

Head-to-head comparison of tau PET tracers across the Alzheimer's disease spectrum: baseline results from the HEAD study



Guilherme Povala^{1*}, Bruna Bellaver^{1*}, Firoza Z. Lussier¹, Livia Amaral¹, Guilherme Bauer-Negrini¹, Pamela C.L. Ferreira¹, Andreia Rocha¹, Emma Ruppert¹, Marina S. Medeiros¹, Cecile Tissot², William J. Jagust², Joseph C. Masdeu³, Juan Fortea⁴, Dana L. Tudorascu¹, David N. Soleimani-Meigooni^{2,5}, Val Lowe⁶, Hwamee Oh⁷, Belen Pascual³, Brian A. Gordon⁸, Pedro Rosa-Neto⁹, Suzanne Baker^{2†}, Tharick A. Pascoal^{1,10†}.

¹University of Pittsburgh, Department of Psychiatry, PA, United States of America; ²Lawrence Berkeley National Laboratory, Berkeley, CA, United States of America; ³Houston Methodist Research Institute, Department of Neurology, Houston, TX, United States of America; ⁴Hospital de la Santa Creu i Sant Pau, Sant Pau Memory Unit, Department of Neurology, Barcelona, Spain; ⁵University of California San Francisco, Memory and Aging Center, San Francisco, CA, United States of America; ⁶Mayo Clinic, Department of Radiology, Rochester, MN, United States of America; ⁷Brown University, Department of Psychiatry and Human Behavior, Providence, RI, United States of America; ⁸Washington University in St. Louis, Department of Radiology, St. Louis, MO, United States of America; ⁹Translational Neuroimaging Laboratory, McGill University Research Centre for Studies in Aging, Douglas Research Institute, Montréal, QC, Canada; ¹⁰Department of Neurology, University of Pittsburgh School of Medicine.



Introduction

Tau PET imaging has emerged as a critical biomarker for Alzheimer's disease, informing diagnosis, staging, and therapeutic selection. However, whether tracer choice meaningfully alters tau detection across the AD spectrum remains incompletely understood. Here, we investigated whether PET tracer selection alters tau prevalence and positivity rates in a large, multicenter cohort.

Methods

We conducted a prospective, multicenter, within-participant comparison of [¹⁸F]Flortaucipir and [¹⁸F]MK6240 in 682 individuals of whom had complete Flortaucipir, MK6240, and Aβ PET, including 38 young adults (aged 19–27), 362 cognitively unimpaired elderly (CU), and 282 cognitively impaired (CI). Tau positivity in the medial temporal lobe (MTL) and neocortex was defined as uptake exceeding mean + 2.5 SD of young adults. Aβ positivity was based on visual reads or Centiloid >20. Prevalence ratios (PR) were estimated with Poisson regression with robust variance adjusting for Centiloid. The number of participants needed to identify one tau-positive case was defined as the inverse of the observed positivity rate (1/prevalence), and the number needed to detect (NND) as the reciprocal of the absolute difference in positivity rates between tracer-discordant groups. Logistic regression modeled tau and cognitive-domain positivity as a function of Centiloid, and group differences across tau positivity categories were assessed by ANOVA with FDR correction.

Results

In CU participants, MK6240 identified twice as many MTL-positive cases as Flortaucipir, corresponding to 23 additional cases per 100 (**Fig. 1**). Neocortical tau positivity was more frequent with MK6240 than with Flortaucipir in CI individuals, identifying 15 additional MCI and 21 dementia cases per 100. Among discordant cases, 75 (89%) were MK6240-positive only and had higher Aβ burden, APOEε4 frequency, and memory impairment than those negative on both tracers (**Fig. 2**). The 50% probability threshold for MTL positivity occurred at 53 Centiloids for MK6240 and 81 Centiloids for Flortaucipir (**Fig. 3**). Both tracers reached MTL tau positivity before the 50% threshold for memory impairment (120 Centiloids). For neocortical regions, thresholds were 129 Centiloids for MK6240 and 171 for Flortaucipir. MK6240 neocortical positivity occurred shortly after memory decline but before impairment in other domains. Flortaucipir neocortical positivity occurred after impairment thresholds for both memory and executive function (132 Centiloids). Representative discordant cases are shown in **Fig. 4**.

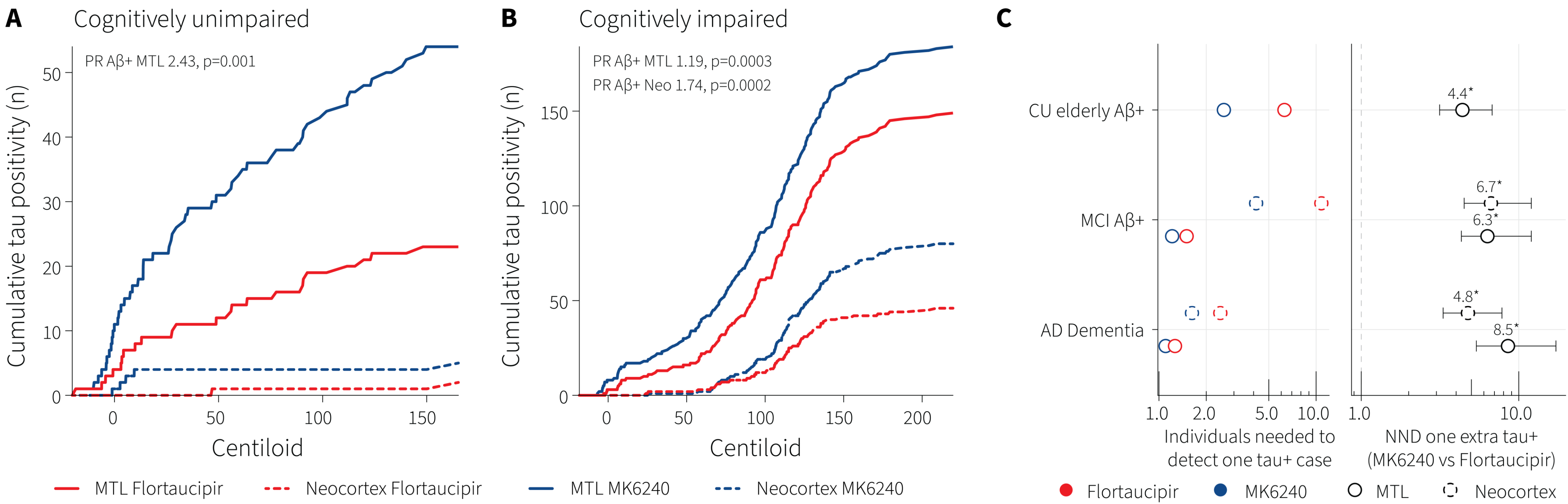


Figure 1. Cumulative proportion of tau-positive individuals in the medial temporal lobe (MTL; solid lines) and neocortex (dashed lines) for Flortaucipir and MK6240, plotted as a function of Centiloids in (A) CU and (B) CI groups. (C) Number of participants needed to identify one tau-positive case and one extra tau-positive stratified by diagnosis and Aβ status.

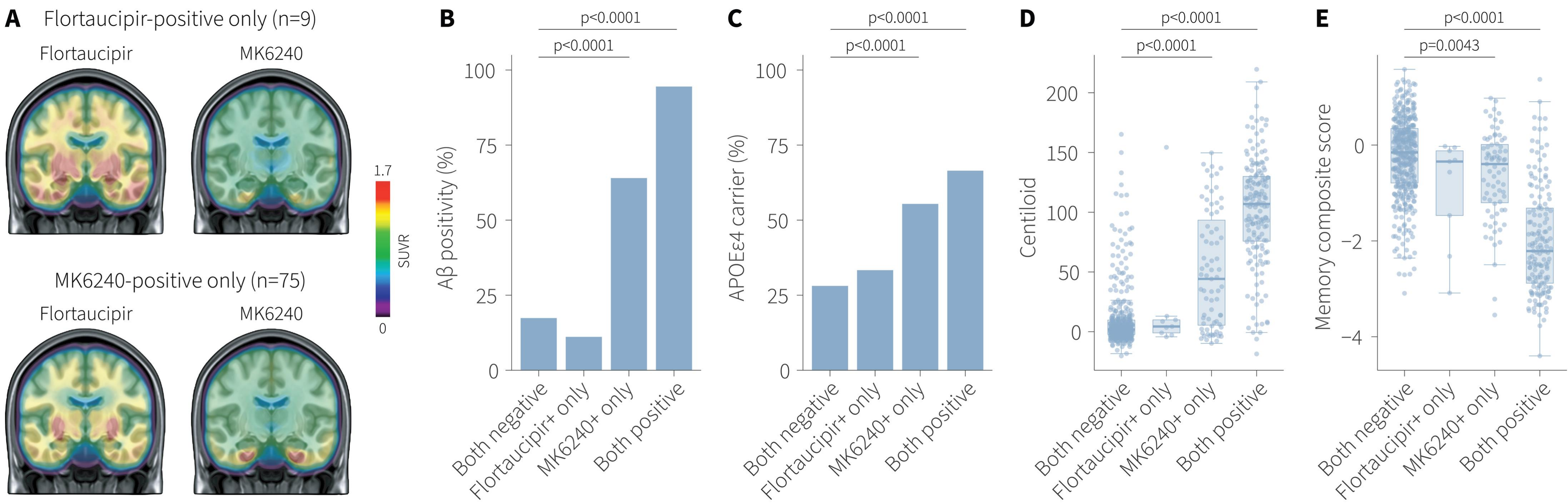


Figure 2. Mean SUVR images for Flortaucipir and MK6240 in Flortaucipir-positive and MK6240-positive only groups (A). Panels B–E display the corresponding distributions of (B) Aβ positivity, (C) APOE ε4 genotype, (D) Centiloid values, and (E) memory composite scores across Flortaucipir and MK6240 groups. Values are presented as median ± interquartile range.

Conclusion

Tau PET tracer selection influences the frequency of tau pathology across the Alzheimer's disease spectrum. Compared with Flortaucipir, MK6240 identified more individuals with tau pathology in CU and CI individuals, with implications for patient stratification in clinical trials and more precise guidance for therapeutic decision-making.

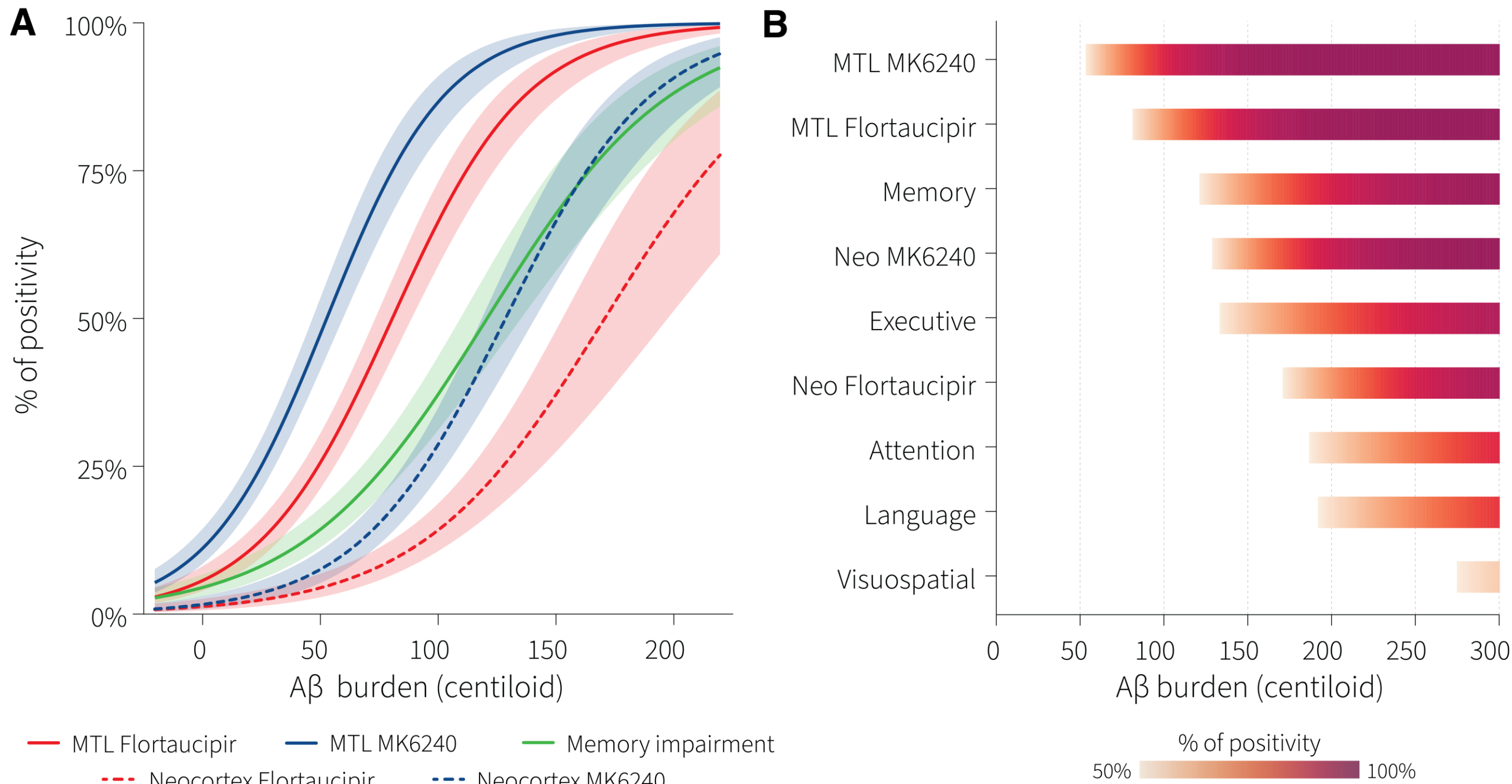


Figure 3. Probability of positivity for Flortaucipir and MK6240 in the MTL (solid lines) and neocortex (dashed lines), shown as a function of Aβ burden (Centiloids) (A). Centiloid thresholds corresponding to a 50% probability of tau positivity for each tracer and for a 50% probability of decline in memory, executive function, attention, language, and visuospatial domains (B).

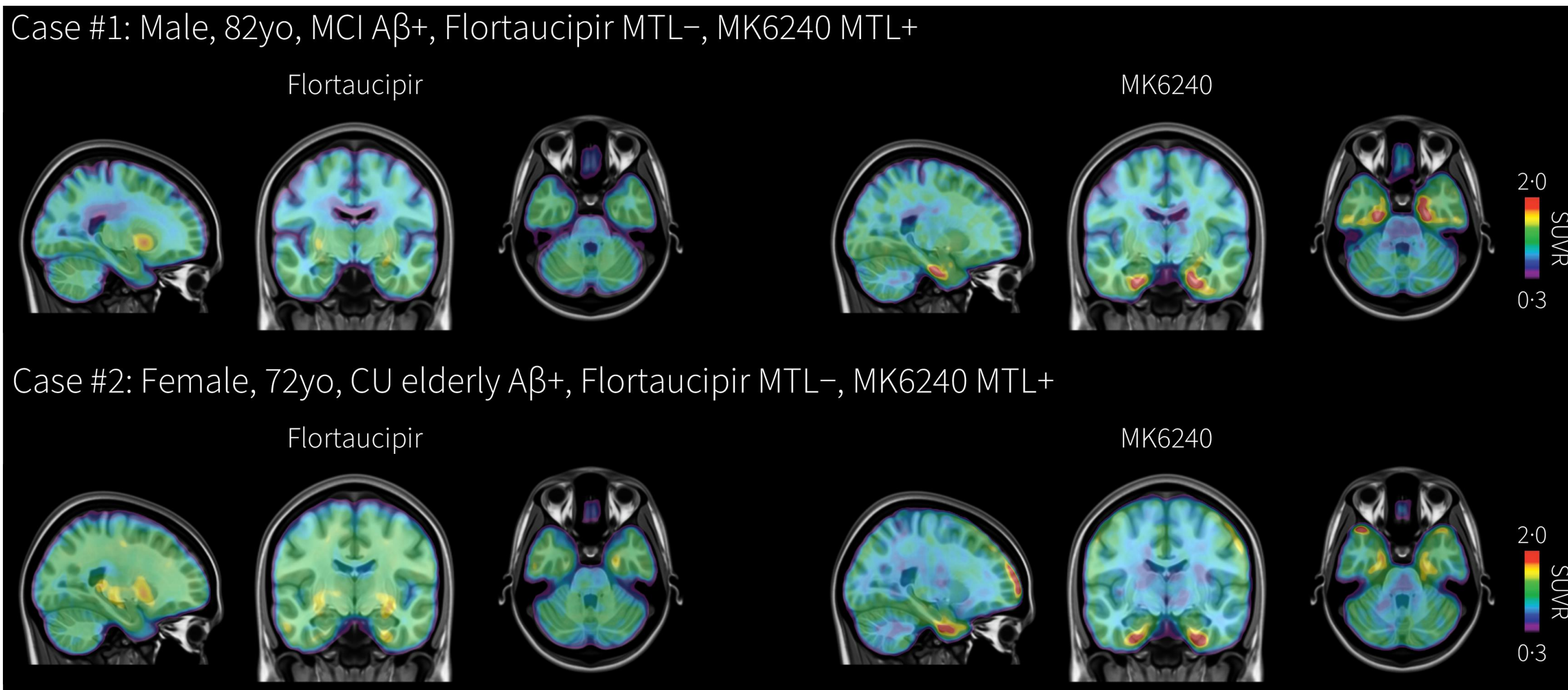


Figure 4. Representative cases of tau PET uptake in individuals scanned head-to-head with Flortaucipir and MK6240.

Acknowledgments:

