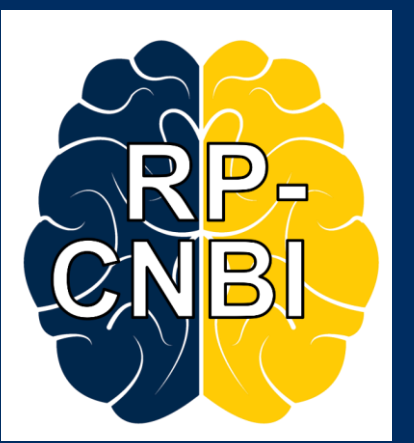


Gray matter microstructural degeneration patterns associated with plasma TDP-43 and pTau-217 in older adults with memory impairments

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Research Program on Cognition and Neuromodulation Based Interventions

Introduction

- Transactive response DNA-binding protein of 43 kDa (TDP-43) proteinopathy is frequently observed in medial temporal lobe (MTL) regions of older adults, leading to the conceptualization of limbic-predominant age-related TDP-43 encephalopathy (LATE)^{1,2}.
- Postmortem* studies showed that LATE neuropathological changes (LATE-NC) were characterized by structural alterations of MTL regions^{3,4}.
- However, the recent emergence of candidate plasma TDP-43 biomarkers raises the possibility of *antemortem* investigations of LATE-NC.

Goals: Examine the relationships between plasma TDP-43, pTau-217, and brain microstructural integrity in older adults with amnesic MCI or dementia of Alzheimer's type (DAT).

Methods

Participants

We enrolled **195** older adults with consensus conference-based diagnosis of aMCI or mild DAT from the Stimulation to Improve Memory study (R01AG058724; NCT03875326; PI: Hampstead) (**Table 1**).

Neuropsychological assessment

We administered a comprehensive neuropsychological assessment including tests from the Uniformed Data Set v3 to each participant to establish their clinical diagnosis (i.e., aMCI or DAT).

Characteristic	Mean (SD) or N (%)
Age (in years)	72.18 (7.08)
Sex (male)	107 (54.88%)
Education (in years)	16.06 (2.50)
Clinical diagnosis (aMCI/DAT)	131 (67.18%)/64 (32.82%)
MoCA total (out of 30)	20.39 (4.52)
TDP-43 (pg/mL)	1,895.90 (2,126.97)
pTau-217 (pg/mL)	1.09 (0.64)
NfL (pg/mL)	20.00 (16.62)

Table 1 – Demographic and clinical characteristics

Plasma analysis

We used single-molecule array (SIMOA®) technology to estimate plasma levels of TDP-43 and pTau-217 on a Quanterix HD-X analyzer.

3T MRI

- We applied the neurite orientation dispersion and density imaging (NODDI) model to diffusion-weighted images, resulting in three parameters (**Figure 1**):
 - Neurite density index (NDI) reflects the density of dendrites and axons.
 - Orientation dispersion index (ODI) reflects the dendritic arborization complexity.
 - Free water fraction (FWF) reflects volume occupied by CSF and is a marker of tissue damage and neuroinflammation.

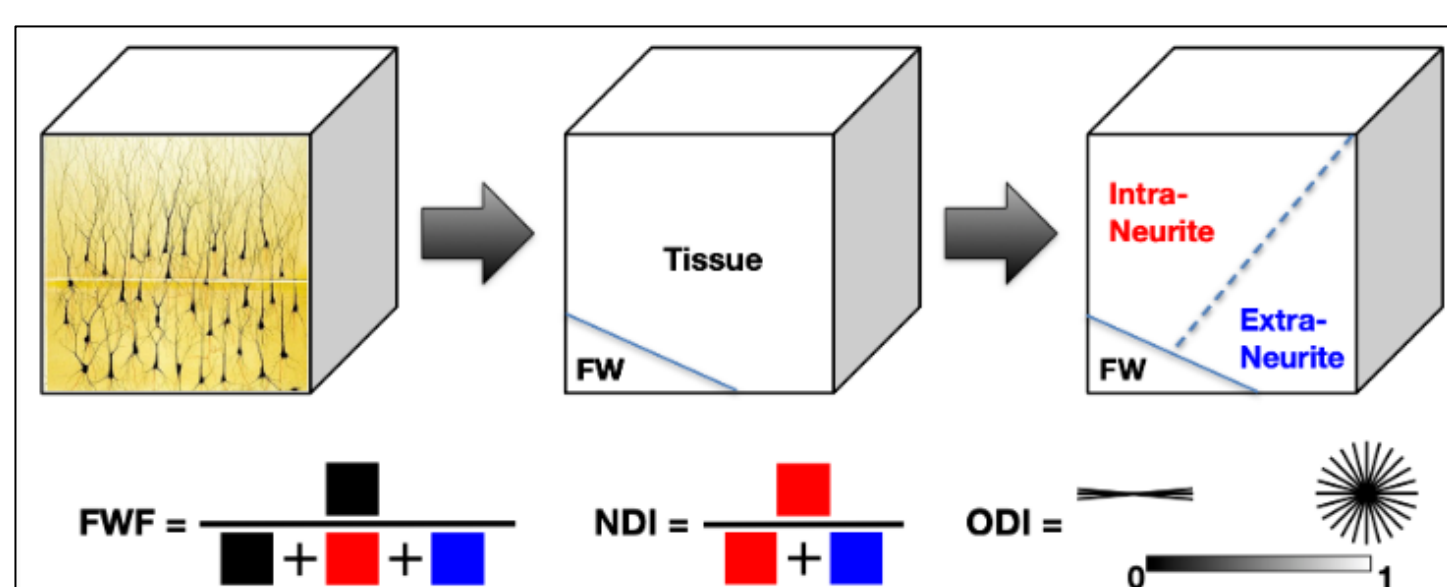


Figure 1 – NODDI parameters

- We segmented MTL regions (i.e., hippocampus, amygdala, parahippocampal cortex (PHC), entorhinal cortex (ERC)) using the Automatic Segmentation of Hippocampal Subfields⁵ (ASHS) pipeline on T1-weighted images. For each MTL region, we calculated averaged NDI, ODI, and FWF across left and right hemispheres.
- We projected NODDI maps onto individual surfaces that were generated from T1-weighted images using the Computational Anatomy Toolbox v12 (CAT12). We then normalized individual NODDI surface maps to a template surface.

Statistical analyses

- For each MTL region, we constructed a linear regression model with plasma TDP-43 or pTau-217 as predictor and average NDI, ODI or FWF as outcome. We set the significance threshold at $p < .05$.
- We also performed surface-based regressions to examine the relationships between plasma TDP-43 or pTau-217 and NODDI parameters in the whole neocortex. We set significance at vertex-level $p < .001$ and cluster-level $p_{FWE} < .05$.
- We controlled for age, sex, and education in all analyses.

Plasma TDP-43 is associated with lower NDI in MTL regions

- Greater plasma TDP-43 was significantly associated with lower NDI in the hippocampus and PHC (**Figures 2 and 3**). Associations remained significant after covarying pTau-217.
- Plasma TDP-43 was not associated with ODI and FWF in MTL regions.
- Surface-based regressions did not show significant associations of TDP-43 with NODDI parameters in the whole neocortex.

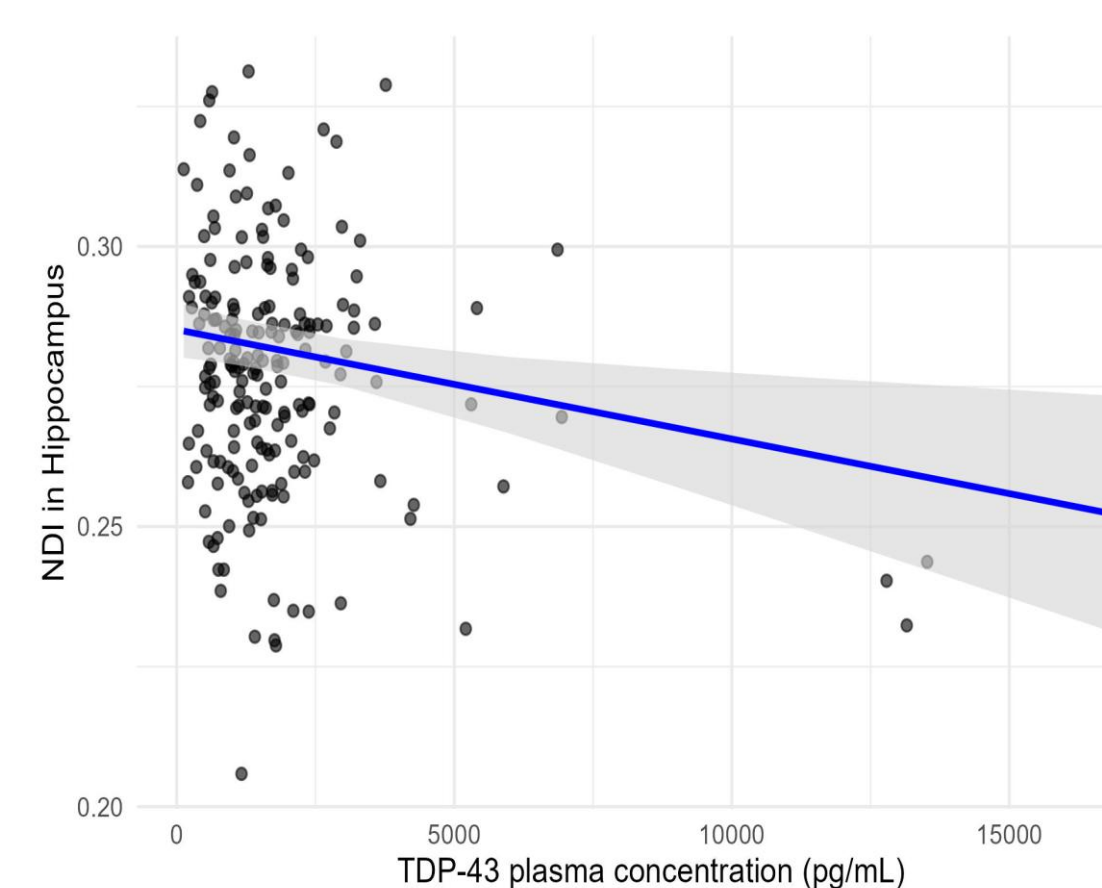


Figure 2 – Relationship between plasma TDP-43 and NDI in the hippocampus.

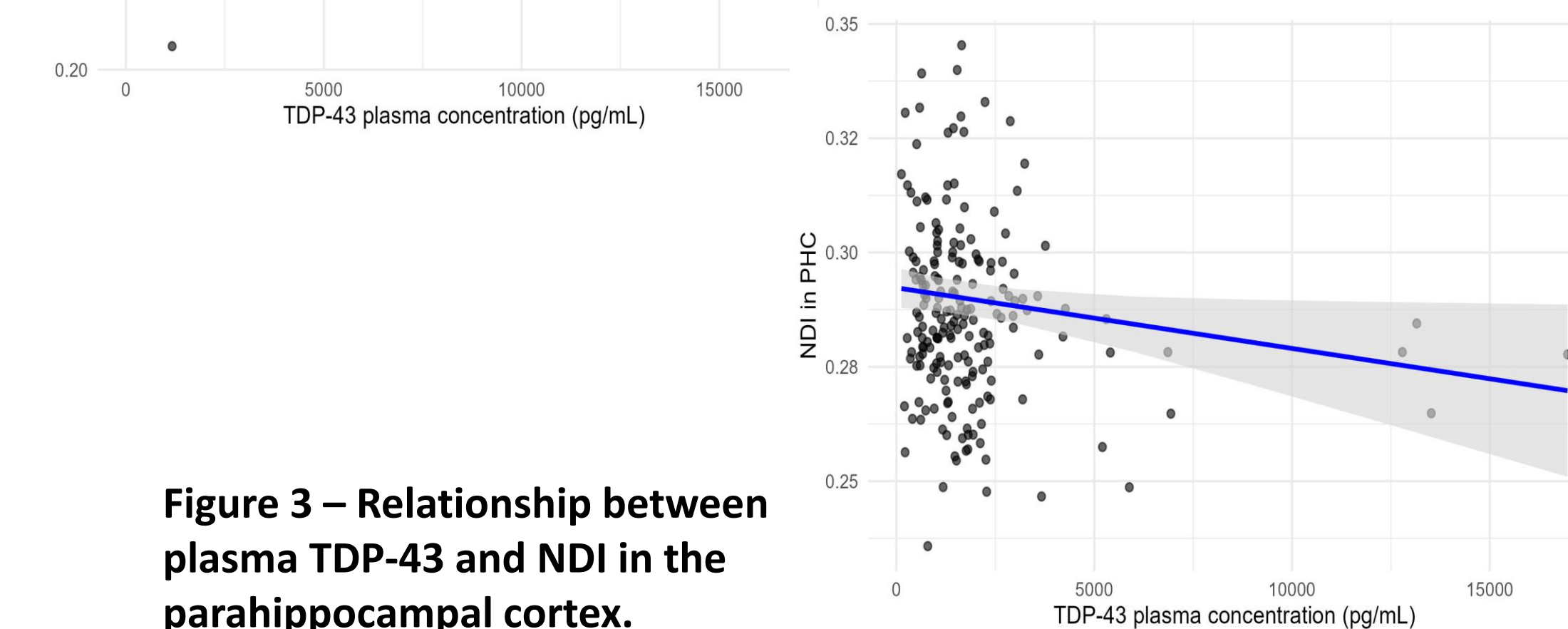


Figure 3 – Relationship between plasma TDP-43 and NDI in the parahippocampal cortex.

Plasma pTau-217 is associated with lower ODI and greater FWF in MTL and neocortical regions

- Greater plasma pTau-217 was significantly associated with lower ODI in PHC and ERC (**Figure 4**) and greater FWF in all four MTL regions (**Figure 5**).
- Surface-based regressions showed that greater plasma pTau-217 was associated with lower ODI and greater FWF in lateral frontal and temporo-parietal regions (**Figure 6**).
- All associations remained significant after covarying TDP-43.

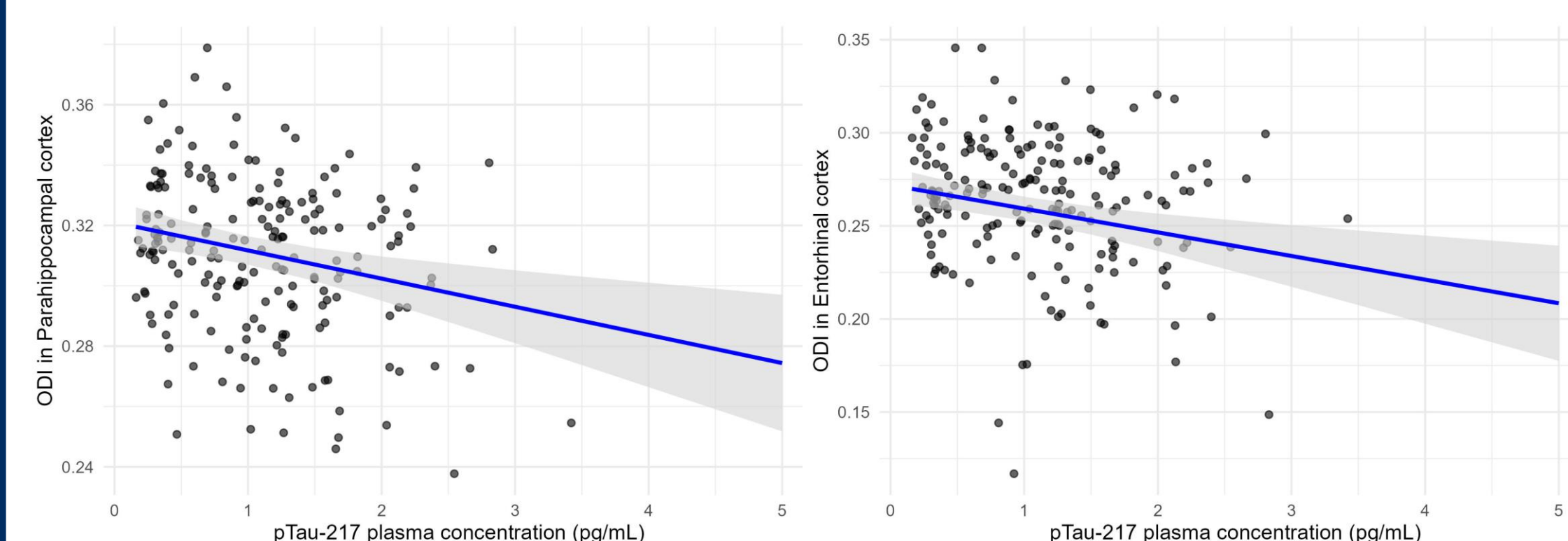


Figure 4 – Relationship between plasma pTau-217 and ODI in the parahippocampal cortex (left) and entorhinal cortex (right).

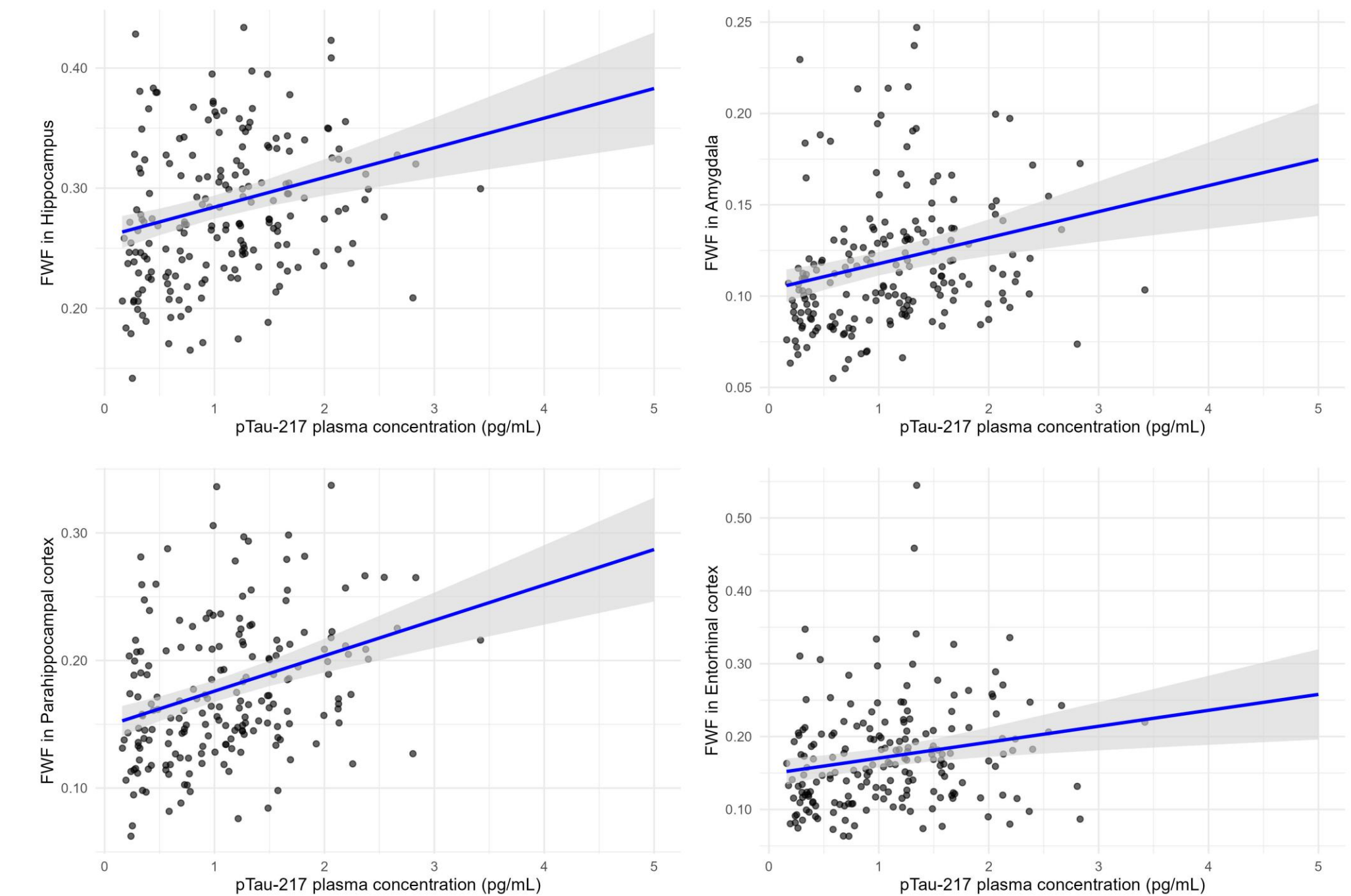


Figure 5 – Relationship between plasma pTau-217 and FWF in MTL regions.

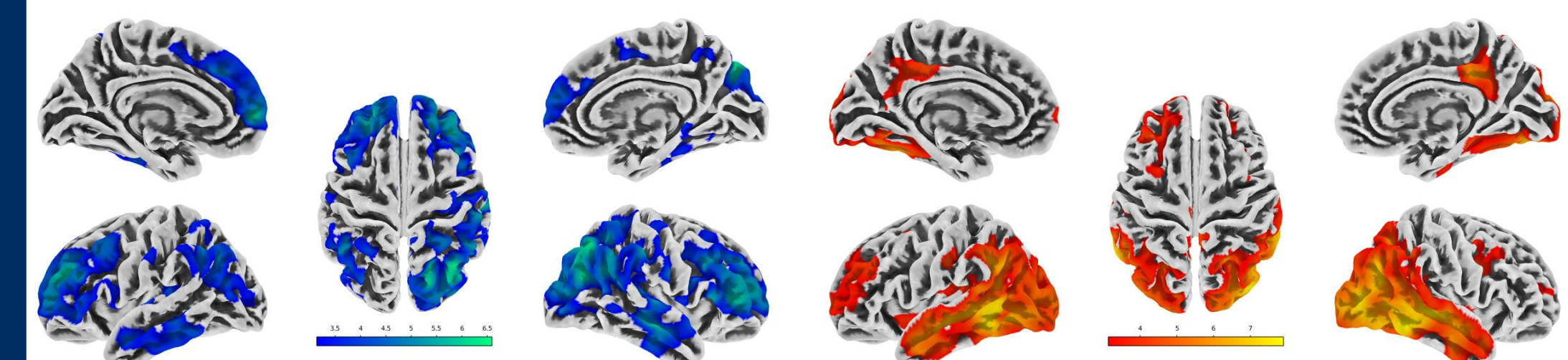


Figure 6 – Relationship between plasma pTau-217 and ODI (left) and FWF (right) in neocortex.

Discussion

- Plasma TDP-43 is associated with lower density of dendrites and axons restricted to MTL regions.
- Plasma pTau-217 is associated with lower dendritic arborization complexity and greater tissue damage and neuroinflammation in MTL regions but also neocortical regions.

Conclusion: Our findings show distinct patterns of GM microstructural alterations associated with plasma TDP-43 and pTau-217, raising the possibility that combining plasma biomarkers and NODDI may help distinguish LATE-NC from Alzheimer's disease neuropathological changes *in vivo*.

References

- Nelson *et al.* *Brain* 2019;142:1503–27.
- Wolk *et al.* *Alzheimer's Dement* 2025;21:e14202.
- Bejanin *et al.* *Brain* 2019;142:3621–35.
- Wesseling *et al.* *Brain* 2025;148:3913–23.
- Xie *et al.* *MICCAI 2016, 19th International Conference, Athens, Greece, October 17-21, 2016, Proceedings, Part II. Lect Notes Comput Sci* 2016;9901:564–71.

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