Journal of Neurology (2019) 266:835–843
https://doi.org/10.1007/s00415-019-09203-5

ORIGINAL COMMUNICATION

Cognitive changes of older adults with an equivocal amyloid load

Kristell Pothier[1,2] · Laure Saint-Aubert[3,4] · Claudie Hooper[1] · Julien Delrieu[1,4] · Pierre Payoux[3,4] · Philipe de Souto Barreto[1,5] · Bruno Vellas[1,5] · MAPT/DSA Study Group

Received: 3 August 2018 / Revised: 5 December 2018 / Accepted: 18 January 2019 / Published online: 28 January 2019

Abstract

Background Observational and interventional studies addressing the link between amyloid (Aβ) burden and cognitive decline are increasing, but a clear definition of amyloid positivity is still lacking. This may represent a great stake for therapeutic studies enrolling Aβ + patients only. The main objective of this study was to define a population with "equivocal" amyloid status, and evaluate their cognitive changes.

Methods Sixty-five participants over 75 years old, from the Control group of the interventional MAPT study, at risk to develop Alzheimer's disease, were included. Participants were classified into three groups in terms of amyloid load: Aβ +, Aβ − and Equivocal participants (according to visual reading, global standardized uptake (SUVR) cut-offs, or a k-mean clustering method). The cognitive changes over time (memory, executive functions, attention and processing speed) of this Equivocal group were then compared to Aβ + and Aβ − participants.

Results When classified by visual read, Equivocal participants' memory scores were comparable to the Aβ- participants, and greater than in Aβ + participants over time. Secondary analyses, using SUVR cut-offs classification, showed different trajectories with Equivocal participants being comparable to the Aβ + participants, and lower than Aβ-, on executive performance over time.

Conclusions This original work pointed out a population that may be of great interest for interventional studies, raising the question of how amyloid status should be defined and integrated in such studies. These findings should be replicated in future studies on larger datasets, to confirm what methodological approach would be the most suitable to highlight this specific neuroimaging entity.

Keywords Amyloid imaging · Memory · Executive functions · Equivocal cases

Kristell Pothier and Laure Saint-Aubert authors have contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09203-5) contains supplementary material, which is available to authorized users.

✉ Kristell Pothier
kristell.pothier@univ-tours.fr

1 Gérontopôle de Toulouse, Centre Hospitalo-Universitaire de Toulouse (CHU Toulouse), Toulouse, France

2 EA 2114, Département de Psychologie-Psychologie des Ages de la Vie et Adaptation, University of Tours, 3, Rue des Tanneurs, 37041 Tours Cedex 1, France

3 Department of Nuclear Medicine, Imaging Pole, Toulouse University Hospital, Toulouse, France

4 Toulouse NeuroImaging Center, Université de Toulouse, Inserm, UPS, Toulouse, France

5 UMR INSERM 1027, University of Toulouse III, Toulouse, France

Introduction

The detection of amyloid-beta (Aβ) load in vivo using positron emission tomography (PET) has proved to be an invaluable tool to increase clinical diagnosis accuracy of probable Alzheimer's disease (AD) [1, 2]. Amyloid burden is present from the preclinical stages of AD [3], allowing very early detection of the underlying pathology. Previous studies have suggested an association between Aβ load and cognitive decline at follow-up in cognitively healthy older adults [4, 5]. However, most studies rely on their own definitions of amyloid positivity (Aβ +), sometimes using visual reading [6, 7], or—more commonly—global cut-offs [8–10]: even when using standardized uptake values ratios (SUVR), studies used various cut-offs ranging from 1.10 [11] to 1.34 [12], most likely due to preprocessing differences, and discard possible regional heterogeneity of tracer uptake. Despite various definitions of a positive status, this dichotomous approach has been largely used to include Aβ + participants in interventional studies. However, this method can lead to important proportions of false negative/positive status that may result in inappropriate follow-ups. This is particularly true in cases being close to a quantitative cut-off, or in absence of an inter-experts consensus for PET scan visual reading: those may be defined as "equivocal" cases. In an exploratory study, using [^{11}C]Pittsburgh Compound B-PET ([^{11}C]PIB-PET) imaging, Mormino and collaborators investigated this equivocal population by classifying older adults without cognitive impairment according to global [^{11}C]PIB index values. When examining the spatial distribution of the tracer, slightly elevated values of [^{11}C]PIB uptake were observed in the equivocal group in regions known to show amyloid deposition, making this specific population biologically relevant [13]. Moreover, a recent cross-sectional study by our group [14], using visual read of [^{18}F]florbetapir amyloid PET scans to classify older adults at risk of cognitive decline according to their amyloid load, showed that subjects with equivocal PET scans (ie, no consensus among three observers on visual rating) seemed to represent an intermediate population, compared to Aβ + and Aβ − older adults, with regards to cognitive scores (MMSE, and memory and executive scores) and amyloid load. Taken together, these results indicate that such equivocal populations, potentially reflecting an early stage of AD development, may be a neuroimaging entity, worth studying over time. These specific individuals might represent a target population for future preventive interventions. Nevertheless, to the best of our knowledge, no study has, to date, evaluated this equivocal population with a careful cognitive follow-up.

The main objective was, therefore, to study the cognitive changes over time, using various neuropsychological measures, of elderly participants at risk of cognitive decline, with an equivocal amyloid load on PET imaging.

Materials and methods

This study is a secondary analysis of the Multidomain Alzheimer Preventive Trial (MAPT), a multicenter, three-year randomized controlled trial designed to test the impact of three different interventions (omega 3 polyunsaturated fatty acid supplementation, multidomain intervention including nutritional and physical counseling and cognitive training, and the combination of both) against placebo on cognitive decline in 1680 older adults [15, 16]. The protocol is registered on a public-access clinical trial database (http://www.clinicaltrials.gov; #NCT01513252) and was approved by the French Ethics Committee in Toulouse (CPP SOOM II). All participants from MAPT study signed an informed consent.

Participants

For this ancillary study, all MAPT participants who underwent a [^{18}F]florbetapir PET scan were included ($n = 271$). Participants included in interventional groups ($n = 187$) were excluded because a positive impact of interventions was previously shown on the cognitive outcome in participants with an amyloid burden [16]. All included participants were above 70 years old, and all met at least one of the following clinical criteria: spontaneous memory complaints, limitation in executing one or more instrumental activity of daily living, or slow walking speed (≤ 0.8 m/s). The main exclusion criteria were: having dementia, cognitive disorders (score at the Mini-Mental State Examination—MMSE—below 24), severe depression, difficulty in basic activities of daily living, taking polyunsaturated fatty acid supplements at baseline. Nineteen participants were excluded from this study: two of them because they had dementia at the moment of their PET scan (score at the Clinical Dementia Rating scale—CDR—above 1), and 17 because they had no cognitive follow-up after their PET scan, leaving a final sample of 65 older adults from the control group of MAPT study for the analyses.

Clinical assessments

Clinical and functional examinations

All participants included in this study underwent a clinical examination (performed the closest to the PET scan evaluation) to assess their physical performance (using the Short Physical Performance Battery—SPPB), their gait-speed, their body-mass index (BMI). Depression was assessed using the Geriatric Depression Scale-15 items (GDS-15). Biological sample was performed to obtain, among others, levels of Omega 3, Vitamin-D, homocysteine, as well as apolipoprotein (APoE) phenotype. Participants were diagnosed as possible MCI if they had a CDR score = 0.5.

Cognitive assessment

Global and specific cognitive functions were evaluated through different neuropsychological tests at baseline, and at 6, 12, 24 and 36 months. For this specific study, only cognitive scores performed closest to the PET scan (± six months from the scan evaluation), and after, were included in the analyses. Global cognition was evaluated by the MMSE score. Episodic memory was assessed by the Free and Cued Selective Reminding Test (FCSRT), for which free recall, and total (free + cued) recall were collected. Executive functions were evaluated through two verbal fluency tests: Controlled Oral Word Association Test (COWAT, numbers of accurate words beginning with a "*P*" in two minutes) and Category Naming Test (CNT, numbers of accurate give animals, in two minutes), as well as the Trail-Making Test part B (TMT-B, time to perform the test, in seconds, specifically evaluating switching). Processing speed was assessed by the Digit Symbol Substitution Subtest of the Wechsler Adult Intelligence Scale-Revised (DSST, number of correct symbols drew in 45 s), and the Trail-Making Test part A (TMT-A, time to perform the test, in seconds).

PET imaging

Acquisitions

[^{18}F]Florbetapir scans were acquired on 5 different hybrid PET-CT scanners, including one PET CT 690 (GE Healthcare; Cleveland, OH), one Discovery RX VCT (General Electric; Fairfield, CT), 2 True Point HiRez (Siemens Medical Solutions; Malvern, PA), and one Biograph 4 Emission Duo LSO (Siemens Medical Solutions). All PET sinograms were reconstructed with a three-dimensional iterative algorithm, with corrections for randomness, scatter, photon attenuation, and decay, which produced images with an isotropic voxel of $2 \times 2 \times 2$ mm^3 and a spatial resolution of approximately 5 mm full width at a half maximum at the field-of-view centre. All cerebral emission scans began 50 min after a mean injection of 4 MBq/kg weight of [^{18}F] florbetapir. For each participant, 10- or 15-min frames were acquired to ensure movement-free image acquisition. PET scans were performed once during the 3-year study, as close as possible to clinical assessments, using whole-body hybrid PET-computed tomography scanners. No partial volume correction was applied.

Classification of the participants

Visual read Following the procedure described in details in Payoux et al. [14], all amyloid scans from MAPT study were visually assessed independently by three trained molecular imaging specialists, blinded to clinical data, and classified into three groups, based on consensus among the observers: 1/Aβ +: the three observers agreed there was significant [^{18}F]florbetapir cortical retention (ie, two or more brain areas in which there was reduced or absent grey/white matter contrast or one or more areas in which grey matter radioactivity was intense); 2/Aβ−: the three observers agreed there was no significant [^{18}F]florbetapir cortical retention (ie, clear grey/white matter contrast); 3/Equivocal PET: there was no consensus among the three observers.

Semi-automated quantitative analysis

To avoid potential subjective interpretation due to visual reading, two other methods of classification have been used to assign participants to subgroups, according to amyloid load: one using SUVR cut-offs, and one data-driven approach, by k-mean clustering (see Fig. 1 for representative images of participants' PET scans).

For both semi-quantitative methods, [^{18}F]florbetapir images were first co-registered with statistical parametric mapping to a [^{18}F]florbetapir template provided by Avid Radiopharmaceuticals (Philadelphia, PA). Mean signal in the global cortex was computed for each participant, with cerebellum as the reference region and, according to the most commonly used cut-offs in research studies, the thresholds of cortical SUVR < 1.10 [11] and SUVR > 1.17 [8] were used to define participants without amyloid burden (Aβ −) and amyloid-positive participants (Aβ +), respectively. Participants with an Equivocal amyloid load were then classified as follow: 1.10 ≤ SUVR ≥ 1.17, which lies in a range similar to what was used in a recent study [17]. Mean signal was also computed in the following predefined anatomical regions of interest (with the cerebellum as the reference region): temporal cortex, parietal cortex, medial orbitofrontal cortex, occipital cortex, precuneus, anterior and posterior cingulate, and hippocampus. The resulting regional SUVR values were used to apply a classic k-mean clustering with $n = 3$ clusters, roughly corresponding to the three groups of amyloid load (Aβ +, Aβ −, 'Intermediate' or "Equivocal" population).

Statistical analysis

Descriptive statistics are presented as means ± standard deviations (SD), or absolute numbers and percentage, as appropriate.

To compare the changes in cognitive performance according to amyloid load, we performed a linear mixed model with participant used as a random effect, cognitive scores (closest to, and after the PET scan) was the dependent variable, and amyloid group, time, time² were the independent variables. The interaction between group × time and group × time² were assessed to compare changes in cognitive scores over time between the three amyloid groups (Aβ +, Aβ − and Equivocal participants), as defined by each classification method (visual reading, SUVR cut-off, or clustering). Age at the moment of the PET scan was added as a confounding variable. The models were repeated with APoE ε4 status (presence of at least one ε4 allele) as an additional confounding variable, but because there was no main effect of APoE ε4 status observed, these models will not be further discussed. Considering the design of the study, we also

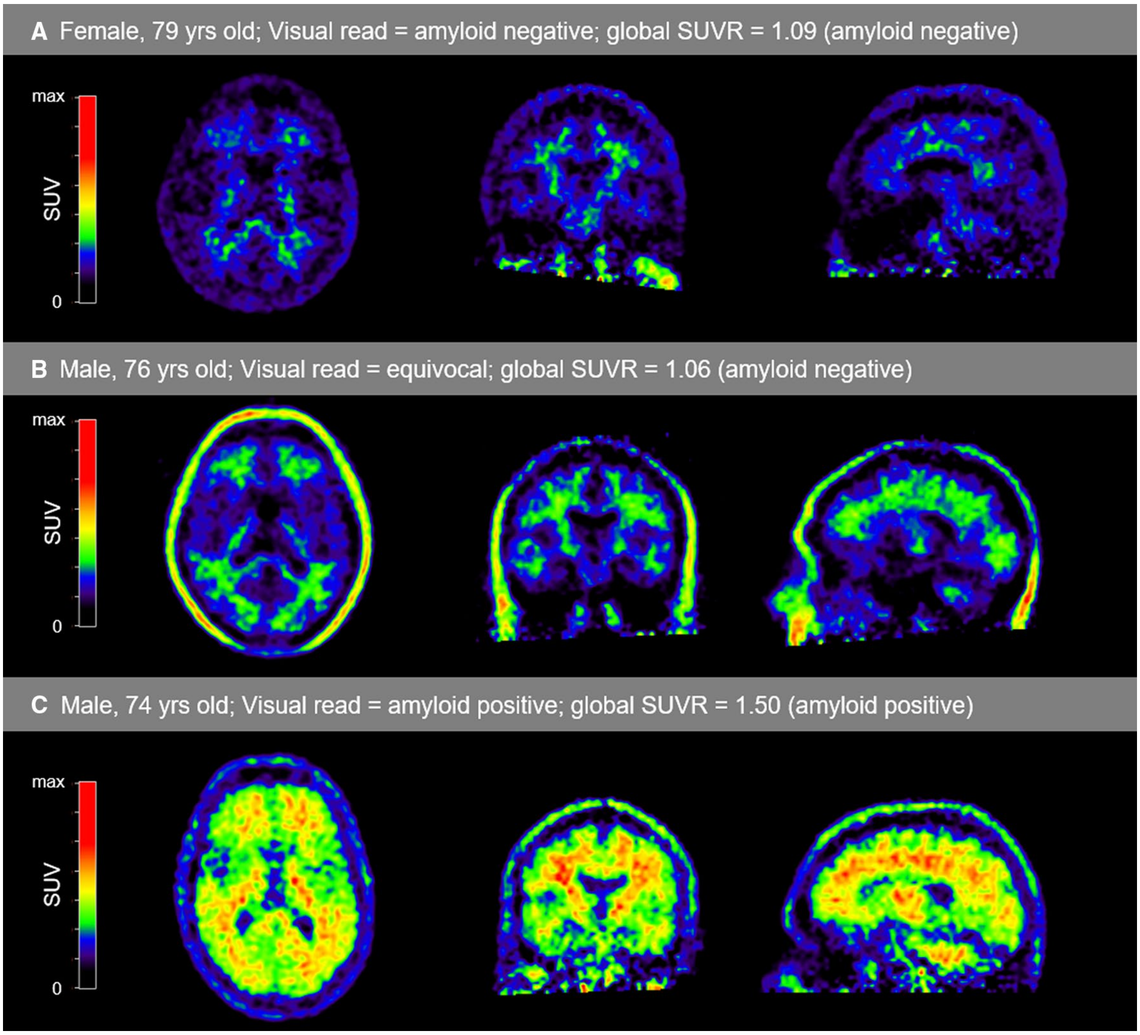

Fig. 1 Representative images in axial (left), coronal (middle) and sagittal (right) view of [18F]florbetapir PET scans of patients with: **A** negative amyloid PET scan on both visual read and global SUVR quantification (< 1.10); **B** equivocal amyloid status on visual read but negative amyloid status on global SUVR quantification; **C** positive amyloid PET scan on both visual read and global SUVR quantification (> 1.17). All three cases were scanned in the same PET centre. Scans are presented as they appeared after reconstruction but prior to any spatial transformation or regional normalization, as this is how raters looked at them for visual read

controlled for the time interval between the post-scan cognitive assessments and the PET scan.

Results

The 65 older adults included in this study (mean age = 76.11 years old ± 4.73, at the time of the scan) were mostly women (60% of the sample). The mean time interval between the inclusion visit at the beginning of the study and the PET scan was 463.29 days (± 260). The first cognitive assessment (post PET scan) was performed at 41.51 (± 66.17) days in average from the scan. The last cognitive evaluation was performed at around 21 months in average from the first cognitive assessment (657.49 ± 234.30 days). Among the 65 participants, two (3.1%) had all five cognitive assessments, 20 (30.7%) had four assessments, 40 (61.5%) had three assessments, and all of them had at least two assessments.

Clinical and demographic characteristics of all study participants (for the whole sample, as well as per amyloid group) at the time of the PET scan are described in Table 1. Figure 2 represents the distribution of participants with Equivocal amyloid status; out of the 65 participants, seven were classified as Equivocal for their amyloid status, based on visual reading. Using the two other methods, eleven were classified as Equivocal participants by global SUVR cut-offs, and 21 with the clustering method. Of note, no participant classified as Equivocal with visual reading was also classified as Equivocal using the global SUVR method, hence

Table 1 Baseline characteristics of equivocal participants, according to the three methods of classification

	All	Equivocal participants		
		Visual read	SUVR cut-offs	Clusters
n	65	7 ($n_{A\beta+}$ =26)	11 ($n_{A\beta+}$ = 32)	21 ($n_{A\beta+}$ = 21)
MCI *n* (%)	31 (47.7%)	0	5 (45.4%)	11 (52.4%)
SUVR	1.2 (0.2)	1.21 (0.2)	1.1 (0.02)	1.2 (0.06)
Age	76.1 (4.7)	74.84 (4.3)	74.3 (3.1)	75.8 (4.2)
Sex *n* female (%)	39 (60%)	3 (42.8%)	8 (72.7%)	14 (66.7%)
Education	3.5 (1.3)	4 (1.1)	3.36 (1.6)	3.6 (1.4)
Clinical and functional assessments				
BMI (kg/m^2)	26.4 (3.6)	24.6 (3.8)	27.2 (4.7)	26.3 (4.1)
Gait speed (m/sec)	1.1 (0.2)	1.2 (0.2)	1.1 (0.3)	1.1 (0.2)
SPPB (/12)	10.4 (1.6)	10.9 (1.9)	10.4 (1.7)	10.7 (1.6)
GDS-15	3 (2.7)	4.3 (3)	1.3 (1.2)	2.8 (2.3)
APoE ε4 *n* (%)	19/57 (33.3%)	5/7 (71.4%)	1/7 (14.3%)	5/17 (29.4%)
Omega 3 index	6.06 (1.5)	6.95 (2)	6.1 (1.3)	5.9 (1.3)
Vitamin D (ng/ml)	21.2 (9.9)	19.8 (1.5)	22 (9.8)	18.9 (9.3)
Total plasma homocysteine (µmol/L)	13.8 (3.2)	10.76 (1.4)	13.2 (2.6)	14.1 (2.6)
Cognitive assessment				
Global cognition				
MMSE (/30)	28.2 (1.5)	28.3 (0.8)	28.2 (1.6)	28 (1.7)
Episodic memory				
FCSRT free recall (/48)	28.3 (8.6)	30.3 (6.8)	32.4 (8.6)	29.8 (8)
FCSRT total recall (/48)	44.2 (4.8)	45.1 (2.8)	45.7 (2.1)	45.2 (3.2)
Executive functions				
COWAT	19.3 (5.8)	22.7 (5.5)	20 (5.8)	20.1 (5.5)
CNT	25.7 (6.4)	28.4 (6.1)	27 (8.5)	27.8 (6.8)
TMT-B (sec)	109 (39)	96.7 (28.6)	105.5 (56.1)	111.8 (50)
Processing speed				
DSST	38.2 (9.3)	39.9 (3.8)	44.8 (9.7)	40.7 (11.4)
TMT-A (s)	40.4 (11.3)	36.4 (7.7)	37.2 (9)	38.3 (8.5)

Values are expressed as mean (standard deviation), unless specified otherwise

APoE ε4 presence of at least one ε4 allele, *BMI* Body Mass Index, *CNT* category naming test, *COWAT* Controlled oral word association test, *DSST* the Digit Symbol Substitution Subtest of the Wechsler Adult Intelligence Scale-Revised, *Education* assessed with a scale from 1 (no diploma) to 5 (highly educated), *FCSRT* Free and cued selective reminding test, *GDS-15* Geriatric Depression Scale-15 items, *MCI* Mild Cognitive Impairment (score = 0.5 on the Clinical Dementia Rating scale), *MMSE* Mini-Mental State Examination, *SPPB* Short Physical Performance Battery scores (over 12 points), *SUVR* standardized uptake values ratios, *TMT* Trail-Making Test

reinforcing the use of the third – data-driven – approach to better characterize what could be this Equivocal population (Fig. 3).

Regarding the change in cognitive scores over time, according to the amyloid burden (see Table 2), a significant group × time interaction was found for the free recall ($p = 0.011$), and for the total recall of the FCRST ($p = 0.001$): using visual reading classification, Equivocal participants' memory scores were comparable to the Aβ − participants, and greater than in Aβ + participants over time. Secondary analyses using the two other methods of classification showed a similar significant group × time interaction for the total recall of the FCRST ($p = 0.037$). The SUVR cut-offs method also showed a significant group × time interaction ($p = 0.032$) for executive switching performance (TMT-B), with Equivocal participants being comparable to the Aβ + participants, with lower performance than Aβ − participants over time (see Fig. 4). All associations on the other tests were non-significant (see Online Resource 1).

Discussion

In this study, we investigated cognitive changes over time in elderly participants at risk of developing AD, and who had Equivocal amyloid status on PET imaging. The main

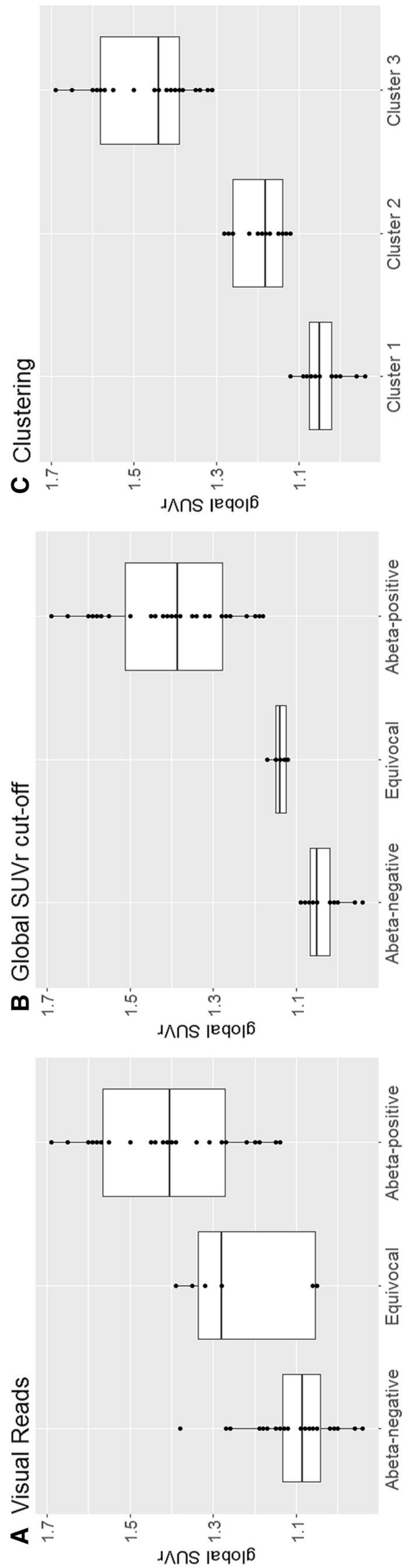

Fig. 2 Distribution of Global SUVR values in the three groups of participants (Aβ +, Aβ − and Equivocal) according to the three classification approaches. *Abeta+* amyloid-beta positive, *Abeta-* amyloid-beta negative, *SUVR* standardized uptake values ratios

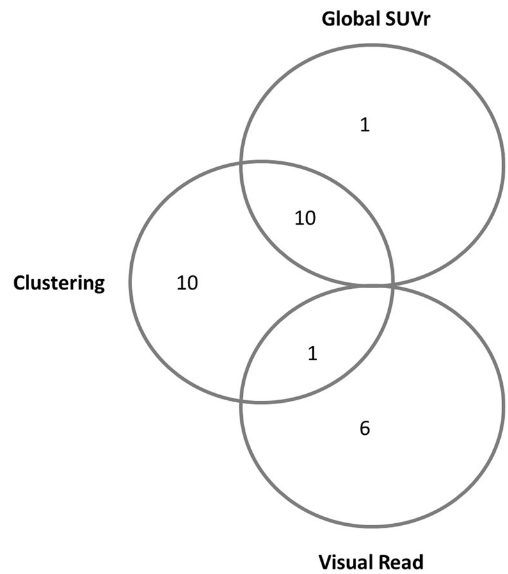

Fig. 3 Venn diagram illustrating the number of participants with Equivocal amyloid status according to the three classification approaches. *SUVR* standardized uptake values ratios

findings revealed similar trajectory between Equivocal and Aβ − participants in memory scores over time, when participants were classified by visual reading. However, when using SUVR cut-offs method, results showed different cognitive trajectories with Equivocal participants being similar to Aβ + participants for executive performance over time.

By comparing visual analysis to two other methods of classification of the amyloid status, this study highlights noteworthy findings on participants with an Equivocal amyloid load. Both visual read and SUVR cut-offs classifications showed a significant difference between the three groups for episodic memory over time, with better performance in the Equivocal and Aβ − populations compared to Aβ +. In contrast, when classified by SUVR cut-offs only, the Equivocal participants, like the Aβ +, showed worse performance over time on one executive test compared to Aβ −. It suggests 1/that the methods used to define the Equivocal population are not equivalent, and 2/that participants with light amyloid load, as observed by PET imaging, have a distinct pattern of cognitive change. Despite inconsistencies across studies, a meta-analysis from 2013 revealed a significant positive association between amyloid positivity and highly integrated processes in cognitively normal individuals [18]. Authors specifically found that increased amyloid burden was associated with decreased performance only in episodic memory and executive functions. Two recent studies also reported such associations between amyloid load and memory [19] or executive functions [20]. The small sample size of the Equivocal group resulting from our visual read and SUVR cut-offs classifications, plus the unexpected

Table 2 Cognitive performance showing different progression over time between three groups of participants (Aβ +, Aβ − and Equivocal), according to the methodological approach

Cognitive domain	Cognitive test	Visual read				SUVR cut-off			
		Main effect (F)	Aβ + vs Equivocal	Aβ − vs Equivocal	Aβ + vs, Aβ −	Main effect (*F*)	Aβ + vs Equivocal	Aβ − vs Equivocal	Aβ + vs Aβ −
Episodic memory	FCRST free recall	**4.893**	**$\beta = -0.061$; $t = -2.50$ ($p = 0.015$)**	$\beta = -0.023$; $t = 1.01$ ($p = 0.316$)	**$\beta = -0.038$; $t = -2.71$ ($p = 0.009$)**	3.097	–	–	–
	FCRST total recall	**7.305**	**$\beta = -0.100$; $t = -3.03$ ($p = 0.004$)**	$\beta = -0.037$; $t = 1.20$ ($p = 0.233$)	**$\beta = -0.063$; $t = -3.33$ ($p = 0.002$)**	**3.484**	**$\beta = -0.056$; $t = -2.44$ ($p = 0.018$)**	$\beta = -0.017$ $t = -0.70$ ($p = 0.482$)	$\beta = -0.040$ $t = -1.92$ ($p = 0.059$)
Executive functions	TMT-B	0.765	–	–	–	**3.656**	**$\beta = 0.0002$; $t = -2.16$ ($p = 0.035$)**	**$\beta = 0.247$; $t = 2.29$ ($p = 0.026$)**	**$\beta = 0.220$; $t = 2.34$ ($p = 0.023$)**

F values as well as post-hoc *β* estimates and *t* values (*p* values) for the significant Group × time interaction are presented. Significant ($p < 0.05$) post-hoc results are mentioned in bold

Aβ + amyloid-beta positive, *Aβ −* amyloid-beta negative, *FCSRT* free and cued selective reminding test, *SUVR* standardized uptake values ratios, *TMT* trail-making test

absence of a main effect of APoE ε4 status in our models, preclude from drawing strong conclusions from our findings. We cannot rule out the possibility that the significant associations observed with specific cognitive scores over time were mainly driven by poor statistical power and noise. However, it is also possible that these classifications were able to target specific populations of interest that may be specific neuroimaging entities [14] that would benefit the most from specific trainings. Conversely, the clustering method, by grouping together a larger number of participants, may have not been able to define a population of real interest. As a consequence, this third, data-driven, method found no significant difference between groups in cognitive performances over time.

While understanding the association between amyloid load and cognitive functioning along time is important for designing effective trials to prevent age-related decline, the crucial question of selecting the best target population for these trials still remains. Previous studies suggested caution regarding the employed methodology used in PET scans research [21, 22]. Indeed, most clinical studies define amyloid status based on quantitative values of global/composite uptake, and all interventional studies fully rely on the subsequent status to enroll patients. Based on our findings, we claim that the term "amyloid-positive status" should be employed cautiously. However, results obtained in our population (relatively young [$m = 76.1 \pm 4.7$], with limited co-morbidity) may not be generalizable to an older population with more concurrent brain pathology. Moreover, some research studies correct the PET images for partial volume effects, to avoid artificial attenuation of the signal due to spill in/spillover effects. We did not correct PET images for partial volume effect in this study, to be consistent with the methodology used by the studies we referred to for SUVR cut-off definition. Such correction would, however, likely modify the final measures and the cut-off, and is another element to keep in mind when discussing amyloid status. Future studies addressing the definition of amyloid status in larger and more fragile population, and more specifically the evolution of individuals with equivocal based on regional cut-offs or other innovative methods are needed. Recent literature suggests a continuum, a dose–response effect between amyloid load and cognitive changes [23, 24], encouraging the use of several PET scans over time to help characterize a population at risk of cognitive decline. McMillan and Chételat [25] recently described the existence of so-called "accumulators" individuals (Aβ accumulation over time, linked to memory decline [19]), which could be the next generation of candidates for amyloid-targeted clinical trials. Nevertheless, the use of a single PET assessment is still frequent in research, mostly for cost reasons, which is why addressing the issue of characterizing an Equivocal (or "intermediate", or "accumulator") population from a single PET scan is essential.

This original study had several strengths to highlight: very few studies have, to date, address the issue of Equivocal/intermediate amyloid load and, to the best of our knowledge, this is the first study that used different methodological approaches to isolate such population and investigate their cognitive changes. The use of the MAPT database allowed us to benefit from several neuropsychological measures, over almost 3 years for some participants. Future large scale, longitudinal studies shall

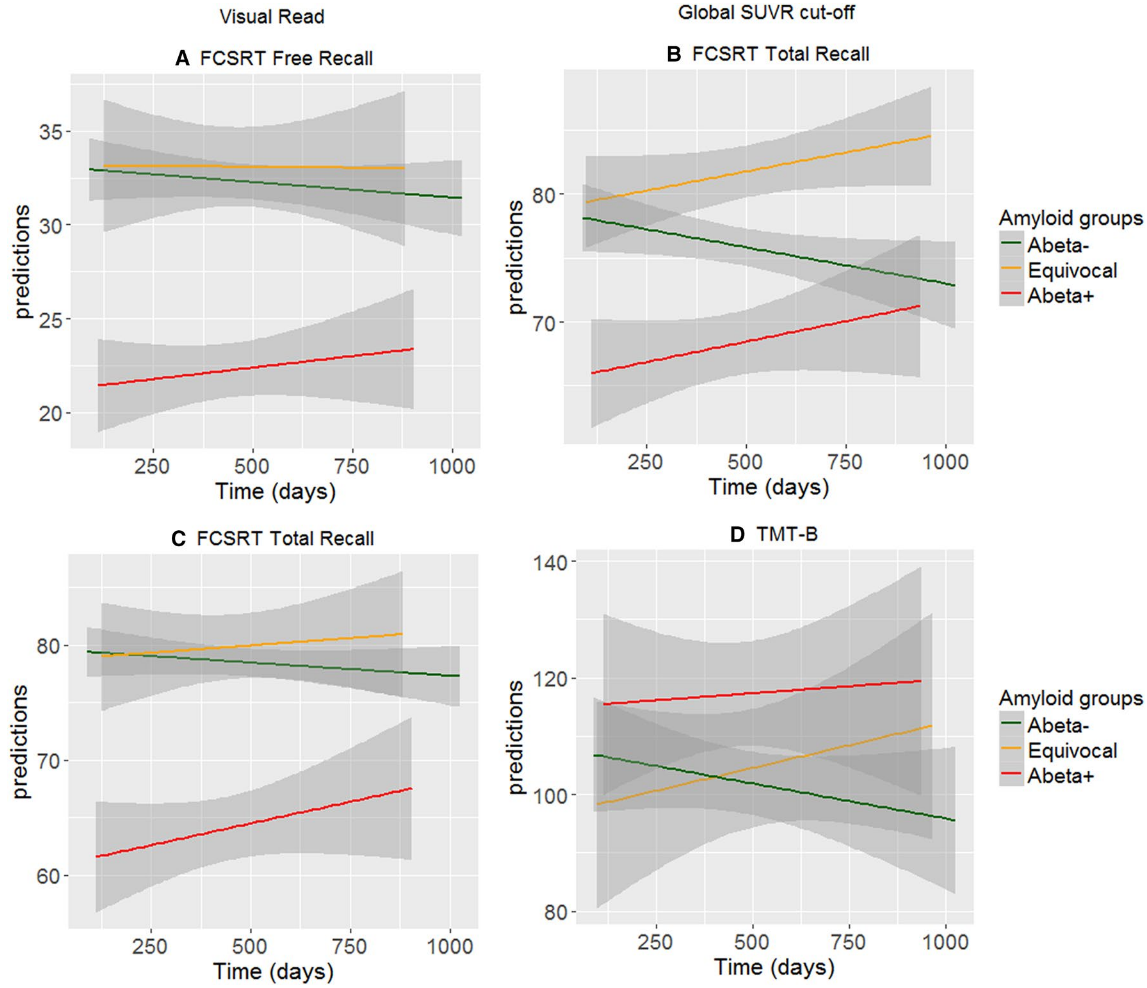

Fig. 4 Significant group differences in cognitive changes over time, using visual read and SUVR cut-offs (C and D) classification approaches. **a** Memory scores (FCSRT, total recall), and **b** executive scores (TMT-B) across time for the three participant groups (Aβ +, Aβ − and Equivocal) classified by the SUVR cut-off method. **c** FCSRT Free and, **d** FCSRT Total scores across time for the three participant groups (Aβ +, Aβ − and equivocal) classified by the visual read method. *Abeta* + amyloid-beta positive; *Abeta* − amyloid-beta negative, *FCSRT* free and cued selective reminding test, *SUVR* standardized uptake values ratios, *TMT* trail-making test

help better characterizing these specific individuals, with a view to possibly including them in future interventional studies to help preventing a potential amyloid spreading.

Acknowledgements This study was supported by grants from the French Ministry of Health (PHRC 2008), and the Institut de Recherche Pierre Fabre. The promotion of this study was supported by the University Hospital Center of Toulouse. Biological sample collection was supported by Exhonit Therapeutics. The AV45-MAPT study was supported by Avid radiopharmaceuticals/Eli Lilly and Company. Authors would like to thank all the members of the MAPT/DSA Study Group.

Funding This work was funded by grants from the Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), Pierre Fabre Research Institute, Exhonit Therapeutics SA, and Avid Radiopharmaceuticals Inc.

Compliance with ethical standards

Conflicts of interest Prof. P. Payoux served on the scientific advisory board of Avid Radiopharmaceuticals and GEHC. Dr. J. Delrieu served on the scientific advisory board of Avid Radiopharmaceuticals. Prof. B. Vellas served on the scientific advisory board of Avid Radiopharmaceuticals. Other authors (Dr K. Pothier, Dr L. Saint-Aubert, Dr C. Hooper, Dr de Souto Baretto) declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Herholz K, Ebmeier K (2011) Clinical amyloid imaging in Alzheimer's disease. Lancet Neurol 10(7):667–670
2. Ma Y, Zhang S, Li J, Zheng DM, Guo Y, Feng J, Ren WD (2014) Predictive accuracy of amyloid imaging for progression from mild cognitive impairment to Alzheimer disease with different lengths of follow-up: a meta-analysis. Medicine 93:27
3. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, … Park DC (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. J Alzheimer's Assoc 7(3):280–292
4. Kemppainen NM, Aalto S, Wilson IA, Nagren K, Helin S, Bruck A et al. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. Neurology. 2007;68:1603–1606. https://doi.org/10.1212/01.wnl.0000260969.94695.56
5. Baker JE, Lim YY, Pietrzak RH, Hassenstab J, Snyder PJ, Masters CL, Maruff P (2017) Cognitive impairment and decline in cognitively normal older adults with high amyloid-β: A meta-analysis. Alzheimer's Dement 6:108–121
6. Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA et al (2011) Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 305:275–283. https://doi.org/10.1001/jama.2010.2008
7. Ng S, Villemagne VL, Berlangieri S, Lee ST, Cherk M, Gong SJ, … Smith C (2007) Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. J Nucl Med 48(4):547–552
8. Fleisher AS, Chen K, Liu X, Roontiva A, Thiyyagura P, Ayutyanont N, Doraiswamy PM (2011) Using positron emission tomography and florbetapir F 18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. Arch Neurol 68(11):1404–1411
9. Landau SM, Mintun MA, Joshi AD, Koeppe RA, Petersen RC, Aisen PS, Jagust WJ (2012) Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Annal Neurol 72(4):578–586
10. Camus V, Payoux P, Barré L, Desgranges B, Voisin T, Tauber C, Mondon K (2012) Using PET with 18 F-AV-45 (florbetapir) to quantify brain amyloid load in a clinical environment. Eur J Nucl Med Mol Imaging 39(4):621–631
11. Joshi AD, Pontecorvo MJ, Clark CM, Carpenter AP, Jennings DL, Sadowsky CH, Saha K (2012) Performance characteristics of amyloid PET with florbetapir F 18 in patients with Alzheimer's disease and cognitively normal subjects. J Nucl Med 53(3):378–384
12. Chiotis K, Saint-Aubert L, Savitcheva I, Jelic V, Andersen P, Eriksson J, Nordberg A (2016) Imaging in-vivo tau pathology in Alzheimer's disease with THK5317 PET in a multimodal paradigm. Eur J Nucl Med Mol Imag 43(9):1686–1699
13. Mormino EC, Brandel MG, Madison CM, Rabinovici GD, Marks S, Baker SL, Jagust WJ (2012) Not quite PIB-positive, not quite PIB-negative: slight PIB elevations in elderly normal control subjects are biologically relevant. Neuroimage 59(2):1152–1160
14. Payoux P, Delrieu J, Gallini A, Adel D, Salabert AS, Hitzel A, Fernandez P (2015) Cognitive and functional patterns of nondemented subjects with equivocal visual amyloid PET findings. Eur J Nucl Med Mol Imag 42(9):1459–1468
15. Vellas B, Carrie I, Gillette-Guyonnet S, Touchon J, Dantoine T, Dartigues JF, Bories L (2014) MAPT study: a multidomain approach for preventing Alzheimer's disease: design and baseline data. J Prevent Alzheimer's Dis 1(1):13
16. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, Desclaux F (2017) Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol 16(5):377–389
17. Grothe MJ, Barthel H, Sepulcre J, Dyrba M, Sabri O, Teipel SJ, Jagust W (2017) In vivo staging of regional amyloid deposition. Neurology 89(20):2031–2038
18. Hedden T, Oh H, Younger AP, Patel TA (2013) Meta-analysis of amyloid-cognition relations in cognitively normal older adults. Neurology 80(14):1341–1348
19. Landau SM, Horng A, Jagust WJ, Alzheimer's Disease Neuroimaging Initiative (2018) Memory decline accompanies subthreshold amyloid accumulation. Neurology 5:10–1212
20. Kemppainen N, Johansson J, Teuho J, Parkkola R, Joutsa J, Ngandu T, Paajanen T (2018) Brain amyloid load and its associations with cognition and vascular risk factors in FINGER Study. Neurology 90(3):e206–e213
21. Cohen AD, Mowrey W, Weissfeld LA, Aizenstein HJ, McDade E, Mountz JM, Williamson J (2013) Classification of amyloid-positivity in controls: comparison of visual read and quantitative approaches. Neuroimage 71:207–215
22. Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD, Jagust WJ, Rowe CC (2015) The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. Alzheimer's Dement 11(1):1–15
23. Farrell ME, Kennedy KM, Rodrigue KM, Wig G, Bischof GN, Rieck JR, Park DC (2017) Association of longitudinal cognitive decline with amyloid burden in middle-aged and older adults: evidence for a dose-response relationship. JAMA Neurol 74(7):830–838
24. Chételat G, Villemagne VL, Villain N, Jones G, Ellis KA, Ames D, Rowe CC (2012) Accelerated cortical atrophy in cognitively normal elderly with high β-amyloid deposition. Neurology 78(7):477–484
25. McMillan CT, Chételat G. Amyloid "accumulators": the next generation of candidates for amyloid-targeted clinical trials? [published online March 23, 2018]. Neurology. https://doi.org/10.1212/WNL.0000000000005362