Robust Detection of Progressive White Matter Abnormalities in mTBI Using DW-MRI

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INTRODUCTION: DW-MRI has been effectively used to detect white matter abnormalities in mild traumatic brain injury (mTBI) [1]. However, the progress of white matter injuries that may occur from repetitive blows to the head has not been evaluated. Building on our study of repetitive blows in contact sports [2-3], we introduce a bootstrapped z-score analysis as a robust voxel-wise statistical analysis method to detect deviations from normal white matter fractional anisotropy. With this approach, we evaluate the progression of changes in fractional anisotropy (FA) over time, using DW-MRI scans from pre-season to post-season. These changes provide strong evidence that contact sports athletes, especially American football players, who receive many blows to the head during the season, exhibit likely chronic white matter injuries.

METHOD: **1) Study Design**: Three populations were evaluated. (a) A sample of four (from a pool of 80) high-school American football players who experienced a wide range of hits to the head during a 12-week football season were selected for evaluation. The players and their associated number of hits to the entire helmet (and number of hits to the top-front of the helmet): P120, 1463 (178) hits; P121, 1783 (302) hits; P204, 533 (33) hits; P125, 223 (12) hits. All players were scanned prior to, during and after the competition season. Players 120, 121 and 204 went through the entire season without being clinically diagnosed with a concussion. Player 125 missed part of two weeks after sustaining a clinically-diagnosed concussion. (b) A control population of 25 (12 male, 13 female) high school-aged non-contact sport athletes, each of whom was scanned on two separate occasions to assess test-retest behavior. (c) A 22 y.o. female equestrian suffering memory problems as a result of multiple concussions from repeated falls from her horse, scanned once within one month of a concussion. **2) Processing**: FA values were extracted from DW-MR images after eddy-current correction was applied. FA images were co-registered using non-linear registration with the FMRIB58 FA template, and aligned into the $1 \times 1 \times 1$mm MNI152 standard space by affine transformation, and a white-matter-mask was applied. **3) Robust Voxel-wise Statistical Analysis "Bootstrapped Z-score Analysis"**: Due to the limited control size (25 individuals, 50 total measurements), the mean and standard deviation of the general population cannot be well-characterized. Therefore, we used a bootstrapped z-score (z_{BS}) to characterize deviant and non-deviant measurements: $z_{BS} = \frac{data - \mathrm{Mean}(\bar{x})}{\mathrm{STD}(\bar{x})}$, where $data$ is the subject's FA measurement, x is voxel-specific FA from the healthy controls, $\bar{x} \in \mathbb{R}^{B\times 1}$, $\bar{x}_b$ is the mean of each set of uniformly sampled data with placement for b = 1,…,B, and B is the number of bootstrapped samples (here B=100). Normally, the 95% confidence interval would be used to identify outliers or, if using an inter-session difference, deviant FA changes. However, we have assumed that the automated registration technique is not perfect, but that resulting errors in FA values are smaller than changes that may occur due to injury. Therefore, we here use a high threshold value, $z_{\alpha/2}$, corresponding to the 99.999% confidence level, to ameliorate the potential confound from mis-registration.

RESULTS AND DISCUSSION: For our control population, the z_{BS} distribution was quite consistent, both across subjects and testing sessions. Conversely, for the American football players, it was consistently found that the width of the z_{BS} distribution was proportional to the number of total hits experienced to the head. Therefore, the number of hits to the head was predictive for the number of abnormally low (decreased) or high (increased) white matter FA values, with these changes being asymmetric—typically exhibiting a greater increase on the *positive* (increased FA) side. It should be noted that Players 120 and 121, who had each experienced more than 1800 hits to the head in the previous season [1], exhibited pre-season measurements that were more deviant (**Fig 1**) than any of the measurements on players 125 and 204, neither of whom experienced such high hit totals in preceding seasons. This suggests that P120 and P121 have chronic levels of white matter damage accrued over previous seasons of participation in football. The tendency of players such as P120 and P121 who experienced large numbers of hits to exhibit *high* as opposed to *low* FA values, suggests that damage (e.g., de-bonding of myelin from axons) to neural tracts that are non-primary to everyday task performance may not achieve complete repair under repeated mechanical stress. Crossing fiber regions may thus exhibit higher-than-expected FA values. The equestrian subject, known to be experiencing long-term memory problems typically associated with significant history of mTBI, exhibited dramatic widening of the z_{BS} distribution, particularly on the negative (decreased FA) side (red, **Fig 1**).

CONCLUSSION: The z_{BS} analysis robustly detects the progress of abnormal white matter FA in mTBI patients. Appreciable differences in distribution between non-contact sport controls and American football players, suggests this may be an effective means of detecting early-stage white matter lesions associated with repetitive blows to the head.

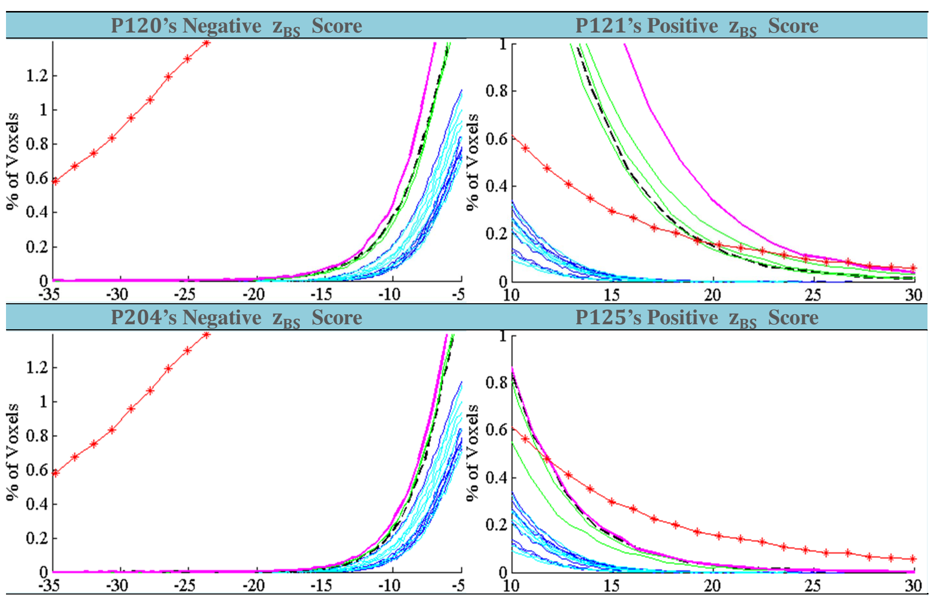

Fig 1. The partial distribution of t_{BS} score comparison **(a)** P120 **(b)** P121 **(c)** P204 **(d)** P125 (Color info.: **Pre**, **In**, **Post**, **Equestrian subj.**, **Cont. 1st scan**, and **Cont. 2nd scan**.)

REFERENCES: [1] M. Lipton, et al., Brain Imag & Beh 2012; 6(2):329. [2] T. Talavage, et al., J Neurotrauma, 2010. [3] E. Breedlove, et al., J Biomechanics 2012; 45(7):1265.