

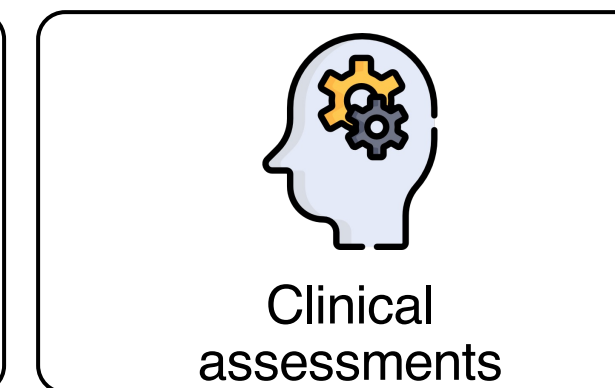
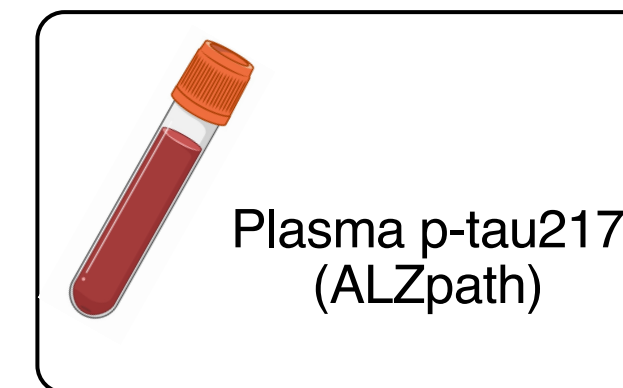
Introduction

Tau phosphorylation and aggregation are hallmark features of Alzheimer's disease pathology (AD). Previous studies have shown that plasma phosphorylated tau (p-tau) at threonine 217 can detect AD-related tau tangle pathology. However, the head-to-head association between p-tau217 and different tau PET tracers still remains unexplored.

Objective

Perform a a head-to-head comparison of the association between plasma p-tau217 and two tau PET tracers, MK6240 and flortaucipir (FTP).

Methods



Statistical analyses:

Aβ positivity (Aβ+): Visual reading.

Voxel-wise linear regression analysis evaluated the associations between tau PET and plasma p-tau217:

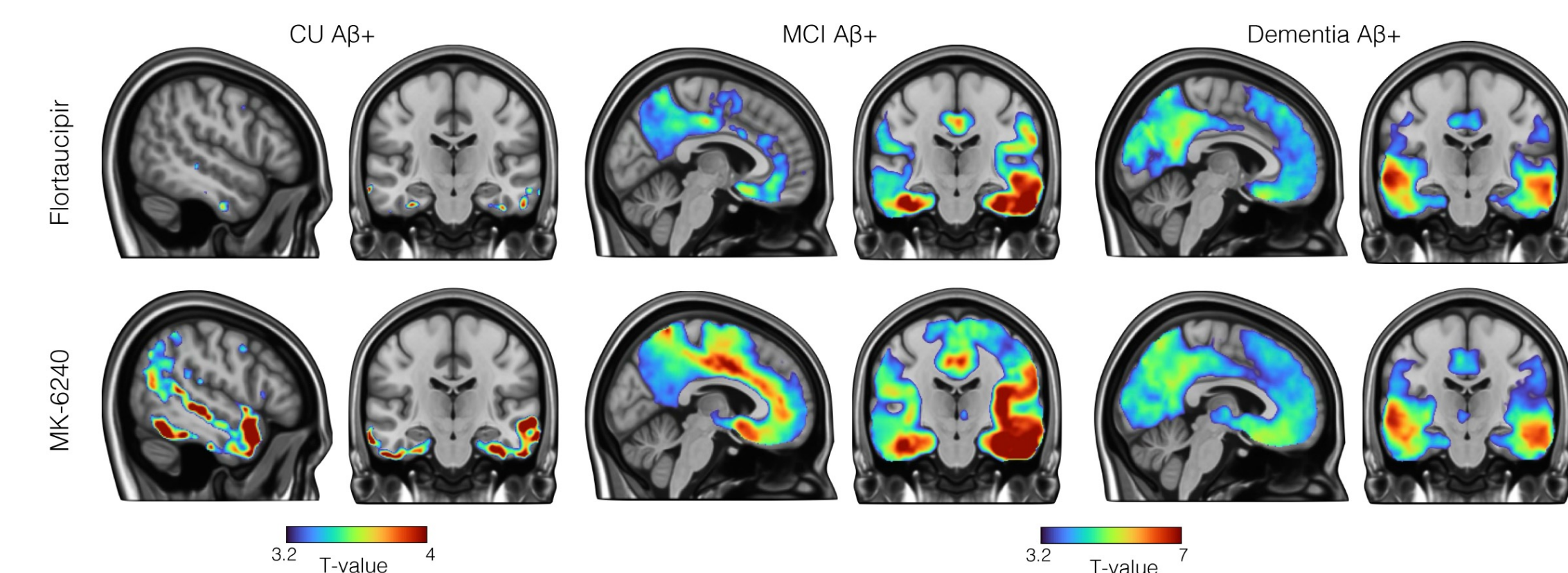
- The extent of the association between tau PET and plasma p-tau217 was determined by the percentage of abnormal voxels (corrected by multiple comparison t-value > 3.2).
- Discriminative performance for predicting tau PET positivity was assessed by logistic regression.

CU = cognitively unimpaired; MCI = mild cognitive impairment; MRI = magnetic resonance imaging;

PET = positron emission tomography.

Results

a Associations between plasma p-tau217 and tau PET tracers across the AD spectrum



b Regional extent of significant associations

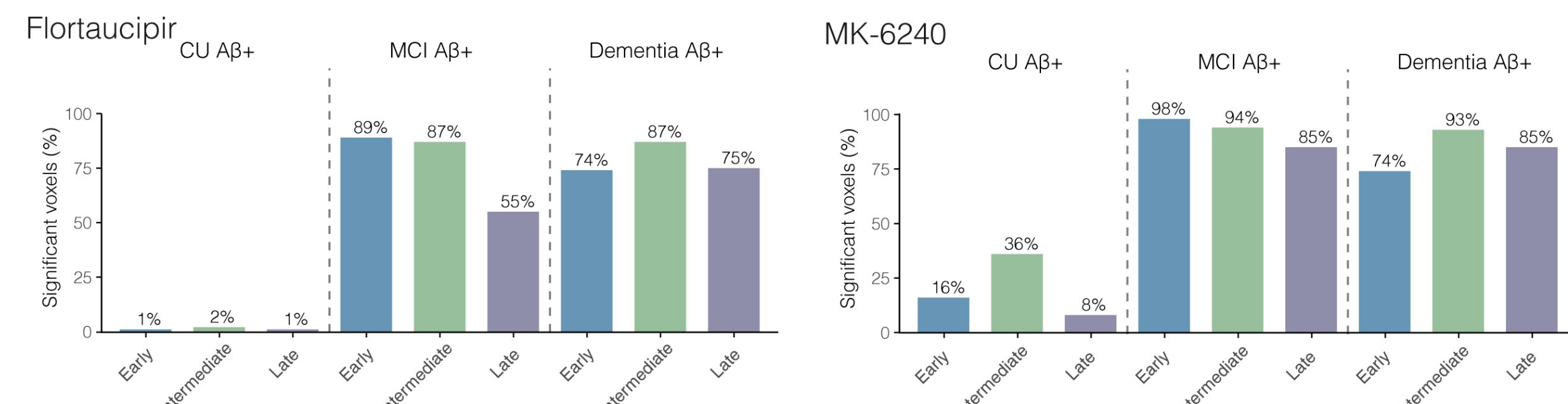


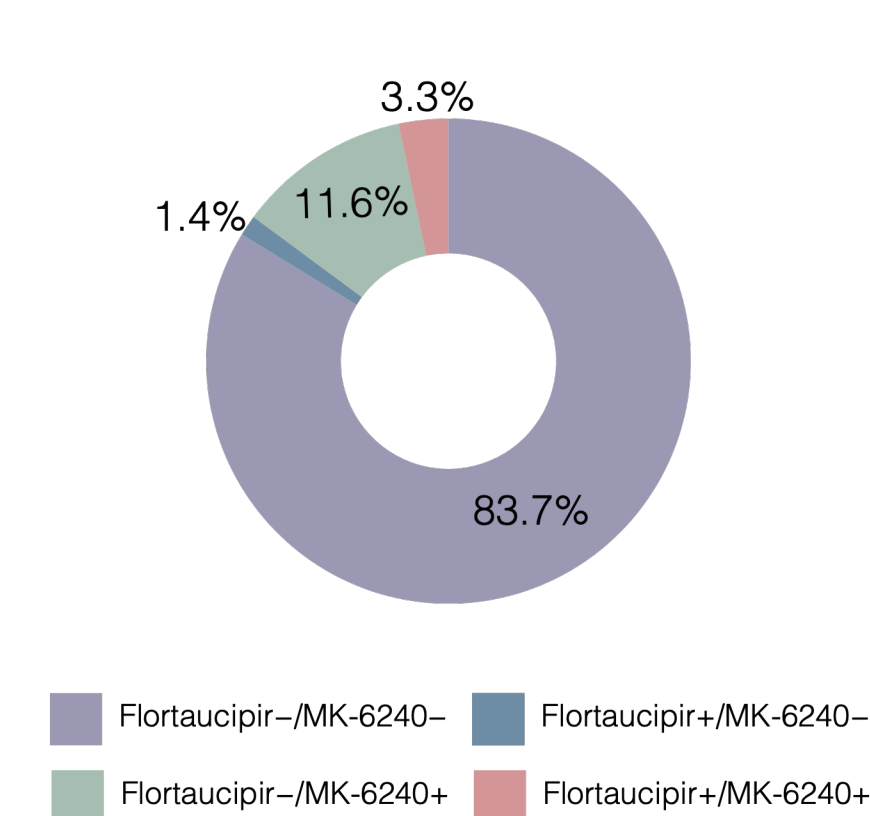
Figure 1. Association between plasma p-tau217 and tau PET tracers across the AD spectrum. (a) Voxelwise t-statistic maps showing associations between plasma p-tau217 and Flortaucipir (top row) and MK-6240 (bottom row) in Aβ-positive CU, MCI, and dementia individuals. **(b)** Proportion of significant voxels for the association between plasma p-tau217 and each tau PET tracer across clinical groups in Aβ-positive individuals. All analyses were adjusted for age, sex, and study site. Early regions correspond to the medial temporal lobe (MTL); intermediate to neotemporal cortex; and late to Braak V–VI regions. Aβ, amyloid-β; CU, cognitively unimpaired; MCI, mild cognitive impairment; MTL, medial temporal lobe; FDR, false discovery rate.

- In the CU Aβ+, MK-6240 showed broader and more widespread associations with plasma p-tau217 than FTP (**Figure 1**).
- In MCI Aβ+ individuals, both tracers demonstrated widespread associations with plasma p-tau217.
- In dementia Aβ+ individuals, both tracers showed extensive and largely overlapping associations throughout the brain.
- No significant** associations were observed on **Amyloid negative** individuals.

Figure 2. Tau PET burden and positivity as a function of plasma p-tau217 levels. (a) Proportion of tau PET MTL-positive individuals for Flortaucipir and MK-6240 across plasma p-tau217 levels. **(b)** Probability of Flortaucipir and MK-6240 positivity as a function of plasma p-tau217 concentrations. Dashed vertical lines indicate the plasma p-tau217 concentration at which each tracer reaches 50% probability of tau PET positivity. Probability curves included the entire population. MTL, medial temporal lobe; SUVR, standardized uptake value ratio; Aβ, amyloid-β.

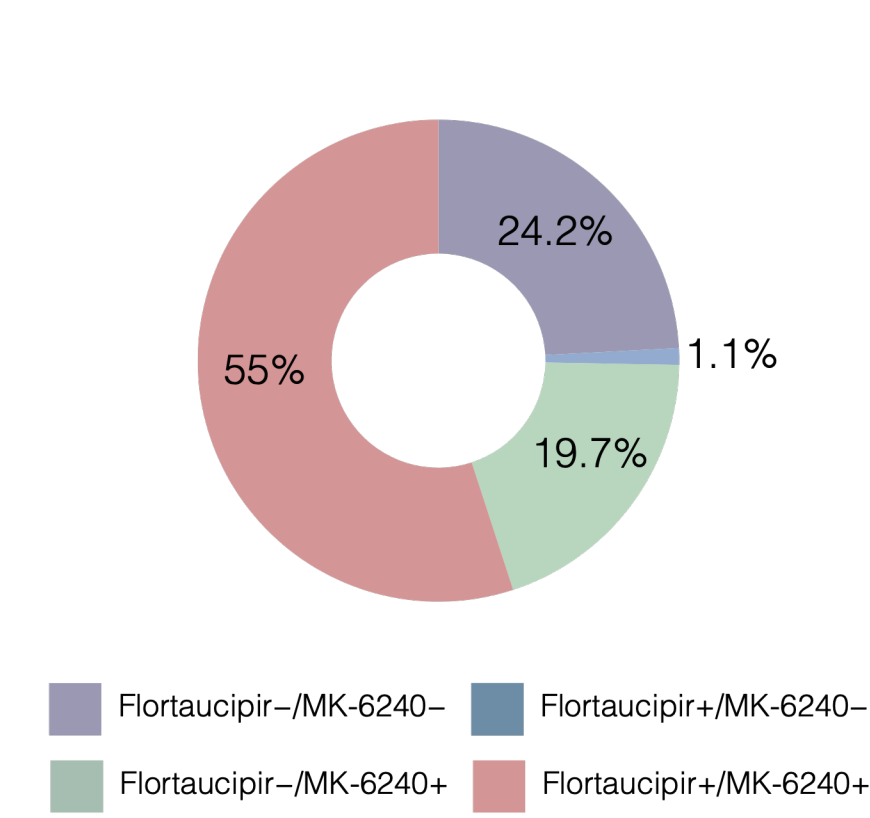
Plasma p-tau217 negative

a Concordance across tau PET status

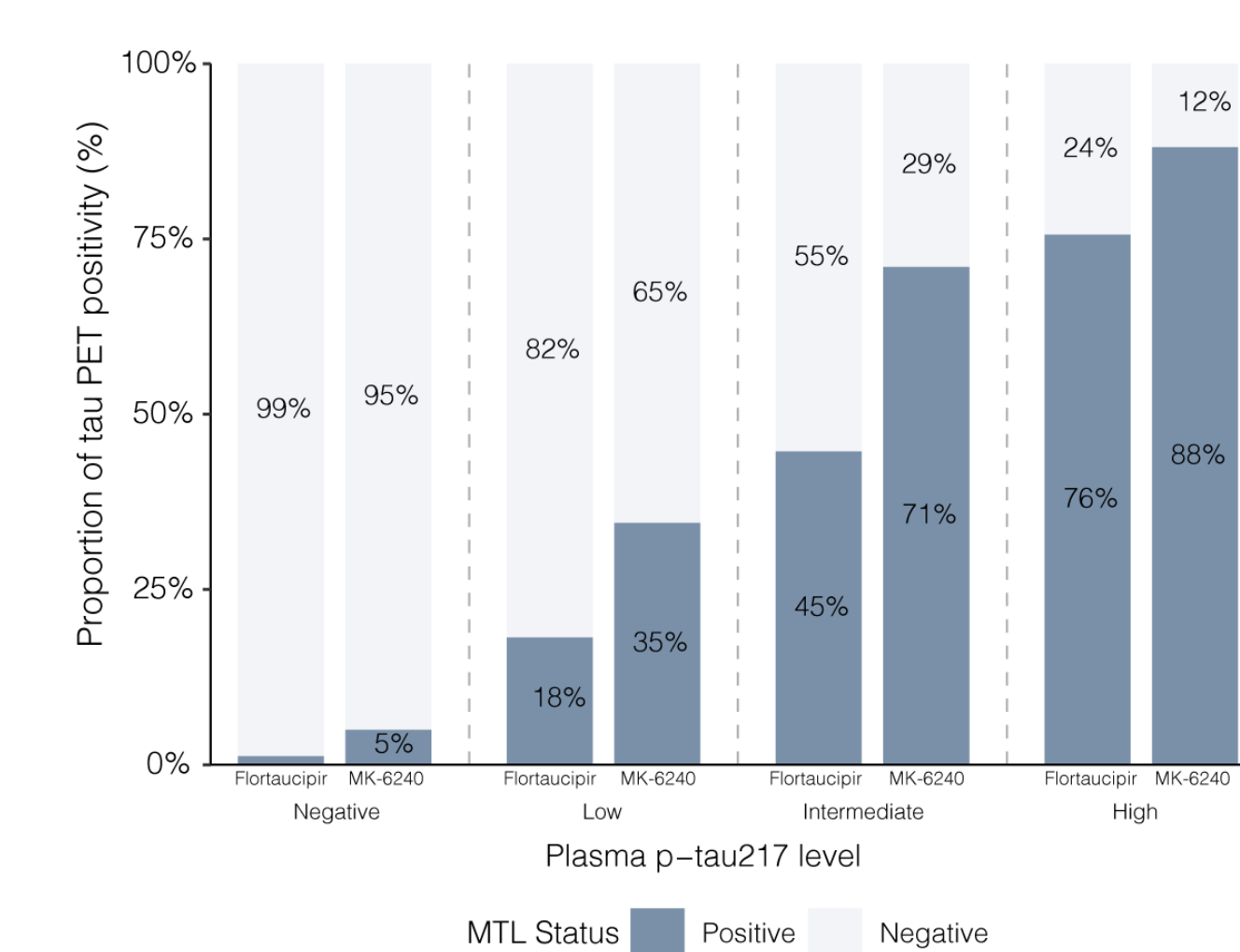


Plasma p-tau217 positive

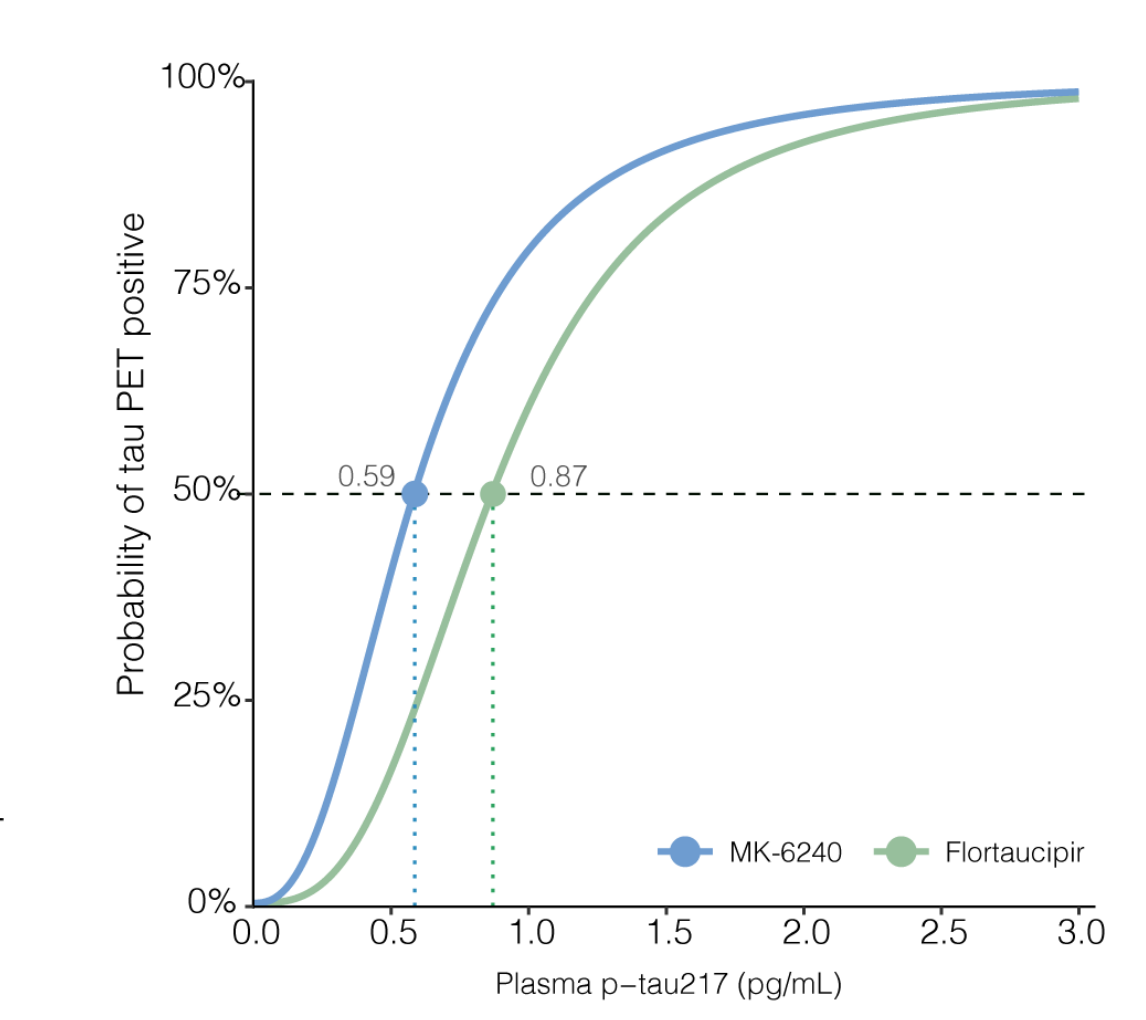
d Concordance across tau PET status



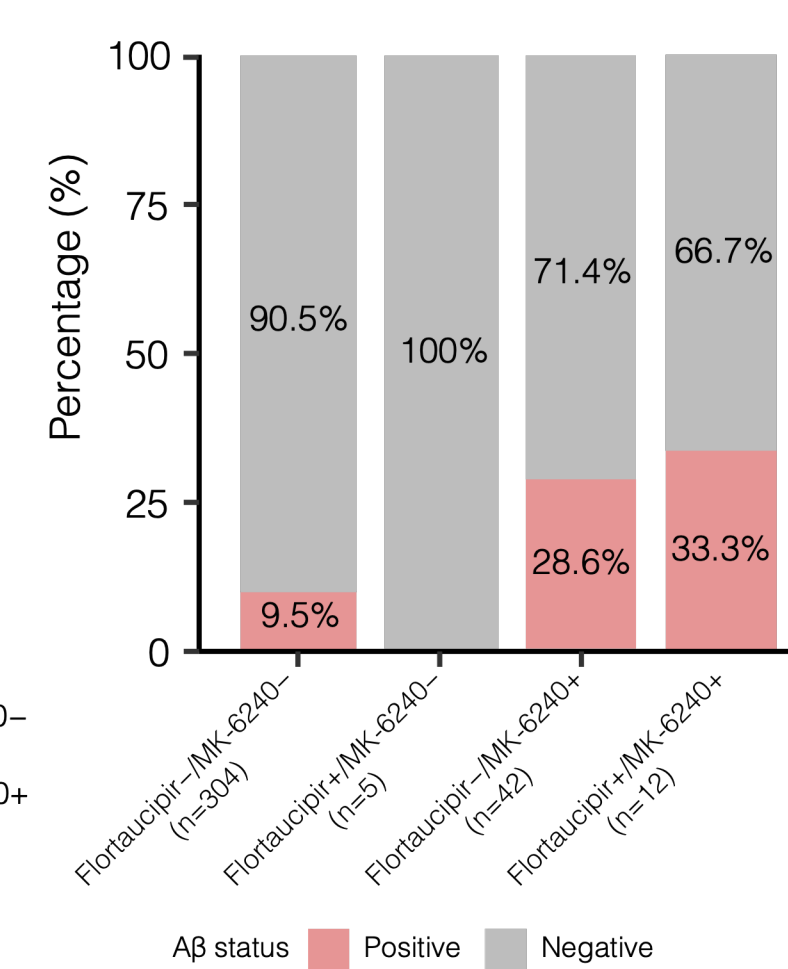
a Tau PET positivity across tracers by plasma p-tau217 levels



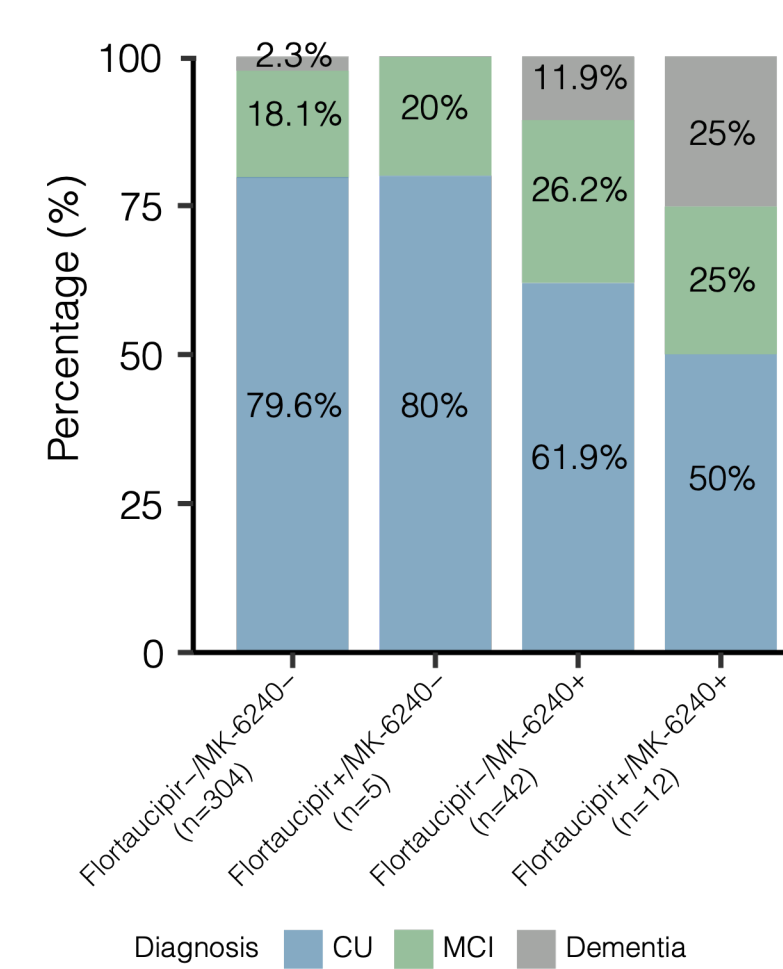
b Probability of tau PET positivity across plasma p-tau217 levels



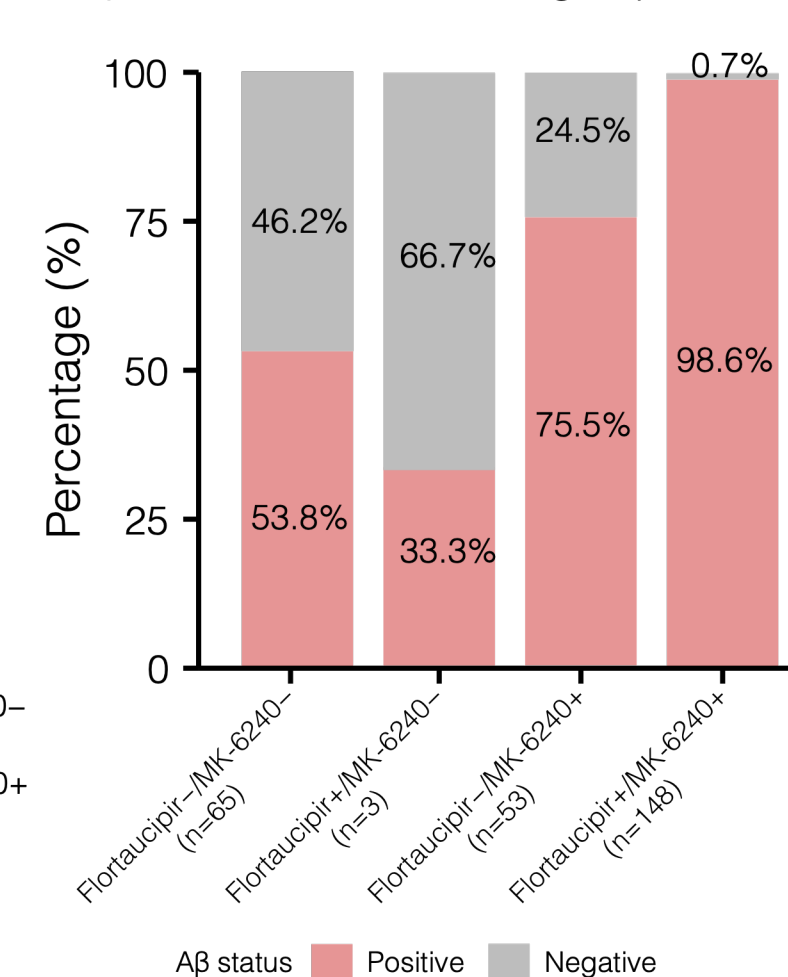
b Aβ status across tau PET groups



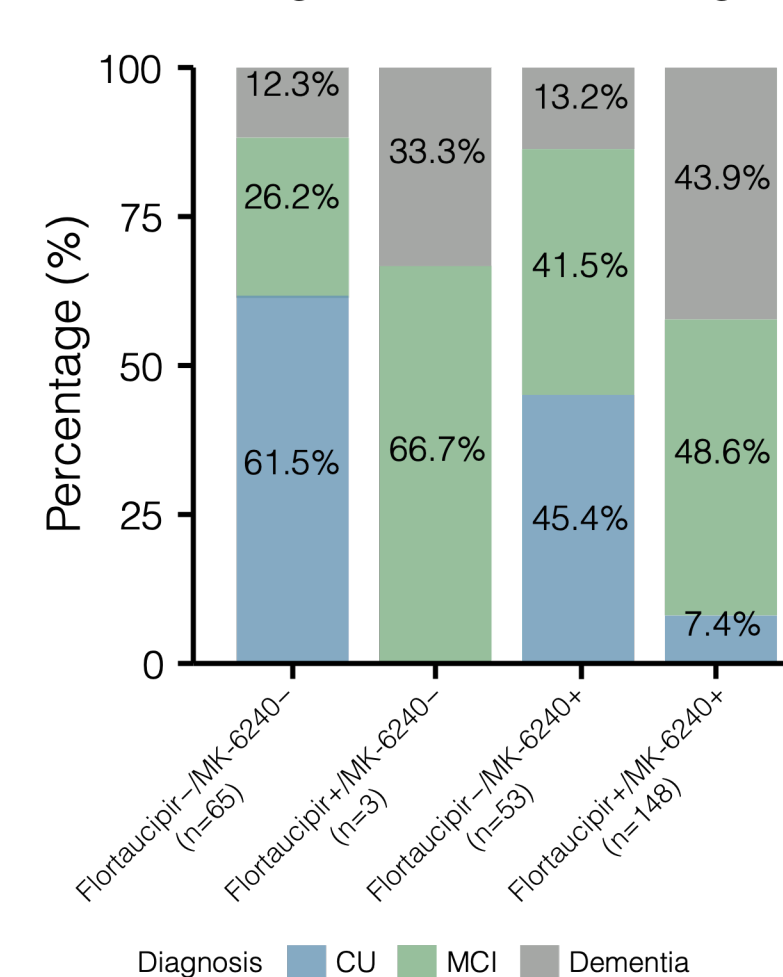
c Clinical diagnosis across tau PET groups



e Aβ status across tau PET groups



f Clinical diagnosis across tau PET groups



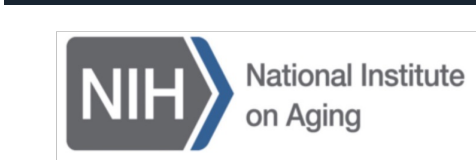
- MK-6240 consistently showed higher positivity rates than FTP (**Figure 2a**).
- MK-6240 reached 50% probability of tau PET positivity at lower plasma p-tau217 concentrations than FTP (**Figure 2b**)
- In both tracers discordant cases were predominantly (**Figure 3**).

Figure 3. Concordance between plasma p-tau217 and tau PET status. Panels **a–c** show analyses in plasma p-tau217-negative individuals. **(a)** Distribution of tau PET concordance groups. **(b)** Amyloid-β status and **(c)** clinical diagnosis across tau PET concordance groups. Panels **d–f** show analyses in plasma p-tau217-positive individuals. **(d)** Distribution of tau PET concordance groups. **(e)** Amyloid-β status and **(f)** clinical diagnosis across tau PET concordance groups. Pearson correlation coefficients and p-values are shown in panels d and i. CU, cognitively unimpaired; MCI, mild cognitive impairment; MTL, medial temporal lobe; SUVR, standardized uptake value ratio.

Conclusion

Our results showed that both MK6240 and FTP tau PET tracers exhibit robust associations with plasma p-tau217. In CU Aβ-positive, a greater extent of association was observed for MK6240 than for FTP, while in MCI and dementia Aβ-positive, the extent was comparable between tracers.

Acknowledgments



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