Longitudinal study of concussion-related diffusion MRI changes in college athletes

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Abstract

Sports-related traumatic brain injuries affect 1.6-3.8 million individuals in the US each year, and diffusion weighted imaging can measure the complex timeline of resulting axolemmal changes. Such longitudinal data is difficult to model statistically, however, given the high-dimensionality, semi-parametric and interdependent scalar values, and non-linear spatial (within-tract) and temporal (across visit) properties. Proposal: hierarchical generalized additive models (HGAMs) are well-suited to fit such data with the requisite flexibility and sensitivity to investigate (a) the spatial and temporal changes of white matter tracts, and (b) how such changes relate to diagnostic assessments. Methods: we utilized MRI and IMPACT data collected from 67 college athletes (9 female, age=19.43[1.68]) at three visits: start-of-season, post-concussion, and return-to-play. Diffusion tensors were modeled via constrained spherical deconvolution and probabilistic tractography from pyAFQ yielded 100 scalar values per white matter bundle. Results: By fitting the scalar profiles with longitudinal HGAMs we detected within-tract changes as a function of visit, revealing distinct patterns of post-injury disruption and recovery. Critically, it is unlikely that such changes would have been detected with standard techniques given their linear assumptions and limited dimensionality. Further, we examined whether these evolving diffusion metrics correlated with cognitive outcomes using HGAM tensor product interaction smooths and found moderate evidence linking white matter alterations to IMPACT composite scores. Merit: HGAMs offer a powerful framework to capture the complex progression of brain injury. Our findings suggest that HGAMs enhance our understanding of the spatiotemporal dynamics of brain injury and may enable more accurate tracking of injury and recovery.

KEYWORDS: DWI, MRI, GAM, TBI

1 Introduction

Introduction here.

2 Methods

2.1 Participants

Participants were recruited from men's football and women's soccer programs at the University of Nebraska-Lincoln, which resulted in a total of 69 (9 female, age = 19.36 $\pm$1.67, range = 17-24) National Collegiate Athletic Association (NCAA) athletes. Due to the limited number of females, and the sport-sex interaction confound, we combined all participants into a single group. Institutional Review Board approval was obtained at the outset of the study, and prior to beginning experimental procedures participants completed informed consent and assent. Magnetic Resonant Imaging (MRI) and clinical assessment (ImPACT, described below) data were acquired at three sessions: enrollment at the beginning of the season (baseline, Base), within 48 hours of diagnosed concussion (post-concussion, Post), and prior to return-to-play (RTP). A number of participants did not contribute data for Base, Post, and/or RTP sessions yielding final counts of Base = 67 (9 female), Post = 65 (8 female), and RTP = 56 (7 female).

2.2 ImPACT

Description of ImPACT.

2.3 MRI Protocol

Magnetic Resonance Imaging data were collected on a 3 Tesla Siemens MAGNETOM Skyra scanner at the Center for Brain, Behavior and Biology (University of Nebraska-Lincoln) utilizing a 32-channel coil. For each of three sessions (Base, Post, and RTP), participants contributed T1 and diffusion weighted images (T1w, DWI). T1w Multi-Echo Magnetization Prepared - RApid GRadient Echo (MEMP-RAGE) structural scans were acquired with the following parameters: TR = 2530 ms, TE = 1.69, 3.55, 5.41, and 7.27 ms, flip angle = 7°, voxel size = 1 mm^3, FoV = 256 × 256, slices = 176 interleaved. DWI scans were acquired via TR = 3000 ms, TE = 95 ms, flip angle = 90°, voxel size = 1.719 × 1.719 × 2.4 mm^3, 134 slices, multi-band acceleration factor = 3, directions = 128, bandwidth = 1500 Hz/Px, shells = 1 (b-value = 1000 s/mm^2), reference volumes = 6 (b-values = 0 s/mm^2; b_0). A set of field maps for the DWI scans were collected using the same acquisition direction (anterior-posterior, AP) and reversed (posterior-anterior, PA).

2.4 MRI Data Processing

Preprocessing and modeling of the DWI data were conducted using FSL v6.0 (Jenkinson et al., 2012) and PyAFQ v1.3.6 (Kruper et al., 2021; Yeatman et al., 2012). First, b_0 volumes from A>>P and P>>A field map files were extracted and combined, as were their acquisition parameters. Next, `topup` calculated a distortion correction matrix from the AP-PA b_0 file. A brain mask was generated via `bet`, and an index file was generated to describe the relationship between the DWI volumes and their acquisition parameters. Preprocessing of DWI was then conducted via `eddy_openmp`, which generated motion- and distortion-corrected diffusion images.

Whole-brain tractography was computed from the preprocessed DWI by PyAFQ. Constrained spherical deconvolution was used to derive the fiber orientation distribution function of each voxel, and probabilistic tractography modeled fiber paths using one seed per voxel for each dimension, a maximum turning angle of 30°, step size = 0.5 mm, and a length range = 50-250 mm. The resulting fibers were then parcellated into individual tracts via *a priori* inclusion (waypoint) and exclusion regions of interest (ROIs); waypoint and exclusion ROIs are moved from MNI atlas into participant space via a symmetric, non-linear diffeomorphic transformation (Wakana et al., 2007). Resulting tracts are then compared to fiber probability maps (Hua et al., 2008), and any fibers which traverse low-probability spaces are removed from the tract. Further, any fibers with a length 4+ standard deviations from the tract average, or 5+ standard deviations from the average path centroid, are removed as well. Lastly, each tract was then resampled into 100 equidistant nodes (according to a Mahalanobis distance metric) for which averaged diffusion values and scalars were calculated. Specifically, for each tract node we extracted averaged axial diffusivity ($\lambda_{\parallel}$; AD), radial diffusivity ($(\lambda_{\perp 1} + \lambda_{\perp 2})/2$; RD), mean diffusivity ($(\lambda_{\parallel} + \lambda_{\perp 1} + \lambda_{\perp 2})/3$; MD), and fractional anisotropy (FA).

2.5 GAM specification

Description of GAM.

3 Results

3.1 ImPACT

Impact results.

3.2 DWI Tracts

Tract results.

3.3 DWI Tracts Interactions - ImPACT

Description of DWI - ImPACT interaction.

3.4 DWI Tracts Interactions - Time

Description of DWI-time interaction.

4 Discussion

Discussion.

Acknowledgments

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5 Supplemental Materials

Supplemental Materials.

5.1 Tables

Supplemental Tables.

5.2 Figures

Supplemental Figures.