A Diffusion MRI-derived Brain Health Summary for Detecting White Matter Abnormalities After TBI

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Motivation

- Diffusion MRI free water volume fraction (FW-VF) can reflect white matter (WM) abnormalities after TBI
- Reference Intervals (RIs), following CLSI guidelines, contextualize patient values against normative variation
- Clinically useful summaries should capture distributed WM abnormalities
- **Objective: Develop a diffusion MRI based WM brain health summary (BHS) for TBI, and test associations with long-term functional and cognitive outcomes**

Materials and Methods

	Controls N (male, female)	Patients N (male, female)	Mean age (min-max)
TRACK-TBI	100 (64, 36)	487 (328,159)	37.7 (18-75)
Penn	46 (29, 17)	86 (65, 21)	38.5 (18-71)
IXI	327 (141, 186)	N/A	51.1 (20-76)
UKBB	12220 (5687, 6533)	N/A	62.1 (45-75)
Total	12693 (5921, 6772)	573 (393, 180)	37.9 (18-75)
Patients w/o lesion and 12-mo f/u		296 (198, 98)	38.0 (18-75)

Table 1. TRACK-TBI and Penn samples were harmonized with a large healthy cohort from IXI and UK Biobank studies.

- Created average and symmetry measurements of FERNET free water volume fraction (FW-VF) within major WM systems of the "Eve" atlas
  - Symmetry = 2*(LH – RH)/(LH + RH)

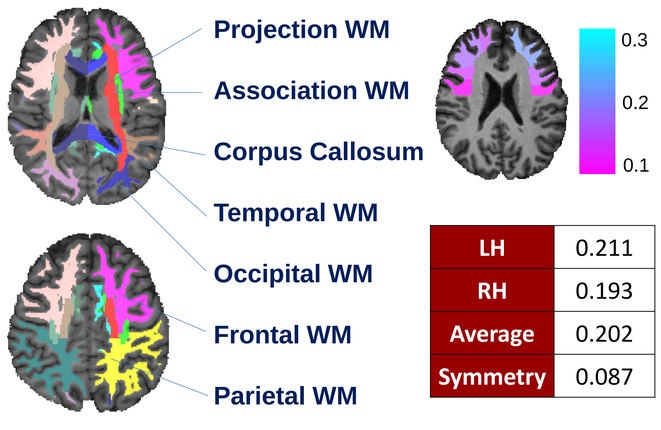
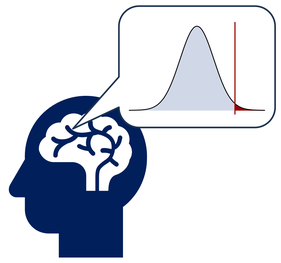


Figure 1. Left: Major WM systems of the Eve atlas. Right: FW-VF values from a 65-year-old female illustrate construction of average and symmetry measurements.

Early elevations in free-water volume fraction across specific white matter systems identify TBI patients at increased risk for impaired 12-month cognitive or functional outcome

Reference Intervals



- Imaging features were harmonized with Longitudinal ComBat
- Age- and sex-specific RIs constructed using ≥120 controls:
  - One RI per sex for ages 18-48
  - For ages 48-76, one RI per-sex and per-year
- RIs and patient measurements form the BHS:
  - Average FW-VF categorized as non-outlier, low or high outliers
  - Symmetry measurements categorized as non-outlier or outlier
- Tested association of 2-week FW-VF outliers with 12-month functional and cognitive outcomes: <10th percentile performance on RAVLT, TMTA, TMTB and GOSE≤6
  - Age- and sex-corrected logistic regression: Outcome ~ Age + Sex + I(Outlier)

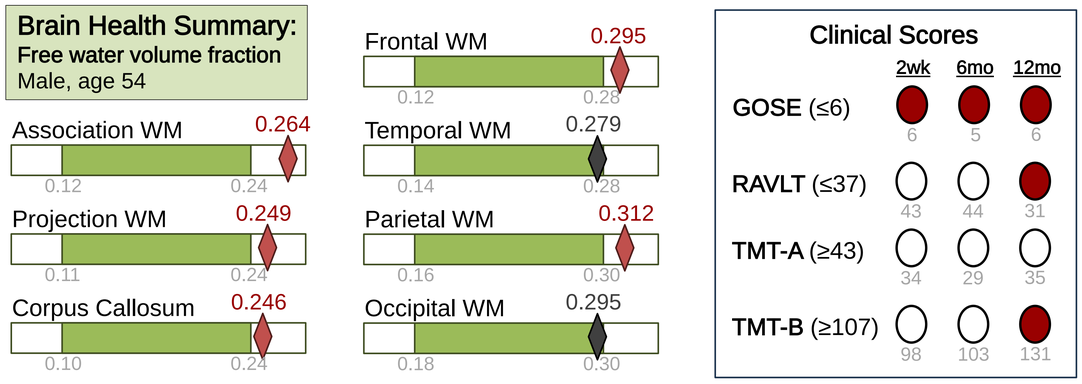


Figure 2. Example Brain Health Summary of a 54-year-old male TBI patient. Left: WM summary FW-VF values compared to demographically matching reference intervals show elevated FW-VF in several WM systems 2 weeks post-injury. Right: Clinical scores for the patient across time, compared to 10th percentile of performance among healthy controls.

Results

WM Region	Clinical test, threshold	Odds Ratio	Conf. int.	P value
Frontal	RAVLT ≤ 37	7.5	1.2-48	0.034*
Corpus Callosum	TMTB ≥ 107	6.9	1.5-32	0.013*
Association	TMTB ≥ 107	4.7	1.1-20	0.037*
Projection	GOSE ≤ 6	3.7	1.3-11	0.015

Table 2. Results of logistic regression analysis. P-values with * survived multiple comparisons correction.

- No significant associations were observed for asymmetry features, or for TMT-A time

Conclusions

- Early FW-VF elevations in corpus callosum, frontal and association WM were associated with poor one-year cognition
- Asymmetry features did not show significant associations with outcomes
- The BHS concisely summarizes patient-specific FW-VF abnormality burden distributed across multiple WM systems
- Results demonstrate feasibility of a diffusion-based brain health summary for prognostic enrichment in TBI research and clinical trial design

Funding

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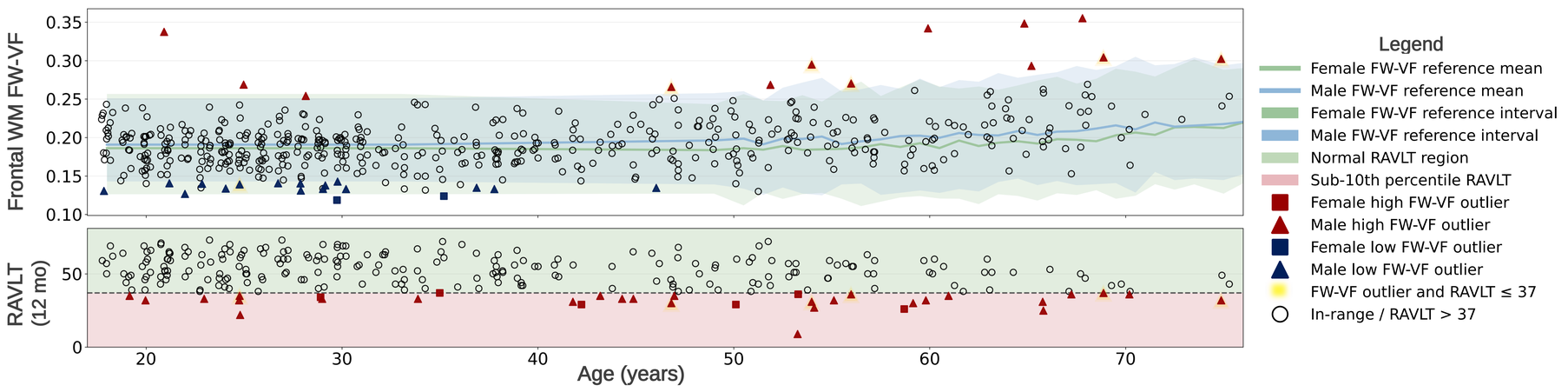

Figure 3. Top: 2-week frontal WM FW-VF values plotted against age with reference intervals for each sex and age shaded. Bottom: 12-month RAVLT plotted against age with 10th percentile shaded red. Outliers indicated by red or blue squares (female) or triangles (male). Common outliers are highlighted in yellow.