UCSF
UC San Francisco Electronic Theses and Dissertations

Title
Diffusion Tensor Imaging Analysis of mTBI in Scholastic Athletes

Permalink
https://escholarship.org/uc/item/7w7946d0

Author
Mallott, Jacob M

Publication Date
2018

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

Diffusion Tensor Imaging Analysis of mTBI in Scholastic Athletes

by

Jacob Mallott

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Biomedical Imaging

in the

GRADUATE DIVISION

Copyright 2018

By

Jacob Mallott

Dedication and Acknowledgements

I would like to dedicate this thesis to the memories of

Ramona H, Amy P, Rachel P, and Jeremy L.

I would like to thank all my professors in the MSBI program, Dr. Eva M Palacios, my thesis committee, and my friends and family.

Diffusion Tensor Imaging Analysis of mTBI in Scholastic Athletes

Jacob Mallott

Mild traumatic brain injury (mTBI) is a major public health concern, linked with post-concussive syndrome and chronic traumatic encephalopathy. At present, standard clinical imaging fails to reliably detect traumatic axonal injury associated with mTBI and post-concussive symptoms. Diffusion tensor imaging (DTI) is an MR imaging technique that is sensitive to changes in white matter microstructure. Prior studies using DTI to investigate mTBI did not separate contact sport athletes, a population at high risk for mTBI and subconcussive head traumas, and there has been a dearth of longitudinal studies of mTBI patients. In this study, we used Tract-Based Spatial Statistics to perform cross-sectional and longitudinal analysis describing changes in DTI scalar parameters in emergency room (ER) patients and in scholastic contact sport athletes. In the acute post-injury period, athletes demonstrated an elevated rate of regional decreases in axial diffusivity compared to controls. These decreases were especially pronounced in the cerebellar peduncles, and were more pronounced in contact sport athletes compared to the ER patient population. These results lend credence to the hypothesis that post-concussive symptoms are caused by shearing of axons of an attention network in the brain with timing mediated by the cerebellum, and warrant further study of the correlation between cerebellar DTI findings and clinical outcomes in mTBI patients.

Table of Contents

List of Tables

List of Figures

Introduction

Over 1.5 million Americans suffer a traumatic brain injury (TBI) each year. Moderate to severe TBI can be diagnosed early through CT and conventional MRI imaging. Mild traumatic brain injury (mTBI), however, make up the majority of TBI, and at present cannot be reliably detected by such imaging techniques, which remain the standard of care.[1]

As a result, such injuries are currently diagnosed and assessed by clinical evaluation of symptoms.[2] Many mTBI patients have transient postconcussive symptoms including headaches, fatigue, insomnia, depression, attention problems, and memory problems.[2] While the majority recover within days or weeks, nearly a third continue to have persistent postconcussive syndrome (PCS).[1] Current assessment cannot reliably predict which mTBI patients will go on to suffer PCS.[3]

Another major concern is the effect of mTBI on future development of neurological conditions including neurodegenerative diseases. Contact sport athletes have a higher incidence of mTBI and sub-concussive head trauma due to repeated impacts to the head.[2] Multiple mTBI over time have been associated with chronic traumatic encephalopathy (CTE), a neuropathological diagnosis with symptoms that can resemble those of other neurodegenerative conditions.[2] To date, CTE can only be conclusively diagnosed on autopsy; as a result, its prevalence in the general population remains unknown.[2] A study of retired National Fooball League (NFL) players' death certificates found an elevated rate of death from Alzheimer's disease and Amyotrophic Lateral Sclerosis (ALS); these diagnoses could also be related to CTE.[4] These results have raised questions about the long-term neurological risks of playing contact sports.[2]

Diffusion weighted imaging methods, including diffusion tensor imaging (DTI), have been applied recently in order to probe white matter changes in mTBI.[5] Traumatic axonal injury (TAI) can sometimes be detected on CT and conventional MRI due to its association with small hemorrhages that those modalities can detect, but DTI can more directly detect changes in white matter microarchitecture.[1] Past studies have found changes in DTI scalar metrics such as fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) in both acute and chronic TBI patients, indicating microstructural alterations to white matter even in cases where CT and MRI scans were negative.[3] In the acute phase, FA has been seen to increase overall, while RD and AD have been seen to decrease. At chronic time points, the opposite effect is seen, with decreases in FA and increases in RD and AD.[1] Abnormal scalar parameter values have been associated with cognitive functioning in mTBI patients.[5]

The description of DTI changes in mTBI has generally not divided its analysis into different sub-populations known to have higher incidence of sub-concussive head trauma. Additionally, there are limited studies that have performed longitudinal analysis in the mTBI patient population. The present research study applied voxel-wise and region-of-interest analysis methods to describe changes in diffusion tensor metrics in scholastic contact sport athletes with mTBI at multiple time points, and to compare those changes to those seen in non-athlete emergency room (ER) patients with mTBI.

Methods

Subject Recruitment

Subject recruitment and MRI imaging were acquired by collaborators at the Brain Trauma Foundation. All subjects were recruited from the New York metropolitan area and gave written consent for the study. In the case of minors, legal guardians gave consent.

Eighteen scholastic athletes between ages 12 and 23 years with suspected mTBI were recruited for imaging, as were 42 ER patients age 7 years and older with suspected mTBI. In addition, 38 control subjects with no prior history of head injury (age 7 years and older) were recruited and received imaging.

For the purposes of the study, a suspected mTBI was defined as a concussive event within two weeks of recruitment with loss of consciousness, post-traumatic amnesia, or at least one of the following symptoms: dizziness, nausea, headaches, balance problems, blurred or double vision, or feeling dazed/confused.

To be considered for the study, subjects were required to have 20/30 or better eyesight and English proficiency. In addition, subjects over 18 were required to have a high school diploma or GED; 18 year olds set to graduate high school on time were also included.

Exclusion criteria for subjects and controls were a prior history of head injury or eye disease, as well as neurological, psychiatric, or substance abuse (for more details, see Table 1). Subjects with contraindications for an MRI were also excluded. For athletes and ER patients, additional exclusion criteria were acute intoxication at time of injury and LOC or PTA for more than 24 hours.

Table 1. *Detailed Exclusion Criteria*

Exclusion	**Details**
Neurological Diagnosis	Prior Diagnosis of one or more of the following: Stroke, multiple sclerosis, epilepsy, brain tumor/cancer, encephalitis, dementia, movement disorder, spontaneous nystagmus
Eye-sight abnormalities	Amblyopia, uncorrected myopia, uncorrected presbyopia, uncorrected farsightedness, astigmatism, color blindness, macular degeneration
Eye Diseases	Cataracts, glaucoma, retinal disorder
Psychiatric History	Any of the following: history of psychiatric hospitalization, history of legal trouble for violence, use of psychotropic medication other than a stable dose of SSRI
Psychiatric Diagnoses	Prior Diagnosis of one or more of the following: Bipolar disorder, eating disorder, substance abuse disorder, personality disorder, sleep disorder, depressive disorder, anxiety disorder, ADHD
Questionnaires	Pediatric Subjects: T-Score≥70 on Conners 3 Inattention Index or Hyperactivity Index, or T-Score ≥65 on BAI-Y or BDI-Y. 18+ Subjects: T-Score≥70 on CAARS ADHD Index, ≥27 on CES-D, ≥26 on BAI.
Alcohol/Drug Abuse	Any of the following: • Score ≥ 6 on alcohol consumption survey • Answering 3 of 7 yes on MINI for alcohol dependence • History of daily/almost-daily use of illicit or prescription drugs • Use of any illicit or prescription drugs in past week • Past hospitalization/rehab for drugs • Past loss of job or suspension/expulsion from school for drugs • Multiple alcohol- or drug-related citation or arrest
MRI Contraindications	Metal in body, claustrophobia, possibility of pregnancy

Magnetic Resonance Imaging Protocols

For each scholastic athlete subject, MR imaging was acquired at multiple timepoints: in the acute post-injury period (within two weeks of suspected mTBI), as well as at one month, 3 months, and one year after the first scan. For ER patients, patients MR imaging studies were acquired at the acute timepoint and at one month follow-up. Control subjects received only one

set of diffusion tensor images. While all subjects received imaging at the acute timepoint, acquisition of follow-up scan data was incomplete; Table 2 shows the number of subjects who received scans at each timepoint.

Table 2. *Number of Patients with Follow-up Scans.*Listed below are the numbers of subjects with scans for each combination of time points; numbers are not exclusive to each combination. As longitudinal data collection was incomplete, longitudinal studies were performed at those time points for which there was sufficient data to power the group comparisons.

	Acute	One Month	Three Month	One Year	One Month & Three Month	1-month, 3-month and 1 year
Athletes (18 total)	18	11	12	6	10	5
Emergency Room (42 total)	42	38	N/A	N/A	N/A	N/A

MR imaging was performed at the Weill Medical College of Cornell, on a 3T Siemens scanner. In each imaging study, whole-brain diffusion tensor imaging was performed using a echo-planar imaging sequence (TE=85ms, TR=7500ms) with one b=0 scan and b=1000 s/mm^2 in 64 diffusion directions. Imaging was performed with 128x128x60 isometric voxels of 2mm dimensions.

Diffusion Tensor Image Processing

Image preprocessing was performed using tools within the Functional MRI of the Brain (FMRIB, Oxford University, Oxford, UK) Software Library.[6,7,8] Correction for eddy currents and subject motion was performed and registered to the b=0sec/mm^2 volume using the FMRIB Linear Image Registration tool.[9] Image volumes were checked for excessive patient movement between diffusion weighted images and were accepted if mean and median movement were less than 2mm.

Non-brain tissue was then eliminated using the FMRIB Brain Extraction tool.[10] Using the diffusion-weighted data, a diffusion tensor model was generated using the FMRIB DTIFit

algorithm, from which fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were determined at each voxel.

Tract-based Spatial Statistics (TBSS) were used to perform non-linear registration on the FA volumes to the FMRIB58_FA standard-space image, constructed from an average of 58 FA images taken of healthy subjects age 20-50. After brain volumes were registered into a common space, a mean FA skeleton was generated using a threshold of FA>=0.2 to limit the analysis to white matter voxels. TBSS alignment and white-matter skeleton generation was performed separately for each of the comparison groups (see *Statistical Analyses*).[11]

In addition to voxel-based analysis, masks were applied corresponding to 27 white matter tracts previously labeled in the Johns Hopkins University (JHU) white-matter labels atlas. The white matter tracts in the atlas were created by hand segmentation of a standard-space average of diffusion tensor maps from 81 subjects. Within each of these regions of interest, mean values for the four DTI scalar parameters were calculated for each subject.

Comparison Groups

A number of different comparison subsets were studied with TBSS. A summary of the different comparison groups can be found in Table 3 below, including the inclusion criteria for each comparison group. Three ER patients of the 42 recruited were removed from analysis due to DTI quality issues.

Table 3. *Comparison Groups for TBSS.* Included are the criteria used to build the studied subsets from the data.

	Group 1	**Group 2**	**Inclusion Criteria**
ER Patients Cross-Sectional	39 ER Patients (acute) age 8-64 yr (21±13.8)	26 Controls age 7-63 yr (30±12.9)	All ER Patients; Control subjects (>40 y.o. excluded except for individuals age-/sex-matched to ER patients)
ER Patients Longitudinal	28 ER Patients (acute) age 8-64 (21.1±14.9)	28 ER Patients (1 month) age 8-64 (21.1±14.9)	All ER Patients with high-quality scans at both time-points
Athletes Cross-Sectional	18 Athletes (acute) age 13-23 (17.7±3.0)	10 Controls age 12-25 (21.2±4.0)	All Athlete subjects; All Control subjects age 12-25
Athletes Longitudinal	10 Athletes (acute) age 13-23 (21.1±14.9)	10 Athletes (1 month)	All Athlete Subjects with high-quality scans at both time-points
	10 Athletes (acute)	10 Athletes (3 month)	
	10 Athletes (1 month)	10 Athletes (3 month)	

Cross-sectional analysis was performed on the 18 scholastic athlete acute post-injury time point scans compared with the scans 10 control subjects of a similar age range. A cross-sectional analysis was performed on the acute scans of the 39 ER patients compared with a set of 26 control scans of a similar age range.

Longitudinal analyses were also performed for the ER patients and athlete group. For the ER patients, longitudinal analyses were performed on 28 patients with DTI imaging at both the acute and one-month time point. For athlete subjects, comparisons were made on the 10 subjects with high-quality scans at the acute, 1-month, and 3-month time points.

Statistical Analyses

For cross-sectional analyses, unpaired two-sided t-tests were performed. For longitudinal analyses, paired two-sided t-tests were performed. In the case of the longitudinal athlete analyses, t-tests were performed comparing all three combinations of time points.

Using the FMRIB Software Library *randomise* tool, permutation tests (n=5000) were performed to evaluate significant differences between groups on a voxel-wise basis, using Threshold-Free Cluster Enhancement, with correction for family-wise error. With family-wise error correction, each volume achieves a 95% confidence interval that there are no false positive voxels in the comparison image.[12] For each comparison group, permutation tests were performed for FA, MD, RD, and AD.

Mean FA, MD, RD, and AD within each of the 27 white-matter ROIs were compared between groups with two-sided t-tests, with false-detection rate (FDR) correction for the multiple comparisons.

In addition to group-wise comparisons with unpaired t-tests, comparisons were made between the number of patients and controls with at least one white matter tract of abnormally high or low parameter values for each of the 4 parameters. For this purpose, an abnormal parameter value was defined as >2.2 control group standard deviations above or below the control mean. Significance of these group differences were determined with Pearson's χ^2 test.

Results

Patient Characteristics

Table 4 summarizes patient characteristics for the ER Patient cross-sectional and longitudinal analyses. Table 5 summarizes patient characteristics for the contact sport athlete

analyses. In the cross-sectional analysis, patient and control age were imperfectly matched, while differences in gender were not significant.

Table 4. *Subject Characteristics for ER Patient Analyses.*

	Cross Sectional Analysis		**Longitudinal Analysis**
	ER Patients (39 Subjects)	**Controls (26 Subjects)**	**ER Patients (28 Subjects)**
Age	8-64 yrs (21±13.8)	7-63 yrs (30±12.9)	8-64 yrs (21.1±14.9)
Gender	18 Female/21 Male	14 Female/12 Male	15 Female/13 Male
Time After Injury	6.1±3.4 days (3-14 days)	N/A	**Acute:** 6.6 ± 3.3 days **One Month:** 32 ± 5.4 days

Table 5. *Subject Characteristics for Contact Sport Athlete Analyses.*

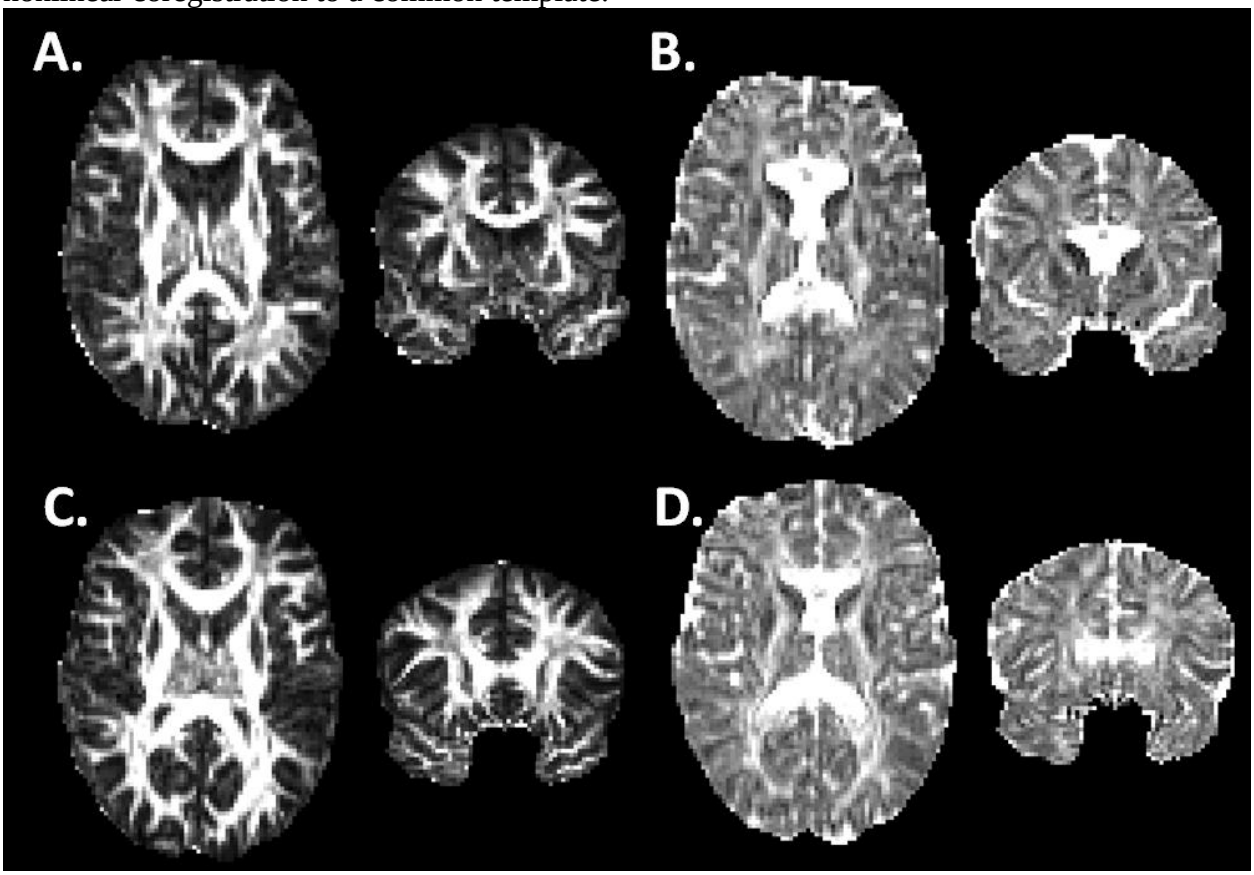
	Cross Sectional Analysis		**Longitudinal Analysis**
	Contact Athletes (18 Subjects)	**Controls (10 Subjects)**	**Athletes (10 Subjects)**
Age	13-22 yrs (17.7±3.0)	13-25 yrs (21.2±4.0)	13-22 yrs (17.4 ± 3.5)
Gender	9 Female/9 Male	5 Female/5 Male	6 Female/4 Male
Time After Injury	5.8 ± 3.5 days (2-14 days)	N/A	**Acute:** 6.6 ± 4.4 days **One Month:** 32 ± 3.8 days **Three Month:** 98 ± 8.6 days

Voxel-Wise Group Comparisons

Figure 1 below illustrates the preprocessed DTI data after motion correction, brain extraction, and calculation of DTI scalar parameters, but prior to TBSS coregistration or

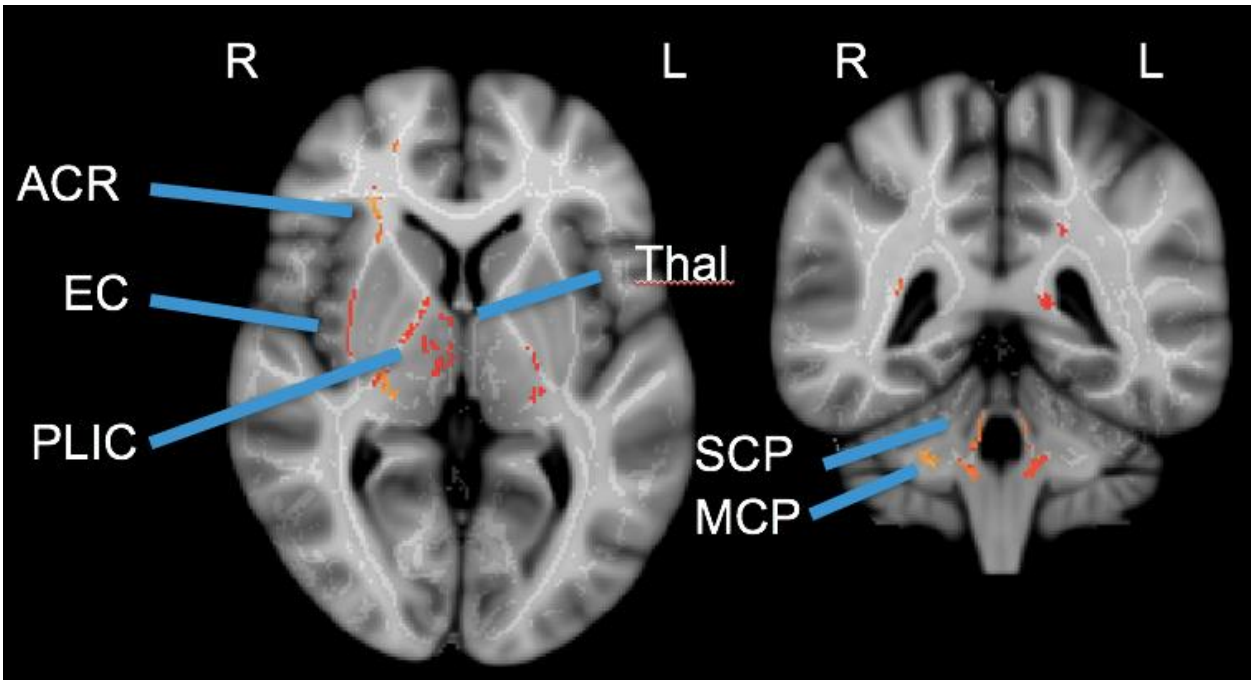
application of white matter skeleton mask. They serve to illustrate image quality; accurate comparisons are not easily drawn between subjects without subsequent alignment steps.

Figure 1. *Fractional anisotropy and Axial Diffusivity in Athlete and Brains.* A-B. Fractional Anisotropy (A) and Axial Diffusivity (B) maps for one of the athlete subjects in horizontal and coronal views. C-D. FA and AD maps for one of the control subjects in horizontal and coronal views. The imaging data has undergone image preprocessing, but has not yet undergone nonlinear coregistration to a common template.



For the cross-sectional analysis between ER patients and controls at the acute time point, no significant differences were found in the voxel-wise comparison. For the cross-sectional analysis between controls and athlete patients at the acute time point, regional significant decreases were observed in the athletes compared to controls in AD (see Figure 2). These differences were seen in the uncinate fasciculus, external capsule, posterior limb of the internal capsule, and regions of the thalamus. All three of the cerebellar peduncles also saw significant decreases in AD.

Figure 2. *Cross-Sectional Voxel-wise Comparison: Control > Patient Axial Diffusivity.* Two cross-sections illustrating regions of significant decrease in athlete AD (acute post-injury time point) compared to controls. TBSS Analysis with Threshold-Free Cluster Enhancement FEW corrected at $p<0.025$. ACR=Anterior Corona Radiata, EC= External Capsule, PLIC=Posterior Limb of Internal Capsule, Thal=Thalamus, SCP=Superior Cerebellar Peduncle, MCP = Medial Cerebellar Peduncle.



Longitudinal comparisons between acute and follow-up time points did not demonstrate significant differences in either ER patients or scholastic athletes between any of the time points compared.

White Matter Tract Comparison

For the cross-sectional analysis between athletes and controls, unpaired t-test comparisons of JHU white matter tract means demonstrated no significant group differences when adjusting for FDR (q=0.2). Similarly, for the cross-sectional analysis between ER patients and controls, unpaired t-test comparisons of JHU white matter tract means demonstrated no significant group differences when adjusting for FDR (q=0.2). Similarly, longitudinal comparisons of JHU tracts did not show differences in any DTI parameters across time points.

Outlier/Abnormal Tract Comparison

For each athlete and control subject in the cross-sectional analysis, the number of high outlier and low outlier regions were counted for each DTI parameter. Using the control means and standard deviations in each JHU white matter tract for each parameter, a high outlier region was defined as a JHU white matter tract whose mean value was >2.2 standard deviations above the control mean, while a low outlier region was defined as one whose mean value was <2.2 standard deviations below the control mean. The numbers of athletes and controls with at least one such region are summarized in Table 6 below.

Table 6. *Proportion of 18 athletes vs 10 controls with one or more abnormally high/low DTI parameter value in a JHU atlas white matter tract.* P-values determined by Pearson's χ^2 test.

SEP	Contains ≥ 1 JHU Tract more than 2.2 SD above control mean	Contains ≥ 1 JHU Tract more than 2.2 SD below control mean
Fractional Anisotropy	Control: 2 (20%) Athlete: 6 (33%) (p=0.47)	**Control: 1 (10%)** **Athlete: 11 (61%) (p=0.007) ****
Mean Diffusivity	Control: 1 (10%) Athlete: 6 (33%) (p=0.19)	Control: 2 (20%) Athlete: 10 (56%) (p=0.07)
Radial Diffusivity	**Control: 0 (0%)** **Athlete: 8 (44%) (p=0.011) ***	Control: 1 (10%) Athlete: 7 (39%) (p=0.11)
Axial Diffusivity	Control: 1 (10%) Athlete: 5 (28%) (p=0.29)	**Control: 2 (20%)** **Athlete: 16 (89%) (p<0.001) ****

Athletes were seen to be more likely to have regional decreases of FA and AD, and increases of RD. The finding of regional decreases in AD is the only one which remains significant after applying a Bonferroni correction. In athletes, the most common tracts with decreased AD were the medial cerebellar peduncle (11 athletes), inferior cerebellar peduncle (8 athletes), superior cerebellar peduncle (8 athletes), uncinate fasciculus (7 athletes), and the superior fronto-occipital fasciculus (5 athletes).

Post-Hoc Follow-Up Analysis

Based on the striking AD results in the outlier analysis, we performed TBSS and outlier analysis on a subset of 18 ER patients, chosen to best match the 18 athlete subjects by age. The resulting subjects ranged in age from 13-25 years (17.1±3.7), with 11 females and 7 males. We compared their acute time point DTI scans to the same set of 10 controls as were used in the athlete analysis.

On voxel-wise comparison and JHU tract group comparisons, we did not see significant differences between the 18 ER patients and controls. As for the outlier analysis, similar trends were seen in the data, with significantly more ER patients demonstrating low FA and low AD in one or more JHU tracts compared to controls. In ER patients, the most common JHU tracts with abnormally low FA were the medial lemniscus (6 patients), posterior thalamic radiation (4 patients), and retrolenticular part of the internal capsule (4 patients). In ER patients, the most common tracts with low AD were the inferior cerebellar peduncle (6 patients), middle cerebellar peduncle (5 patients), and the uncinate fasciculus (4 patients). Table 7 below summarizes the outlier analysis results.

Table 7. *Proportion of 18 ER patients vs 10 controls with one or more abnormally high/low DTI parameter value in a JHU atlas white matter tract.* P-values determined by Pearson's χ^2 test.

	Contains ≥ 1 JHU Tract more than 2.2 SD above control mean	Contains ≥ 1 JHU Tract more than 2.2 SD below control mean
Fractional Anisotropy	Control: 2 (20%) ER Patient: 8 (44%) (p=0.21)	**Control: 0 (0%)** **ER Patient: 11 (61%) (p<0.001)**
Mean Diffusivity	**Control: 0 (0%)** **ER Patient: 6 (33%) (p=0.04)**	Control: 2 (20%) ER Patient: 7 (39%) (p=0.32)
Radial Diffusivity	**Control: 0 (0%)** **ER Patient: 9 (50%) (p=0.005)**	Control: 1 (10%) ER Patient: 5 (28%) (p=0.29)
Axial Diffusivity	Control: 1 (10%) ER Patient: 8 (44%) (p=0.065)	**Control: 2 (20%)** **ER Patient: 11 (61%) (p=0.038)**

Finally, we performed an analysis comparing the 18 athlete subjects against the 18 age-matched ER patients. In the outlier analysis we treated the ER patients as "controls" for determining the means and standard deviations in each JHU tract.

No significant differences were seen between the patient groups in voxel-wise or tract-wise comparison. There was a significant difference in the number of patients with one or more tracts with decreased AD. The athletes had the most low-AD outliers in the fornix/stria terminalis (4 athletes), middle cerebellar peduncle (4 athletes), and the superior cerebellar peduncle (3 athletes). Table 8 below summarizes the results of the resulting outlier comparison between athletes and ER patients.

Table 8. *Proportion of 18 athletes vs 18 ER patients with one or more abnormally high/low DTI parameter value in a JHU atlas white matter tract.* P-values determined by Pearson's χ^2 test.

	Contains ≥ 1 JHU Tract more than 2.2 SD above ER mean	Contains ≥ 1 JHU Tract more than 2.2 SD below ER mean
Fractional Anisotropy	Athletes: 7 (39%) ER Patients: 4 (22%) (p=0.29)	Athletes: 7 (39%) ER Patients: 3 (17%) (p=0.15)
Mean Diffusivity	Athletes: 4 (22%) ER Patients: 4 (22%) (p=1)	Athletes: 5 (28%) ER Patients: 2 (11%) (p=0.22)
Radial Diffusivity	Athletes: 5 (28%) ER Patients: 3 (17%) (p=0.44)	Athletes: 6 (33%) ER Patients: 3 (17%) (p=0.26)
Axial Diffusivity	Athletes: 3 (17%) ER Patients: 4 (22%) (p=0.68)	**Athletes: 9 (50%)** **ER Patients: 3 (17%) (p=0.034)**

Discussion

The present study shows regional white matter changes in mTBI patients in the acute post-injury period. We observed greater frequency of regional disruptions in DTI parameters with our outlier analysis. This method of performing region-of-interest analysis was modeled on that of Niogi et al (2008) for chronic MTBI and Yuh et al (2014) for acute mTBI, in which high and low outliers in FA were compared between controls and patient subsets.[3,13] This method of

classifying patients as having or lacking abnormal tracts can account for spatial heterogeneity of mTBI.

Of particular note are our results demonstrating AD decreases in acute mTBI patients, both in the ER cohort and our athlete cohort. The vast majority of athletes had at least one JHU tract with a markedly low AD value, and while these decreases were spatially heterogeneous, there were a striking number of low AD values in all of the cerebellar peduncles. There was a decrease in AD during our follow-up analysis of ER patients as well, though our direct comparison of ER patients and athletes suggested that the contact athlete mTBI patient was more prone to this particular finding.

This study builds on others that have seen effects of TBI on DTI parameters in the cerebellar peduncles. Pediatric patients of TBI have been seen to have a lasting decrease in white matter volume following their injury.[14] Wang et al (2016) looked specifically at cerebellar FA in mTBI patients and found increases at the acute phase, which was associated with worse neurocognitive testing scores.[15]

A 2011 study of American soldiers with blast-related TBI found a marked decrease in FA at an acute time point, though no directional change in AD. These patients all had confounding brain traumas in addition to their primary blast injury, a situation similar in some ways to contact sports athletes, though the type and severity of injuries sustained by combat soldiers is likely different and could account for some of the differences.[16]

Our findings in the cerebellar peduncles provide some support to the hypothesis of predictive brain state disruption in TBI.[17] By this hypothesis, the collection of post-concussive symptoms we observe clinically could be explained by disruptions in an attention network in the brain with timing mediated by the cerebellum.[17] (It should be noted that our analysis was data-

driven and not driven by any hypothesis.) To further test this hypothesis, future studies can and should attempt to correlate our cerebellar DTI findings to clinical outcomes.

In our longitudinal analyses, we expected to see changes in DTI parameters in line with previous studies. In the acute post-injury period, prior studies have found increases in FA along with decreases in RD and AD, while at chronic time points reversals of such trends have been described. We did not observe such time progression in group-wise comparisons.

There are multiple possible explanations for the failure of longitudinal studies to find significant differences at different time points, despite previous literature. One issue is the spatial heterogeneity of mTBI, which can require a larger sample size to achieve the necessary power to see group differences in individual voxels or white matter tracts.

Another concern, specific to our dataset, is the relatively wide window of what is defined as an "acute" post-injury scan time. Anything within two weeks of injury was considered within the acute phase. However, the differences between DTI parameters two days after mTBI and 14 days after mTBI could be significant, especially when comparing subjects between the acute and one-month time point. In addition, with regards to the athletes, it is possible that repeated sub-concussive blows to the head could lead to a variable time course of recovery.

There are several limitations to the present study. First, age matching between patients and controls was imperfect. On the whole, the control population was older than the subject population, and there were insufficient control subjects to choose a suitably large control group that was well-matched to the subject data. Performing a linear regression treating age as a covariate was not a good option for dealing with the discrepancy, as that would rely on the assumption that DTI parameters vary linearly with age. It has previously been shown that age-related changes in DTI measures are not linear.[18]

Overall sample size was small, especially considering continued sub-concussive traumas sustained by athletes as a confounding factor to the time course of mTBI recovery. A larger study size could increase power and allow for detection of more subtle group differences.

In designing future studies of athlete populations, it would perhaps be best to design image acquisition protocols that allow for more advanced diffusion models than diffusion tensor imaging. For instance, neurite orientation dispersion and density imaging (NODDI) uses high angular resolution diffusion data with multiple b-values, and applies a three-compartment model that takes into account the brain anatomy in describing the diffusion pattern within a voxel.[19] The NODDI model rests on certain assumptions regarding normal brain physiology, so in studying pathology such as mTBI it is possible that the resulting NODDI parameters do not accurately describe the underlying brain architecture. However, in a preprint study Palacios et al have shown greater sensitivity in mTBI when studying changes in NODDI parameters compared to the DTI parameters analyzed in this study.[20]

Conclusion

The present study found marked decreases in AD in the acute period post-mTBI in scholastic contact sport athletes compared to controls, particularly in the cerebellar peduncles. Similar results were seen in an ER patient population, though with less frequency. Future studies are warranted to confirm these findings in larger patient populations and to correlate the findings with symptoms and clinical outcomes. These findings could lead both to better our understanding of the etiology of mTBI post-concussive symptoms and also to aid in development of imaging biomarkers in mTBI. In addition, characterizing mTBI in the athlete population could lead us to better understand how frequent exposure to mTBI and subconcussive head trauma affects the brain and can lead to CTE.

References

1. Niogi SN, Mukherjee P. Diffusion tensor imaging of mild traumatic brain injury. J Head Trauma Rehabil. 2010 Jul-Aug;25(4):241-55.

2. Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. Mol Cell Neurosci. 2015 May;66(Pt B):75-80.

3. Yuh EL, Cooper SR, Mukherjee P, Yue JK, Lingsma HF, Gordon WA, Valadka AB, Okonkwo DO, Schnyer DM, Vassar MJ, Maas AI, Manley GT; TRACK-TBI INVESTIGATORS. Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: a TRACK-TBI study. J Neurotrauma. 2014 Sep 1;31(17):1457-77.

4. Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. Neurology. 2012 Nov 6; 79(19): 1970-1974.

5. Oehr L, Anderson J. Diffusion-Tensor Imaging Findings and Cognitive Function Following Hospitalized Mixed-Mechanism Mild Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. 2017 Nov;98(11):2308-2319.

6. Mori et al., MRI Atlas of Human White Matter. Elsevier, Amsterdam, The Netherlands (2005).

7. Wakana et al., Reproducibility of quantitative tractography methods applied to cerebral white matter. NeuroImage 36:630-644 (2007)

8. Hua et al., Tract probability maps in stereotaxic spaces: analysis of white matter anatomy and tract-specific quantification. NeuroImage, 39(1):336-347 (2008)

9. Andersson JL, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage. 2003 Oct;20(2):870-88.

10. Smith SM. Fast robust automated brain extraction. Human Brain Mapping, 17(3):143-155, November 2002.

11. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TEJ. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. NeuroImage, 31:1487-1505, 2006.

12. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. NeuroImage 2014;92:381-397.

13. Niogi SN, Mukherjee P, Ghajar J, Johnson C, Kolster RA, Sarkar R, Lee H,Meeker M, Zimmerman RD, Manley GT, McCandliss BD. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. AJNR Am J Neuroradiol. 2008 May;29(5):967-73.

14. Spanos GK, et al. cerebellar atrophy after moderate-to-severe pediatric traumatic brain injury. AJNR Am J Neuroradiol. 2007 Mar;28(3):537-42.

15. Wang Z, et al. Altered Cerebellar White Matter Integrity in Patients with Mild Traumatic Brain Injury in the Acute Stage. Yap P-T, ed. PLoS ONE. 2016;11(3):e0151489.

16. Mac Donald CL, et al. Detection of blast-related traumatic brain injury in U.S. military personnel. N Engl J Med. 2011 Jun 2;364(22):2091-100.

17. Ghajar J, Ivry RB; Cognitive and Neurobiological Research Consortium. The predictive brain state: timing deficiency in traumatic brain injury? Neurorehabil Neural Repair. 2008 May-Jun;22(3):217-27.

18. Lebel C, Beaulieu C. Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci. 2011 Jul 27;31(30):10937-47.

19. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage. 2012 Jul 16;61(4):1000-16.

20. Palacios E, Owen JP, Yuh EL, Wang MB, Vassar MJ, Ferguson AR, Diaz-Arrastia R, Giacino JT, Okonkwo DO, Robertson CS, Stein MB, Temkin N, Jain S, McCrea M, Mac Donald CL, Manley GT, Mukherjee P, TRACK-TBI Investigators. The Evolution of White Matter Microstructural Changes After Mild Traumatic Brain Injury: A Longitudinal DTI and NODDI Study. BioRxIV (preprint), posted June 14, 2018.

Publishing Agreement

It is the policy of the University to encourage the distribution of all theses, dissertations, and manuscripts. Copies of all UCSF theses, dissertations, and manuscripts will be routed to the library via the Graduate Division. The library will make all theses, dissertations, and manuscripts accessible to the public and will preserve these to the best of their abilities, in perpetuity.

I hereby grant permission to the Graduate Division of the University of California, San Francisco to release copies of my thesis, dissertation, or manuscript to the Campus Library to provide access and preservation, in whole or in part, in perpetuity.

Author Signature  Date 9/6/2018