Unique Changing Patterns of DTI Parameters Associated with Sport-Related Concussions from Wild Bootstrap Analysis

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Introduction: Diffusion tensor imaging (DTI) can be used to study sports related concussions (also known as mild Traumatic Brian Injury [mTBI]). DTI Fractional Anisotropy (FA) was reported as either decreased [1,2] or increased [3] in internal capsule during different post-concussion period, reflecting the complex nature of the underlying pathological processes. The mechanical forces during concussion not only cause axonal injury of common pattern in vulnerable brain regions but may result in subject-dependent impact. In this study, we applied a wild bootstrap based analysis [4, 5] for voxel-wise statistical comparisons between longitudinal DTI data of an individual subject, in a group of high school hockey or football players to investigate the subject-dependent patterns of changes of DTI parameters. The cross-subject common patterns were further investigated by a second-level statistics based on the results of the wild bootstrap statistics of the individuals.

Methods: Seven young athletes (1 hockey and 6 football players) and two non-participating controls (all neurologically normal) were scanned pre- and post-season within a three-month interval. During the season, one athlete was diagnosed with mTBI (scanned within 72 hours of injury) and the other six suffered between 26 and 289 subconcussive head blows. All images were obtained on a Siemens 3T Trio system. DTI sequence parameters were: TR/TE=10s/100ms, isotropic 2x2x2 mm voxel, iPAT (GRAPPA) acceleration factor=2, 60 diffusion gradient directions with b=700 s/mm^2 and one average, b=0 images with 10 averages. 3D MP-RAGE T1W image (1x1x1mm) and dual-echo GRE images were also acquired for spatial normalization and susceptibility corrections. Home-built software was used for post-processing with eddy-current and field inhomogeneity corrections and tensor calculations. *Wild bootstrap:* The bootstrap samples were generated to approximate the real situation when numerous repeated measurements were performed [4,5]. A statistical comparison was performed to detect the changes in FA or MD over time for each subject by comparing the bootstrap samples at each time point. *Two-level Statistics:* For each subject, the data from one time point was randomly selected to register to the other time point data. For the first level statistics in each subject, 250 bootstrap samples of FA or MD were generated voxel-wise for pre- and post-season DTI data. A non-parametric permutation t-test with 2500 permutations based on SnPM toolbox [6] were then performed at each voxel, using a model of single subject, two-condition with replications and an exchangeability block size of 2. The resulted permutation T statistic maps represent the statistical significance of changes in FA or MD between two time points for each subject. The spatial distributions as well as the levels of the significant FA/MD changes were quantitatively evaluated as the {total number of significant voxel / total non-CSF brain volume} (**Total FA%** in Tab.1), and the ratio between the numbers of voxels with increased or decreased FA values (**FA+/FA-** in Tab.1). FA and MD changes within previously reported regions [1,2,3] (Fig1.A), such as anterior corpus callosum (ACC), were also evaluated. For the second level statistics, each individual's contrast image was normalized and further compared by a Multi-subject One-Sample T-test model from SnPM for the common change patterns among subjects.

Results: An example from the first level statistics is shown as the coefficient of variation (CV) map for FA (Fig1.B). CV maps calculated voxel-wisely from 250 bootstrap samples describe the uncertainty level of DTI measurement. FA and MD changes in both directions (increase or decrease) were detected post the season in comparison to the pre-season data. However, in 5 out of 7 athletes studied, the number of pixels with the elevated FA or reduced MD is on average 1.7 to 2.9 times of the number of pixels with the decreased FA or increased MD, listed as **FA+/FA- and MD-/MD** in Tab.1. The athlete with mTBI had the largest number of voxels with DTI changes. For five previously reported regions with DTI changes under mTBI, only very small portion in each region has significant DTI changes with a maximum value in ACC of 10±7%. Additional regions with elevated FA (Fig2.A) or decreased MD (Fig2.B) in post-season data include posterior region of corona radiata (yellow arrow) and inferior longitudinal fasciculus (blue arrow). There is also a noticeable bilateral asymmetry (**L/R Asymmetry** in Tab.1) in total number of voxels with significant changes potentially reflecting the different mechanical impact, such as location and intensity, for each individual. In contrast to the injured athletes, controls show much fewer numbers of voxels with significant FA or MD changes, have approximately equal number of pixels with increase or decrease DTI parameters when comparing pre- and post- season scans, and no L/R asymmetry was detected. For cross-validation, no difference was found in statistical results when the data set of either time point from controls was selected as the reference set during registration. No significant differences in DTI parameters were detected from the second level statistics among the subjects.

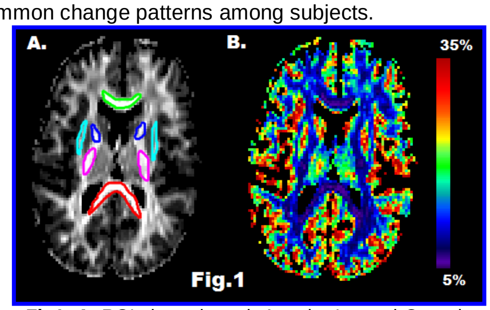

Fig1: **A.** ROIs investigated: Anterior Internal Capsule -- Blue, Posterior Internal Capsule -- Magenta, Anterior Corpus Callosum-- Green, Posterior Corpus Callosum– Red and External Capsule– Cyan. **B.** FA CV map. (CSF has been removed)

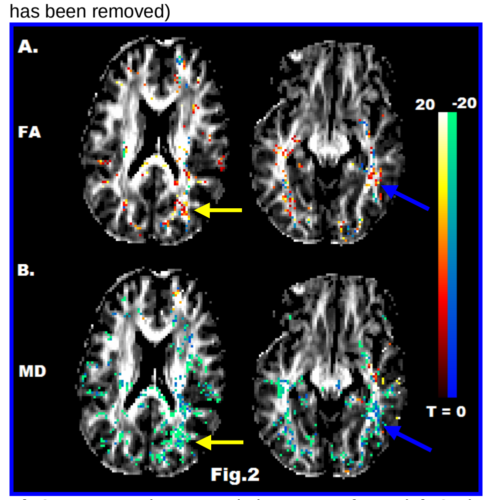

Fig2: Permutation T-statistic maps of FA (**Fig2.A**) and MD (**Fig2.B**) from the athlete with mTBI superimposed on the FA map. Red/Green: DTI parameters Elevated/Reduced in the post-season scan.

Discussions: The wild bootstrap analysis of longitudinal DTI data in young athletes enable a subject-specific investigation of the changing patterns of DTI parameters due to sports concussions. The spatial locations as well as the levels of DTI changes are shown to be subject-dependent that are not easily detected by a ROI-based or group analysis. Even in the previously reported vulnerable regions, DTI changes are small in scale and highly variant in locations among subjects. Therefore, the presented bootstrap-based method potentially provides complementary information for better characterizing the pathological changes that occur after concussion and subcomcussive head blows. Unique patterns of elevated FA and reduced MD under concussion presented here are most likely due to the axonal swelling during the process of axonal injury [3].

Reference: [1]. Arfanakis K et al. AJNR, 2002; 23(5): 794-802; [2]. Inglese M et al. J Neurosurgery, 2005; 103(2): 298-303; [3]. Bazarian J. et al., J Neurotrauma, 2007; 24:1447-1459. [4]. Chung S. et al., Neuroimage 2006; 33(2): 531-541. [5]. Whitcher B., et al. Human Brain Mapping. 2007. In Press. [6]. Nichols TE., et al., Human brain mapping, 2001; 15:1-25.

Table 1 : Wild bootstrap analysis of pre- and post season data.

	Controls	mTBI	Athlete 1	Athlete 2	Athlete 3	Athlete 4	Athlete 5	Athlete 6
Total FA %	0.18%	3.19%	0.88%	1.33%	0.68%	0.77%	1.03%	1.63%
FA+/FA- (post vs. pre)	≈1	1.86	1.81	2.28	1.90	≈1	1.86	≈1
Total MD%	0.41%	3.44%	1.29%	1.78%	1.01%	1.28%	1.34%	2.19%
MD-/MD+ (post vs. pre)	≈1	3.55	1.53	6.35	3.71	≈1	3.02	0.89
L/R Asymmetry	≈1	0.81	1.03	0.7	0.88	1.21	1.10	0.97