

Introduction

Alzheimer disease (AD) biological staging is defined by the progression of **amyloid (A)** and **tau (T)** accumulation, but the exact mechanisms driving downstream **neurodegeneration (N)** and **neuroinflammation (I)** remain unclear (Jack et al., 2024).

- The **biological mechanisms** impacting neuronal health and clinical progression remains unclear.
- Objective: investigate the spatiotemporal impact of A/T pathology on microstructural health.

Gray/White Interface (GWI) and **Superficial White Matter (SWM)**: Highly plastic zone of late-myelinating fibers and glia uniquely vulnerable to AD structural reorganization (Phillips et al., 2016)

- Amyloid deposits directly within the SWM, disrupting tissue and inciting inflammation.
- Tau heavily accumulates in white matter interstitial neurons.

Diffusion imaging: tracks disease progression and detects presymptomatic disruption in cortical and SWM networks (Jefferson et al., 2015; Torso et al., 2023; Weston et al., 2015).

- Previous Work**: We established that standard **Diffusion Tensor Imaging (DTI)** captures these presymptomatic GWI alterations:.
 - Amyloid drives widespread changes in high-order association cortices
 - Tau drives focal medial temporal decline.
- DTI lacks biological specificity**: conflating distinct pathologies like edema, glial proliferation, and axonal injury

Generalized diffusion basis spectrum imaging (g-DBSI): overcomes this by decomposing the diffusion signal into distinct, histologically validated compartments (Wang et al., 2026).

Mapping biologically specific g-DBSI metrics to amyloid and tau at the GWI will elucidate the microstructural cascade driving AD progression and clinical decline

Methods

Imaging & Processing Pipelines:

- T1-weighted MRI**: Processed using the FreeSurfer Desikan-Killiany atlas and FSL FAST for tissue segmentation.
- PET Imaging**: Processed using the PUP PET Pipeline to generate regional amyloid and tau Standardized Uptake Value Ratios (SUVR).
- Diffusion MRI**: Multi-shell diffusion data were modeled using the generalized Diffusion Basis Spectrum Imaging (g-DBSI) to generate voxel maps:
 - RAF (Restricted Anisotropic Fraction)**: Neuronal Wiring (*Axon & dendrite integrity*)
 - RIF (Restricted Isotropic Fraction)**: Total Cellularity (*Glial cells & cell bodies*)
 - HIF (Hindered Isotropic Fraction)**: Extracellular Fluid (*Edema & tissue swelling*)
 - PF (Perfusion Fraction)**: Vascular Health (*Blood flow & BBB permeability*)

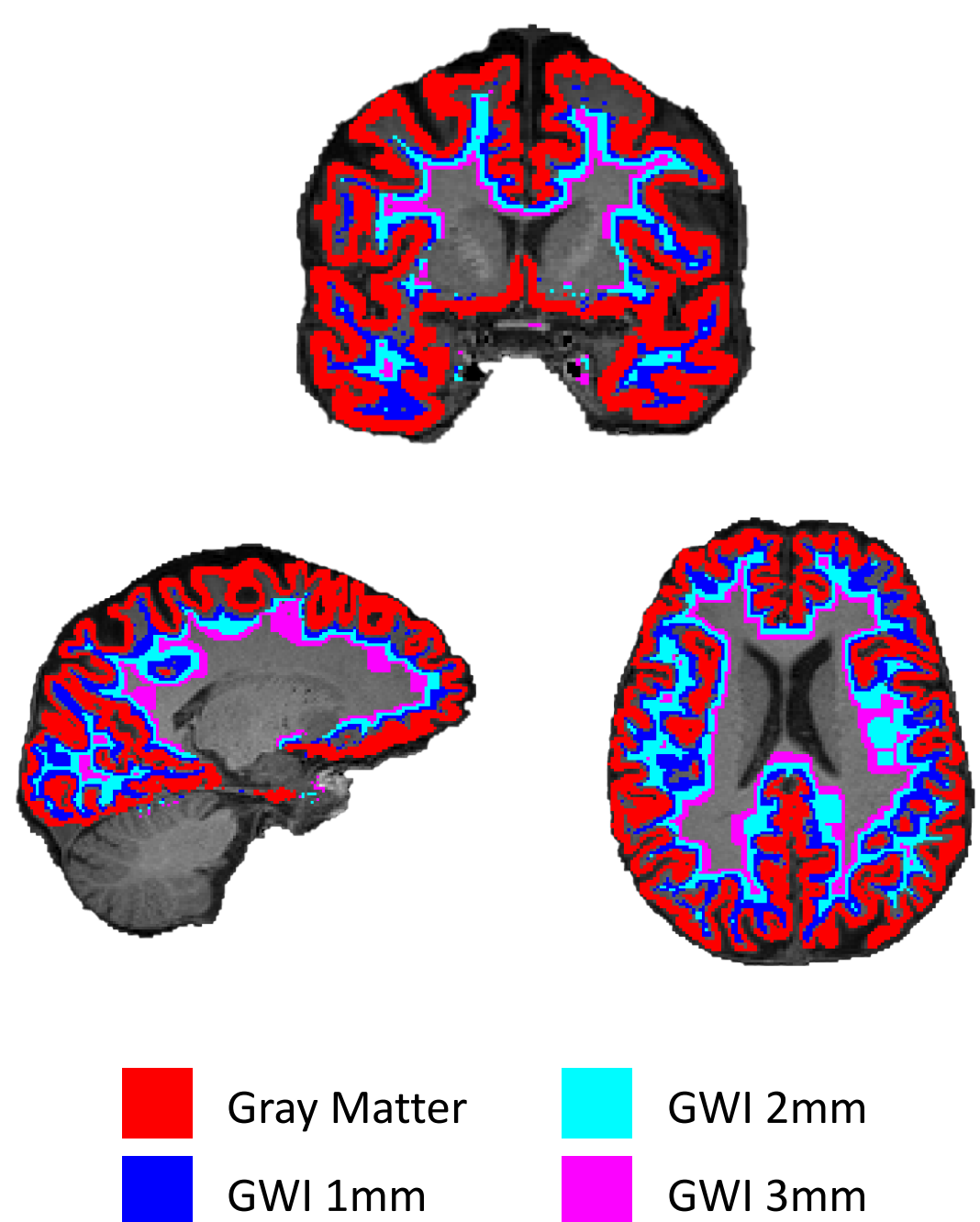
GWI Extraction Workflow: Each FS cortical gray matter region was dilated by 3mm into white matter. These regions were then registered into the participant's diffusion space to extract g-DBSI metrics

Statistical Analysis: General linear models computed in R assessed the regional effects of protein burden on microstructural integrity.

- Model**: gDBSI ~ PET SUVR + Age

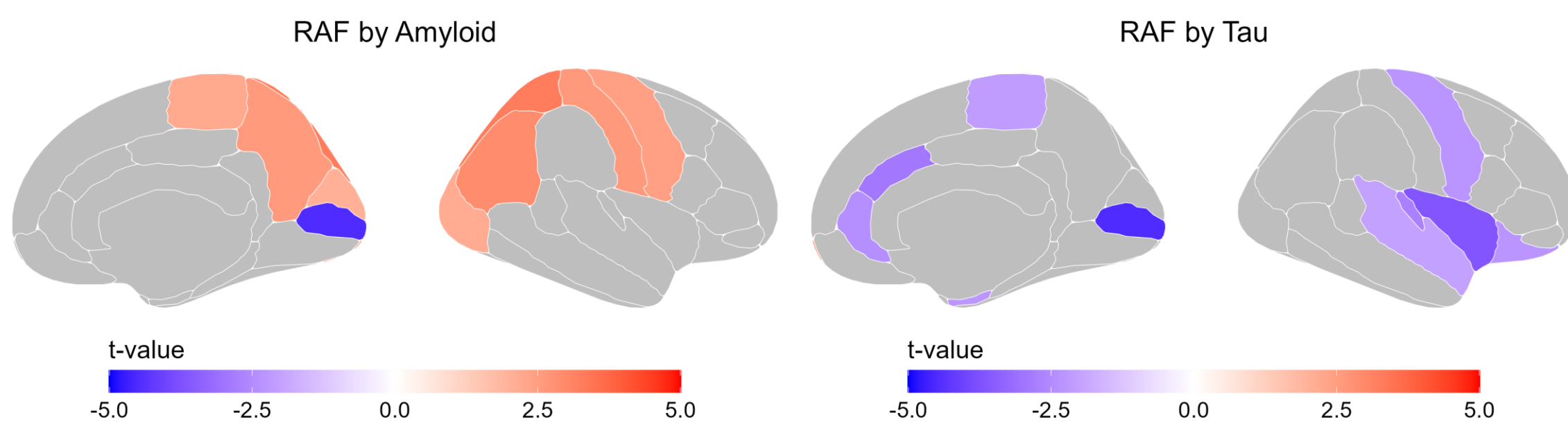
Participant Demographics and Clinical Characteristics	
Knight ADRC Cohort	
Characteristic	N = 162 [†]
Age (Years)	69.2 (8.9)
Sex	
F	91 (56%)
M	71 (44%)
Race/Ethnicity	
White	145 (90%)
Black	16 (9.9%)
Other	1 (0.6%)
Education (Years)	16.3 (2.2)
Clinical Dementia Rating	
CDR = 0	148 (91%)
CDR > 0	14 (8.6%)
Amyloid Status	
A-	121 (75%)
A+	40 (25%)

[†] Mean (SD); n (%)



Results

Restricted Anisotropic Fraction (RAF): Neurofilament Density



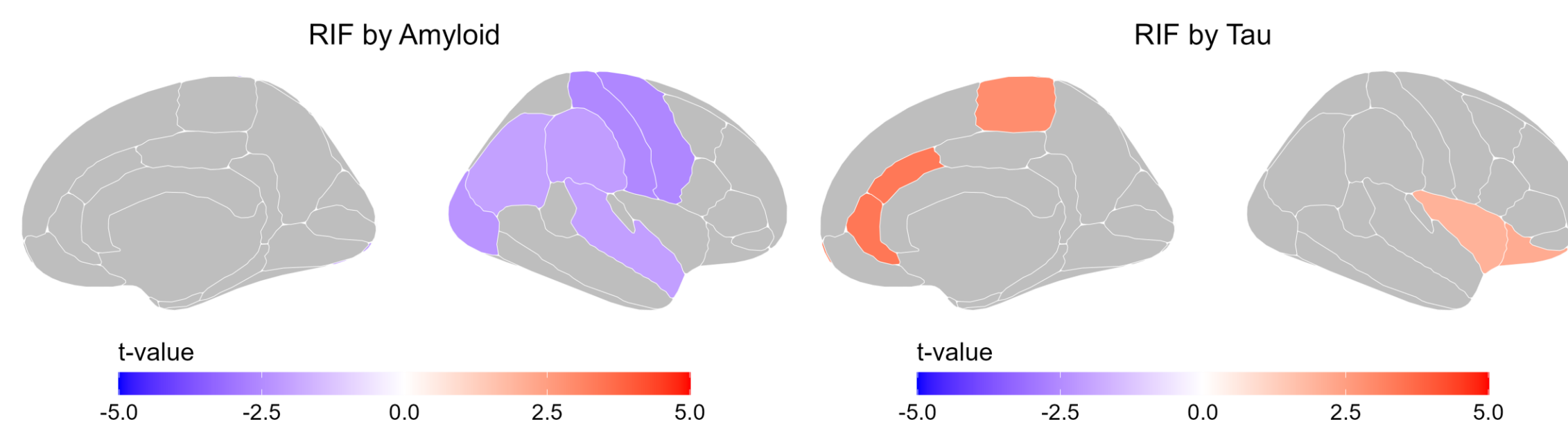
Amyloid: Widespread increases (parietal/frontal) and focal decreases (medial occipital) reflect early compensatory dendritic sprouting and astrocyte expansion mimicking higher neurofilament density.

Tau: Marked decreases (anterior cingulate, insular, temporal) capture the early breakdown of neuronal fibers, marking the onset of microstructural decline.

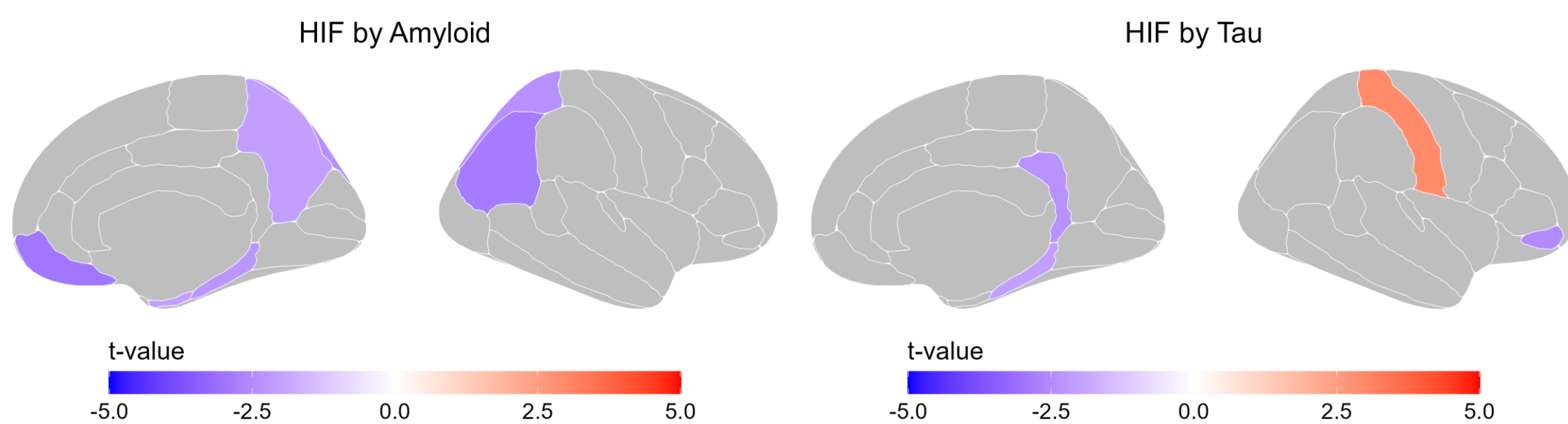
Restricted Isotropic Fraction (RIF): Cellularity

Amyloid: Widespread decreases (parietal/temporal) reflect early reductions in total cellularity, capturing initial cellular vulnerability before the onset of active inflammation.

Tau: Localized increases (anterior cingulate, medial frontal) map emerging microglial and astrocytic proliferation, signaling a shift toward active neuroinflammation.



Hindered Isotropic Fraction (HIF): Extracellular Edema



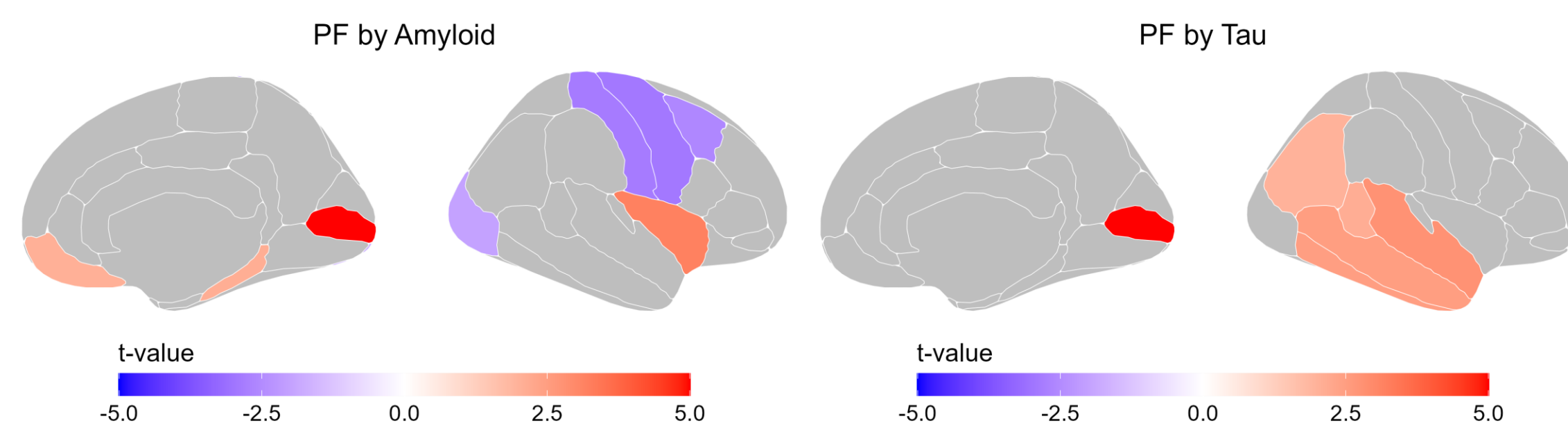
Amyloid: Decreases (entorhinal/parietal/orbitofrontal) indicate that early amyloidosis is not yet characterized by extracellular swelling reflecting a state of dense tissue packing before active inflammation begins.

Tau: While dense packing persists in the highly vulnerable MTL, focal increases (sensory) capture early extracellular swelling (edema), distinctly separating the tau response from the amyloid phase.

Perfusion Fraction (PF): Cerebrovascular Perfusion

Amyloid: Divergent regional changes (sensorimotor/frontal decreases vs. orbitofrontal/insular increases) reflect an early, localized vascular response.

Tau: Widespread increases (lateral temporal/inferior parietal) reflect elevated blood flow and increased vascular permeability during initial neuroinflammation.



Discussion

g-DBSI distinguishes two distinct stages of neurodegeneration (N) and neuroinflammation (I) at the gray/white interface (GWI):

- Amyloid Phase (Early N & I)**: Initial cellular vulnerability (**early N**; ↓RIF) and dense tissue packing (↓HIF) trigger a compensatory structural immune response via localized astrocytic expansion (**early I**; ↑RAF).
- Tau Phase (Active N & I)**: Propagating tau overwhelms this defense, driving glial proliferation and vascular permeability (**active I**; ↑RIF, ↑PF) and active neuronal fiber destruction (**active N**; ↓RAF).

g-DBSI provides stage-specific, biologically grounded biomarkers for Alzheimer disease monitoring.

- By directly disentangling these specific stages of (N) and (I), g-DBSI overcomes the confounding limitations of traditional DTI.

Yields noninvasive targets to evaluate disease-modifying therapies, predict clinical progression, and track treatment-emergent neuroinflammatory adverse events.

References

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