European Journal of Neurology

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE OPEN ACCESS

Tau PET Imaging With [^{18}F]MK-6240: Limited Affinity for Primary Tauopathies and High Specificity for Alzheimer's Disease

Thomas Gérard[1,2] | Lise Colmant[2,3] | Vincent Malotaux[2] | Yasmine Salman[2] | Lara Huyghe[2] | Lisa Quenon[2,3] | Emilien Boyer[2,3] | Laurence Dricot[2,3] | Adrian Ivanoiu[2,3] | Renaud Lhommel[1,2] | Bernard Hanseeuw[2,3,4,5]

[1]Nuclear Medicine Department, Cliniques Universitaires Saint Luc, Brussels, Belgium | [2]Institute of Neurosciences, Université Catholique de Louvain, Brussels, Belgium | [3]Neurology Department, Cliniques Universitaires Saint Luc, Brussels, Belgium | [4]WELBIO Department, WEL Research Institute, Wavre, Belgium | [5]Department of Radiology, Gordon Center for Medical Imaging, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence: Thomas Gérard (thomas.gerard@uclouvain.be)

Received: 22 August 2024 | **Revised:** 3 January 2025 | **Accepted:** 23 January 2025

Funding: This work was funded by the Fonds National pour la Recherche Scientifique/Belgian Fund for Scientific Research (FNRS/F.R.S), a WelBio Starting Grant (#40010035), and the StopAlzheimer Foundation (grant SAO-FRA #20210026).

Keywords: Alzheimer's disease | MK-6240 | neurodegenerative diseases | Tau PET | tauopathy

ABSTRACT

Introduction: Second-generation tau-PET tracers like [^{18}F]MK-6240 are increasingly used both for diagnosing and quantifying Alzheimer's Disease (AD) tauopathy. However, while [^{18}F]MK-6240 tau-PET has demonstrated excellent sensitivity for AD tauopathy, data assessing its specificity and binding in non-AD tauopathies are still scarce.

Methods: Participants were assigned to exclusive categorical diagnoses based on their amyloid (Aβ) and cognitive status. We quantified mesiotemporal (MTL) and neocortical [^{18}F]MK-6240 tau-PET signal in 28 Aβ− cognitively impaired (CI) patients presenting various non-AD neurodegenerative disorders. Tau-PET quantifications were compared with Aβ− cognitively unimpaired (CU) subjects ($n = 51$) and Aβ+ CI patients ($n = 77$).

Results: Among the 28 Aβ− impaired subjects, only five presented significant and isolated mesiotemporal signal, most of them being suspected of primary age-related tauopathy (PART). Only two Aβ− impaired patients (7%) presented positive neocortical signal, both being diagnosed with fronto-temporal degeneration (FTD). The Tau-PET results of all the remaining Aβ− patients were comparable to the CU population, including eight other FTD patients. Importantly, 4R-only tauopathies (CBD and PSP) and sv-PPA were negative.

Conclusion: [^{18}F]MK-6240 tau-PET has a special affinity for tauopathies involving 3R/4R paired helical filaments: AD, PART (Aβ− subjects with MTL-restricted tau-PET signal) and some forms of FTD while most primary tauopathies do not exhibit significant cortical signal. Positive neocortical scans are therefore highly specific for AD tauopathy. Based on those and previous results, we propose a diagnostic flowchart for MCI subjects suspected of AD or another tauopathy which may significantly reduce the need for amyloid PET or CSF measurement.

Renaud Lhommel and Bernard Hanseeuw jointly supervised the work.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2025 The Author(s). *European Journal of Neurology* published by John Wiley & Sons Ltd on behalf of European Academy of Neurology.

1 | Introduction

Positron Emission Tomography (PET) has emerged as a powerful imaging modality for studying and diagnosing various neurodegenerative disorders, particularly Alzheimer's disease (AD) and primary tauopathies [1]. The recent development of radiotracers specific for tau tangles has significantly enhanced the capability to visualize and quantify pathological processes leading to tau protein aggregation in vivo. Among these radiotracers, [^{18}F]MK-6240 has shown great promise due to its high affinity for tau protein aggregates in AD [2].

AD is a progressive neurodegenerative disorder characterized by a complex interplay of pathological processes, including amyloid plaque formation, tau neurofibrillary tangles, and neurodegeneration. These three hallmarks have become the basis for a biomarker classification [3]. Amyloid pathology is the first to arise and amyloid biomarkers are commonly used nowadays for AD diagnosis. However, cognitive impairment is more closely associated with tau pathology [4, 5]—especially in the mesiotemporal lobe where it appears very early in the neurodegenerative process, before the occurrence of clinical symptoms [5, 6]. As such, observing and quantifying AD specific tauopathy could become a crucial staging biomarker for early AD. However, while the great sensitivity of [^{18}F]MK-6240 tau PET for AD diagnosis is now well documented [7–10], the specificity of the tracer for AD—and conversely its sensitivity for non-AD tau pathologies—remains to be determined. Could non-AD tauopathies benefit from this imaging technique, and if so, which ones? In vitro studies have shown little affinity of tau PET tracers for non-AD tauopathies [11], but in vivo studies with [^{18}F]MK-6240 in non-AD patients are scarce.

This study aimed to analyze [^{18}F]MK-6240 tau-PET quantification—both in the mesiotemporal lobe (MTL) and in the entire neocortex—in a group of patients presenting with various non-AD neurodegenerative disorders. We defined "non-AD" as a low level of amyloid pathology (Aβ−) to ensure independence with the tau-PET examination. Our main objective was to determine the affinity of the tracer for different types of tau pathologies, and consequently, the specificity of the tracer for AD tau tangles.

2 | Methods

2.1 | Participants

The study included a total of 177 subjects (age 45–91). One hundred and eleven patients were recruited at the Memory Clinic of the Cliniques Universitaires Saint-Luc (Brussels, Belgium), while 66 volunteers were recruited from a pool of clinically normal older adults participating in research studies at the university. The volunteers' group was enriched in Apolipoprotein E4 (ApoE4) carriers to match the prevalence observed in the AD group. Recruitment and examinations took place between June 2019 and March 2024. Exclusion criteria were focal brain lesions, major depression or psychiatric diseases and alcohol or drug abuse. All participants provided informed consent in accordance with the Declaration of Helsinki. Ethical approval for the study was granted by the Ethics Committee of the Catholic University of Louvain (Date: 13 May, 2019; Eudra-CT number: 2018-0034/73-94) (Figure 1).

Participants were categorized based on a bioclinical algorithm, which included amyloid status (Aβ) and cognitive assessments. The following biomarkers were conducted in clinics, as ordered by the attending neurologist: lumbar puncture with total tau (t-tau), p-tau^{181} (p-tau) and Aβ42 cerebrospinal fluid (CSF) measures, Amyloid PET, FDG PET, clinical MRI, neuropsychological assessment, and ApoE genotyping. Volunteers underwent amyloid-PET, structural MRI, and neuropsychological assessment with ApoE genotyping conducted prior to the study [12].

Amyloid status was determined for each subject, either by amyloid PET (vide infra) or CSF measurement. Subjects were considered to be Aβ+ (suggesting AD pathology) if at least one of these three conditions was met: PET Centiloid > 25 [13]; CSF Aβ42 < 437 pg/mL; [437 pg/mL < CSF Aβ42 < 650 pg/mL]; and CSF P-tau > 61 pg/mL [14] (this latter condition concerned six patients). If both biomarkers were performed and discordant, the amyloid PET result was considered decisive.

Categorial diagnoses were initially based on amyloid status (Aβ−/+), which indicated whether the subject fell within the AD spectrum, and neuropsychological evaluations, which classified subjects as unimpaired, mildly cognitively impaired (MCI), or demented. A participant was classified as MCI if its Mini Mental State Examination (MMSE) score was ≥ 24/30 accompanied by impaired performance in at least one of the four tested cognitive domains (episodic memory, executive, visuospatial, and language). The cutoff criteria were set at −1.5 *Z*-score for every cognitive domain, except for language which was not considered if the testing language was not the patient's mother tongue [15]. All demented individuals had an MMSE score < 24 and functional impairment in everyday life.

The four first categories were as follows:

- Cognitively unimpaired Aβ− subjects (Aβ− CN)
- Cognitively unimpaired Aβ+ subjects (excluded, vide infra)
- Cognitively impaired Aβ+ amyloid positive subjects (Aβ+ impaired)
- Cognitively impaired Aβ− subjects (Aβ− impaired)

The Aβ+ impaired group served as a positive control for studying Aβ− cognitively impaired subjects. Cognitively unimpaired Aβ+ subjects (preclinical AD, $n = 21$) were excluded because they represented a heterogeneous group whose tau burden could range from Aβ− CN to AD levels.

The Aβ− impaired subjects were then assigned a specific etiological diagnosis when possible. Diagnoses included Frontotemporal degeneration (FTD), Corticobasal dementia (CBD), Progressive supranuclear palsy (PSP), and Hydrocephalus. The remaining subjects whose diagnosis could not be precisely determined were classified as Aβ− undefined-MCI (Aβ− uMCI). None of them was demented.

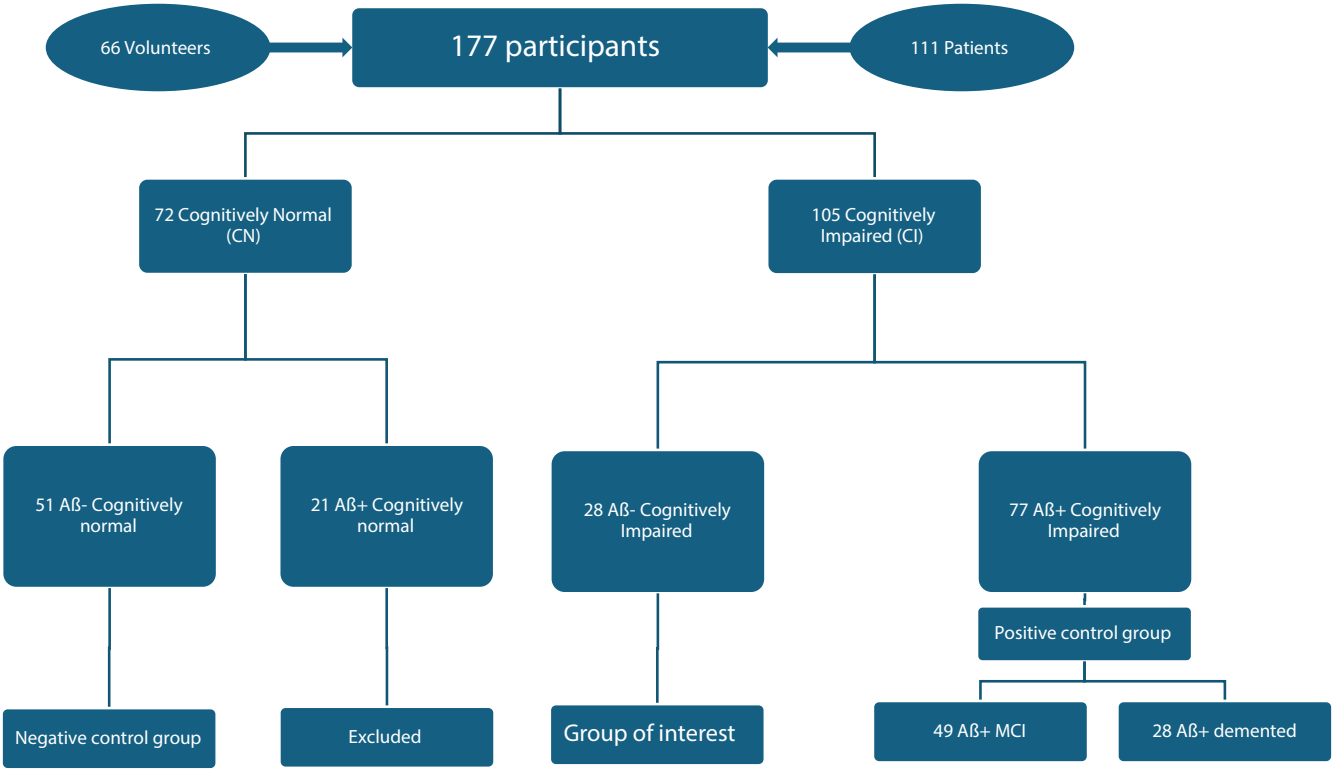

FIGURE 1 | Distribution of the participants in the different bioclinical categorical groups.

Subjects with mixed pathologies including AD (e.g., one case with a clinical diagnosis of Lewy body dementia with high-Aβ) were assigned to the AD group as they were expected to present AD tauopathy on [^{18}F]MK-6240 tau PET-scan.

2.2 | PET and MRI Acquisition

All participants underwent a 3DT1 MRI and an [^{18}F]MK-6240 tau PET. Acquisition parameters and processing were similar to our previously published study [10]. White Matter Hypointensities (WMH) data were extracted from the MRI acquisition with Freesurfer v7.2 software. Tau PET scans were quantified in terms of Extent Of Tauopathy (EOT) in the region Braak $1+2$ (Braak ≤ 2, roughly the MTL) and the region Braak $1+2+3+4+5+6$ (Braak ≤ 6), which includes the entire neocortex and some gray nuclei [10]. EOT corresponds to the proportion of voxels greater than to 1.3 SUVr, considered as significant.

Amyloid PETs were acquired with two different tracers: [^{18}F] Flutemetamol and [^{11}C]PIB. The acquisition procedure was similar for both tracers and was previously detailed [13]. Amyloid PETs were quantified on the centiloid scale with a positivity cutoff set at >25 [10].

2.3 | Neuropsychological Assessment

All participants underwent a comprehensive neuropsychological evaluation. *Z*-scores were computed for four cognitive domains: episodic memory (Free and Cued Selective Reminding Test, French version [16]), language (Lexis Naming Test, the Category Fluency Test for animals, and the Letter Fluency Test for the letter "P" [17]), executive functions (Trail Making Test [18], Luria's Graphic Sequences [adaptations in French, unpublished]), and visuospatial functions (Clock Drawing Test and the Praxis part of the CERAD battery [19, 20]). Each cognitive domain was assessed based on three measures (for additional details refer to [15]). A global cognitive *Z*-score was calculated by averaging the *Z*-scores from these four cognitive domains, and this score was used as a proxy for cognitive performance/impairment. Three Aβ+ demented subjects and two Aβ− demented subjects were unable to complete all the tasks; therefore, a cognitive score could not be calculated for those subjects.

2.4 | Statistics

All statistics were calculated with Graphpad Prism 10 software (Graphpad LLC, Boston, MA). The characteristics of the participants were compared to those of the Aβ− CN group and Aβ+ impaired group using Mann–Whitney tests.

To compare the different Aβ− impaired subgroups with both the Aβ− CN (negative control group) and AD-impaired (positive control group), results were tested with Kruskal–Wallis test and Dunn's multiple comparison.

ROC curves were generated to assess the diagnostic performances of [^{18}F]MK-6240 tau PET quantification as a tool for diagnosing Alzheimer's Disease (AD) in a CI population.

Finally, simple linear regressions and Spearman's correlations were calculated to explore the relation between the tau PET quantification results and the cognitive performances in the Aβ− population (CN and clinically impaired).

3 | Results

3.1 | Characteristics of the Participants

The 177 subjects were assigned to one of four categorical diagnoses: 51 were Aβ− CN, 21 Aβ+ CN, 77 Aβ+ impaired, and 28 Aβ− impaired. As explained in the methods, the 21 Aβ+ CN were excluded from this study. The Aβ− impaired individuals were then classified into Aβ− uMCI ($n=12$), FTD ($n=10$), CBD ($n=3$), PSP ($n=1$), and hydrocephalus ($n=2$) (Table 1).

Characteristics of the Aβ− impaired group, which is the primary group of interest, were compared to the other groups. The Aβ+ impaired group was further subdivided into MCI ($n=49$) and demented ($n=28$) to provide a more relevant comparison of the cognitive deficits.

The Aβ− impaired group was slightly younger (67 vs. 71 years old) and had a lower proportion of ApoE4 carriers (23% vs. 66%) than the Aβ+ impaired group. MMSE scores were similar between Aβ− and Aβ+ MCI (circa 26/30), although the global cognitive score was slightly lower in the Aβ+ MCI group (Z-score = −0.91 vs. −1.36), primarily due to lower scores in memory and executive function. Conversely, language Z-scores were lower in the Aβ− than in the Aβ+ MCI group (−1.60 vs. −1.00), consistent with the inclusion of patients with primary progressive aphasia in the FTD subgroup. There were no significant differences in visuospatial scores between the Aβ− and Aβ+ MCI groups. Amyloid PET centiloid values were by definition higher in the Aβ+ groups; they were also slightly lower in the Aβ− impaired group than in the Aβ− CN (Centiloid = −2.5 vs. 6.3). CSF data were only significantly different in the Aβ+ group. Regarding WMH—used as a proxy for cerebrovascular disease—no significant differences were observed between groups.

3.2 | [^{18}F]MK-6240 Tau PET Results

In the Braak ≤ 2 region, only two Aβ− CN subjects exhibited a tau burden exceeding the previously defined cutoff for this MTL region (extent = 24.8% of voxels with above-threshold SUVRs, best cutoff to distinguish between Aβ− CN and CI AD patients [10]). Almost every Aβ+ CI individual had a mesiotemporal EOT > 24.8% and the group had significantly higher tau burden than the Aβ− CN group ($p<0.0001$). Regarding the Aβ− impaired subjects, the results were heterogeneous. CBD, PSP, and hydrocephalus subjects, all presented an [^{18}F]MK-6240 signal in the Aβ− CN range, showing no significant mesiotemporal tauopathy. Most of the FTD subjects also remained in the Aβ− CN range; however, two FTD subjects presented significant mesiotemporal tauopathy (55.3% and 99.0%). The Aβ− uMCI group was the most heterogeneous with EOT values widely ranging from 2% to 81%, straddling both sides of the cutoff line: Five out of 13 (38%) Aβ− uMCI had positive tau-PET signal in the MTL (Figure 2).

When examining neocortical tauopathy in the Braak ≤ 6 region, only one Aβ− CN subject showed a slightly elevated value (13.2%) compared to the established cutoff (12.1%, value which best distinguishes between Aβ− CN and symptomatic AD [10]). Most Aβ+ cases had EOT values well above the cutoff with a mean value of 44.9%. In contrast, Aβ− patients were all under the cutoff, except for two FTD subjects. The five Aβ− uMCI with positive tau-PET signal in the MTL all had very little tau-PET signal in the neocortex. Notably, in the Aβ− impaired group, the demented subjects did not present higher neocortical tau-PET signal than participants with milder cognitive impairment, suggesting that neocortical [^{18}F]MK-6240 signal may not be an accurate measure of non-AD tau pathology progression.

We performed additional analysis to evaluate the impact of ApoE status on tau-PET signal. In the Aβ− CN and Aβ− CI groups, we did not observe any significant differences between ApoE4 carriers and noncarriers. However, we observed a significant difference among the Aβ+ impaired subjects both in region Braak ≤ 2 ($p=0.0002$) and Braak ≤ 6 ($p=0.018$). Complete data are displayed on a figure in Supporting Information. Of note, the ApoE effect was predominant in the MTL (also visible in Aβ− CI, although it did not reach statistical significance).

3.3 | ROC Curves

ROC curves analysis to diagnose AD (Aβ+) pathology in a CI population with [^{18}F]MK-6240 EOT quantification demonstrated good performances with an area under the curve of 0.90 and 0.91 for the Braak ≤ 2 and Braak ≤ 6 regions, respectively. For Braak ≤ 2 region, the optimal performance was achieved with a cutoff < 55.6% (Sn: 92.9% and Sp: 80.5%) and for Braak ≤ 6 with a cutoff < 12.5% (Sn: 92.9% and Sp: 87.0%). This 12.5% cutoff almost matches the previously established cutoff to best distinguish Aβ+ impaired subjects from the Aβ− CN population. In contrast, the Braak ≤ 2 cutoff is much higher indicating that some Aβ− individuals may have moderately high tau-PET signal in the MTL. Using SUVr instead of EOT provided similar results with a threshold of 1.68 SUVr in the MTL (Sn: 92.9% and Sp: 79.2%) and 1.03 SUVr in the entire neocortex (Sn: 92.9% and Sp: 81.8%) to distinguish Aβ+ from Aβ− CI patients (Figure 3).

3.4 | Simple Linear Regressions and Correlations Between Tau-PET Signal and Cognition

Simple linear regression between [^{18}F]MK-6240 tau PET quantitative data and the global cognitive Z-score in the Aβ− population was slightly significant for the Braak ≤ 2 region ($R^2=0.13$; $p=0.001$), mostly driven by a few Aβ− uMCI and two FTD subjects. Among the specific cognitive domains, only episodic memory was significantly associated with MTL tauopathy ($R^2=0.31$; $p<0.0001$). Otherwise, no other significant linear regression or correlation was observed between cognition and tauopathy in the Aβ− population (Figure 4).

Of note, there was no significant influence of the education level on the correlation between tau-PET signal and the global cognitive Z-score (tested on the entire population, data not shown).

3.5 | Tau-PET in CSF-Tau Positive and Negative Aβ− Impaired Individuals

Among the Aβ− impaired subjects, we compared EOT values between individuals who were CSF total tau+ (> 381 pg/mL)

TABLE 1 | Characteristics of the participants. All groups were compared to the group of interest (Aβ− impaired) with Mann–Whitney tests. *p*-values are displayed as * when significant.

		Aβ− CN	Aβ− impaired	Aβ+ MCI	Aβ+ demented	Aβ+ impaired
Demographics	Number included	51	28	49	28	77
	Age (years) (SD; min–max)	67.1 (8.87; 45–86)	66.8 (9.61; 48–91)	72.3 (7.54; 54–87)**	68.6 (8.09; 51–83)	70.9 (7.99; 51–87)*
	ApoE ε4 carriers (%)	51*	23	65**	70**	66***
	ApoE missing data	0	2	1	5	6
	Gender (% female)	59	50	59	50	56
	Education level (NSC 1–3)	2.78	2.75	2.53	2.54	2.53
Cognition	MMSE (SD)	28.8 (0.99)****	25.8 (4.39)	26.1 (1.91)	19.6 (3.14)****	23.8 (3.97)**
	Global cognitive *Z*-score (SD)	0.17 (0.34)****	−0.91 (0.85)	−1.36 (0.86)**	−3.04 (0.97)****	−1.93 (1.20)****
	Memory *Z*-score (SD)	0.33 (0.64)****	−1.51 (1.63)	−3.15 (1.89)***	−4.53 (1.63)****	−3.59 (1.92)****
	Language *Z*-score (SD)	−0.06 (0.88)****	−1.60 (1.46)	−1.00 (0.85)*	−1.96 (1.06)	−1.32 (1.02)
	Executive *Z*-score (SD)	0.30 (0.31)**	−0.21 (1.05)	−0.97 (1.39)**	−2.68 (1.72)****	−1.52 (1.69)****
	Visuospatial *Z*-score (SD)	0.10 (0.46)***	−0.63 (1.21)	−0.61 (1.08)	−2.82 (2.18)****	−1.38 (1.87)***
	Cognitive *Z*-score missing data	0	2	0	3	3
MRI imaging	White matter hyperintensities (SD)	2704 (3649)	4782 (8373)	4853 (9183)	4803 (6393)	4834 (8206)
	Missing data	4	3	2	0	2
Amyloid imaging	Amyloid PET centiloid value	6.28**	−2.48	68.5****	104.0****	80.2****
	Centiloid missing data	2	14	35	21	56
CSF	P-tau^{181} (SD) (cutoff: 61 pg/mL)	40.7 (15.1)	39.1 (18.6)	94.0 (50.6)****	110.0 (57.0)****	100 (53.4)****
	T-tau (SD) (cutoff: 381 pg/mL)	315 (107)	332 (145)	596 (263)****	718 (358)****	643 (306)****
	AB42 (SD) (cutoff: 437 pg/mL)	942 (255)	739 (373)	396 (156)***	355 (159)***	380 (157)****
	CSF missing data	48	8	6	1	7

Abbreviations: ApoE, apolipoprotein E; Aβ, amyloid; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, mini-mental score examination.

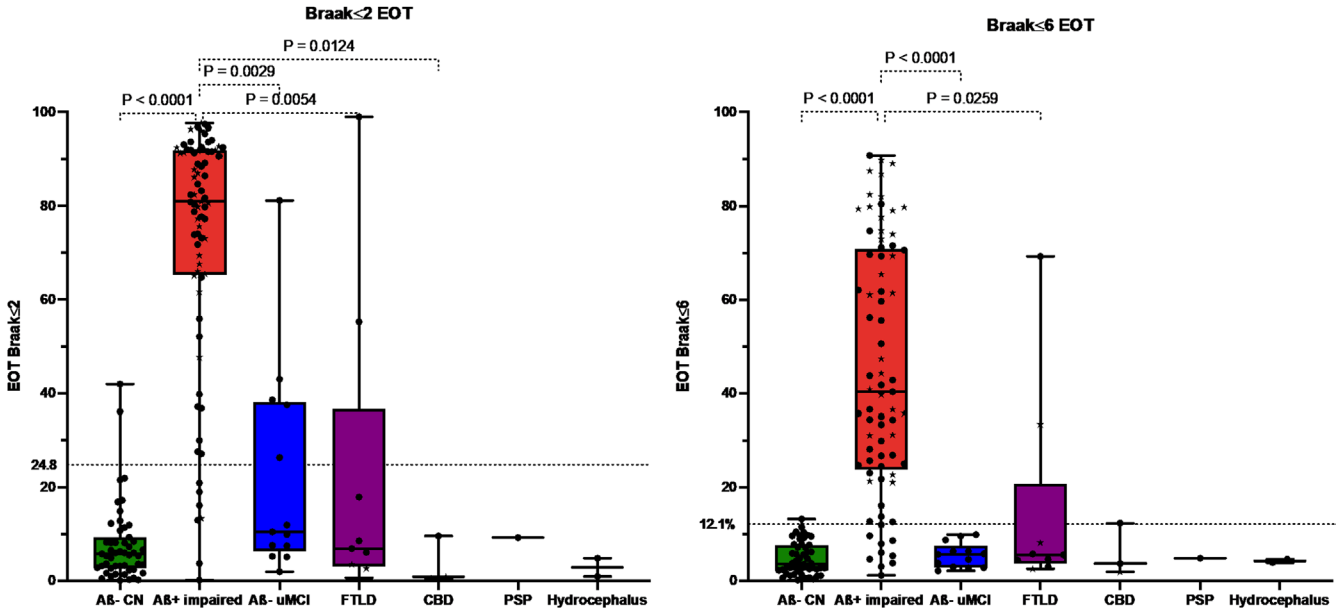

FIGURE 2 | Graphic of EOT values in regions Braak ≤ 2 and Braak ≤ 6 for the different diagnostic groups (and subgroups for the Aβ− impaired subjects). Positivity cutoff is displayed as a dotted line. Demented subjects are displayed as ★. Groups are compared with Kruskal–Wallis test and Dunn's multiple comparison. Significant results are displayed. EOT, extent of tauopathy (in %). Braak ≤ 2: region corresponding to the mesiotemporal lobe. Braak ≤ 6: region corresponding to the whole neocortex and some gray nuclei. Aβ− uMCI, amyloid negative undefined MCI; Aβ, amyloid; CBD, corticobasal degeneration; CN, cognitively normal; FTLD, frontotemporal lobar degeneration; PSP, progressive supranuclear palsy.

and CSF total tau− (< 381 pg/mL). CSF data were available for 20 subjects, including eight CSF tau+ and 12 CSF tau−. EOT Braak ≤ 2 values were significantly higher in CSF tau+ (median: 9.8%) than in CSF tau− (median: 4.2%) individuals ($p = 0.039$ Mann–Whitney). EOT Braak ≤ 6 values were also significantly different between CSF tau+ (median: 6.0%) and CSF tau− (median: 4.2%) individuals ($p = 0.016$ Mann–Whitney). Notably, even though CSF tau+ individuals had greater EOT values than CSF tau−, differences were moderate and all medians stayed below the positivity cutoff, highlighting the weak association between CSF total tau values and tau-PET signal, in Aβ− CI individuals.

3.6 | Subgroup Analyses

3.6.1 | Aβ− uMCI

Among the Aβ− uMCI, five subjects presented mesiotemporal tauopathy. All of them are illustrated in Figure 5. We discuss two distinct scenarios for these cases based on their Aβ pathology levels (either clearly negative or close to the Aβ threshold).

- Aβ− uMCI 13 was a 70-year-old man presenting a cortical tauopathy slightly extending beyond the Braak ≤ 2 region and visually classified as Braak 3. He had 27/30 on the MMSE and a global cognitive *Z*-score of −0.59 (mean of CN = 0, SD = 1). His primary deficit was in episodic memory (−1.44 *Z*-scores). We have no CSF data for this patient but a borderline amyloid PET (centiloid +20.8). This single patient may be considered as having MCI due to AD if we lower our Centiloid threshold to 20 (instead of 25).
- The other Aβ− uMCI Braak ≤ 2 positive cases all presented a similar pattern with different levels of mesiotemporal tauopathy. The diagnosis of Primary Age-Related Tauopathy (PART) was suggested since Aβ pathology was excluded based on PET or CSF results.

3.6.2 | FTD

Among the 10 subjects diagnosed with FTD, four had a behavioral phenotype, five had a PPA phenotype (with two out of five with semantic variant), and one an amnestic presentation. Two out of the 10 FTD patients exhibited both Braak ≤ 2 and Braak ≤ 6 significant tauopathy while all the remaining cases fell within the Aβ− CN range (Figure 6):

- FTD8 was a 73-year-old man. He was followed for more than 10 years at the time of his tau-PET. He was confirmed as amyloid negative through lumbar puncture (Aβ42 measured at 934 pg/mL, normal > 437) and an amyloid PiB-PET 4 years later (centiloid value: −11.3). He had a global cognitive *Z*-score at −2.40 at the time of the tau PET with severe impairment in episodic memory (−7.12 *Z*-score). C9orf72 mutation was absent. The tau-PET revealed a high tau burden in the MTL and both temporal lobes, with corresponding mirror hypometabolism observed on FDG-PET in the [^{18}F]MK-6240-positive regions.
- FTD9 was a 48-year-old woman. She developed a Primary Progressive Aphasia (PPA). Her global cognitive score remained normal at −0.81, mainly lowered by her performances in language tasks (−1.48 *Z*-score). Her lumbar puncture showed normal AB42 (1029 pg/mL), but increased

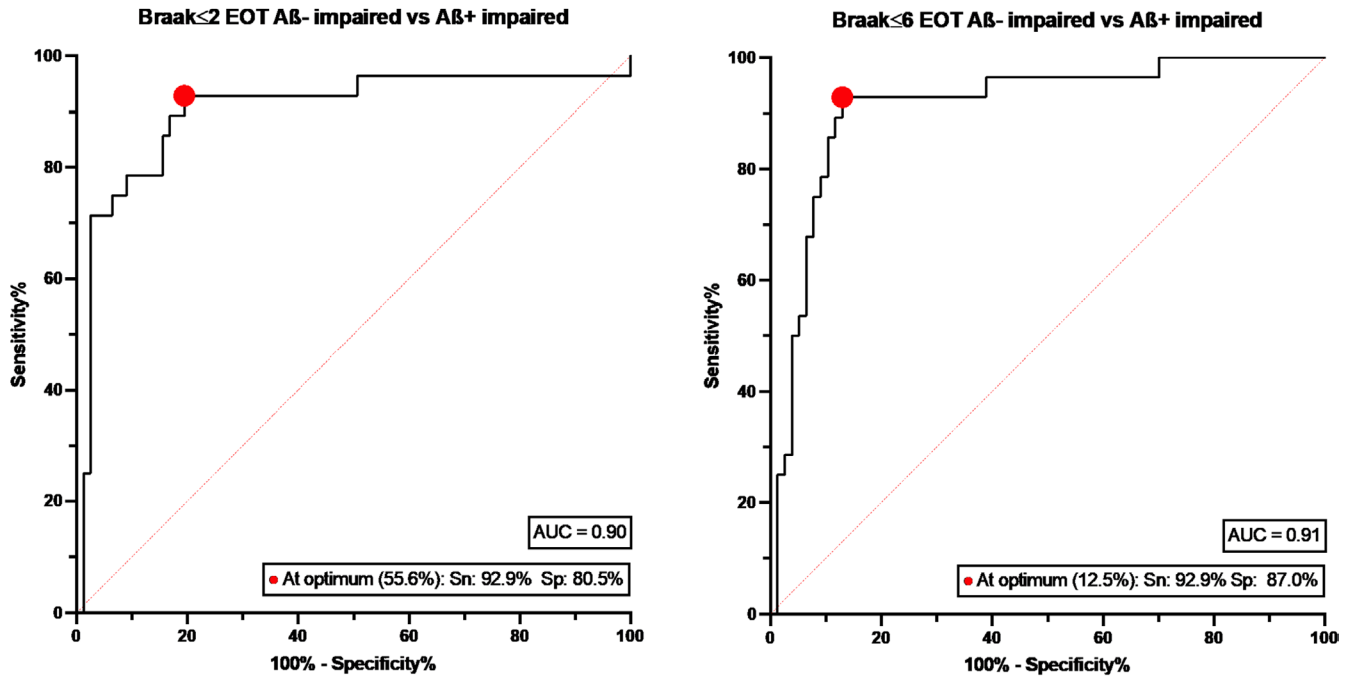

FIGURE 3 | ROC curves calculating the diagnostic performances of [^{18}F]MK-6240 to distinguish amyloid positive from amyloid negative subjects among a cognitively impaired population. EOT, extent of tauopathy (in %). Braak ≤ 2: region corresponding to the mesiotemporal lobe. Braak ≤ 6: region corresponding to the whole neocortex and some gray nuclei. Aβ, amyloid; AUC, area under the curve; Sn, sensitivity; Sp, specificity.

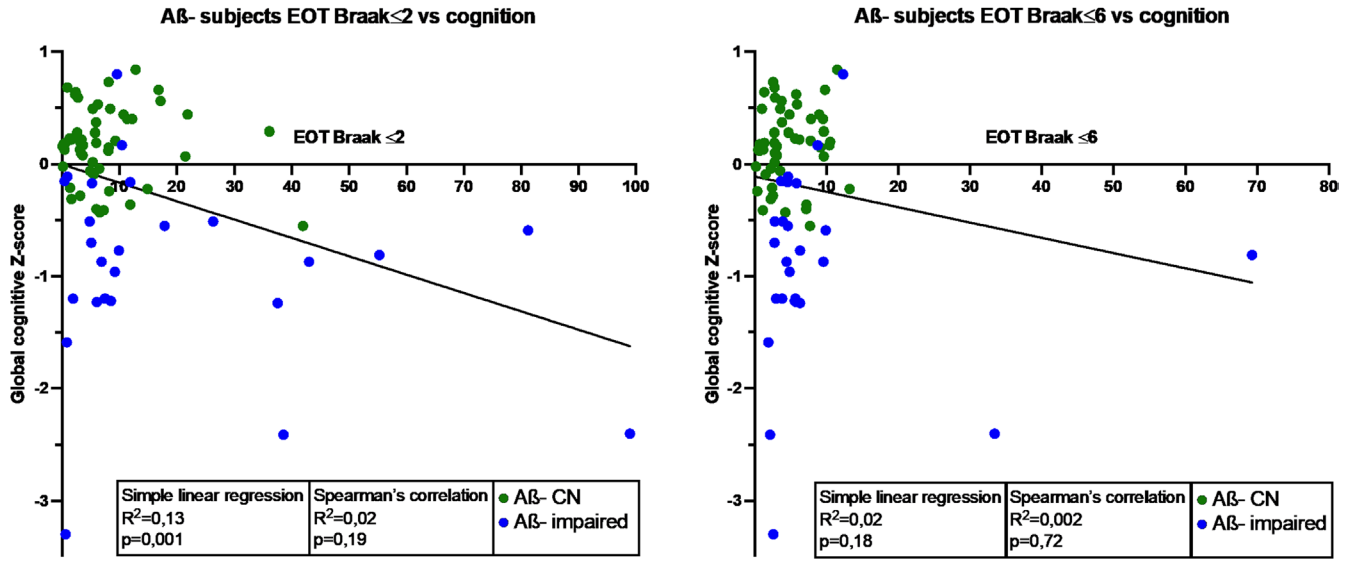

FIGURE 4 | Graph presenting the relation between the global cognitive *Z*-score and extent of tauopathy (EOT) in the regions Braak ≤ 2 and Braak ≤ 6 in the amyloid negative (Aβ−) population (Cognitively normal and cognitively impaired). Simple linear regression and Spearman's correlation results are displayed. Braak ≤ 2: region corresponding to the mesiotemporal lobe. Braak ≤ 6: region corresponding to the whole neocortex and some gray nuclei.

t-tau (572 pg/mL, normal < 381), and p-Tau (64 pg/mL, normal < 61 pg/mL), suggesting a non-AD tauopathy. Amyloid PET 2 years after the tau-PET confirmed the Aβ− status with a −11.0 centiloid score. The [^{18}F]MK-6240 tau-PET showed diffuse neocortical tauopathy. Most of FTD-related mutations were tested and excluded: C9orf72, GRN, MAPT (ex1, ex9−13), and VCP.

3.6.3 | Parkinsonian Syndrome

One of the Aβ+ impaired subjects also presented with parkinsonian syndrome and was eventually diagnosed with Dementia with Lewy Bodies (DLB). Among the Aβ− impaired individuals, four had parkinsonian syndrome: three patients diagnosed with CBD and one with PSP.

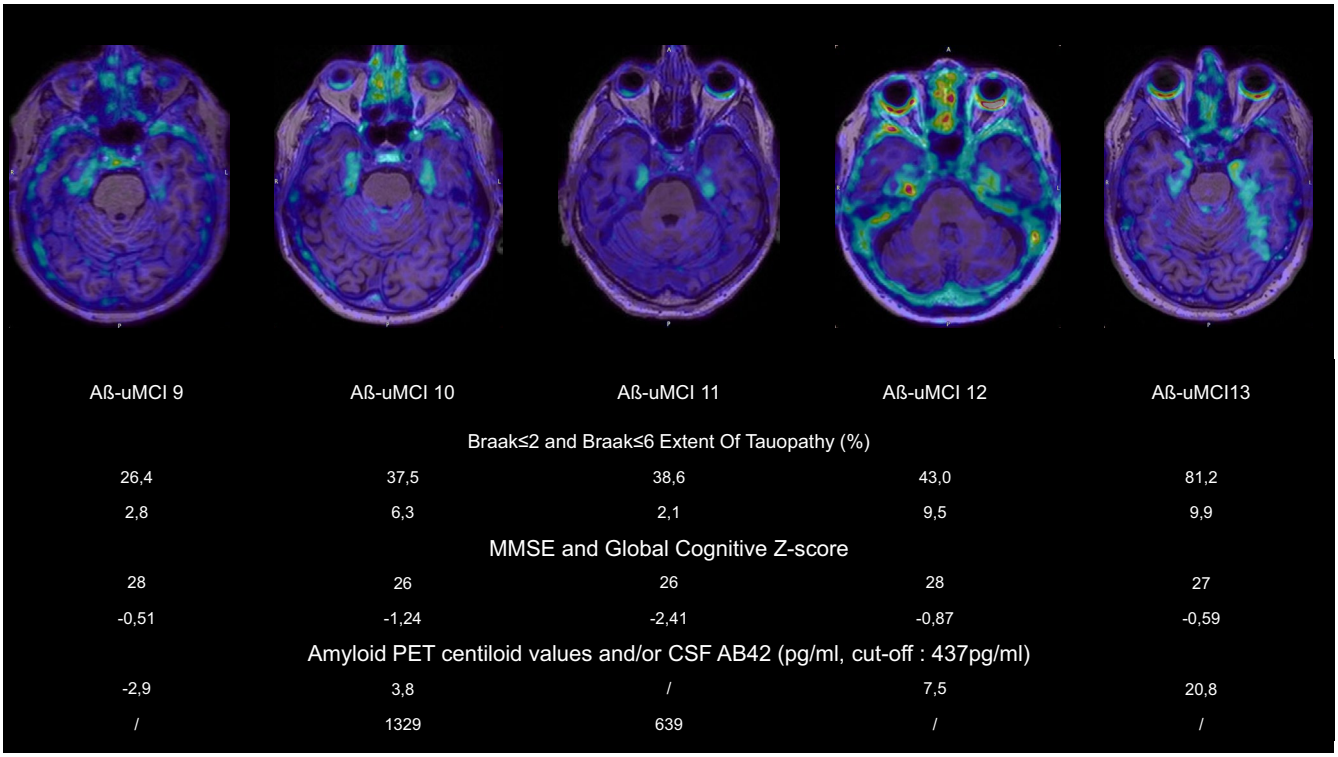

FIGURE 5 | [^{18}F]MK-6240 PET-MR fused images of five etiologically undefined mild cognitively impaired amyloid negative subjects (Aβ− uMCI). Aβ− uMCI 13 is suspected of early Alzheimer's disease and the remaining four are suspected of Primary age-related tauopathy (PART). Quantitative [^{18}F]MK-6240 PET data, cognitive tests results, Amyloid PET, and CSF results are displayed. Braak ≤ 2: Region corresponding to the mesiotemporal lobe. Braak ≤ 6: Region corresponding to the whole neocortex and some gray nuclei. CSF, cerebrospinal fluid; MMSE, mini-mental score examination.

3.6.4 | Vascular Disease

Among the Aβ− uMCI subjects, one individual had high WMH (29366). After genetic testing, he was confirmed to suffer from Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). He did not present significant tau PET signal (Braak ≤ 2 EOT 1.9% and Braak ≤ 6 EOT 5.6%).

4 | Discussion

This study aimed to investigate the specificity of [^{18}F]MK-6240 tau PET for AD versus non-AD tauopathy. While the sensitivity of the tracer for AD tauopathy was already explored in previous works [7–10], the present study focused on a Aβ− heterogeneous group ($n = 28$) including CI patients presenting with different neurodegenerative disorders suggestive of non-AD tauopathies. Among these subjects, significant neocortical [^{18}F]MK-6240 signal was only observed in two FTD subjects (while eight other subjects diagnosed with FTD remained negative). Additionally, five Aβ− uMCI subjects (out of 12 scanned) exhibited significant mesiotemporal tauopathy, most of whom are suspected to have PART.

Interestingly, the three types of tauopathies exhibiting significant [^{18}F]MK-6240 cortical signal are those involving (or potentially involving, in certain FTD subtypes) 3R/4R tau protein aggregates forming paired helical filaments (PHF). A recent study using cryoEM technique [21] showed how [^{18}F]MK-6240 specifically binds the PHFs in AD. Based on our findings, we hypothesize that [^{18}F]MK-6240 has a particular affinity for this form of tau aggregate, which is present in these tauopathies. From a diagnostic standpoint, the most challenging part is to distinguish the few [^{18}F]MK-6240-positive FTD subjects from AD pathology. Levy et al. demonstrated in 2022 [22] that some forms of genetic FTD with MAPT P301L or R406W mutations presented a certain degree of binding with [^{18}F]MK-6240. Furthermore, [^{18}F] Flortaucipir PET binding has also been reported in MAPT mutation carriers, especially those causing 3R/4R tauopathies [23]. Regarding our two subjects, no FTLD-related mutations were found. More specific FTD-centered studies with [^{18}F]MK-6240 are needed to fully understand the biological processes of the disease and subsequent tracer binding ability.

The presence of mesiotemporal tauopathy in Aβ− subjects raises the question of PART and its pathophysiological classification. As discussed by Duyckaerts et al. [24], should PART be considered a limited, non-amyloid driven, form of AD? We believe that this question would benefit from longitudinal clinical and imaging studies to enlighten the evolution of those subjects compared with typical prodromal AD controls. Early work using Flortaucipir-PET suggests that they have lower risk of progression than their Aβ+ MCI counterparts [25].

4.1 | Tau-PET Imaging: A New Diagnostic Tool?

Quantification in the region Braak ≤ 6 provided the most accurate diagnostic performances with a 12.5% positivity cutoff to distinguish Aβ− from Aβ+ CI patients. This 12.5% cutoff matches the previously established cutoff to distinguish Aβ+ impaired subjects from the Aβ− CN population (Figure 7).

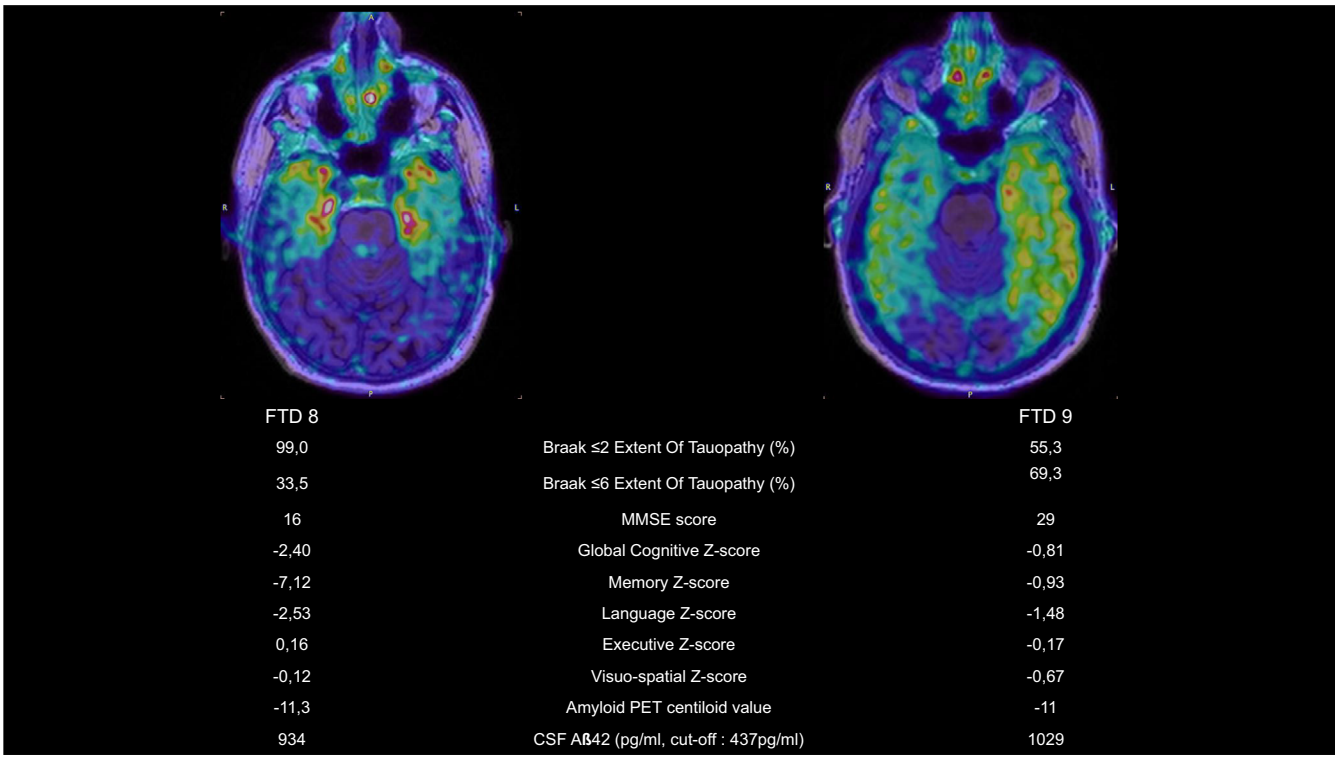

FIGURE 6 | [^{18}F]MK-6240 PET-MR fused images of the two (out of nine) subjects diagnosed with frontotemporal dementia (FTD) and presenting significant neocortical signal. Quantitative [^{18}F]MK-6240 PET data, cognitive tests results, Amyloid PET, and CSF results are displayed. Braak ≤ 2: Region corresponding to the mesiotemporal lobe. Braak ≤ 6: Region corresponding to the whole neocortex and some gray nuclei. CSF, cerebrospinal fluid; MMSE, mini-mental score examination.

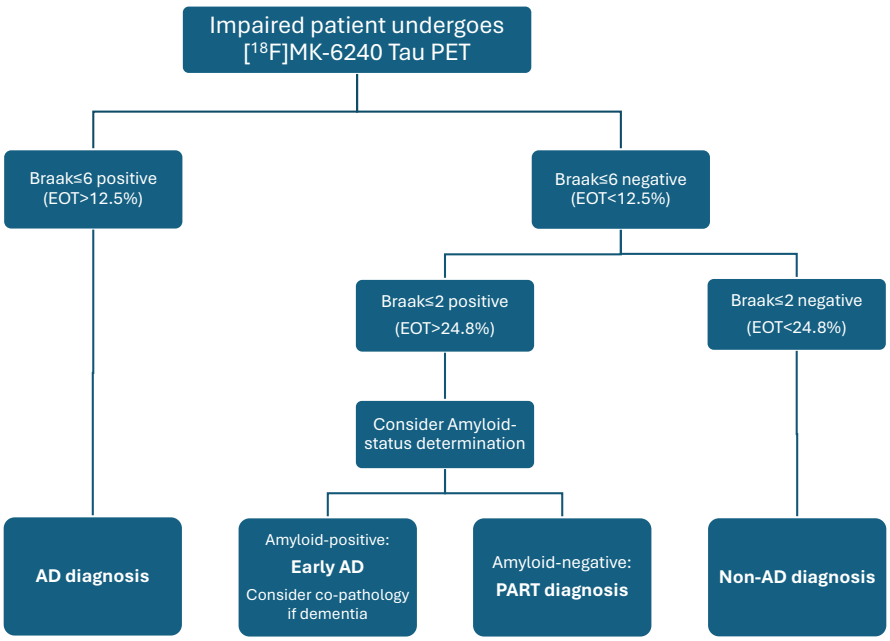

FIGURE 7 | Diagnostic flowchart for MCI patient suspected of Alzheimer's disease (AD). EOT, extent of tauopathy (in %). Braak ≤ 2: Region corresponding to the mesiotemporal lobe. Braak ≤ 6: Region corresponding to the whole neocortex and some gray nuclei. PART, primary age-related tauopathy.

Using this threshold, [^{18}F]MK-6240 tau PET has the potential to replace amyloid PET as the primary diagnostic tool for patients clinically suspected of AD. Indeed, our previous research demonstrated that if a subject had clinical impairment due to AD (Aβ+ MCI), we systematically observed positive [^{18}F]MK-6240 signal [10]. Conversely, if CI subjects do not exhibit significant tauopathy on tau-PET, they are likely to be Aβ− and cognitive impairment should be attributed to another neurodegenerative

disorder. Amyloid status determination may still be relevant for subjects with MTL-limited tauopathy to distinguish between PART and early AD. Based on our findings, we propose a diagnostic flowchart (Figure 7). Following this flowchart, amyloid PET may have a much more limited place to assess MCI patients suspected of AD if [^{18}F]MK-6240 tau PET is available, especially given the rise of blood-based biomarkers [26, 27]. When applying the flowchart to our cohort of 105 CI subjects, only 13 (12.4%) would have required amyloid PET, as they exhibited positive MTL but negative neocortical tau-PET signal. When applying the flowchart to the 21 CN Ab+ participants, 14 (66.7%) were considered as not having AD (negative tau-PET in both MTL and neocortex), five (23.8%) were considered as having AD (positive tau-PET in both regions), and two (9.5%) required amyloid-PET to determine whether they had AD (as they had positive MTL, but negative neocortical tau-PET). Applying tau-PET in the general CN population is unrealistic, but it is more feasible to confirm AD after positive plasma test and cognitive assessment. While amyloid PET results are mostly dichotomous, tau PET has the advantage of providing the extent of the disease.

4.2 | Limitations

Our Aβ− group was relatively small, with a limited number of patients in each subgroup representing different tauopathies. However, we could find a clear-cut separation between 3R/4R PHF tauopathies, which exhibited specific neocortical signal and all other tauopathies that did not. To further validate these findings, autopsy-proven studies of FTLD cases are needed to determine the specific types of tau isoforms aggregating in [^{18}F]MK-6240-positive FTD cases.

5 | Conclusion

[^{18}F]MK-6240 tau PET demonstrated high specificity for cerebral AD tauopathy compared to non-AD tauopathies. Aside from AD subjects, specific cortical signal was observed, limited to the MTL, in five out of 12 Aβ− MCI subjects, mostly suspected of PART, and in two out of 10 subjects diagnosed with FTD. These three neurodegenerative processes: AD, PART, and certain FTD cases share a common feature: They are driven by 3R/4R PHF, which appears to be the specific target of this tracer.

Consequently, [^{18}F]MK-6240 tau PET emerges as a highly specific tool for diagnosing AD tauopathy, particularly when neocortical signal is observed. Combined with its previously established high sensitivity, this tracer represents a reliable diagnostic tool for identifying AD in an MCI population.

Author Contributions

Thomas Gérard: writing – review and editing, writing – original draft, methodology, data curation, formal analysis, conceptualization, investigation. **Lise Colmant:** resources. **Vincent Malotaux:** resources. **Yasmine Salman:** resources. **Lara Huyghe:** resources. **Lisa Quenon:** resources. **Emilien Boyer:** resources. **Laurence Dricot:** resources. **Adrian Ivanoiu:** resources, project administration. **Renaud Lhommel:** project administration, resources, writing – review and editing, supervision, validation, funding acquisition. **Bernard Hanseeuw:** resources, project administration, funding acquisition, writing – review and editing, supervision, validation.

Acknowledgments

This work has been supported by the Fonds National pour la Recherche Scientifique/Belgian Fund for Scientific Research (FNRS/F.R.S).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

References

1. H. Wilson, M. Politis, E. A. Rabiner, and L. T. Middleton, "Novel PET Biomarkers to Disentangle Molecular Pathways Across Age-Related Neurodegenerative Diseases," *Cells* 9, no. 12 (2020): 2581, https://doi.org/10.3390/cells9122581.

2. M. L. Malarte, A. Nordberg, and L. Lemoine, "Characterization of MK6240, a Tau PET Tracer, in Autopsy Brain Tissue From Alzheimer's Disease Cases," *European Journal of Nuclear Medicine and Molecular Imaging* 48, no. 4 (2021): 1093–1102, https://doi.org/10.1007/s00259-020-05035-y.

3. C. R. Jack, D. A. Bennett, K. Blennow, et al., "A/T/N: An Unbiased Descriptive Classification Scheme for Alzheimer Disease Biomarkers," *Neurology* 87, no. 5 (2016): 539–547, https://doi.org/10.1212/WNL.0000000000002923.

4. P. T. Nelson, I. Alafuzoff, E. H. Bigio, et al., "Correlation of Alzheimer Disease Neuropathologic Changes With Cognitive Status: A Review of the Literature," *Journal of Neuropathology and Experimental Neurology* 71, no. 5 (2012): 362–381, https://doi.org/10.1097/NEN.0b013e31825018f7.

5. B. J. Hanseeuw, R. A. Betensky, H. I. L. Jacobs, et al., "Association of Amyloid and Tau With Cognition in Preclinical Alzheimer Disease," *JAMA Neurology* 76, no. 8 (2019): 915–924, https://doi.org/10.1001/jamaneurol.2019.1424.

6. H. Braak, D. R. Thal, E. Ghebremedhin, and K. Del Tredici, "Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years," *Journal of Neuropathology and Experimental Neurology* 70, no. 11 (2011): 960–969, https://doi.org/10.1097/NEN.0b013e318232a379.

7. T. J. Betthauser, K. A. Cody, M. D. Zammit, et al., "In Vivo Characterization and Quantification of Neurofibrillary Tau PET Radioligand ^{18}F-MK-6240 in Humans From Alzheimer Disease Dementia to Young Controls," *Journal of Nuclear Medicine* 60, no. 1 (2019): 93–99, https://doi.org/10.2967/jnumed.118.209650.

8. T. A. Pascoal, M. Shin, M. S. Kang, et al., "In Vivo Quantification of Neurofibrillary Tangles With [^{18}F]MK-6240," *Alzheimer's Research & Therapy* 10, no. 1 (2018): 74, https://doi.org/10.1186/s13195-018-0402-y.

9. G. Vanderlinden, N. Mertens, L. Michiels, et al., "Long-Term Test-Retest of Cerebral [^{18}F]MK-6240 Binding and Longitudinal Evaluation of Extracerebral Tracer Uptake in Healthy Controls and Amnestic MCI Patients," *European Journal of Nuclear Medicine and Molecular Imaging* 49, no. 13 (2022): 4580–4588, https://doi.org/10.1007/s00259-022-05907-5.

10. T. Gérard, L. Colmant, V. Malotaux, et al., "The Spatial Extent of Tauopathy on [^{18}F]MK-6240 Tau PET Shows Stronger Association With Cognitive Performances Than the Standard Uptake Value Ratio in Alzheimer's Disease," *European Journal of Nuclear Medicine and Molecular Imaging* 51, no. 6 (2024): 1662–1674, https://doi.org/10.1007/s00259-024-06603-2.

11. C. Aguero, M. Dhaynaut, A. C. Amaral, et al., "Head-to-Head Comparison of [^{18}F]-Flortaucipir, [^{18}F]-MK-6240 and [^{18}F]-PI-2620 Postmortem Binding Across the Spectrum of Neurodegenerative Diseases," *Acta Neuropathologica* 147, no. 1 (2024): 25, https://doi.org/10.1007/s00401-023-02672-z.

12. L. Colmant, A. Bierbrauer, Y. Bellaali, et al., "Dissociating Effects of Aging and Genetic Risk of Sporadic Alzheimer's Disease on Path Integration," *Neurobiology of Aging* 131 (2023): 170–181, https://doi.org/10.1016/j.neurobiolaging.2023.07.025.

13. B. J. Hanseeuw, V. Malotaux, L. Dricot, et al., "Defining a Centiloid Scale Threshold Predicting Long-Term Progression to Dementia in Patients Attending the Memory Clinic: An [^{18}F] Flutemetamol Amyloid PET Study," *European Journal of Nuclear Medicine and Molecular Imaging* 48, no. 1 (2021): 302–310, https://doi.org/10.1007/s00259-020-04942-4.

14. J. L. Bayart, B. Hanseeuw, A. Ivanoiu, and V. Van Pesch, "Analytical and Clinical Performances of the Automated Lumipulse Cerebrospinal Fluid Aβ42 and T-Tau Assays for Alzheimer's Disease Diagnosis," *Journal of Neurology* 266, no. 9 (2019): 2304–2311, https://doi.org/10.1007/s00415-019-09418-6.

15. A. Ivanoiu, L. Dricot, N. Gilis, et al., "Classification of Non-Demented Patients Attending a Memory Clinic Using the New Diagnostic Criteria for Alzheimer's Disease With Disease-Related Biomarkers," *Journal of Alzheimer's Disease* 43, no. 3 (2015): 835–847, https://doi.org/10.3233/JAD-140651.

16. M. Van der Linden, F. Coyette, J. Poitrenaud, et al., "L'évaluation des troubles de la mémoire: présentation de quatre tests de mémoire épisodique (avec leur étalonnage)," in *L'épreuve de rappel libre/rappel indice à 16 items (RL/RI-16)*, ed. M. Van der Linden, S. Adam, A. Agniel, C. Baisset Mouly, and les membres du GREMEM (Solal Editeur, 2004), 25–47.

17. M. P. de Partz de Courtray, V. Bilocq, V. De Wilde, X. Seron, and A. Pillon, "Lexis. Tests pour le diagnostic des troubles lexicaux chez le patient aphasique" (2001), https://dial.uclouvain.be/pr/boreal/object/boreal:90447.

18. R. M. Reitan, "The Relation of the Trail Making Test to Organic Brain Damage," *Journal of Consulting Psychology* 19, no. 5 (1955): 393–394, https://doi.org/10.1037/h0044509.

19. I. Rouleau, D. P. Salmon, N. Butters, C. Kennedy, and K. McGuire, "Quantitative and Qualitative Analyses of Clock Drawings in Alzheimer's and Huntington's Disease," *Brain and Cognition* 18, no. 1 (1992): 70–87, https://doi.org/10.1016/0278-2626(92)90112-y.

20. J. C. Morris, R. C. Mohs, H. Rogers, G. Fillenbaum, and A. Heyman, "Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Clinical and Neuropsychological Assessment of Alzheimer's Disease," *Psychopharmacology Bulletin* 24, no. 4 (1988): 641–652.

21. P. Kunach, J. Vaquer-Alicea, M. S. Smith, et al., "Cryo-EM Structure of Alzheimer's Disease Tau Filaments With PET Ligand MK-6240," *bioRxiv* (2023), https://doi.org/10.1101/2023.09.22.558671.

22. J. P. Levy, G. Bezgin, M. Savard, et al., "^{18}F-MK-6240 Tau-PET in Genetic Frontotemporal Dementia," *Brain* 145, no. 5 (2022): 1763–1772, https://doi.org/10.1093/brain/awab392.

23. E. E. Wolters, J. M. Papma, S. C. J. Verfaillie, et al., "[^{18}F]Flortaucipir PET Across Various *MAPT* Mutations in Presymptomatic and Symptomatic Carriers," *Neurology* 97, no. 10 (2021): e1017–e1030, https://doi.org/10.1212/WNL.0000000000012448.

24. C. Duyckaerts, H. Braak, J. P. Brion, et al., "PART Is Part of Alzheimer Disease," *Acta Neuropathologica* 129, no. 5 (2015): 749–756, https://doi.org/10.1007/s00401-015-1390-7.

25. A. Costoya-Sánchez, A. Moscoso, J. Silva-Rodríguez, et al., "Increased Medial Temporal Tau Positron Emission Tomography Uptake in the Absence of Amyloid-β Positivity," *JAMA Neurology* 80, no. 10 (2023): 1051, https://doi.org/10.1001/jamaneurol.2023.2560.

26. R. Ossenkoppele, R. van der Kant, and O. Hansson, "Tau Biomarkers in Alzheimer's Disease: Towards Implementation in Clinical Practice and Trials," *Lancet Neurology* 21, no. 8 (2022): 726–734, https://doi.org/10.1016/S1474-4422(22)00168-5.

27. L. Colmant, E. Boyer, T. Gerard, et al., "Definition of a Threshold for the Plasma Aβ42/Aβ40 Ratio Measured by Single-Molecule Array to Predict the Amyloid Status of Individuals Without Dementia," *International Journal of Molecular Sciences* 25, no. 2 (2024): 1173, https://doi.org/10.3390/ijms25021173.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.