Improve Diagnosis of Sport-related Sub-concussive Injury of Individual Football Athletes: Changes in DTI and Mechanical Impact Metrics from Real-time Recording

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Introduction: Recent autopsies of ex-NFL players suggest that repetitive sub-concussive head blows (SHB) contribute to early-onset dementia (chronic traumatic encephalopathy, CTE) [1]. The public health impact of brain injury from SHB is potentially dramatic. The diagnosis of concussion depends on the athlete (or a witness) to report a brief loss of consciousness or period of amnesia. However, athletes tend to underreport symptoms to avoid being taken out of the game and even head blows that do not result in concussion may cause brain injury. Moreover, mechanical forces not only cause axonal injury of common pattern in vulnerable regions but also may result in subject-dependent impact. Diffusion tensor imaging (DTI) has been used as an objective and non-invasive approach to study brain injury associated with concussions [2, 3]. In this study, we conducted three longitudinal DTI studies of a group of 10 college football players before and after a regular season, along with mechanical force data recorded by helmet-embedded sensors throughout the season. Subject-dependent patterns of longitudinal DTI changes were analyzed with a bootstrap-permutation analysis of each individual [4] and further associated with impact force metrics to aim at identifying key factors in sport-related brain injury.

Methods: 10 college football players (all males, age between 20 and 23) and five age-matched male healthy controls were studied between Aug 2011 and May 2012. All 15 subjects underwent a battery of tests including cognitive and balance testing, DTI scanning and serum collection, at the start of the football season (T1), immediately (T2) and 6 months (T3) after the season. In addition, these players were fitted specially designed helmets with embedded sensors (**Fig.1A**) that recorded the linear and rotational acceleration of every impact incurred during the season. *Metrics for impact force*: Five commonly used metrics of impact intensity, peak linear acceleration (PL), peak rotational acceleration (PR), head injury criterion (HIC), Gadd Severity Index (GSI), Head Impact technology severity profile (HITsp), were calculated based on data from helmet accelerometers over the course of the season. *MR imaging:* All images were obtained on a Siemens 3T Tim Trio system. DTI parameters were: TR/TE=10s/89ms, 2x2x2 mm voxel, 60 diffusion directions with b=1200s/mm^2 and one average, b=0 images with 10 averages. Home-built software based on tools in FSL was used for eddy-current and susceptibility corrections and tensor calculations. For each subject, FA images of each time point were aligned to each other to identify the "most representative" one as the template for achieving spatial correspondence among the three longitudinal DTI data. *Wild bootstrap:* The bootstrap samples were generated to approximate the real situation when numerous repeated measurements were performed [5]. Empirical distributions with 250 bootstrap samples of FA/MD for each longitudinal data of the same subject were generated. *Detect longitudinal DTI changes of each individual:* Pair-wise statistical comparisons (T1vs.T2, T2vs.T3, and T1vs.T3) among longitudinal DTI data with permutation t-test [6] (2500 permutations) were conducted based on bootstrap samples using Randomise in FSL. A cluster-based threshold (with a cluster size of 10) was used for multiple-comparison correction. Using FA as the example, spatial distributions as well as intensity of the significant longitudinal FA change were quantitatively evaluated as {Total FA%=number of significant WM voxel / total WM} (**Fig.1B**), and as the percentage of voxels with increased or decreased FA values (FA+%, FA-% in **Tab.1**) **in comparing DTI data at later and earlier times**. *Association between DTI and impact metrics*: For each pairwise comparison of DTI using bootstrap-permutation test, the level of FA changes, represented by FA+% and FA-%, are associated with impact metrics using Spearman correlation coefficient.

Results: Athletes incurred between 431 and 1850 SHBs, and none were diagnosed with concussions. *DTI analysis (**Fig.1**)*: we investigated longitudinal DTI data of ***individual*** subjects to detect subject-specific DTI changes before and after head impacts. Our results show that the football players had a significantly higher mean percent of WM voxels with significant changes in FA (0.55±0.13% vs. 0.09±0.03%, p<0.00001) and in MD (2.32±0.50% vs. 0.78±0.23%, p<0.0001) compared to controls, for which only a very small proportion of WM with a statistically significant longitudinal change were detected (**Fig.1B**). Examples of WM regions with significant FA change between pre- and post-season (T1 vs. T2) of three athletes and one control are illustrated in **Fig.1C**. Red/blue dots indicate voxels with significantly increased/decreased FA in post-season data. For the athletes, voxels with significant FA changes tend to be clustered, in contrast to sparse and isolated voxels in the control data (indicating random errors due to the bootstrap sampling procedure). *Correlation between DTI and impact metrics (**Tab.1**)*: The total number of hits during the season did not significantly correlate with any DTI results, nor did the overall net changes in DTI (Total FA% and MD%) correlate strongly with any impact metrics. However, the number of hits above certain thresholds for most impact metrics (such as PL>50 indicating #hits with peak linear acceleration larger than 50g), did positively associate with FA-% between T1 vs. T2 (i.e. significantly reduced FA in post-season DTI data). In addition, there are also significant negative associations between MD-% (i.e. significantly reduced MD in post-season DTI data) and many impact metrics. Previous studies of head injuries reveal two possible change patterns of FA/MD associated with possibly different pathological changes after impact: FA🡣/MD🡡 (associated with axonal injury or demyelination) and FA🡡/MD🡣 (indicating axonal swelling). Our findings suggest that more severe impacts are more likely associated with axonal injury while less severe but repetitive impacts might instead induce axonal swelling.

Discussions: Combining advanced DTI technique, novel bootstrap-permutation analysis and real-time recording of impact force data, this study enabled us to monitor individual athletes for potential brain injury, and relate injury to various metrics from mechanical impact measurements. Despite a small sample size, the study finds that certain DTI measurements and mechanical force metrics show strong correlations during the first phase (T1 vs. T2) of this study. Pending confirmation in a larger cohort, our results suggest that repetitive sub-concussive head hits may adversely result in DTI-detectable brain damage. Results from this study provide useful information for better management of athletes playing sports involving repeated head impacts.

Table 1: Correlation between DTI changes and mechanical impact metrics from sensors. (pre- vs. immediately post-season)

Spearman Correlation Coefficients	Total Hits	Mean Linear	Mean Rotation	Mean HITsp	HIC>150	GSI>150	HITsp>50	PL>50	PR>4500
Total FA %	0.03	0.07	0.03	0.09	0.07	0.04	0.01	0.09	0.05
Total MD%	-0.11	-0.42	-0.37	-0.33	-0.46	-0.48	-0.44	-0.32	-0.47
FA-%	0.33	**0.64**	0.55	**0.58**	**0.76**	**0.85**	**0.64**	**0.77**	**0.91**
MD+%	-0.20	0.18	0.22	0.28	0.14	0.01	0.22	-0.19	-0.12
FA+%	-0.21	-0.35	-0.43	-0.30	**-0.57**	**-0.63**	-0.52	-0.54	**-0.64**
MD-%	-0.01	**-0.68**	**-0.62**	**-0.66**	**-0.64**	**-0.55**	**-0.67**	-0.32	-0.46

(Red indicates significant correlations: p<0.05. Blue indicates close to significant correlation, p<0.1.

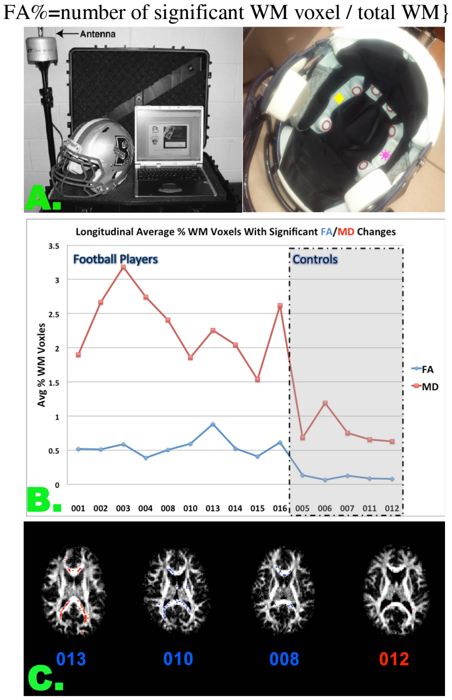

Fig1: A. The mechanical impact recording system (left) with six accelerometers/sensors embedded in helmet (right) to record impact information in real time during practice/games. **B.** Average values of Total FA% (blue curve) and Total MD% over three longitudinal DTI sets. Shaded area represents data from five healthy control subjects. **C.** Examples of WM regions with significant FA changes in the post-season data (red indicates increased FA and blue indicates decreased FA) from three athletes (008, 010 and 013) and one control (012).

Reference: [1]. McCrory P et al., Sport Med 2007; 36:467-476. [2]. Arfanakis K et al. AJNR, 2002; 23: 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]. Bazarian J. et al., Magn Reson Imaging 2012; 30:171-180. [5]. Zhu et al., Neuroimage 2008; 40:1144-1156. [6]. Nichols TE., et al., Human brain mapping, 2001; 15:1-25.