Longitudinal Study of Concussion-Related Diffusion MRI Changes in College Athletes: Modeling Tracts via Hierarchical Generalized Additive Models

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Introduction

- **Background**: 1.6-3.8 million sports-related TBIs per year, mTBI associated with negative MRI findings. Histologically, mTBI associated with traumatic axonal injury.
  - Damaged axolemma, axonal beading, axotomy (or recovery).
- DWI MRI is sensitive to changes in axonal water permeability, diffusion.
- **Issue**: Modeling within-tract DWI data is complicated due to interdependent nodes, non-linear tract profiles, semi-parametric scalar distributions, injury across multiple tracts, creeping Type-I error and/or large MC corrections.
- **Proposal**: Model whole-brain, longitudinal data with Hierarchical Generalized Additive Models (HGAM; Fig 1).
  - Accounts for semi-parametric distributions, non-linear interactions, high-dimensionality, and node interdependence. Obviates need for large MC corrections.
  - Facilitates multimodal interaction models via tensor product interaction smooths.

Methods

- **Participants**: 69 NCAA athletes recruited from UNL men's football and women's soccer programs; 9 female, age=19.36(1.67), range = 17-24.
- Three sessions: start of season (Base), 0-48 hours after diagnosed concussion (Post), and Return-To-Play (RTP).
  - DWI MRI data and ImPACT responses collected at all three sessions.
- **DWI Model**: Constrained Spherical Deconvolution, probabilistic tractography, tracts divided into 100 equidistant nodes (PyAFQ).
- **Statistical Models**: HGAMs to test for concussion- and recovery-related changes.
  - Model 1: Longitudinal whole-brain FA changes (Fig 2).
  - Model 2: Longitudinal tract-specific scalar changes (Fig 3).
  - Model 3: Longitudinal multimodal interactions (Fig 4).

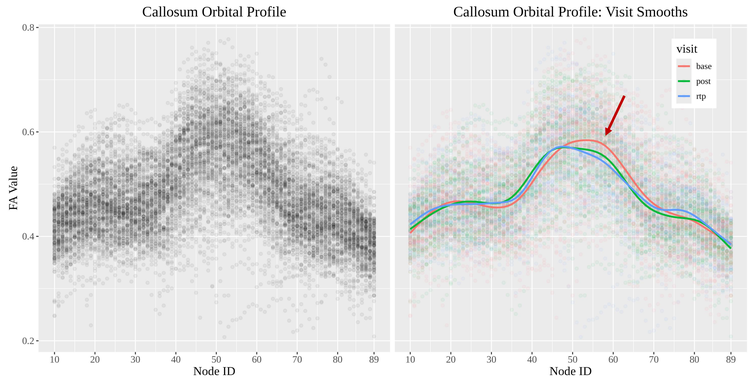


Fig 1. HGAMs fit longitudinal scalar data to detect subtle within-tract changes.

Results

- Whole-brain models show changes in FA values relative to Base (Fig 2).
- **Tract-specific scalar models help elucidate source of FA changes (Fig 3).**
  - Right Cingulum shows evidence of recovery by RTP (node 35).
  - Possible evidence of edema around node 60.
- **Tensor product interaction smooths identify associations between ImPACT metrics with changes to tract FA values (Fig 4).**
  - Post Callosum Occipital node-FA interactions with visual motor statistically differs from the Base interaction, while RTP does not.
  - Similar pattern for Callosum Superior Parietal interaction with total symptoms.

Whole-brain models detect injury and recovery.

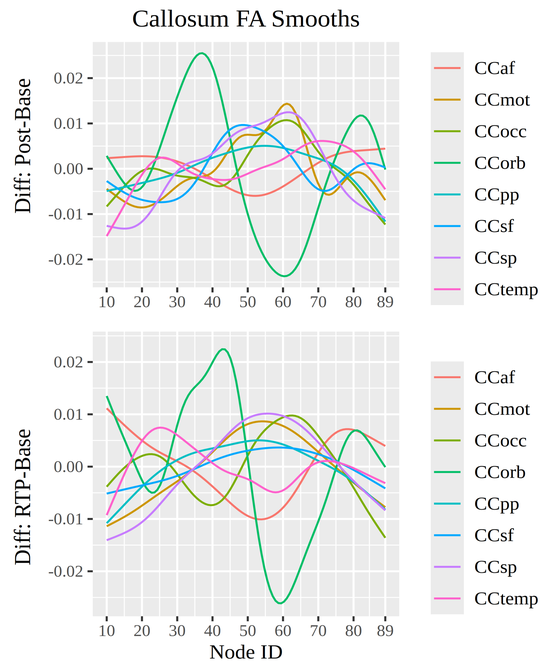
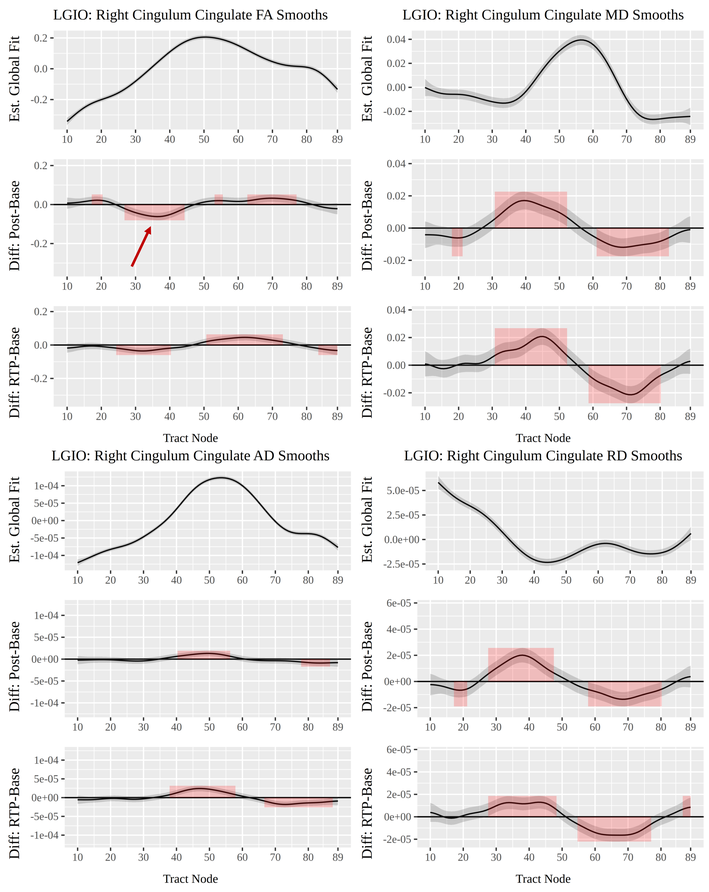


Fig 2. Concussion- and recovery-related changes in tract FA values (selected). Difference smooths indicate regions (nodes) where Post and RTP differ from Base. Confidence intervals omitted for clarity.

Tract-specific models implicate axolemmal changes.



Interactions are present between tract FA values and ImPACT metrics.

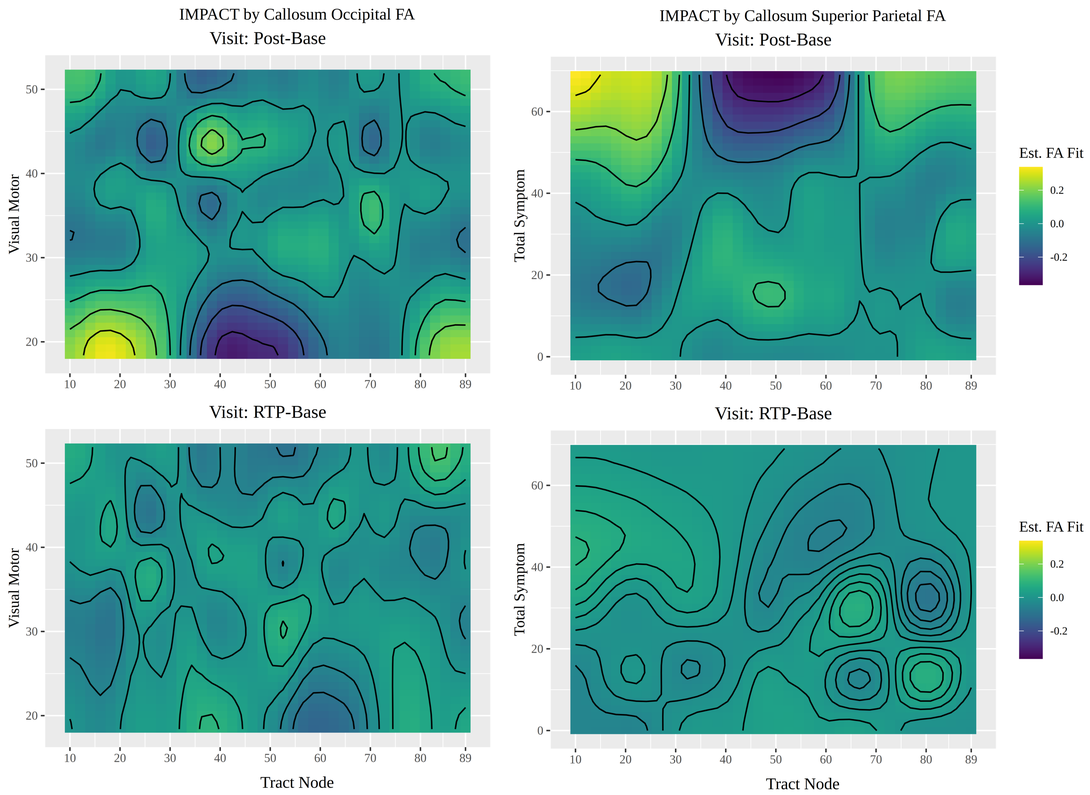


Fig 4 (above). **Left**: Worse visual motor performance at Post is associated with decreased FA values in the Callosum Occipital tract around node 45 (top). By RTP (bottom), visual motor performance recovers and this association is no longer apparent. **Right**: An increase in reported symptoms is related to decreased FA values around node 50 (and increased around node 15) of the Callosum Superior Parietal tract at Post (top). Upon recovery (RTP, bottom), this relationship is no longer apparent. Tensor product interaction smooths are difference interactions from Base.

Fig 3 (left). Evidence of recovery in right Cingulum (selected). Decreases in FA values at Post relative to Base is evident around node 35 (red arrow), which appears to resolve by RTP. Increased RD, and not decreased AD, is the source of FA decrease. Possible edema is evident at RTP around node 65, resulting in increased FA values (and decreased RD). Models were conducted for each scalar: FA (**Top Left**), MD **(Top Right)**, AD **(Bottom Left)**, and RD **(Bottom Right)**. Red boxes indicate nodes where smooths differ statistically from Base. Session difference smooths are plotted in global domain to show relative fit contribution.

Discussion

- **HGAMs sensitively model complex, high-dimensional data with non-linear interactions.**
  - Capable of detecting concussion- and recovery-related DWI scalar changes.
- **Changes in RD drives FA changes in sports-related mTBI.**
  - Implicates axolemmal damage/permeability and edema.
  - Lack of decreased AD relevant for faster recovery, AD related to axonal microtubule and cytoskeletal disruption.
- **HGAMS facilitate linking tissue damage to clinical assessment metrics via high dimensional tensor product interaction smooths.**
  - Weak relationship between ImPACT and DWI scalars, most interaction surfaces did not show expected interaction pattern.
- Limitations:
  - Running tractography multiple times adds approximately 10% variance, tract dependent.
  - Scan-rescan variance is likely due to inherent thermal properties.
  - Injury is heterogeneous, due to mechanism of injury and type of sport.
- Future work:
  - Extend approach to m/s TBI, other clinical assessments and link to epidemiologic factors.

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