DOI: 10.1002/alz.091032

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POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

NEUROIMAGING

A clock model of regional tau-PET accumulation and cognitive decline in sporadic early-onset Alzheimer's disease

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Abstract

Background: The timing of tau-PET accumulation and cognitive decline in sporadic early-onset Alzheimer's disease (eoAD, age-at-onset<65) has not been established and is needed to optimize tau-PET as an outcome measure in clinical trials. Here we leverage large-sample, longitudinal data from the Longitudinal Early-onset Alzheimer's Disease Study (LEADS) to model tau-PET accumulation in three regions relative to cognitive decline.

Method: Longitudinal [^{18}F]Flortaucipir-PET (FTP) and CDR-SB scores were acquired in 195 amyloid-PET-positive, sporadic eoAD patients with MCI or mild dementia due to AD at baseline (Table 1). FTP scans were referenced against inferior cerebellar GM, and mean SUVRs calculated in three meta-ROIs comprising temporal, parietal, and frontal association cortices (Figure 1A). Generalized additive models estimated nonlinear relations between: (1) baseline SUVRs and annualized rates-of-change in each meta-ROI, and (2) baseline CDR-SB and annualized rates-of-change in cognition. Integrating these baseline-by-change functions yielded regional FTP and CDR-SB trajectories over time. An exhaustive search algorithm identified optimal time-shifts between each regional tau trajectory and CDR-SB progression that minimized the error between model-predicted and observed data at baseline. This time-shifting procedure was repeated in a held-out dataset of 184 eoAD patients to assess out-of-sample reproducibility (Table 1).

Result: FTP SUVRs and CDR-SB scores increased longitudinally in most patients (Figure 1B,C). Baseline SUVR by rate-of-change associations were inverted U-shaped in each meta-ROI (Figure 1D), and similar associations were found for CDR-SB

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progression (Figure 1E). Time-shift estimation in the training dataset converged on a single, best-fitting model in which temporal and parietal FTP accumulation led clinical onset by 4.5 years, while frontal FTP accumulation began 0.5 years before clinical onset (Figure 2A). The replication dataset yielded nearly identical results (Figure 2B). We estimate that the full timecourse of FTP accumulation and cognitive decline occurs over ~16 years from earliest detectable change in FTP.

Conclusion: Tau-PET accumulation in the frontal meta-ROI immediately precedes cognitive decline and tracks closely with clinical progression in eoAD, while temporoparietal tau-PET is prominent at clinical onset and plateaus as dementia worsens. For clinical trials in symptomatic patients, temporal and parietal tau-PET may therefore aid staging and inclusion criteria, while frontal tau-PET is likely superior for monitoring longitudinal change.

	Training Set: N = 195 eoAD patients	Test Set: N = 184 eoAD patients
Age at baseline	59.3 ± 4.0 (range: 45-65)	58.9 ± 4.0 (range: 49-65)
Sex (F/M)	105/90	95/89
APOE-ε4 carriers (No/Yes/Unknown)	83/95/17	30/47/107
CDR-SB at baseline	3.6 ± 1.7	4.2 ± 2.0
MMSE at baseline	21.8 ± 5.0	20.9 ± 5.6
Aβ-PET Centiloids at baseline	95.3 ± 25.5	94.9 ± 25.5
FTP scans per patient	2.5 ± 0.7 (range: 2-4)	1
Inter-scan interval (FTP)	1.3 ± 0.4	-
CDR exams per patient	3.0 ± 0.9 (range: 1-5)	1.2 ± 0.5 (range: 1-4)
Inter-test interval (CDR)	1.2 ± 0.4	1.3 ± 0.5

Table 1. Patient demographics. Values are mean ± SD across patients. The training set included all eoAD patients with 2+ FTP scans. The test set was limited to all eoAD patients with only 1 FTP scan (either due to recent enrollment or study dropout).

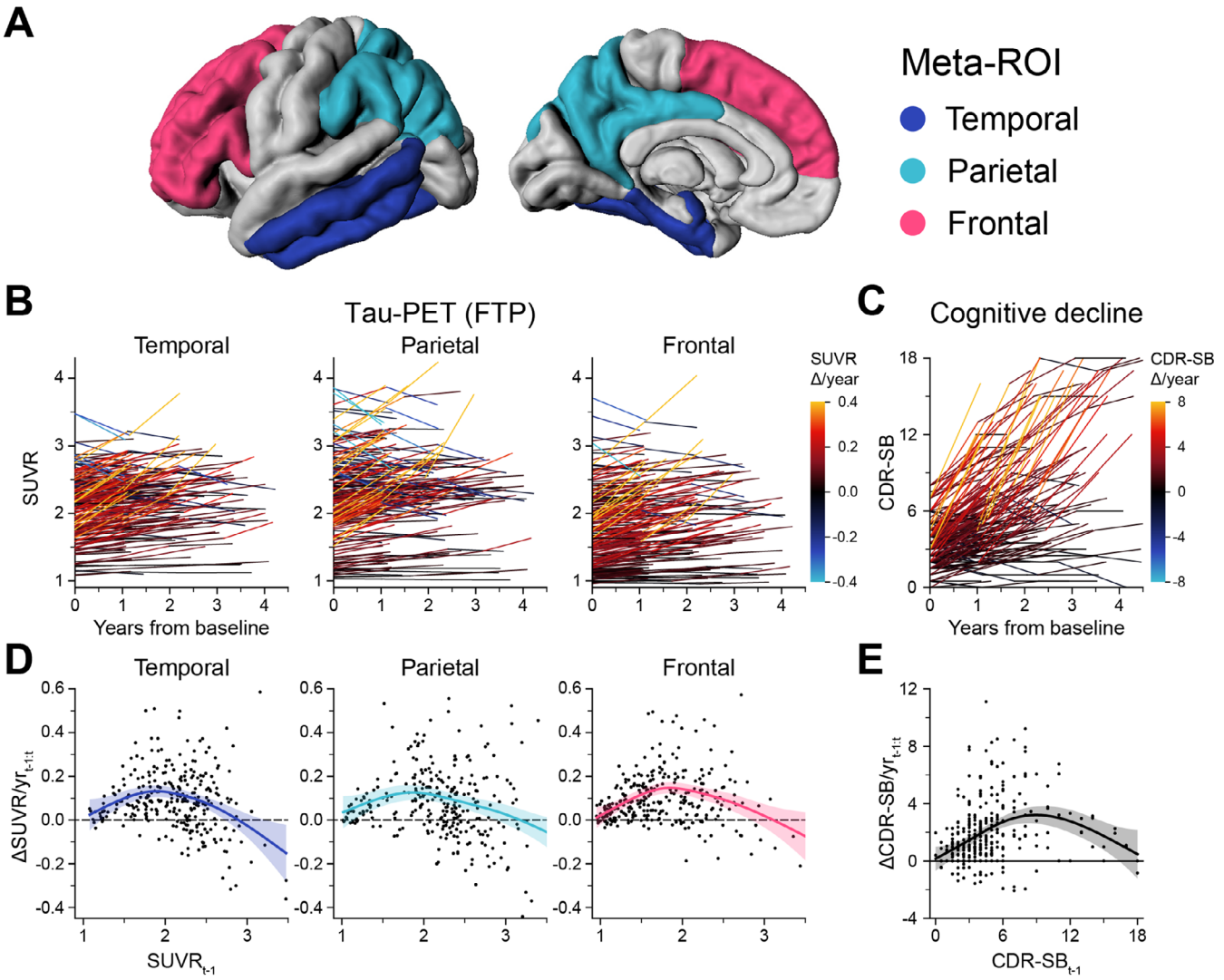


Figure 1. Longitudinal tau-PET SUVRs and CDR-SB scores. (A) Bilateral meta-ROIs are shown in one hemisphere for comparison. **(B,C)** Spaghetti plots show mean FTP SUVRs (**B**) and CDR-SB scores (**C**) in 195 eoAD patients over time. **(D,E)** Baseline by annualized rate-of-change associations are shown for FTP meta-ROIs (**D**) and CDR-SB scores (**E**). Each point = 1 timepoint from 1 patient. Generalized additive model fits with 95% confidence intervals are overlaid on each scatterplot.

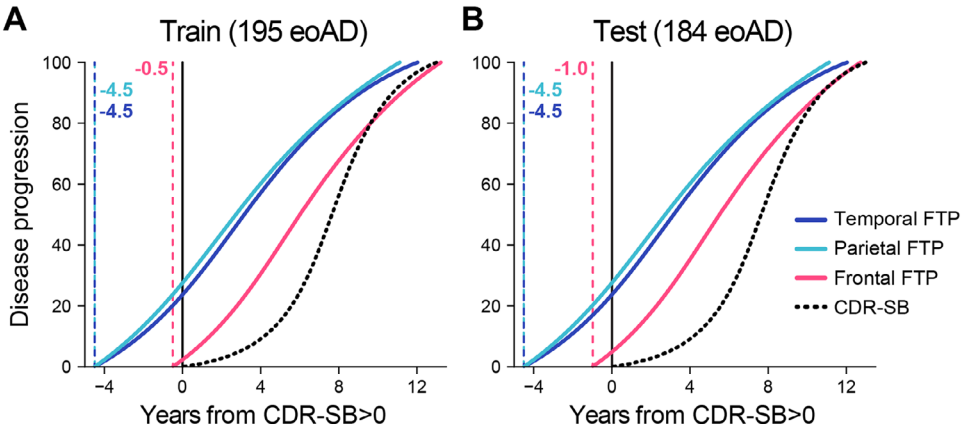


Figure 2. Clock models of tau-PET accumulation and cognitive decline. Best-fitting models of regional FTP accumulation and CDR-SB progression are shown in separate training (**A**) and testing (**B**) datasets of sporadic eoAD patients. SUVR and CDR-SB scores are rescaled from 0 (SUVR=1.22, CDR-SB=0) to 100 (SUVR=2.72, CDR-SB=18) for purpose of visualization. For SUVR, this corresponds to the range at which FTP signal was increasing longitudinally with ≥95% confidence across patients.