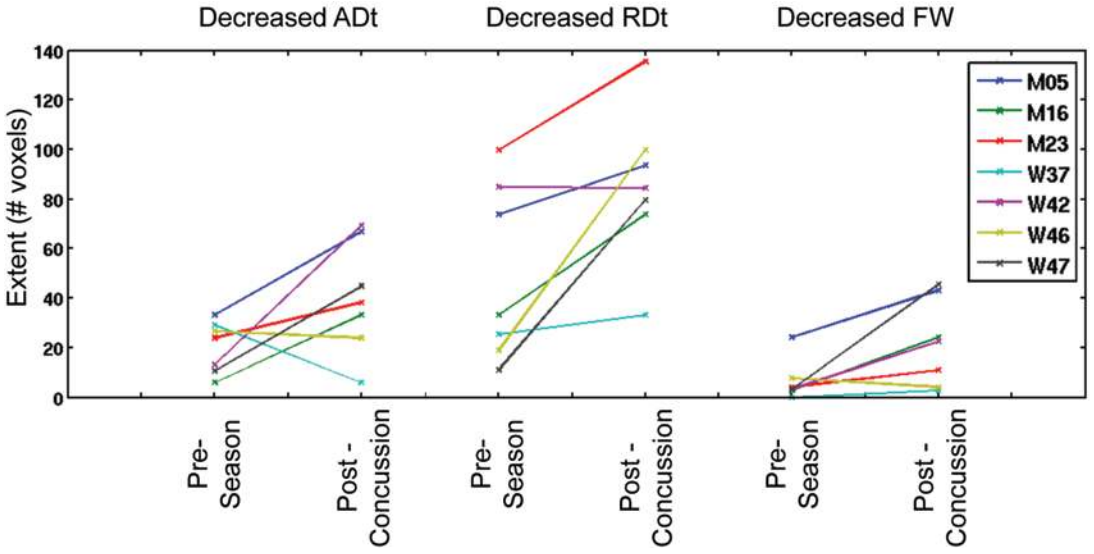

Fig. 5. Individual differences in ADt, RDt, and the free-water measure. The decreases in the extent of decreased ADt, RDt, and free-water were consistent in the 7 concussed players. The degree of change varied across the players.

the entire white matter skeleton. These consistent alterations across the group of concussed players suggest that similar microstructural changes occurred, yet probably not in the same brain location. This is not surprising since brain injury is heterogeneous, and population-based studies may not find group differences because such differences are less detectable when variability within the group increases.[9,17,32] Importantly, individual-based analyses focus on the individual profile of injury, and this information can then be used to make group comparisons, as we have done here.

Fractional anisotropy is currently the most studied DTI-derived parameter in concussion and other TBI studies.[35] Many studies have reported a decrease in FA associated with dysfunctions following injury.[16,35] Nevertheless, increased FA is often reported as an additional finding,[16,35] especially in the acute stages following injury. In our results, we observed increased FA, but we did not find decreased FA. It is not yet clear what the pathological sources are that lead to increased FA; however, swelling or cytotoxic edema have been suggested as the main causes of increased FA,[4,22] especially in the acute stage. Using free-water imaging, we were able to provide additional information regarding the possible source of the increased FA. We found that the free-water measure, which is sensitive to changes in the extracellular space, was reduced following concussion, suggesting that the volume of the extracellular space was reduced. Following free-water elimination, the postconcussion FAt measure was no longer significantly increased. This finding suggests that the extracellular differences account for the anisotropy changes that are evident in the FA measure.

Using free-water elimination and comparing tensor indices obtained from the tissue compartment, we identified alterations in the tissue vicinity affecting RDt and ADt. Both measures were decreased following concussion in the subjects studied. As with most imaging studies, it was not possible to determine, based on imaging alone, the exact pathology that occurred. However, we were able to identify that changes did occur, and these changes could be used to guide future studies, which will likely better characterize the acute pathological changes identified here.

The decrease in RDt and the decrease in the free-water measure could be explained by axonal swelling.[4] However, it is less likely to explain the decrease in ADt because the geometry along the fibers should not necessarily change in swelling. On the other hand, decreased ADt and a decrease in the free-water measure could be due to an increased number of glial cells. The increase in glial cells is likely to be part of a neuroinflammatory response[43] common in the acute and subacute stages following concussion,[6] where the glial cells swell and migrate to injured areas.[15,39] An increase in the number and size of glial cells would decrease the extracellular volume (that is, decreased free-water measure) and would decrease axial diffusivity, since the diffusivity within glial cells is more restricted than the diffusivity along the axons. However, such a change in glial cells is not expected to change the radial diffusivity. We therefore suggest that the ADt, RDt, and free-water changes that we observed might be connected to both processes: swelling and increased cellularity. These processes could happen at the same place or separately in different brain locations. We note that both swelling and increased cellularity might be a normal response of the immune system,[8,39] and further studies would be required to determine whether these changes lead to long-term symptoms or not.

The construction of the atlas provides a new way to identify characteristic alterations that are associated with brain disorder, even if the abnormalities are not co-localized. Here, we used the extent measure to quantify deviations from the atlas,[9,18] and using the measure we demonstrated statistically significant alterations that occur following a concussion. However, the extent measure compares the tails of the distributions (that is, the extreme values), and it is possible that other measures that quantify other aspects of the z-score distributions could add additional insights and identify further alterations that occur in the brain following injury.

Typically, an atlas is built with a group of healthy controls.[9,18] In our study, however, we used scans obtained in hockey players before the beginning of the season to construct the atlas. These hockey players may already have had brain pathology related to concussive or subconcussive blows sustained before the beginning of the study. This might explain the absence of decreased FA/FAt findings, as well as the reduction in the extent measure that was evinced in a small number of players following concussion. On the other hand, the ability to follow each player longitudinally instead of comparing the subjects cross-sectionally adds more validity to the findings and to their association with concussion. We note that this study is one of the first studies to apply the atlas tool in a longitudinal design. We relate the longitudinal changes that we found here to concussion. However, as in all longitudinal studies, these changes could also be attributed to other time-dependent changes that consistently affect all subjects. These could include hardware changes, although we made sure that there were no hardware or software changes within the period of the reported data. It could also include consistent changes that happened to the subjects, such as normal aging, but we did not find the extent measure to correlate with the time that passed between scans. In future studies our findings should be further verified by comparing concussed players with a matching longitudinal acquisition of controls or nonconcussed players. Such controls were not available for the current study.

The use of the atlas, the longitudinal design, and free-water imaging was designed to increase the specificity of subtle brain alterations. However, the relatively small number of players who sustained a concussion may limit the statistical power and hence the sensitivity of the method in detecting brain changes. Nevertheless, the present study, as well as previous and additional studies in this collection, demonstrates clear evidence of microstructural and hemodynamic alterations that occur following concussion.[14,19,34] It is our hope that these studies will help increase the awareness of the possible results of concussions and in this way act as an enticement for future participation in similar studies. We expect that with a larger sample the methods described here may identify

additional microstructural alterations that occur following a concussion.

Conclusions

We present results that demonstrate acute microstructural changes in the brains of ice hockey players following a concussion. These findings support the hypothesis that concussion introduces organic changes to the brain, which could then evolve into long-term pathologies or be resolved. Neuroinflammation is likely involved in either scenario, and dMRI acquisition, complemented by free-water imaging and the atlas tool used in the present study, provides an opportunity to follow the evolution of neuroinflammation and other possible alterations that occur due to concussions. Taken together with other reports in this collection of studies, there is converging evidence to suggest that the alterations we observed may or may not persist, with those that do persist leading possibly to other types of brain changes that can be detected in later stages following the concussion.[19,34] This collective information may lead to a better understanding of the pathophysiology of concussion, which could help with informed decisions in the management of sports-related and other types of concussions.

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