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Use of diffusion tension imaging in the evaluation of pediatric concussions

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ABSTRACT

Objective: To evaluate whether quantitative metrics of white matter fractional anisotropy (FA) and mean diffusivity (MD) were different in patients presenting to our clinic with persistent symptoms after a concussion.
Design: Matched control retrospective study.
Setting: Primary not-for-profit Institution.
Patients: Consecutive patients seen at a primary care institution's Sports Concussion Clinic for sport-related concussion that underwent diffusion tensor imaging. **Interventions (Independent variables)**: Type of sports, days from Injury, number of symptoms, weeks out when Magnetic Resonance Imaging (MRI) ordered, history of psychological issues, length of symptoms, age, sex, MRI imaging data.
Main outcome measure: Difference in white matter FA and MD.
Results: Seventeen concussion patients, ages 9 and 17 (average = 12.5 years; median = 13 years, 11 males and 6 females), were matched with age and gender controls who had an MRI following a complaint of headache. Patients reported an average of 11.5 concussion symptoms, out of a total possible 22 and were seen at an average of 30 days post injury. No region met tract based spatial statistics criteria for significant differences between concussed and healthy control groups (all $p > 0.05$). Similarly, when comparing group averages from the atlas based regional summaries, no region met the 0.2 false discovery rate (FDR) threshold for significant differences (the smallest unadjusted p-values were 0.02 for MD and 0.14 for FA).
Conclusions: Our results did not show measurable diffusion tensor imaging (DTI) changes with standard clinical data acquisition and quantitative processing for the individual patient. At this time DTI should not be considered a technique that can diagnose concussion within an individual subject.

1. Introduction

A concussion is a form of mild traumatic brain injury (mTBI), which is defined as a complex pathophysiological process resulting from direct or indirect traumatic biomechanical forces to the head (McCrory et al., 2017). It is estimated that there are at least 1.6–3.8 million sports related concussions yearly in the United States (Daneshvar et al., 2011). Diagnosis of this condition remains largely clinical as standard imaging modalities, such as structural MRIs and CT scans, rarely show individual abnormality (Rugg-Gunn et al., 2001; Bonow et al., 2017).

Of newer techniques, diffusion tensor imaging (DTI) has been utilized in a broad range of studies to infer disruption in white matter structure via changes in regional water mobility (Zappalà et al., 2012; Jones et al., 2005). Diffusion imaging has been found to be useful in such medical conditions as stroke and cerebrovascular diseases, neoplasia, gross inflammation and demyelination, infection, seizure disorders, and head trauma (Jones et al., 2005). Given that the integrity of while matter tracts are disturbed following significant brain injury, its use has increasingly been examined for biomarker status in milder insults (Gardner et al., 2012).

Diffusion of water molecules in white matter axons favors movement along the axon shaft, with the motion being both non-random and non-uniform. DTI is often quantified or reported by its sub-terms fractional anisotropy (FA) and mean diffusivity (MD). FA values range from 0 to 1.0 with higher numbers related to greater directional water movement. MD is a directionless unit that describes the total or bulk level of diffusion. In traumatic brain injury, FA often decreases (as water movement becomes less organized) and MD increases (since

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water can diffuse more freely). Sometimes the sub-component metrics (e.g. main diffusion directional vectors (longitudinal vs radial) or compartments (white/gray matter) are evaluated, though degrees of freedom and partial volume can impact measurement precision.

Since a common concussion patient-type who presents to the sports-medicine clinic have persistent symptoms (e.g. headache), we wanted to compare a convenience sample with sex and age matched controls to evaluate for measurable brain differences. Two analytic approaches were utilized. The first was tract based spatial statistics (TBSS), a method used in similarly sized literature samples to discriminate regional differences, and a second, leave-one-out analyses, designed as a way to test and minimize false positives that can bias whole-brain level parametric interpretations (Ivesmäki et al., 2014).

2. Methods

After IRB approval, we reviewed 17 consecutive patients who were treated for sports-related concussions in the Concussion Clinic at our institution from July 2013 to July 2014. A sports-related concussion was defined as a concussion that occurs during organized sports or recreational activities. Age and sex matched controls scanned over the same interval for brain evaluation/headache were selected for comparison. Headache was the reason for the MR brain exam in all controls, and in 14 out of 17 subjects this was the only complain. Control patients had no documented history of previous concussions. For the injury group, diagnosis was made by sports medicine providers (physicians and physician assistants) trained in concussion management with diagnosis criteria consistent with the 2012 Fourth International Conference on Concussion in Sport (McCrory et al., 2013). Symptoms were evaluated by the concussion symptom inventory (CSI) (Randolph et al., 2009), which is based on the SCAT3 (Sideline Concussion Assessment Tool 3), a standard battery of 22 symptoms in which patients reported 1 to 22 concussion symptoms with a Likert scale 0 to 6. Symptoms in controls were not collected in the retrospectively collected control sample.

2.1. MR imaging data acquisition and analysis

DTI and conventional clinical MR imaging were performed by using a Siemens (Erlangen, Germany) Trio 3T scanner. Axial DTI images were acquired by using a single-shot echo-planar imaging sequence. The imaging parameters were as follows: repetition time (TR): shortest possible, echo time (TE): 92 ms; number of signal intensity-intensity averages: 2. The gradient (b-values) for diffusion-weighting were 0, 1000 s/mm2, with 10 gradient-encoding directions. Data were obtained with a matrix size of 128 × 128 and 1.8 × 1.8 mm in-plane resolution. Section thickness was 3.5 mm, with 40–45 slices covering the entire brain. Clinical imaging protocol included a high-resolution sagittal longitudinal (T1), axial transverse relaxation (T2)-weighted sequence, and axial fluid-attenuated inversion recovery (FILAIR) sequences.

For tract based spatial statistical analyses (TBSS) and reduction of data into regions for leave-one-out analyses, the FSL toolbox (FMRIB Software Library, Version 4.1; FMRIB, Oxford, United Kingdom) (Smith et al., 2004). In brief, the raw diffusion data were first corrected for the effects of eddy currents and automatic brain extraction was performed. Next, a nonlinear registration was performed, aligning all subjects' FA images into a common space, and a mean FA image of all subjects was created. This mean FA image was then thinned to create a mean FA skeleton, representing the centers of all tracts common to all subjects. Aligned FA images of each subject were then projected onto this skeleton for voxel-wise cross-subject statistics. Analysis of the MD data was performed by applying a nonlinear registration to the data and projecting these data onto the original mean FA skeleton, by using the FA data to find the projection vectors; the resulting data were used for pairwise evaluation.

For leave-one-out analyses, 48 regions were first compared via paired *t*-test with p-values adjusted for multiple testing using a False Discovery Rate (FDR) (Benjamini and Hochberg, 1995) threshold of 0.2. This paralleled TBSS maps for between group comparisons. A cross-validated outlier analysis was then performed. For each region, all FA or MD values were pooled for cases and controls together and leave-one-out ("studentized") residuals were calculated for each participant and regions. Outliers were defined as those meeting a False Discovery Rate (FDR) of < 0.2[11], after adjusting for the multiplicity of tests across participants and regions.

3. Results

The study included 17 consecutive cases seen at a tertiary care institution's Sports Concussion Clinic for sport-related concussion. They were between ages 9 and 17 (median = 13 years, 11 males and 6 females). All cases were diagnosed with concussion as per criteria noted above. Three of them had a history of a previous concussion but they were not receiving ongoing care at the time of the subsequent concussion. Five had a history of psychiatric diagnosis such as depression, anxiety, or ADD/ADHD, however their findings did not differ from the others. Patients were seen 14–78 days (median = 28 days) post-concussion for MRI. Symptoms were evaluated by the concussion symptom inventory (median = 12, out of a total possible 22 symptoms) at the visit when the MRI was ordered. Concussion symptoms lasted 2–32 weeks (median = 8 weeks) after injury. Demographic information is described in Table 1.

Table 1
Demographic characteristics.

Subject #	Sport	Days from Injury	Number of Symptoms	Weeks out when MRI ordered	Psych Past	Length of symptoms (weeks)	Age	Sex
1	Baseball	19	10	1	no	5	9	Male
2	Basketball	18	8	2	anxiety, depression	6	12	Male
3	Basketball	20	10	8	no	12	14	Female
4	Basketball	28	9	4	no	6	10	Male
5	Cheerleading	78	21	8	no	12	16	Female
6	Football	25	21	3	no	8	16	Male
7	Football	14	1	4	no		17	Male
8	Football	34	20	2	ADHD.	5	12	Male
9	Gym class	27	4	4	no	10	13	Female
10	Football	23	16	3	ADD	8	15	Male
11	Skiing	31	6	3	no	5	14	Male
12	Soccer	37	12	4	anxiety	8	13	Female
13	Soccer	28	6	3	anxiety, depression	4	12	Female
14	Swimming	30	14	4	no	10	16	Female
15	Tag	28	17	4	no	24	10	Male
16	Wrestling	49	15	4	no	6	15	Male
17	Wrestling	21	1	4	no	32	14	Male

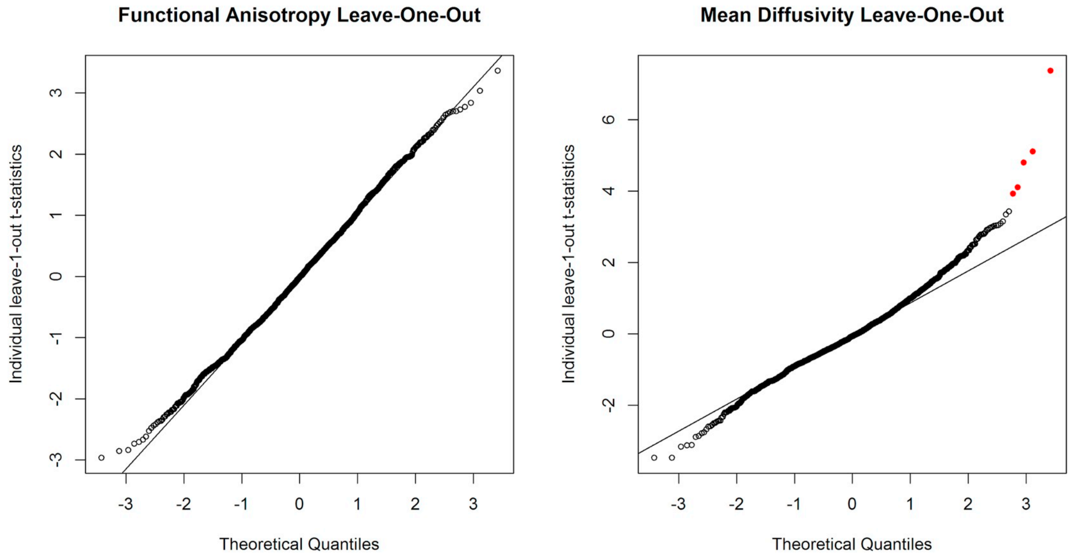

Fig. 1. Functional Anisotropy and Mean diffusivity.

Cases were compared with an age-sex matched cohort of healthy controls. All control scans were read as normal, with no subject having follow-up brain imaging.

No region met TBSS criteria for significant differences between concussed and healthy control groups (all p's $>$ 0.05). Similarly, when comparing group averages from the atlas based regional summaries, no region met the 0.2 FDR criteria for significant differences (the smallest unadjusted p-values were 0.02 for MD and 0.14 for FA). Among individual leave-one-out regional t-statistics, there were no significant FA outliers at the 0.2 FDR level. In fact, the curve of leave-one-out FA statistics closely matched the theoretical t-distribution supporting lack of any measured differences between groups (Fig. 1). For MD, there were five high outliers. However, all outliers came from a single case and a single control, with the largest high value (t = 7.4) belonging to the control subject.

4. Discussion

There are multiple studies that report white matter FA and MD changes within concussed subjects compared to controls (Caeyenberghs et al., 2014; Chamard et al., 2013; Davenport et al., 2014; Lipton et al., 2013; Toth et al., 2013; Virji-Babul et al., 2013; Wu et al., 2017). However, there are also studies failing to demonstrate DTI differences, even when the severity extends into the mild traumatic brain injury spectrum (Ivesmäki et al., 2014). Our study used an image processing technique that is commonly employed, and follow-up analyses designed to minimize false positives as shown in past work to bias results (Watts et al., 2014). Both approaches found no significant difference between the 17 concussed athletes and their age and gender matched clinical controls. Indeed, when considering outlier diffusion metrics for MD, both control and concussed data were equally skewed.

Our study has definitive limitations. The sample size was small, it was retrospective and the timing of obtaining the MRI was late in the disease process. It remains possible that the MRI, on average four weeks after time of injury, might have been more discriminatory if performed in the acute period. However, there are studies showing DTI differences in the post-acute period, with subjects experiencing lasting symptoms likely to exhibit brain alterations (Trifan et al., 2017). Enrolling a more homogeneous concussion sample and minimizing other confounding factors such as history of prior concussion and psychiatric illness, would further reduce error variance.

The information available about the control group might be partial. We selected controls with no history of concussion but given the difficulty in diagnosing this type of injury, it could be possible that patients reporting headaches in the control group might have had an undiagnosed concussion. There could have also been unmeasured confounding variables that were not reported by the controls.

With imaging methods, it is enticing to imagine that sequence improvements, increased field strength, or advancement in reconstruction methodology might unmask the sub-threshold injury that is present. For example, with DTI, acquiring a larger number of diffusion directions, varying the gradient strength, and increasing the magnetic field (e.g. 1.5T $<$ 3T $<$ 7T) would improve data-quality and by extension the possible conclusion that could be drawn. That said, the optimal DTI acquisition parameters for accurate modeling of in-vivo realities are still uncertain and overlap to gold-standard in-vivo realities remains limited at best (Thomas et al., 2014).

The 5th International Conference on Concussion in Sport found that advanced neuroimaging, including DTI, requires “further validation to determine clinical utility in evaluation of SRC (sports related concussion)” (McCrory et al., 2017). While it is certain that DTI has utility in severe diseases states like stroke and severe trauma, it is not clear whether changes are always present in concussion. The regional heterogeneity of head injury also likely will make finding and substantiating biomarkers a difficult task. Future studies could explore measuring interindividual differences as the best way to understand the brain effects of concussion (Wolfers et al., 2018). We look forward to future studies that will help to clarify the utility of DTI as a biomarker in this type of injury.

Conflicts of interest

The authors do not have conflict of interests with this study.

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Appendix A. Supplementary data

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