Sex-Stratified Analysis of the Association Between Elevated GFAP Levels and Quantitative Anisotropy in Trauma Survivors

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BACKGROUND

- Female patients with mild traumatic brain injury (TBI) report worse symptoms compared to male patients[1]

- Female axons have smaller cross-sectional area and contain fewer microtubules relative to male axons; in vitro models suggest they may be more vulnerable to stretch injury[2]

- Using acute glial fibrillary acidic protein (GFAP) levels as an objective proxy for potential TBI, are there sex-specific white matter disruptions among trauma survivors?

METHODS

- Trauma survivors (18–75 years old) were recruited to the AURORA study[3] from participating emergency departments (ED) within 72 hours of a qualifying traumatic event (Fig 1; Table 1)

- Plasma samples collected in the ED were assayed for glial fibrillary acidic protein (GFAP) using Quanterix GFAP Discovery Kits on a Quanterix HD-X Analyzer

- A subset of participants were recruited for diffusion neuroimaging at two-weeks post-trauma at one of five AURORA deep phenotyping sites

- There were twenty (20) participants (11F/9M) with diffusion data and elevated GFAP levels (>268 pg/mL) who were matched to low-GFAP trauma-exposed controls using optimal case-control matching with the *ccoptimalmatch* R package[4] (Fig 2)

Figure 2. Matching overview
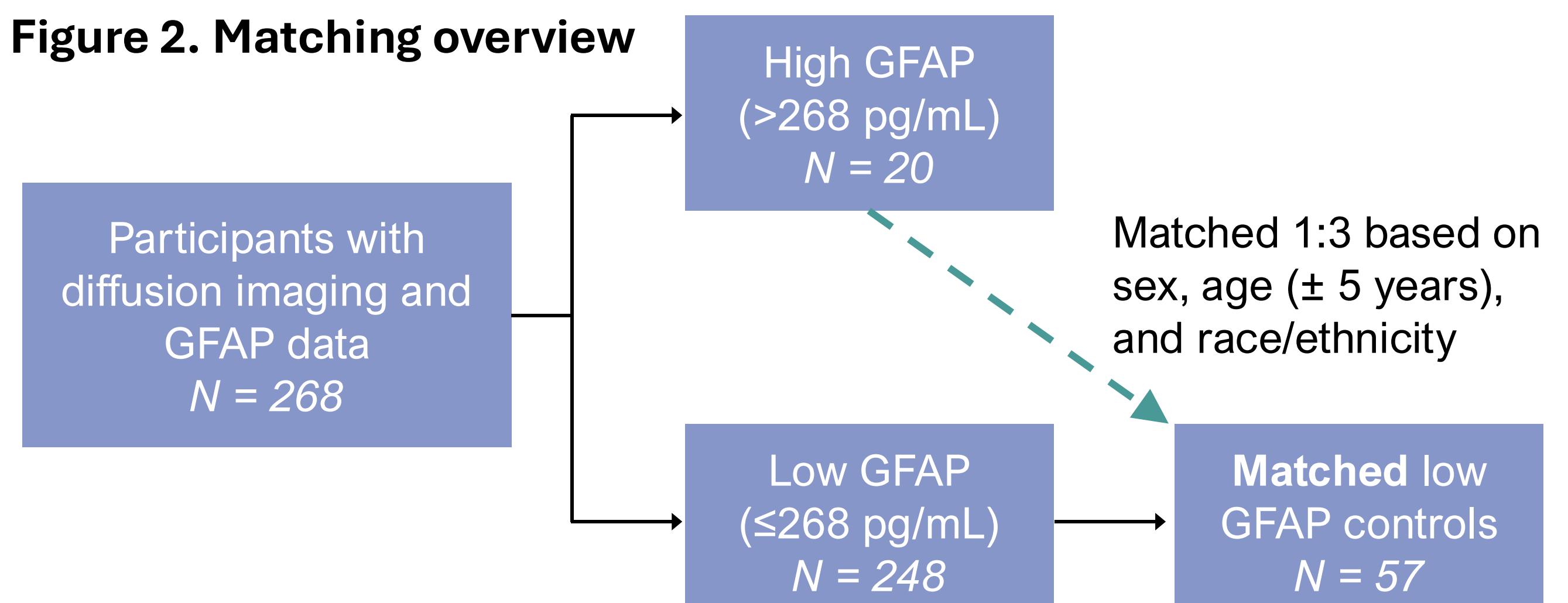
- We conducted a sex-stratified, whole-brain connectometry analysis in DSI Studio (FDR < 0.05, T-threshold = 2.5, minimum length = 30 voxels, 4,000 permutations) to examine the association between tract quantitative anisotropy (QA) and GFAP level (high vs. low)

Among female trauma survivors, elevated acute plasma GFAP levels were associated with reduced white matter integrity at two-weeks post-trauma.

### Figure 1. Study design.
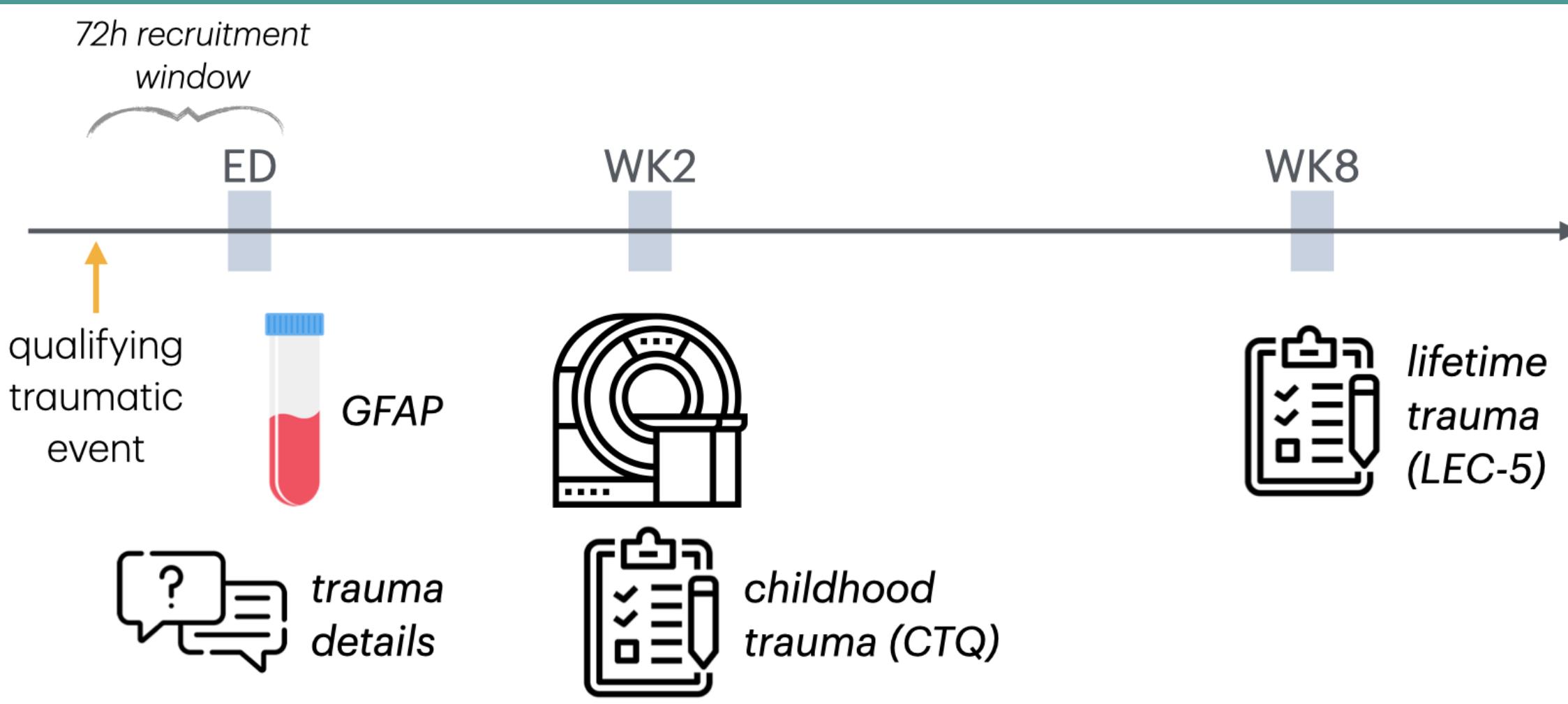
Figure 3. Tracts with reduced QA in female trauma survivors with high acute GFAP levels relative to low GFAP levels. No tracts had increased QA in the high-GFAP group compared to the low-GFAP group.
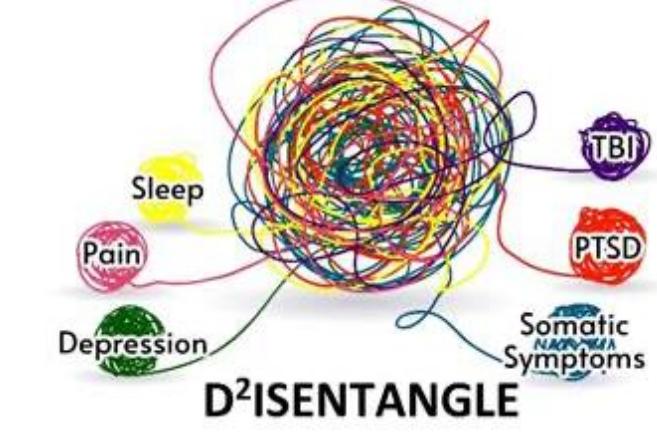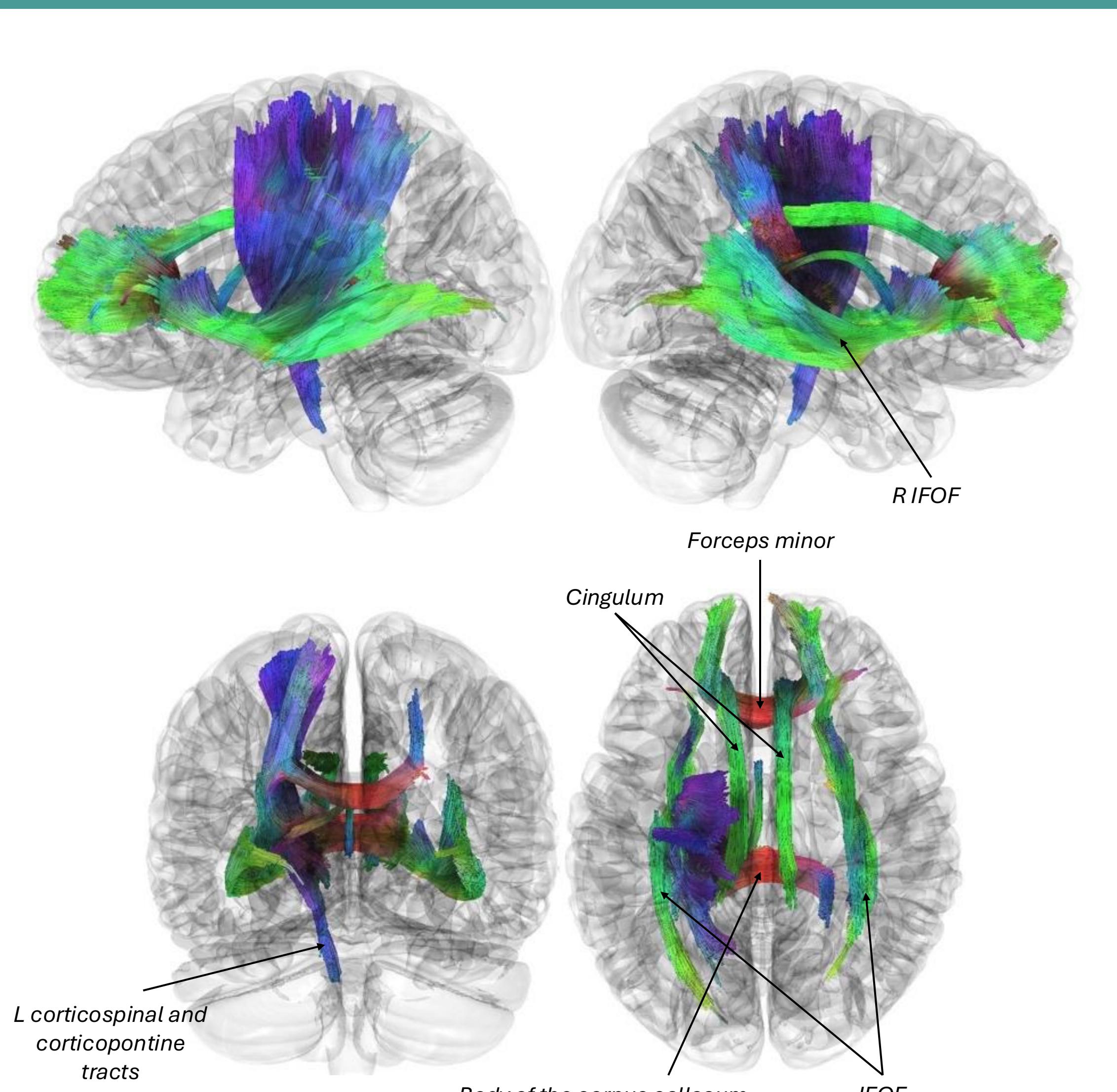

Table 1. Demographics and trauma characteristics

Variable	Male		Female	
	Low-GFAP	High-GFAP	Low-GFAP	High-GFAP
N	27	9	30	11
Age, M±SD	38.1±15.2	37.1±16.1	42.1±15.8	40.7±16.2
Race/ethnicity, Hispanic/Non-Hispanic Black/Non-Hispanic White/Non-Hispanic Other Race	4/5/17/1	2/2/4/1	0/16/14/0	0/6/5/0
Lifetime trauma types, M±SD	4.5±3.7	4.0±3.2	4.2±2.6	2.4±1.6
CTQ score, M±SD	12.9±11.1	6.4±10.4	7.1±6.8	5.1±6.3
Injury Severity Score, M±SD	2.4±2.4	3.7±2.1	2.2±1.9	4.4±4.3
Motor vehicle collision, n (%)	17 (63.0%)	4 (44.4%)	22 (73.3%)	4 (36.4%)

RESULTS

- No differences in QA by GFAP level were detected among **male** trauma survivors

- Tracts with reduced QA were detected in the high-GFAP group relative to the low-GFAP group among the **female** trauma survivors (Figure 2)

DISCUSSION

- Results are consistent with in vitro and computational models[2] and studies of sex differences in the association between white matter integrity and repetitive head impact exposure[5,6]

- Future work could examine GFAP as a continuous independent variable and the potential moderating effect of steroid hormones (e.g., estradiol, progesterone) on white matter integrity

For more information about the AURORA study:

References: [1] Levin et al., 2021 *JAMA Netw Open*; [2] Dollé et al., *Exp Neurol*; [3] McLean et al., 2020 *Mol Psychiatry*; [4] Mamouris et al., 2021 *BMC Med Res Methodol;* [5] Rubin et al., 2018 *Radiology*; [6] Sollmann et al., 2018 *Neuroimage Clin*

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