

Amsterdam Neuroscience

Characterizing tau-PET negative individuals with symptomatic Alzheimer's disease

Roos M. Rikken¹, Emma M. Coomans¹, Lotte de Koning¹, Denise Visser¹, Sander C.J. Verfaillie¹, Sophie E. Mastenbroek^{1,2}, Anouk den Braber^{2,3}, Lyduine E. Collij¹, Frederik Barkhof¹, Philip Scheltens², Wiesje M. van der Flier^{2,4}, Ronald Boellaard¹, Rik Ossenkoppele^{2,5}, Everard G.B. Vijverberg², Bart N.M. van Berckel¹, Elsmarieke van de Giessen¹

¹ Department of Radiology & Nuclear Medicine, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands
² Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands
³ Department of Biological Psychiatry, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
⁴ Department of Epidemiology & Data Science, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands
⁵ Clinical Memory Research Unit, Lund University, Lund, Sweden



Introduction

- Alzheimer's disease (AD) is characterized by the neuropathological accumulation of amyloid- β (A β) plaques and tau tangles. Tau tangles can be visualized and quantified in vivo using the tau-binding radiotracer [¹⁸F]flortaucipir.
- Recently, a method for visual assessment of [¹⁸F]flortaucipir (tau-)PET scans was approved for clinical use by the US FDA to support the diagnosis of AD dementia (PMID: 33573211).
- We and others previously observed that not all A β positive AD patients are tau-PET positive (PMID: 33215319).

Aim: to characterize visual read tau-PET negative AD patients

Methods

- Tau-status was defined by [¹⁸F]Flortaucipir PET visual read (positive/negative) by consensus read of two trained nuclear medicine physicians according to FDA guidelines.
- Since the FDA-approved visual read method does not take MTL regions into account, we quantified tracer binding (SUVr) in the MTL to explore whether tau-PET visual read negative individuals did have tau in MTL regions by comparing this between the groups
- For the subset that had longitudinal data available (N=85), we used linear mixed models with age and sex as covariates to assess [¹⁸F]Flortaucipir accumulation over time in the MTL.
- MRI images were visually rated for white matter hyperintensities, microbleeds or lacunes to assess the potential role of comorbid pathology.

Results

- All MCI/AD A+T- participants remained tau negative after ± 2 years.

	Overall (N=190)	Control A-T- (N=93)	MCI/AD A+T- (N=12)	MCI/AD A+T+ (N=85)	P-value
Age (mean (SD))	67.6 (7.7)	69.8 (7.2)	72.8 (5.3)	64.5 (7.3) ^{ab}	<0.001
Sex, n female (%)	89 (46.8)	45 (48.4)	1 (8.3) ^{ac}	43 (50.6)	0.021
Education in years (Verhage) (mean (SD))	5.5 (1.2)	5.6 (1.2)	5.50 (1.0)	5.5 (1.2)	0.810
APOE $\epsilon 4$ status, n carrier (%)	94 (52.5)	27 (31.4) ^{bc}	10 (83.3)	57 (70.4)	<0.001
MMSE (mean (SD))	25.4 (4.83)	29.0 (1.1)	24.0 (3.6) ^{ac}	21.6 (4.5) ^{ab}	<0.001

Table 1: Demographics across different groups ^a Significantly different from CU A-T- ^b Significantly different from MCI/AD A+T- ^c Significantly different from MCI/AD A+T+

- Compared to MCI/AD A+T+, MCI/AD A+T- were older (p<0.001) and more often male (p=0.015) (Table 1).
- MCI/AD A+T- had on average a higher MMSE in comparison to MCI/AD A+T+ participants (P=0.017) (Table 1).

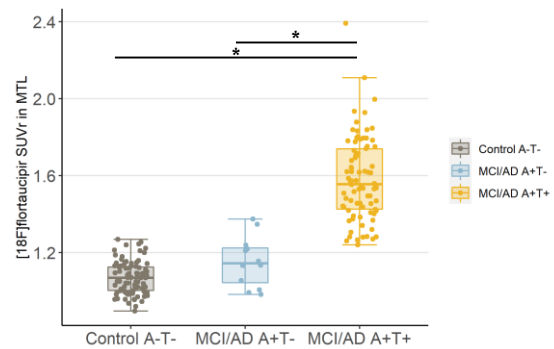


Fig 1: Flortaucipir SUVr in MTL across different groups

- Compared to MCI/AD A+T+, MCI/AD A+T- had a lower MTL [¹⁸F]Flortaucipir SUVr (p<0.001) (Figure 1).
- MCI/AD A+T- participants did not significantly differ in MTL [¹⁸F]Flortaucipir SUVr compared to CU A-T- (p= 0.076) (Figure 1).

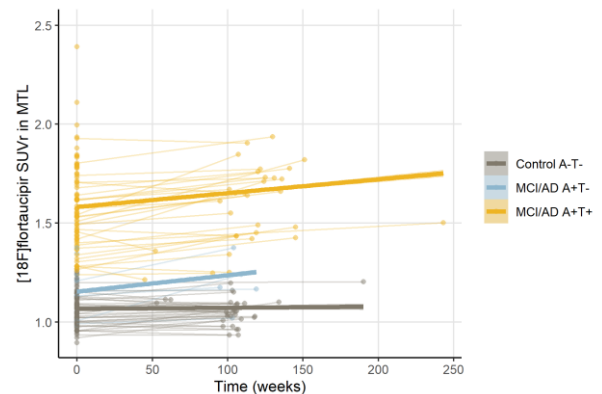


Fig 2: Flortaucipir SUVr in MTL over time across different groups

- Over time, MCI/AD A+T- had a larger SUVr increase in the MTL compared to the CU A-T- group (p= 0.031) (Figure 2).
- Interestingly, tau accumulation over time did not differ between MCI/AD A+T- and MCI/AD A+T+ (p=0.651) (Figure 2).
- No differences were found in the amount of vascular pathology among all groups.

Conclusion

Tau-negative MCI/AD individuals were older and more often male compared to tau-positive MCI/AD. Although visual read tau-PET status remains stable over time in tau-negative MCI/AD, these individuals do show more tau accumulation in the MTL compared to CU A-T- individuals. This indicates that tau-PET negative but A β positive MCI/AD patients are slowly accumulating tau over time. This should be taken into account when evaluating such an individual in the clinic and for clinical trials.