

Extra-Axonal Diffusivity MRI as a Myelin-Sensitive Biomarker of Cognitive and Functional Decline in the Clinical Alzheimer's Disease Continuum

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Background

- Demyelination is a core feature of Alzheimer's disease (AD) with evidence demonstrating its implications in cognitive and functional decline during normative aging¹. However, human evidence for scalable myelin biomarkers remains limited, especially across the clinical AD continuum.
- Myelin water fraction (MWF) is a highly specific MRI measure of myelin². However, it requires specialized sequences, hampering its integration in large multisite cohorts.
- Extra-axonal diffusivities (radial [$De_{\perp}$] and global [De]), derived from widely integrated multishell diffusion MRI sequence, have been shown to be selectively sensitive to demyelination *via* changes in extra-axonal space tortuosity³. However, validation against myelin-specific measures and large-scale human studies have been lacking.

➔ We used the GESTAMP cohort to validate $De_{\perp}$ and De 's in-vivo sensitivity to myelin.

➔ We leveraged ADNI data to investigate the associations of $De_{\perp}$ and De with longitudinal changes in cognition and daily functioning in cognitively normal (CN) and cognitively impaired (CI) adults.

Methods

GESTAMP cohort (biomarkers validation study):

- 74 participants underwent multishell diffusion MRI and BMC-mcDESPOT imaging.
- Extra-axonal diffusivity metrics (radial, $De_{\perp}$, and global, De) were derived using the Standard Model of Imaging (SMI)³.
- MWF was derived using BMC-mcDESPOT⁴.
- Pearson correlations were used to assess associations between $De_{\perp}$ or De and MWF.

ADNI cohort (clinical relevance study):

- 299 CN and 178 CI (predominantly MCI, N = 154) participants with baseline multishell diffusion MRI and longitudinal Clinical Dementia Rating-Sum of Boxes (CDR-SB) assessments were included.
- $De_{\perp}$ and De were derived using SMI³.
- Linear mixed-effects models examined whether baseline $De_{\perp}$ or De biomarker predict longitudinal changes in CDR-SB, adjusting for age, sex, diagnosis (CN, CI), time, and biomarker-by-time interactions, with subject-specific random intercepts.
- Parallel analyses were performed for amyloid-PET or tau-PET in participants with available PET data.

Results & Discussion

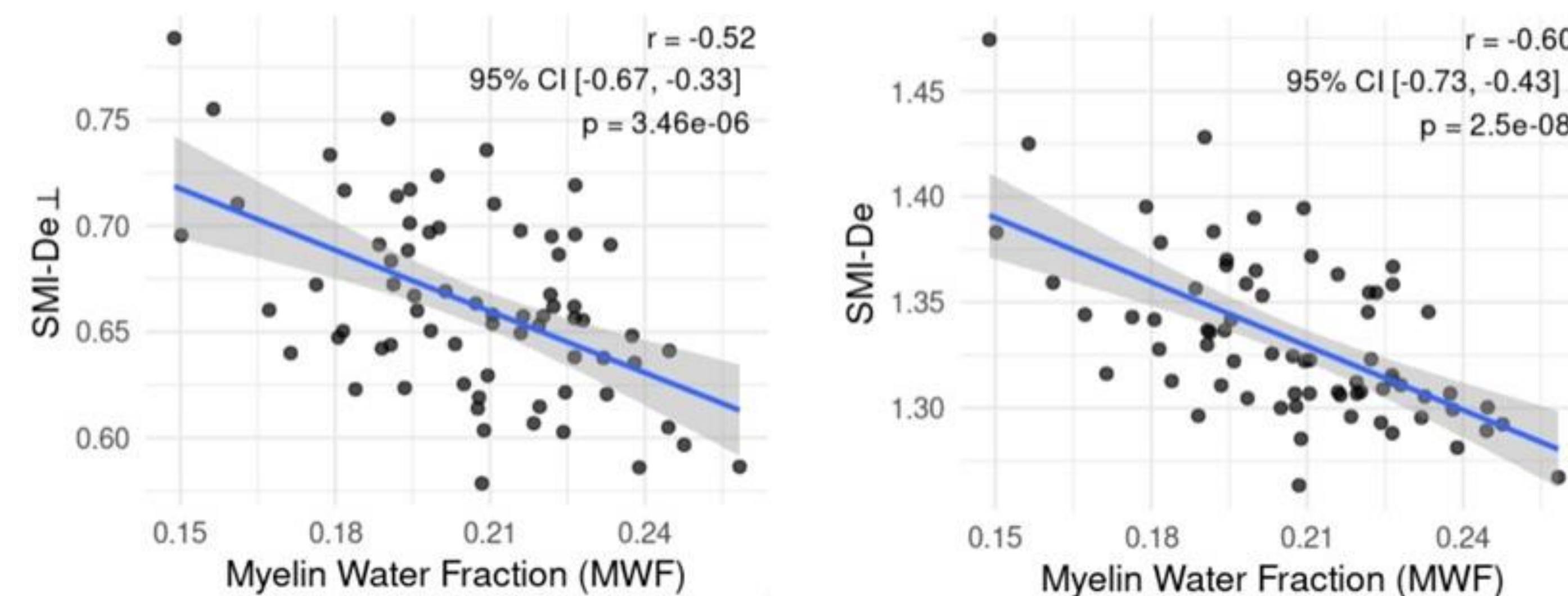


Figure 1. Pearson correlation between $De_{\perp}$ or De and MWF.

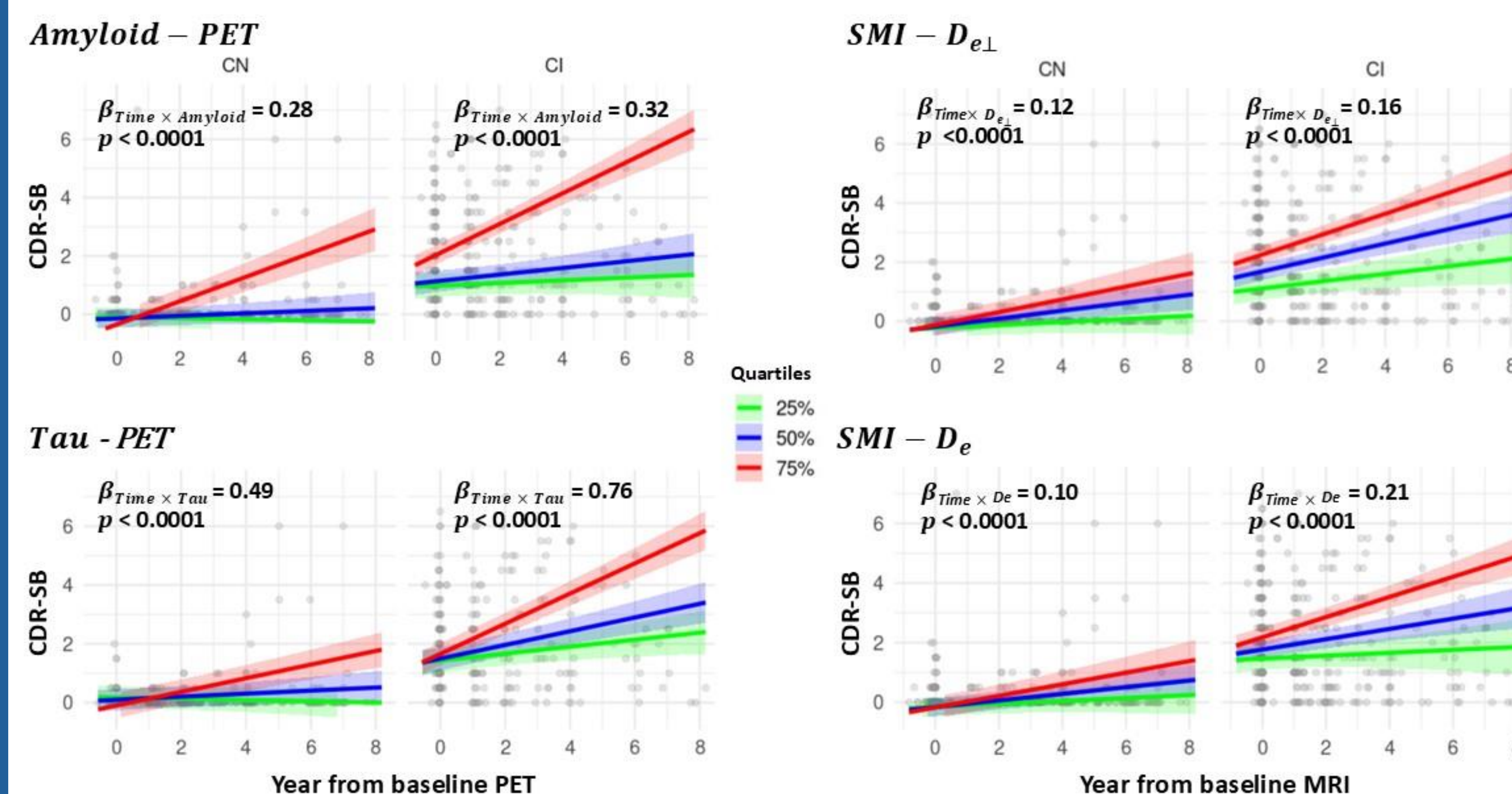


Figure 2. Baseline $De_{\perp}$, De , amyloid-PET or tau-PET association with longitudinal changes in CDR-SB. Predicted CDR-SB trajectories as a function of time are shown for 3 quantiles for the CN and CI groups.

❖ $De_{\perp}$ and De showed strong correlations with MWF with, as expected, higher $De_{\perp}$ or De values associated with lower MWF values (Fig1), supporting their sensitivity to myelin differences.

❖ Higher baseline $De_{\perp}$ and De predicted faster CDR-SB progression in CN and CI, with larger effect size seen in CI (Fig. 2).

❖ Amyloid-PET and tau-PET showed only modest CDR-SB increases except in the highest quartile, consistent with prognostic value only when pathology is severe (Fig. 2).

➔ Strong inverse associations with MWF support the physiological sensitivity of extra-axonal diffusivities ($De_{\perp}$ and De) to myelin integrity *in vivo*.

➔ Higher baseline $De_{\perp}$ and De predicted faster cognitive and functional decline across the AD continuum, linking demyelination-related white matter differences to clinical progression.

➔ Extra-axonal diffusivity may provide a scalable, noninvasive myelin-sensitive biomarker for monitoring disease progression in aging and AD.

¹ Gong et al. A&D 2023 (PMC10387505)

² Bae et al. NeuroImage 2026 (PMC13084559)

³ Coronado-Leija et al. Imaging Neuroscience 2024 (PMC12272244)

⁴ Bouhrara et al. NeuroImage 2016 (PMC4854306)