Diffusion Tensor Imaging of Sports-Related Concussion in Adolescents

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ABSTRACT

Concussion is among the least understood neurologic injuries. The impact of concussion on the adolescent brain remains largely unknown. This study sought to establish short-term changes in white-matter integrity after sports-related concussion in adolescents, and examine the association between changes in white-matter integrity and a clinical measure of concussion. Twelve adolescents, aged 14-17 years with a sports-related concussion within 2 months, and 10 age-matched adolescents with no history of concussion were evaluated with the Sports Concussion Assessment Tool 2 and diffusion tensor imaging. Two measures compared the two groups: fractional anisotropy and mean diffusivity. Whole-brain fractional anisotropy values significantly increased ($F(1,40) = 6.29, P = 0.010$), and mean diffusivity values decreased ($F(1,40) = 4.75, P = 0.036$), in concussed athletes compared with control participants. Total scores on the Sports Concussion Assessment Tool 2 were associated with whole-brain fractional anisotropy. Mean diffusivity values with lower scores were associated with higher fractional anisotropy ($R^2 = 0.25, P = 0.017$) and lower mean diffusivity ($R^2 = 0.20, P = 0.038$). We provide evidence of structural changes in the integrity of white matter in adolescent athletes after sports-related concussion.

Introduction

An estimated 173,285 sports-related and recreation-related traumatic brain injuries in children and adolescents are treated in emergency rooms in the United States annually [1]. These data likely underestimate the actual number of injuries, because many are not reported or are treated outside the emergency room, making traumatic brain injuries a significant public health issue. In Canada, an estimated 98,440 people (2.4% of the population aged at least 12 years) sustained an injury between 2009 and 2010. Of those, 23% ($n = 22,720$) were adolescents [2].

The risk of concussion in youth is of particular concern because the brain is still developing throughout adolescence and may be more susceptible to hypoxia, ischemia, and traumatic axonal injury [3,4]. Although physical features resolve within 2-10 days in the majority of adults who sustain a single concussion [5-7], school-aged children demonstrate postconcussive features for a longer period. Barlow et al. [8] reported that 3 months after injury, 14% of children aged more than 6 years remained symptomatic. The frontal and temporal lobes appear most vulnerable to injury, and damage to these areas is associated with impairments of executive function, learning, and memory, along with behavioral disturbances [9-11]. Impairments in executive functioning during the adolescent phase of development may involve long-term implications for quality of life and future developmental processes. However, associations between behavioral sequelae and underlying structural brain changes after concussion have been difficult to establish.

Growing interest has developed in the use of newer imaging technologies, such as diffusion tensor imaging, which is particularly sensitive to changes in the
Concussion Assessment Tool 2) was examined. Importantly, diffusion tensor imaging detects subtle reductions in white matter integrity that correlate with function [13]. This study sought to investigate structural changes in the brains of adolescents who had sustained a sports-related concussion within a 2-month period, using diffusion tensor imaging, compared with age-matched control subjects with no history of concussion. In addition, the association between specific diffusion tensor imaging measures and a clinical assessment tool (Sports Concussion Assessment Tool 2) was examined.

Methods

Participants

Ten healthy, physically active adolescents with no previous history of concussion and 12 adolescents who had experienced a sports-related concussion within the past 2 months (in ice hockey, rugby, or baseball) were recruited (see Table 1 for participants’ demographics). Adolescents with other focal neurologic deficits and pathology and those receiving prescription medications for neurologic or psychiatric conditions were excluded. Recruitment for control adolescents and ice hockey players was administered through British Columbia Hockey. Parents signed an informed consent form that was approved by the Clinical Research Ethics Board of the University of British Columbia. All participants also provided assent.

Sports Concussion Assessment Tool 2

Trained examiners tested all participants via the Sports Concussion Assessment Tool 2 [7]. The Sports Concussion Assessment Tool 2 is used for sideline and clinical assessment of concussion by determining (number of symptoms and severity of symptoms), physical signs regarding loss of consciousness or balance problems, the Maddock score (assessment of orientation), the Standardized Assessment of Concussion (orientation, immediate memory, concentration, and delayed recall), a modified Balance Error Scoring System, and a coordination examination (finger-to-nose). The maximum score for the Sports Concussion Assessment Tool 2 is 100.

Magnetic resonance imaging scanning protocol

Whole-brain, high-angular resolution diffusion imaging was performed at the University of British Columbia 3T Research Facility on a Philips Achieva 3.0 T magnetic resonance imaging scanner (Phillips Healthcare, Andover, MD), using an eight-channel sensitivity encoding head coil and parallel imaging. Participants first underwent a high-resolution anatomic scan (TR/TE = 12.4/5.4 ms, flip angle θ = 8°, FOV = 256 mm, 170 slices, 1-mm thickness). Two diffusion-weighted scans were performed with a single-shot echoplanar imaging sequence (TR/TE = 7465/75 ms, FOV = 212 × 212 mm, 60 slices, voxel dimension = 2.2 mm³, scan time = 7 minutes/scan). Diffusion weighting was performed across 60 different noncollinear orientations (b = 700 seconds/mm²), with 10 minimally weighted diffusion images acquired (b = 0). The scanning time totaled 45 minutes for each participant.

The software package ExploreDTI [14] was used for diffusion imaging data preprocessing and analysis. Initially, the data were corrected for subject motion and eddy current-induced geometric distortions, using a weighted linear tensor estimation approach, and were rigidly transformed to standard Montreal Neurologic Institute space. Whole-brain tractography was then performed, using a deterministic streamline approach. The fractional anisotropy thresholds for initiating and continuing tracking were set to 0.2, and the tract-turning angle threshold was set to 30 degrees. Fiber tract pathways of interest for each hemisphere were then extracted individually, using standard atlas labels [15-17]. Whole-brain hemispheric tract reconstruction was chosen a priori, based on the theorized diffuse nature of the effects of concussion on the brain. Fractional anisotropy involves

Table 1. Subject demographics

<table>
<thead>
<tr>
<th>Subject Identification Code</th>
<th>Sex</th>
<th>Age</th>
<th>Total score on SCAT2</th>
<th>Number of Concussions</th>
<th>Time After Concussion</th>
<th>Whole-Brain Fractional Anisotropy</th>
<th>Average Mean Diffusivity</th>
</tr>
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Abbreviations:

F = Female
M = Male
SCAT2 = Sports Concussion Assessment Tool 2
a scalar value commonly used to quantify the directionality and magnitude of water diffusion, and can range from zero to one. Multiple structural features of white matter influence fractional anisotropy, including axonal membrane status, myelin sheath thickness, number of intracellular neurofilaments and microtubules, and axonal packing density [18]. Mean diffusivity constitutes an index of the rate of diffusion averaged over all directions. Mean fractional anisotropy and mean diffusivity comprised the primary diffusion tensor imaging-derived measures used to quantify white-matter microstructure status.

Data analysis

All data analyses were blinded with respect to participants’ characteristics. Differences between groups in Sports Concussion Assessment Tool 2 scores were examined using an independent-samples t test (two-tailed significance, $P < 0.05$). Two-way group (concussion vs control) by hemisphere (right vs left) multivariate analyses of variance were performed to assess differences in whole-brain fractional anisotropy and mean diffusivity (critical $\alpha$-level, $P = 0.05$). Linear regression analyses were performed to assess associations between measures of whole-brain white matter integrity (fractional anisotropy and mean diffusivity) and Sports Concussion Assessment Tool 2 scores. We assessed the data for outliers (>3 standard deviations from the mean), normality, linearity, and homoscedasticity, to meet the assumptions for linear regression analysis. No outliers were identified according to these standard criteria.

Results

Sports Concussion Assessment Tool 2 testing

Table 1 lists the demographics and scores on the Sports Concussion Assessment Tool 2 for each group. Although a trend toward a difference between groups was observed, that difference did not achieve statistical significance ($t(20) = 1.60, P = 0.126$).

Diffusion tensor imaging-derived measures of white matter tract integrity

White matter integrity was significantly different between groups (Wilks $\lambda = 0.847, F(2,39) = 3.53, P = 0.039$). Significantly increased whole-brain fractional anisotropy values (difference, 0.011; 95% confidence interval, 0.020-0.004; $F(1,40) = 6.29; P = 0.010$) and decreased mean diffusivity values (difference, $1.81 \times 10^{-2}$; 95% confidence interval, $3.43 \times 10^{-7}$ to $3.59 \times 10^{-7}$; $F(1,40) = 4.75; P = 0.036$) were observed in the concussion group compared with the control group (Fig 1). Differences in whole-brain fractional anisotropy for a representative participant from each group are depicted in Fig 2. A main effect of hemisphere was demonstrated ($Wilks\: \lambda = 0.787, F(2,39) = 5.29, P = 0.009$), but a significant group by hemisphere interaction effect was not observed ($P = 0.721$).

Association between Sports Concussion Assessment Tool 2 and white matter integrity

Sports Concussion Assessment Tool 2 was a significant predictor of variance in whole-brain fractional anisotropy ($R^2 = 0.25, \beta = -0.50, P = 0.017$) and mean diffusivity ($R^2 = 0.20, \beta = 0.45, P = 0.038$) where lower Sports Concussion Assessment Tool 2 scores were associated with higher fractional anisotropy and lower mean diffusivity values, respectively, across participants (Figs 3 and 4). For every unit increase in the total Sports Concussion Assessment Tool 2 score, whole-brain fractional anisotropy decreased by 0.00093 units (95% confidence interval, −0.00167 to −0.000185). For every unit increase in the total Sports Concussion Assessment Tool 2 score, mean diffusivity increased by 0.000017 units (95% confidence interval, 0.0000001-0.0000032).

Discussion

We observed significantly higher whole-brain fractional anisotropy values and lower whole-brain mean diffusivity values in concussed adolescents, compared with healthy, active, nonconcussed adolescents. Importantly, the Sports Concussion Assessment Tool 2 was a significant predictor of whole-brain fractional anisotropy values. To our knowledge, these preliminary data reveal for the first time that sports-related concussion in adolescents is associated with widespread changes in white matter microstructure integrity up to 2 months after injury, and that specific diffusion tensor imaging measures are associated with scores on the Sports Concussion Assessment Tool 2.

The Sports Concussion Assessment Tool 2 score for the control group in our study averaged 89 out of a possible 100. The same average score was reported by Jinguji et al. [19] in a group of high school athletes aged 13-19 years and with no previous concussions. The score in our group

![Figure 1](image-url)
of concussed athletes averaged 84. Although the difference between the control and concussed group scores was not statistically significant, the lower scores may indicate changes in features and function after a concussion.

Concussion induces very subtle changes in the brain that have been difficult to study. The heterogeneity of the location and severity of injury, the stage of recovery, and variability in experimental procedures and analyses have led to apparent discrepancies in reported diffusion abnormalities in the concussion literature. For example, Maugans et al. [20] reported no significant differences in any diffusion tensor imaging-related measures, using a region of interest approach. Other studies reported evidence of damage to the white matter tracts, and have been associated with both increases [21] and decreases [22,23] in fractional anisotropy values. Our results are in agreement with recent work demonstrating higher fractional anisotropy values after concussions in adolescents with mild traumatic brain injury [24-26] and adults with mild traumatic brain injury in both the acute and chronic stages of injury [19]. Mechanical forces resulting from mild traumatic brain injury may stretch the axons and supporting structures, causing changes in the ion channels that could ultimately lead to an increase in intracellular water and a decrease in extracellular water. The decrease in extracellular water may be reflected as a decrease in radial diffusivity, i.e., diffusivity perpendicular to the axon [27]. These changes may be related to processes associated with subtle tissue injury such as inflammation and cytotoxic edema, and together reflect a general pattern of increased fractional anisotropy and decreased radial diffusivity [25,26], suggesting an increase in the directionality of diffusion and the restriction of overall diffusion [28,29].

Our findings of increased fractional anisotropy up to 2 months after injury suggest that pathologic processes and changes in cerebral microstructure related to an initial injury persist well beyond the initial event. However, our understanding of these processes remains limited. Work from the animal literature suggests that continuing axonal pathology may follow the initial injury during a 4-6 week period, and may contribute to late changes in cognition after a concussion [30].

The primary limitations of this preliminary study include its small sample size, the types of sports that resulted in the concussion, and the variability in number of concussions and time since concussion. Although the statistical power of our results is limited by the small sample size, the pattern of results we observed is similar to that reported in recent studies. The majority of concussions in our sample occurred within the sport of ice hockey. We also included two athletes who sustained a concussion while playing rugby, and one athlete who sustained a concussion while playing baseball. The mechanism of injury in these sports may be different from those in ice hockey, and could have led to some variability in the sample. The number of concussions in our sample ranged from 1-4. These numbers are similar to those cited in other studies, and are in fact quite typical of the numbers reported in athletes who engage

![Figure 2. Whole-brain diffusion tensor imaging tractography for one healthy adolescent (left) and one adolescent after concussion (right). Warmer colors indicate higher fractional anisotropy, whereas cooler colors indicate lower fractional anisotropy values. Diffuse increases in white matter tract fractional anisotropy are present after injury compared with an uninjured brain, likely reflecting subtle tissue damage associated with concussion.](image)

![Figure 3. Whole-brain fractional anisotropy vs Sports Concussion Assessment Tool 2. Blue squares represent values for concussed athletes. Red squares represent values for control athletes.](image)
in high-level sports. In addition, the length of time between concussion and magnetic resonance imaging varied, largely because of practical recruitment issues. These variations in time may have affected our data. However, we demonstrated significant group differences between adolescents with and without concussions regardless of these factors. Future studies with larger sample sizes should allow for better stratifications of participants, based on the nature of, number of, and time after concussions.

The increased incidence of sports-related concussions and the potential serious long-term consequences of injury to the developing brain may exert enormous clinical, societal, and economic impacts. Despite these potential impacts, our understanding of the nature of concussion-related brain injury, the risk factors associated with injury, and the mechanisms of recovery in the pediatric population remains limited. The Canadian Pediatric Society recently recommended that “return to sport decisions should be more conservative, cautious and individualized in pediatric athletes” [31]. Our preliminary findings support this recommendation, and illustrate that adolescent athletes exhibit changes in their brains for a longer period than was previously known. These results provide evidence for the need for age-specific diagnostic guidelines that are applied across the disciplines of neurology, physical medicine, rehabilitation, and sports medicine.

Future studies will provide new information on the impact of brain injury on function, and will help in understanding the risks of returning to play and sustaining additional concussions. This information will assist in the development of improved clinical practice guidelines in physicians’ management of sport concussion, including return-to-play decisions.

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References


