

ALTERATIONS IN THE INTEGRITY OF MAJOR WHITE MATTER PATHWAYS IN VETERANS WITH GULF WAR ILLNESS (GWI)

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Objective

To assess the integrity of the major white-matter pathways in the brain for microstructural changes that may have resulted from being in the 1991 Gulf War.

Introduction

Approximately one third of veterans who deployed to the 1991 Gulf War suffer from a chronic disorder called Gulf War Illness (GWI) which is characterized by symptoms including cognitive dysfunction, debilitating fatigue, joint and muscle pain, skin rashes, and gastrointestinal problems. Meta-analyses of cognitive data from these veterans has shown significant decrements in visuospatial skills, executive function, attention, and learning and memory. Magnetic Resonance Imaging (MRI) of veterans with GWI have found reduced white matter volumes in the brain. In order to better understand of the nature of the changes that may have taken place in the white matter, we assessed the major white-matter pathways using diffusion-weighted MRI (DWI). Data were obtained from veterans of the 1991 Gulf War by the Boston University Gulf War Illness Consortium (GWIC). These analyses will help us to better understand if the microstructural integrity of the white matter has been disrupted in individual with the clinical features of GWI.

Participant Information

Participants were part of the Gulf War Illness Consortium (GWIC) study run through the Boston University. The participants were scanned at the Center for Biomedical Imaging (CBI) at the BU School of Medicine on a 3T Philips Achieva System with a 32-channel head coil. We used the images from 60 participants, 12 healthy and 48 participants with symptoms of Gulf War Illness (GWI).

* $p < 0.05$

Methods

T1-Weighted: Magnetic resonance imaging (MRI) was performed on a Philips 3 Tesla Achieva (Philips, Best, Netherland) and included a three-dimensional (3D) structural T1-weighted FFE (Fast Field Echo) scan using a repetition time = 6.8ms, echo time = 3.1ms, flip angle = 9 degrees, and a voxel size = .98 x .98 x 1.2mm

HARDI: Tractography was conducted on the 64 direction HARDI scan with a diffusion weighting of $b=3000$. All MRI data was converted to FSL-NIFTI prior to analysis.

- A high resolution T1-Weighted image and HARDI scan were acquired on each subject.
- T1-Weighted was used to co-register individual data.
- Tract density, volume, mean diffusivity (DA), and quantitative anisotropy (QA) were generated.
- Freesurfer v6 TRActs Constrained by UnderLying Anatomy (TRACULA) function was used to reconstruct 18 major pathways in the brain of each subject, the tracts reconstructed were:
 - Forceps Major & Minor
 - Left & right Anterior Thalamic Radiation
 - Left & right Cingulum-Angular Bundle
 - Left & right Cingulum-Cingulate Gyrus
 - Left & right Corticospinal Tract
 - Left & right Inferior Longitudinal Fasciculus
 - Left & right Superior Longitudinal Fasciculus – Parietal
 - Left & right Superior Longitudinal Fasciculus – Temporal
 - Left & right Uncinate Fasciculus
- For each pathway, we obtained measures of average Fractional Anisotropy (FA), Radial Diffusivity (RD) and Mean Diffusivity (MD).
- Independent samples student's t-tests were used to identify differences between the groups.

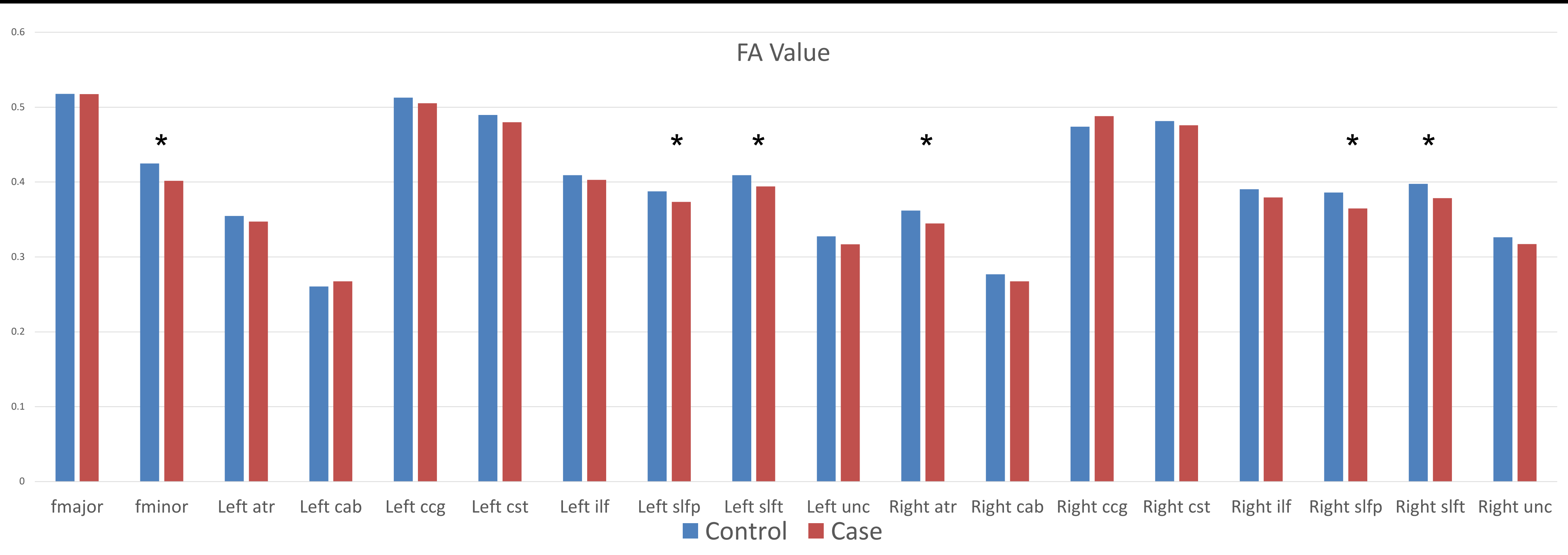
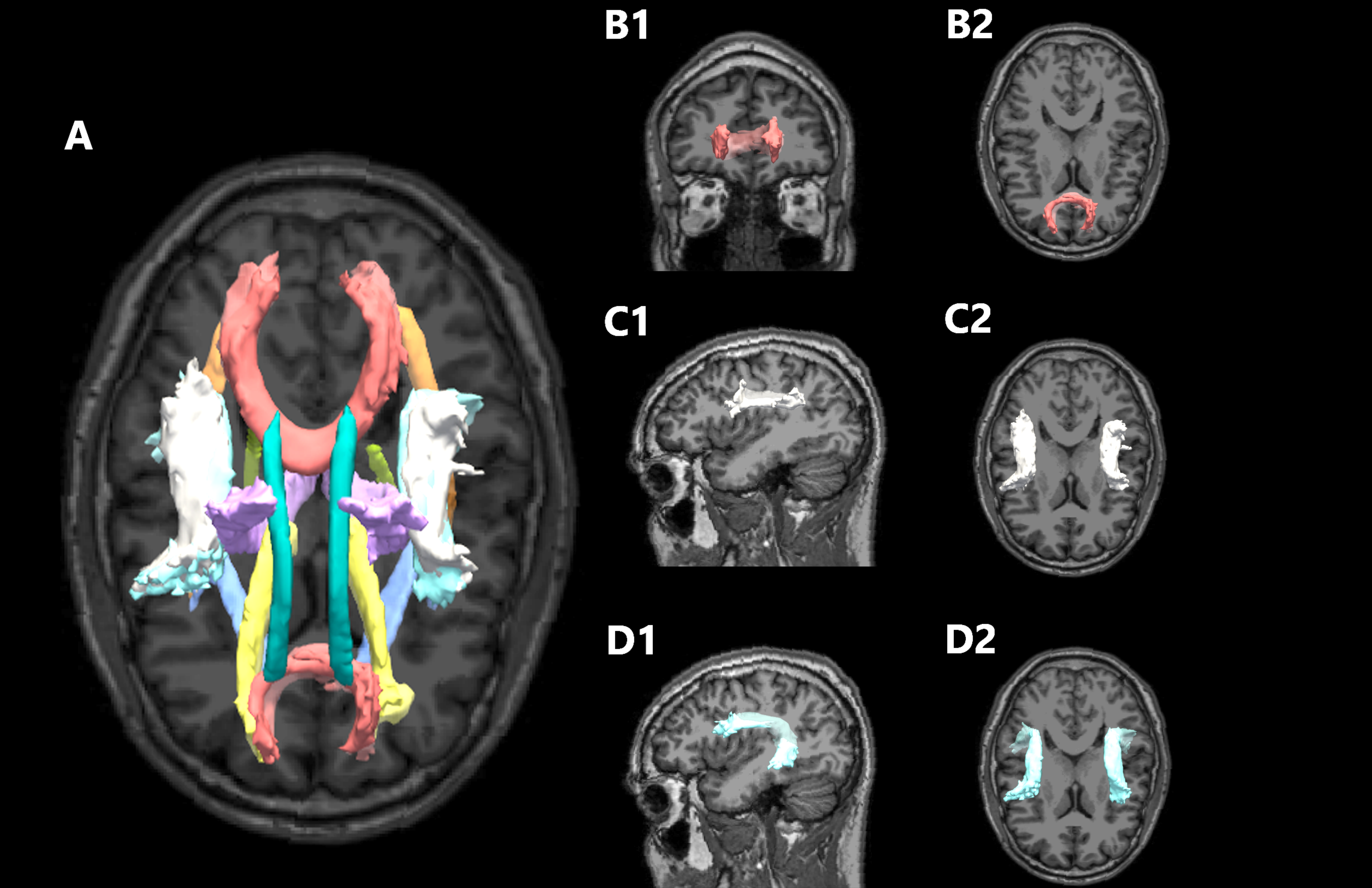


Figure A represents all 18 tract outputs from TRACULA with each color corresponding to the table to the right. Figure B1 and B2 are coronal and transverse views of the forceps minor, which contain fibers connecting the lateral and medial surfaces of the frontal lobes. Figure C1 and C2 are sagittal and transverse views of the SLF-T, which contain fibers from frontal and temporal lobes. Figure D1 and D2 are sagittal and transverse views of the SLF-P which contain fibers from frontal and parietal lobes.

Summary

- These findings suggest that the microstructural integrity of the Superior Longitudinal Fasciculus (SLF) temporal and parietal, was compromised in veterans with GWI.
- Future direction will be to use neurite orientation dispersion and density imaging (NODDI) in accordance with TRACULA in visualizing tract integrity.

RESULTS

Independent samples student's t-tests were used to identify differences between the groups. These analyses revealed that the microstructural integrity of the Superior Longitudinal Fasciculus (SLF) [temporal and parietal tracts] along with the Anterior Thalamic Radiation (ATR) was compromised in veterans with GWI. These results add to the increasing evidence indicating that alterations to the white matter of the brain is an essential component of GWI. The relationship between these alterations in white matter microstructure and the complex clinical profile of GWI requires further investigation.

| FA | CONTROL | CASE | P-VALUE | |
|------------|------------|------------|------------|----------|
| fminor | 0.42469708 | 0.40168909 | 0.00357009 | Two Tail |
| Left slfp | 0.38744392 | 0.37347 | 0.04386888 | Two Tail |
| Left slft | 0.40921192 | 0.39397824 | 0.01774871 | Two Tail |
| Right slfp | 0.38583275 | 0.36457422 | 0.01467554 | Two Tail |
| Right slft | 0.39761633 | 0.37859472 | 0.00295428 | Two Tail |
| Right atr | 0.36188475 | 0.34473761 | 0.03079892 | Two Tail |
| fmajor | 0.51766583 | 0.51735824 | 0.98675532 | Two Tail |
| Left atr | 0.35478892 | 0.34727078 | 0.33777416 | Two Tail |
| Left cab | 0.26064633 | 0.26748637 | 0.44762086 | Two Tail |
| Left ccg | 0.51277325 | 0.50521587 | 0.44858154 | Two Tail |
| Left cst | 0.48957458 | 0.479966 | 0.13778691 | Two Tail |
| Left ilf | 0.4091355 | 0.40288611 | 0.51083635 | Two Tail |
| Left unc | 0.32760733 | 0.31676113 | 0.2954191 | Two Tail |
| Right cab | 0.27693933 | 0.26734954 | 0.31572544 | Two Tail |
| Right ccg | 0.47373233 | 0.48792685 | 0.10648293 | Two Tail |
| Right cst | 0.48144317 | 0.47566263 | 0.30383399 | Two Tail |
| Right ilf | 0.39025417 | 0.37934241 | 0.16282782 | Two Tail |
| Right unc | 0.32609675 | 0.31713978 | 0.42029286 | Two Tail |

Average FA values of Control Vs. Case for each major white-matter pathway present. Values highlighted in yellow represent those showing statistical significance without correction for multiple comparisons. Significant pathways are marked with an asterisk (*)