Robust Detection of Axonal Abnormalities in High School Collision-Sport Athletes: Longitudinal Single Subject Analysis

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INTRODUCTION: Diffusion-weighted MR imaging (DW-MRI) has been used to detect abnormal changes in white matter for subjects with mild traumatic brain injury (mTBI) [1]. A single subject-based approach is proposed here to detect athletes exhibiting longitudinal deviations in fractional anisotropy (FA) as observed by paired tract-based spatial statistics (TBSS). High-school aged (male) football and (female) soccer athletes were scanned longitudinally three times during the course of a competition season, during which they experienced multiple collisions to the head or whiplash-like acceleration events. Significant increases in FA were observed in the second half of the season, relative to the pre-season measures, for most asymptomatic soccer players. Additionally, this analysis yielded the expected result that symptomatic brain injury is associated with a significant falloff in FA.

METHOD: 1) Participants: Eighteen male high school football players (*FB;* ages: 15-18; mean = 16.3) and fifteen female high school soccer players (*SC*; ages: 14-17; mean = 15.8) volunteered for this study. An additional ten male high school non-collision sport players (ages: 14-18; mean = 16.7) were recruited to form a control group. All *FB* and *SC* athletes participated in three imaging sessions taking place before pre-season practices (*Pre*), during the first half of the season (*In1*), and during the second half of the season (*In2*). All controls were scanned twice during their training period. Note that none of the participants reported having experienced a concussion prior to the study. **2) Data Acquisition:** MR imaging was conducted using a 3T GE Signa HDx with a 16-channel Nova Medical brain array. Diffusion weighted images were acquired using a spin-echo echo-planar sequence with parameters: TR/TE = 12,000/83.6ms, 30 diffusion angles, 24cm FOV, 46 axial slices, 2.5mm isotropic resolution. Imaging session *In1* was conducted a median of 54 days after the *Pre* scan, and *In2* was conducted a median of 93 days after the *Pre* scan. For controls, the median interval between the two sessions was 58 days. **3) Processing:** Image processing was primarily performed based using TBSS in the FSL toolbox [2]. After correcting for effects of head movement (b-matrix rotation and FLIRT) and eddy-currents, brain images were segmented and fractional anisotropy (FA) values were estimated. FA values were co-registered with the JHU ICBM-DTI-81 FA template using nonlinear registration (FNIRT). After calculating the mean of all FA images, it was thresholded (FA > 0.25) to create the mean white matter (WM) skeleton. The aligned FA image for each subject was projected onto this mean WM skeleton. Significantly-deviant voxels on the WM tracts in the skeletonized FA images were identified by a randomization-based paired *t*-test. These voxels were then passed into the single-subject analysis.

ANALYSIS: 1) Paired TBSS Analysis: To test longitudinal WM changes, a paired difference analysis was used on three comparison sets: *Pre* vs *In1*, *Pre* vs *In2*, and *In1* vs *In2*. A randomization-based paired *t*-test was performed with threshold-free cluster enhancement (TFCE) and multiple group correction across voxels (10,000 permutations). The skeletonized-FA voxels with a family-wise error rate corrected *p*-value of $p_{\mathrm{FWER}} < 0.15$ were considered to show significant differences. A stringent threshold for p_{FWER} is not necessary here as we are trying to detect subtle variations and are willing to accept the cost of an increase in type I error [3]. **2) Paired Single-Subject Analysis:** At each of the deviated FA voxel locations defined by paired TBSS analysis, each individual subject in the comparison set has multiple FA measurements (one per measurement session). With these multiple measurements, each subject can be considered as a group in a paired difference analysis. A permutation-based paired t-test (50,000 permutations) was applied across multiple subjects with a detection threshold of $p_{\mathrm{FWER}} < 0.05$. Such detected players were "flagged" as candidates for exhibiting significant differences in FA across the sessions (at the given locations).

RESULTS: The paired-TBSS analysis of the control group exhibited no significant FA changes, suggesting that DW-MRI is sufficiently reproducible for application of this approach. *FB* athletes—who experienced a lower rate of head collisions than in previous seasons of this long-term study (e.g., [4])—likewise exhibited no statistically significant alteration in FA in any paired comparison sets. Conversely, significant FA changes were detected (Fig. 1) for all 15 *SC* athletes between *Pre* and *In2* sessions, but not in other paired comparisons. The *SC* athletes in this study experienced notably higher rates of collision events than in previous seasons. 14 of the 15 *SC* athletes exhibited statistically significant increases in FA during the second half of the season. The remaining *SC* athlete exhibited a statistically significant decrease in FA at her planned second half assessment, which was conducted two weeks after a diagnosed concussion.

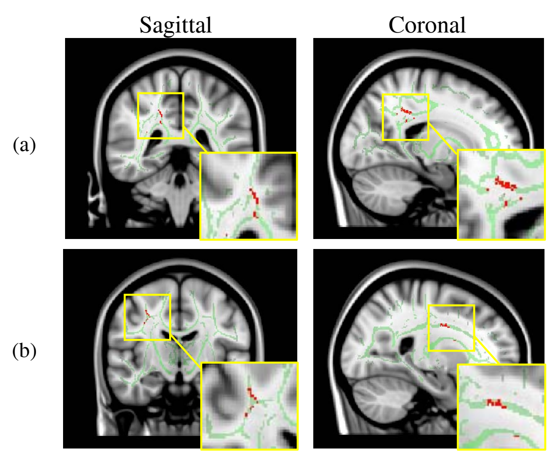

Fig 1. Detected locations having deviant FA ($p_{\mathrm{FWER}} < 0.15$)

DISCUSSION: Novel analysis of diffusion-weighted imaging measurements suggests that head-collisions may have more short-term, local effects on axonal health in female soccer athletes (who do not wear head protection) than in male football athletes (who wear energy-absorbing helmets). In general, the female soccer athletes exhibited FA increases within 93 days of the onset of the competition season. FA increases do not necessarily imply injury of cellular membranes, but are hypothesized to reflect local inflammation [5]. The one *SC* athlete who exhibited a decrease in FA was also the only athlete in this study who was diagnosed with a concussion—an injury typically associated with a decrease in FA.

CONCLUSSION AND FUTURE WORK: Findings suggest that head collision events result in a slow accumulation of altered white matter health, even in the absence of symptoms. If repair/return to health is likewise a slow process, previous observation of persistent impairments beyond the competition schedule [6] could be explained.

REFERENCES: [1] M. Murugavel, et al. *J Neurotraum* ja (2014). [2] S. Smith*, Hum. Brain Mapp.* (2002), 17 (3), 43–155. [3] C. Bennett, et al. *Soc. Cogn. Affect. Neur.* (2009), 4(4), 417-422. [4] E.L. Breedlove, et al. *J Biomech* 45.7 (2012): 1265-1272. [5] J. Povlishock & D. Katz, *J Head Trauma Rehab.* (2005) 20(1), 76–94. [6] K.M. Breedlove, *Athl Train Sports Health Care*, (2014): 119-127.