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External Validation of Joint Propagation Model-Based Tau PET CenTauR units

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Background

- **Tau PET imaging** enables *in vivo* quantification of tau pathology in Alzheimer's disease and is increasingly used in clinical trials for staging and outcome assessment.
- Variability in tracers, acquisition, and processing complicates comparisons of tau PET results across studies and trials.
- The **CenTauR approach**, recently developed by the CPAD Consortium, provides a standardized framework to harmonize tau PET quantitative metrics.

Aim

- **To explore the validitiy of the CenTauR harmonization approach for tau PET in independent datasets.**

Methods

- We analyzed **head-to-head (n=118)**, **anchor point (n=368)**, and **test-retest (n=65)** tau PET datasets (*Leuzy et al., Alzheimers Dement. 2024*) covering five radiotracers: [^{18}F]flortaucipir, [^{18}F]MK-6240, [^{18}F]PI-2620, [^{18}F]GTP-1, and [^{18}F]RO948, to develop the **CenTauR harmonization approach**.
- **SUVRs were computed using a standardized quantification pipeline**, based on the Centiloid framework and predefined CenTauR ROIs (*Villemagne et al., Alzheimers Dement (Amst). 2023*) (**Fig. 1A**).
- The **Joint Propagation Model (JPM)** (*Leuzy et al., Alzheimers Dement. 2024*, **Fig. 1B**)— updated to account for tracer-specific variability in the CenTauR scale—was used to derive linear equations for converting SUVRs into CenTauR units.
- External validation of JPM-based conversion equations was conducted using **three matched cohorts (N = 535 per cohort, 1:1 based on age, clinical diagnosis, and Aβ status,) scanned with 3 different radiotracers**: [^{18}F]flortaucipir (ADNI, A05, SCAN), [^{18}F]MK-6240 (CPAS, SCAN), and [^{18}F]PI-2620 (HABS-HD, LMU, SCAN) **(Table 1)**.
- **Tau PET positivity frequencies**, established with binary (meta-temporal ROI) or staging-based (mesial-temporal and temporoparietal ROIs, *Jack et al. Alzheimers Dement. 2024*) approaches, were compared across the cohorts to assess the robustness of CenTauR harmonization.

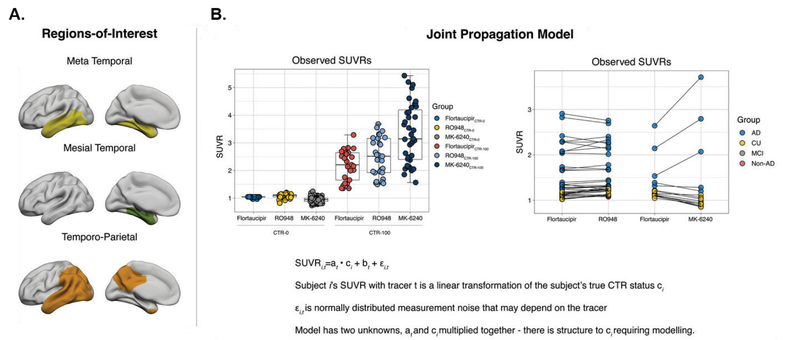

Figure 1. A) Surface-based projections of the CenTauR regions of interest ROIs (Villemagne et al., *Alzheimers Dement (Amst)*. 2023). **B)** Schematic of the Joint Propagation Model (JPM) for between-tracer harmonization of tau PET SUVR data.

	Cognitively Unimpaired			Cognitively Impaired (MCI or AD dementia)		
	[^{18}F]Flortaucipir (ADNI, A05, SCAN)	**[^{18}F]MK-6240 (CPAS,SCAN)**	**[^{18}F]PI-2620 (HABS-HD, LMU, SCAN)**	**[^{18}F]Flortaucipir (ADNI, A05, SCAN)**	**[^{18}F]MK-6240 (CPAS,SCAN)**	**[^{18}F]PI-2620 (HABS-HD, LMU, SCAN)**
N	412	412	412	123	123	123
Age	69.9 (6.4)	69.3 (6.9)	69.0 (7.0)	72.7 (8.0)	72.1 (7.8)	72.4 (7.9)
Aβ-positive N, (%)	75 (18%)	75 (18%)	75 (18%)	112 (91%)	112 (91%)	112 (91%)

Table 1. Characteristics of the participants from the matched external cohorts used for validation of CenTauR harmonization.

Results

- We chose a meta-temporal ROI cut-off of 17.4 CenTauRs for binary classification, based on ROC analysis distinguishing visually positive vs. negative cognitively impaired individuals using the FDA-approved [^{18}F]flortaucipir method (N=553; ADNI & A05).
- For staging, we defined CenTauR values of 26 (mesial temporal) and 13.9 (temporoparietal) corresponding to 2 CenTauRz, and a 'High' category at 41.6 CenTauRs in the temporoparietal ROI (6 CenTauRz).

- CenTauR harmonization yielded highly consistent tau PET positivity frequencies across Aβ− CU, Aβ+ CU, and Aβ+ CI groups (≤3% difference between tracers; **Fig. 2A**. Compared to a CenTauRz ≥2 cut-off, CenTauR harmonization provided more consistent estimates (**Fig. 2B**).

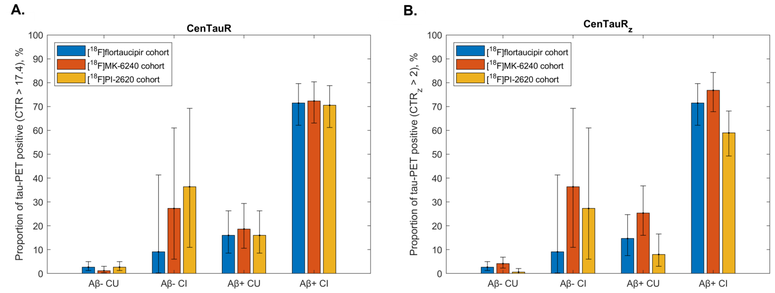

Figure 2. Frequency of tau PET positivity across the different diagnostics groups, as defined using either CenTauR (17.4; panel A) or CenTauRz (2 z-scores; panel B).

- Similarly, CenTauR-based harmonization resulted in highly consistent tau-PET based biological stages of Alzheimer's disease across the different radiotracer datasets (≤ 9% difference between tracers; **Fig. 3**).

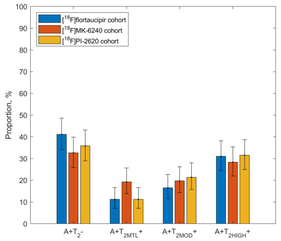

Figure 3. Frequency of tau PET positivity across biological stages of Alzheimer's disease.

Conclusions

- **External validation in matched cohorts scanned with different tau PET tracers showed consistent CenTauR-based positivity rates, supporting the method's robustness and utility for multi-tracer harmonization in clinical trials.**

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