

Regional tau thresholds that mark transitions across the Alzheimer's disease continuum

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BACKGROUND

Clinical progression along the Alzheimer's disease (AD) continuum is a key secondary endpoint in anti-amyloid and anti-tau therapeutic trials. However, the regional tau burden required to drive transitions between clinical stages remains poorly defined.

Here, we used the CenTauR (CTR) scale to examine the level of tau at the time of clinical progression at different stages of Alzheimer's disease clinical continuum.

METHODS

- Participants (n = 188): From the Australian Imaging, Biomarker and Lifestyle (AIBL) Flagship Study of Ageing, Alzheimer's Disease Neuroimaging Initiative (ADNI) and A4 placebo arm:



- Inclusion:

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Who were Aβ-PET positive (Centiloid >25) & progressed ≥ 0.5 on CDR:

- CDR 0→≥0.5 (n=108); CU-Progression
- CDR 0.5→≥1 (n=62); MCI-Progression
- CDR 1→≥2 (n=18); Dementia-Progression

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Level of tau (MK6240 & FTP) and other measures at the visit immediately preceding clinical progression were compared.

RESULTS

	CU-Progression	MCI-Progression	Dementia-Progression
Number (n = 188)	108	62	18
Sex, Female% (n)	52% (55)	39% (21)	50% (8)
YoE, years	16.0 [14.0, 18.0]	15.0 [13.0, 17.0]	15.0 [13.25, 16.0]
APOE e4% (n)	68% (73)	66% (37)	62% (10)
0 e4 / 1 e4 / 2 e4 / missing	34 / 71 / 2 / 1	19 / 30 / 7 / 6	6 / 6 / 4 / 2
Age, years	73.63 [70.42, 78.02]	75.0 [69.0, 77.91]	71.36 [68.09, 77.16]
Mesial Temporal tau, CTR	16.66 [4.03, 35.84]	57.73 [35.57, 73.32]	55.0 [36.71, 64.6]
Meta Temporal tau, CTR	16.66 [4.66, 29.2]	71.77 [31.25, 94.64]	69.18 [44.18, 100.0]
Temporo-Parietal tau, CTR	6.9 [-2.09, 16.08]	43.14 [14.58, 81.33]	58.91 [32.93, 114.46]
Frontal tau, CTR	-1.29 [-8.1, 8.34]	18.03 [-2.98, 58.04]	41.57 [24.5, 106.01]
Tau acquisition interval, years	1.61 [1.38, 1.61]	1.42 [1.09, 2.19]	1.14 [1.02, 1.39]
Δ Mesial tau/year	3.32 [0.55, 8.23]	2.13 [-2.44, 9.63]	2.85 [-5.83, 8.38]
Δ Temporoparietal tau/year	2.69 [-0.03, 5.26]	4.78 [0.95, 10.26]	8.11 [-0.13, 15.88]
Δ Frontal tau/year	0.94 [-0.99, 4.49]	5.62 [0.81, 12.54]	7.31 [0.52, 16.88]
Centiloid	74.76 [50.57, 102.23]	101.08 [77.21, 120.55]	130.33 [112.32, 139.89]
Cohort	A4: 70, ADNI: 25, AIBL: 13	ADNI: 33, AIBL: 22, A4: 7	ADNI: 14, AIBL: 4
Tracer	FTP: 95, MK6240: 13	FTP: 40, MK6240: 22	FTP: 14, MK6240: 4
CDR category transitions (n)	0.0 → 0.5 (106) 0.0 → 1.0 (2)	0.5 → 1.0 (53) 0.5 → 2.0 (8) 0.5 → 3.0 (1)	1.0 → 2.0 (18)

KEY FINDINGS:

- CU-Progression:** Modest tau elevation mainly confined to **Mesial Temporal (17 [4–36] CTR)**, with minimal neocortical involvement (**Temporo-Parietal: 7 [-2–16] CTR**; **Frontal: -1 [-8–8] CTR**).
- MCI-Progression:** Higher **Mesial Temporal tau (58 [36–73] CTR)** with emerging **Temporo-Parietal involvement (43 [15–81] CTR)**; **Frontal** tau remains modest (**18 [-3–58] CTR**).
- Dementia-Progression:** Elevated tau across all regions, including prominent **Frontal involvement (42 [24–106] CTR)**, alongside **Mesial Temporal (55 [37–65] CTR)** and **Temporo-Parietal (59 [33–114] CTR)**.

DISCUSSION

- Each clinical progression along the AD continuum appears to be driven by tau reaching specific regional thresholds.
- Progression from CU occurred with modest level of tau confined to the Mesial Temporal ROI, indicating that only a small amount in this region is sufficient to precipitate decline.
- Progression from MCI required tau presence in the Temporo-Parietal cortex.
- Progression from mild to moderate dementia required tau increase in the Frontal cortex.
- The results support that a Temporo-Parietal threshold of ~60 CTR may be a meaningful cut point for discriminating moderate from high tau in biological PET staging of AD.**