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Relationship between brain AD biomarkers and episodic memory performance in healthy aging

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ABSTRACT

The presence of brain biomarkers can be observed decades before the first clinical symptoms of Alzheimer's disease (AD). We aimed to determine whether associations between biomarkers and episodic memory performance already exist in a healthy late middle-aged population or only in participants over 60 years old. Performance at the Free and Cued Selective Reminding Test [FCSRT], the Logical Memory test and the Mnemonic Similarity Task [MST] was determined in sixty healthy participants (50–70 y.) with a negative status for amyloid-beta (Aβ) biomarker. We assessed Aβ cortical level and tau/neuroinflammation burden using PET scanner, and hippocampal atrophy with MRI scanner. Generalized linear mixed models showed that MST scores (recognition and pattern separation) were positively associated with hippocampal volume in participants over 60 years. No association between memory performance and Aβ and tau/neuroinflammation burden was found in the older or in the younger age group. This suggests that visual recognition memory and discrimination of lures may constitute early cognitive markers of memory decline in an older population.

1. Introduction

Episodic memory changes are the initial cognitive deficits observed in typical Alzheimer's disease (AD) and its prodromal stage (McKhann et al. 2011). Subtle memory impairment can also be seen when patients are still in the preclinical stages (Schindler et al. 2017). Consequently, it is essential to distinguish preclinical manifestations from normal episodic memory difficulties that accompany healthy aging for a better detection of people at risk for AD (Tromp et al. 2015). In healthy aging, some aspects of episodic memory decline more than others (Nyberg et al. 2003). Typically, episodic memory decline starts to accelerate over 60 years, with decreased immediate and delayed free recall for verbal information, while recognition memory remains mostly preserved (Albert 1997). In addition, a prominent difficulty in the ability to discriminate similar memory traces is found in healthy aging (Toner et al., 2009; Holden et al., 2013).

One way to identify the nature of memory changes associated with incipient Alzheimer pathology is to characterize memory performance of healthy older individuals in relationship to the presence of AD biomarkers: β-amyloid (Aβ) deposits (Buckner, 2005; Palmqvist et al., 2017), tau neurofibrillary tangles (Braak and Del Tredici 2015) and hippocampal atrophy (Sarazin et al. 2007). Indeed, these neuropathological signs are observed decades before cognitive symptoms (Jack et al. 2010, 2013) and affect brain areas that are part of the episodic memory network (Rugg and Vilberg 2013).

Along those lines, the presence of AD biomarkers in healthy aging match memory changes at the group level in standard neuropsychological tests. Cross-sectional studies reported that, in middle-aged and older participants (mean age: 60 ± 8.4 years), high level of CSF tau/Aβ42 was associated with decreased verbal episodic memory performance in the Free and Cued Selective Reminder Test (FCSRT-free recall) and Logical Memory (Schindler et al. 2017). A positive association was also observed between hippocampal volume and performance in verbal and visual memory tasks in older adults (O'Shea et al. 2016). In addition, *in vivo* PET imaging studies in cognitively normal adults aged 65 years and older reported that early tau staging in the hippocampus and

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entorhinal cortex (Braak and Braak 1995) predicts decrease in an episodic memory composite score (Schöll et al., 2016; Maass et al., 2018). In contrast, other studies in similar populations failed to demonstrate a direct association between global cortical Aβ and episodic memory performance (Mormino et al., 2009, 2011; Maass et al., 2018). Altogether, these studies suggest that the presence of regional tau deposits in the medial temporal lobe (MTL) is mainly associated with decreased episodic memory performance, an impairment also associated with hippocampal atrophy.

Additionally, there is growing interest for a specific episodic memory process called behavioral pattern separation which more specifically recruits the hippocampus (Marks et al. 2017). Behavioral pattern separation refers to the capacity to discriminate between similar memory events (Yassa and Stark 2011) and is typically assessed with the Mnemonic Similarity Task (Stark et al. 2019). In healthy aging, the ability to identify similar lures in an object recognition memory task is positively associated to the volume of the hippocampus, specifically the combined dentate gyrus (DG) and CA3 subfields, and the subiculum (Stark and Stark 2017). Moreover, the association between lure discrimination and hippocampal volume was mediated by the presence of tau in the medial temporal lobe as assessed with tau PET imaging (Marks et al. 2017). Impaired lure discrimination was also observed in patients with Mild Cognitive Impairment (MCI) (Stark et al. 2013). Decreased performance of object pattern separation and recognition memory are respectively associated with decreased DG and CA3 volumes in a group of older adults (over 60 y.) including 18% of MCI (Dillon et al. 2017).

Interestingly, a recent study combining quantitative MRI for hippocampal volume and Aβ in cerebrospinal fluid (CSF) reported that hippocampal atrophy is the main predictive factor for memory decline in older adults (mean age 77 ± 3.5 years), and CSF Aβ levels in a slightly younger population (mean age: 69 ± 2.1 years) (Svenningsson et al. 2019). These results suggest that relationships between memory performance and AD biomarkers are sensitive to age. Intriguingly, previous cross-sectional and longitudinal studies including middle-aged participants (before 60 y.) failed to report associations between hippocampal atrophy and decreased verbal and visual episodic memory performance (Charlton et al., 2010; Paul et al., 2011; Gorbach et al., 2017). Similar results were observed for Aβ deposits (Okonkwo et al., 2014; Mielke et al., 2016), suggesting that sensitivity of AD-related biomarkers to memory performance is lesser during middle, compared to older, age (≥60 y.).

In this context, the aim of the present study was to assess the relationship between several AD biomarkers (Aβ, tau/neuroinflammation, hippocampal atrophy) and several episodic memory processes (free recall, recognition memory, behavioral pattern separation), and to determine whether these associations already exist in a group comprising healthy late middle-aged participants, rather than only in an older population (above 60 y.), as suggested in the literature.

2. Methods

2.1. Participants

Sixty healthy French-speaking community dwelling participants in their late middle-age (50–69 y, Table 1) were enrolled in a multimodal cross-sectional study on the relationships between AD biomarkers, sleep-related processes and cognitive aging (COFITAGE). Participants were recruited in senior facilities, by advertising in local newspapers and by word of mouth. No participant reported recent history of psychiatric and neurological disorders, or were taking medication likely to affect the central nervous system. However, participants with controlled hypertension and hypothyroidism for more than 6 months were included. All participants had normal or corrected-to-normal vision and hearing. Other exclusion criteria were sleep apnea/hypopnea index ≥ 15/h assessed during an in-lab night of sleep under polysomnography, body mass index < 18 and > 29 kg/m^2, smoking, psychoactive drug consumption, excessive consumption of caffeine (>4 cups/day) or alcohol (>14 units/week), diabetes, and shift-work. Participants with high levels of depressive and anxiety symptoms, as assessed respectively by the Beck Depression Inventory (Beck, 1961) and the 21-item self-rated Beck Anxiety Inventory (Beck et al. 1988), and/or with ongoing pharmacological treatment were excluded (i.e. score > 17). All participants showed normal performance on the Mattis Dementia Rating Scale [i.e. score > 130] and/or Mini Mental state examination [i.e. score > 27]. All participants signed a consent form and received financial compensation. This research was approved by the Ethics Committee of the Faculty of Medicine at the University of Liège, Belgium.

Table 1
Descriptive statistics of demographic characteristics, cognitive scores (n = 60; except for Logical Memory: n = 55), volumetric MRI and PET data.

	Mean	± SD	Min	Max
Demographic data				
Age (years)	59.65	5.25	50	69
Sex, *female, n (%)*	43 (71.6%)			
Ethnicity, *caucasian, n (%)*	60 (100%)			
Education (years)	15.30	3.08	9	25
Memory performance				
FCSRT (Delayed free recall: 0–16)	13.32	2.00	9	16
Logical Memory (items delayed recall: 0–25)	12.51	3.57	3	21
RM	0.80	0.13	0.18	1
BPS	0.21	0.18	−0.16	0.64
BPS-1	0.11	0.14	0.17	0.42
BPS-5	0.30	0.29	−0.31	0.85
AD biomarkers				
THK-PET in Braak I/II ROIs	2.26	0.21	1.83	2.77
CL Aβ-PET in Thal I/II ROIs	3.58	6.92	−27.07	16.24
Hippocampal volume (mm^3)	5149.26	523.68	3671.93	6271.42

SD: standard deviation, FCSRT: Free and Cued Selective Reminding Test, RM: Recognition Memory, BPS: Behavioral Pattern Separation, BPS-1: Behavioral Pattern Separation score for most similar items, BPS-5: Behavioral Pattern Separation score for the most dissimilar items.

2.2. Episodic memory assessment

As part of a larger neuropsychological evaluation, participants were administered the French version of the FCSRT (Van der Linden et al., 2004) the Logical Memory task of the Weschsler Memory Scale (WMS-R) (Wechsler and Stone 1987), and the *Mnemonic Similarity Task* (recognition memory and behavioral pattern separation) (Stark et al. 2015). The first two tests provided standard measures of verbal recall and the last one assessed the specific process of pattern separation in visual memory.

2.2.1. Free and cued selective reminding test – FCSRT

The test consisted in learning of 16 words, presented 4 by 4 on separate sheets. In the encoding phase, the participant was asked to name aloud each item according to its semantic category. The study of each card was followed by an immediate cued recall test. If a subject was unable to recall an item following presentation of its category cue, the procedure was repeated. When the 16 words were correctly encoded, a 20-sec distracting task consisting in backward counting was proposed followed by a 2-minute free recall phase for the 16 items. For non-recalled items, cued recall based on the category was proposed. The distraction task - free recall – cued recall cycle was repeated twice. The delayed free recall test was performed after 20-min, followed by a cued recall for items not retrieved. Measure of performance considered herein was the delayed free recall score.

2.2.2. Logical memory

The Logical Memory subtest of the WMS-R is a standardized assessment of narrative episodic memory. A short story was orally presented,

and the participant was asked to recall the story verbatim (immediate recall). Approximately 20 min later, a second free recall of the story was performed (delayed recall). Memory score consists in the total number of story elements provided during delayed recall.

2.2.3. Mnemonic similarity task

The Mnemonic Similarity Task (MST) is a visual recognition memory task that puts emphasis on very specific memory traces to correctly distinguish similar stimuli (*i.e.* "lure") from those that were identical to stimuli previously encountered (*i.e.*, "old") (Stark et al. 2013). In the study phase, 128 common objects were randomly presented for 2 s (with a 0.5 s inter-stimulus interval) and participants had to judge if the object is more commonly used "indoor" or "outdoor" (incidental encoding phase). Next, participants were administered a recognition memory test consisting in the presentation of 192 objects: 64 were old and seen in the incidental encoding phase (target items), 64 objects were similar but not identical to the one presented in the encoding phase (lure items), and 64 were new objects (foil items). Participants had to indicate whether the object was new (*i.e.*, foil item), old (*i.e.* target item) or similar but not identical (lure items). Lure trials were sorted, according to similarity with the target item (color, texture or orientation) with 5 similarity levels, from bin 1 being the most similar compared to the original studied object to bin 5 being the most dissimilar. Measures considered for statistical analysis were (1) the behavioral pattern separation score (BPS; calculated as the difference between the rate of calling lure items "Similar" minus the rate of calling novel foils "Similar" [P("Similar"|Lure)-P("Similar"|Foil)]); (2) the recognition memory (RM) score which corresponds to the difference between the rate of calling a target item "Old" minus the rate of calling a foil item "Old" [P("Old"|Target)-P("Old"|Foil)] (Stark et al., 2013; 2015). Moreover, based on studies showing that the BPS score for most dissimilar items (BPS-5) is more sensitive to age-related pattern separation deficits than the BPS score for the most similar items (BPS-1) (Yassa et al., 2010; Reagh et al., 2018), these two measures were also considered in the analysis.

2.3. Neuroimaging

2.3.1. Volumetric MRI for hippocampus

For each participant, a T2-weighted MRI (TR = 9240 ms/TE = 80 ms, *acquisition matrix* = 448×448×60, *voxel size* = 0.4×0.4×1.2 mm^3) was acquired with a 3-Tesla MR scanner (MAGNETOM Prisma, Siemens) in a total acquisition time of approximately 8 min, in an oblique-coronal plane perpendicular to the long axis of hippocampus and positioned to cover the entire structure. T1-weighted images were also acquired (TR = 1900 ms, TE = 2.19 ms, *acquisition matrix* = 240 × 256 × 224, *voxel size* = 1 × 1 × 1 mm^3). The quality of each image was systematically visually checked, especially the T2-MRI that is highly sensitive to movement, so that it could be reacquired immediately if visual inspection of the data indicated to do so. Hippocampal volumes were automatically segmented in each hemisphere separately with ASHS (Automatic Segmentation of Hippocampal Subfields) using T2 images (Yushkevich et al. 2015). Whole hippocampal volume consisted in the sum of the left and right hippocampal volumes. Intracranial volume (ICV) was also automatically estimated by ASHS. Hippocampal volumes were corrected for ICV using a regression-based method to account for differences in brain size between participants, as previously described (Yeung et al. 2017). Based on visual quality control, two participants have been excluded from the analyses due to missing hippocampal slices.

2.3.2. MRI neuroimaging for PET analysis

Quantitative multi-parametric MRI acquisition was performed on a 3-Tesla MR scanner (Siemens MAGNETOM Prisma, Siemens Healthineers, Erlangen, Germany). Structural and quantitative maps of T1, T2*, proton density (PD) and magnetization transfer (MT) were calculated from a multi-parameter protocol based on a 3D multi-echo fast low angle shot (FLASH) sequence (Weiskopf and Helms 2008). Three co-localized 3D multi-echo FLASH data sets were acquired with predominantly proton density weighting (PDw: TR/FA = 23.7 ms/6°), T1 weighting (T1w: TR/FA = 18.7 ms/20°), and MT weighting (MTw: TR/FA = 23.7 ms/6°; excitation preceded by an off-resonance Gaussian MT pulse of 5 ms duration, 220° nominal flip angle, 2 kHz frequency offset) in a total acquisition time of approximately 19 min, with a voxel size of 1 mm^3 isotropic. Two calibration sequences were acquired to correct for inhomogeneities in the radio frequency (RF) transmit field. Before proceeding to further processing, quantitative multi-parametric volumes (PDw, T1w, MTw) were auto-reoriented into MNI template with manual quality check. Then, quantitative multi-parametric maps (MT, PD, R1, R2*) were generated using the hMRI toolbox (Tabelow et al. 2019) (http://hmri.info) implemented in MATLAB 2013a (MathWorks Inc., Natick, MA, USA). First, MT maps were segmented into grey, white, and CSF tissue class maps using Unified Segmentation (US) within SPM12 (Ashburner and Friston 2005). Whole-brain segmentation outputs were diffeomorphically registered to create a study-specific template, compatible with the MNI space, created using the Diffeomorphic Anatomical Registration Through Exponentiated Algebra (DARTEL) toolbox in SPM12 (Ashburner 2007) in order to generate deformation fields that were used to warp MT maps into the study-specific template space.

2.3.3. Amyloid-β and tau PET neuroimaging

Aβ-PET imaging was performed with radiotracers [^{18}F]Flutemetamol (n = 63) or [^{18}F]Florbetapir (n = 3), while tau/neuroinflammation-PET imaging was performed with radiotracer [^{18}F]THK-5351 (n = 66), on an ECAT EXACT + HR scanner (Siemens, Erlangen, Germany). For all radiotracers, participants received a single dose of the respective radioligands in an antecubital vein (target dose app. 185 MBq). Aβ-PET image acquisitions started 85 min after injection, and 4 frames of 5 min were obtained, followed by a 10-minute transmission scan (with Germanium-68), with a total duration spent in scanner of app. 30 min. For [^{18}F]THK-5351-PET, a 10-minute transmission scan was acquired first, and dynamic image acquisitions started immediately after injection, consisting of 32 frames (with increasing time duration), with a total duration spent in scanner of approximately 100 min. All PET images were reconstructed using filtered back-projection algorithm including corrections for measured attenuation, dead time, random events, and scatter using standard software (Siemens ECAT - HR + V7.1, Siemens/CTI, Knoxville, TN, USA).

Before proceeding with further PET processing, a PET average image was created using all frames for Aβ-PET, and using the 4 frames corresponding to the time window between 40 and 60 min for [^{18}F]THK-5351-PET (Lockhart et al. 2016). Averaged PET images were manually reoriented and automatically coregistered (rigid coregistration) to the structural MT map in individual space. The averaged coregistered PET images were then normalized to the MNI space using the flow-field deformation parameters obtained from the DARTEL spatial normalization of the MT maps and the study-specific template. Standardized uptake value ratio (SUVR) was calculated using the whole cerebellum as the reference region for Aβ-PET (Klunk et al. 2015), and cerebellum grey matter for [^{18}F]THK-5351-PET (Ishiki et al. 2018). Volumes of interests (VOIs) were determined using the masks provided by automated anatomical labeling (AAL) atlas. As Aβ-PET images were obtained using 2 radiotracers, their SUVR values were scaled to Centiloid units (CL) for common scale (Klunk et al., 2015; Battle et al., 2018; Navitsky et al., 2018). Finally, for Aβ-PET, a mask overlapping the medial and lateral prefrontal cortex, precuneus, posterior cingulate, lateral parietal, middle temporal, and medial temporal cortices for SUVR computation (corresponding to ThalII/II (Thal et al. 2002) was applied (Mormino et al. 2011), whereas for [^{18}F]THK-5351-PET, a mask corresponding to Braak stages I/II was used (Braak and Braak, 1991; Schöll et al., 2016). Three participants with more than 30 CL for Aβ-PET (corresponding to +2.9 standard deviation based on our sample; the cut-off of CL 30 indicates

the presence of established pathology (Salvadó et al. 2019)) have been excluded. One subject with high [^{18}F]THK-5351-PET (SUVR = 3.32; +4SD) was considered as an outlier and has been removed from the analysis.

As previously discussed in Van Egroo et al. (2019), the first two generations of tau protein radiotracers, including [^{18}F]THK5351 were criticized for their off-binding to monoamine oxidase B (MAO-B) *in vivo*, particularly over the basal ganglia (Chiotis et al., 2018; Murugan et al., 2019). However, [^{18}F]THK5351 would be not only a marker of phosphorylated tau, but also a substantial marker of neuroinflammatory elements such as reactive astrocytes, which increase together with tau pathology (Harada et al. 2018). The use of [^{18}F]THK5351 can thus be considered as relevant for the objective of the study.

2.4. Statistical analyses

All statistical analyses using Generalized Linear Mixed Models (GLMM; PROC GLIMMIX) were performed with SAS 9.4 for Windows (SAS Institute, Cary, USA). Graphics were computed with GraphPad Prism®. Distribution of dependent variables were determined using 'allfitdist' function on MATLAB R2013a (MathWorks Inc., Natick, USA). GLMMs were adjusted for sex, age and educational level, while subject (intercept) effect was included as a random factor. We computed 6 separate models corresponding to memory scores used as dependent variable: FCSRT [free delayed recall], Logical Memory [delayed recall], MST [RM, BPS, BPS-1 and 5]. GLMMs evaluated the association between memory scores and hippocampal structural volume, tau deposition in Braak stages I/II regions (hippocampus and enthorinal cortex) (Braak and Braak, 1991; Schöll et al., 2016) and Aβ load in regions sensitive to early accumulation stages (neocortical regions and MTL) (Mormino et al. 2011). Statistical analyses were first performed on the whole sample. We next perform an interaction test on each model to examine if group status (under vs. over 60 y.) lead to specific associations between memory scores and biomarkers. Finally, in an exploratory analysis in a subset of participants, subjective age was considered as a proxy of brain aging (Kwak et al., 2018), and entered in the models including the interaction term and showing significant association with memory performance. Degrees of freedom (DF) were estimated using Kenward-Roger's correction. Semi-partial R2 ($R^2\beta^*$) values were computed to estimate effect size of significant fixed effects in all GLMMs as previously described (Jaeger et al. 2017). The statistical threshold for significance was set at $p < 0.05$. To exclude the possibility that an absence of significant relationship is due to a low statistical power, the magnitude of observed effects was estimated using 95% confidence intervals (Levine & Ensom, 2001).

3. Results

3.1. Relationship between AD biomarkers and memory performance in late middle-aged healthy participants (50–69 y.)

Demographic characteristics, memory performance and AD biomarker values are presented in Table 1.

The GLMM analysis showed no significant association between AD biomarkers (tau/neuroinflammation, Aβ and hippocampal atrophy) and memory performance at the FCSRT, Logical Memory and MST in the whole group of participants (Table 2). The observation of 95% confidence intervals indicated that the possibility that there is no difference between groups should not be ruled out for low statistical power (Levine & Ensom, 2001).

3.2. Relationship between AD biomarkers and memory performance in younger and older healthy participants (below and over 60 y.)

The second set of analyses was performed by including the group status (under vs. over 60 y. (n = 31 and n = 29 respectively). Demographic characteristics, memory performance and AD biomarker values are presented in Table 3. The proportion of response "New",

Table 2
Statistical outcomes of the GLMMs seeking for associations between AD biomarkers and delayed recall at FCSRT and logical Memory tasks, as well as RM, BPS, BPS-1 and 5 at the MST (dependent variables; each column corresponds to one model) in late middle-aged and older participants (50–69 y.). For the FCSRT and MST n = 60 (n = 59 for RM due to one outlier) and for the Logical memory, n = 55 (5 missing values). Estimate ± SE are presented. 95% confidence intervals are presented in brackets.

	FCSRT	Logical Memory	RM	BPS	BPS-1	BPS-5
Sex	0.18 ± 0.61 $F_{1, 53} = 0.09$ $p = 0.77$ [−1.1 1.4]	−0.23 ± 1.17 $F_{1, 48} = 0.04$ $p = 0.84$ [−2.59 2.13]	−0.004 ± 0.0.3 $F_{1, 52} = 0.01$ $p = 0.91$ [−0.07 0.06]	−0.07 ± 0.06 $F_{1, 53} = 1.51$ $p = 0.22$ [−0.18 0.04]	0.019 ± 0.043 $F_{1, 53} = 0.21$ $p = 0.65$ [−0.07 0.10]	−0.12 ± 0.09 $F_{1, 53} = 1.84$ $p = 0.18$ [−0.30 0.057]
Chronological age	−0.06 ± 0.0.06 $F_{1, 53} = 1.03$ $p = 0.31$ [−0.17 0.06]	0.04 ± 0.11 $F_{1, 48} = 0.14$ $p = 0.71$ [−0.18 0.26]	−0.003 ± 0.003 $F_{1, 52} = 0.96$ $p = 0.33$ [−0.009 0.003]	0.0003 ± 0.005 $F_{1, 53} = 0.00$ $p = 0.95$ [−0.01 0.01]	−0.005 ± 0.004 $F_{1, 53} = 1.50$ $p = 0.23$ [−0.01 0.003]	−0.005 ± 0.008 $F_{1, 53} = 0.44$ $p = 0.51$ [−0.02 0.01]
Educational level	−0.007 ± 0.09 $F_{1, 53} = 0.01$ $p = 0.94$ [−0.19 0.18]	0.11 ± 0.17 $F_{1, 48} = 0.39$ $p = 0.53$ [−0.24 0.46]	−0.002 ± 0.005 $F_{1, 52} = 0.18$ $p = 0.67$ [−0.01 0.007]	0.10 ± 0.008 $F_{1, 53} = 1.42$ $p = 0.24$ [−0.007 0.03]	0.006 ± 0.006 $F_{1, 53} = 0.89$ $p = 0.35$ [−0.007 0.018]	0.012 ± 0.013 $F_{1, 53} = 0.83$ $p = 0.37$ [−0.01 0.04]
THK-PET in Braak I/II ROIs	−1.93 ± 1.33 $F_{1, 53} = 2.11$ $p = 0.15$ [−4.60 0.74]	3.04 ± 2.57 $F_{1, 48} = 1.40$ $p = 0.24$ [−2.13 8.20]	−0.04 ± 0.07 $F_{1, 52} = 0.41$ $p = 0.53$ [−0.18 0.09]	−0.06 ± 0.12 $F_{1, 53} = 0.21$ $p = 0.65$ [−0.30 0.18]	0.009 ± 0.092 $F_{1, 53} = 0.01$ $p = 0.92$ [−0.18 0.19]	−0.009 ± 0.19 $F_{1, 53} = 0.00$ $p = 0.96$ [−0.39 0.37]
CL Aβ-PET in Thal I/II ROIs	−0.04 ± 0.04 $F_{1, 53} = 0.01$ $p = 0.92$ [−0.08 0.07]	−0.03 ± 0.08 $F_{1, 48} = 0.13$ $p = 0.72$ [−0.18 0.12]	−0.001 ± 0.002 $F_{1, 52} = 0.49$ $p = 0.48$ [−0.005 0.003]	0.003 ± 0.004 $F_{1, 53} = 0.61$ $p = 0.44$ [−0.004 0.01]	0.005 ± 0.003 $F_{1, 53} = 0.03$ $p = 0.87$ [−0.005 0.006]	−0.01 ± 0.008 $F_{1, 53} = 0.31$ $p = 0.58$ [−0.01 0.008]
Hippocampal volume (mm^3)	0.0002 ± 0.0005 $F_{1, 53} = 0.19$ $p = 0.67$ [−8E−4 1E−3]	−0.0003 ± 0.001 $F_{1, 48} = 0.09$ $p = 0.77$ [−0.003 0.002]	0.00 ± 0.00 $F_{1, 52} = 1.52$ $p = 0.22$ [−2E−5 8E−5]	7.46E−6 ± 4.9E−5 $F_{1, 53} = 0.02$ $p = 0.88$ [−9E−5 1E−4]	−5E−5 ± 4E−5 $F_{1, 53} = 1.84$ $p = 0.18$ [−1E−4 2E−5]	8.3E−5 ± 7.7E−5 $F_{1, 53} = 1.16$ $p = 0.29$ [−7E−5 2E−4]

FCSRT: Free and Cued Selective Reminding Test, RM: Recognition Memory, BPS: Behavioral Pattern Separation, BPS-1: Behavioral Pattern Separation score for most similar items, BPS-5: Behavioral Pattern Separation score for the most dissimilar items.

Table 3
Descriptive statistics of demographic characteristics, cognitive scores, volumetric MRI and PET data in participants from 50 to 60 y. (n = 29; excepted for Logical Memory: n = 28) and participants over 60y. (n = 31; excepted for Logical Memory: n = 27).

	Younger Participants from 50 to 60 y.		Older Participants over 60 y.	
	Mean (SD)	**Min-Max**	**Mean (SD)**	**Min-Max**
Demographic data				
Age (years)	55.14 (2.67)	50–59	63.87 (3.08)	60–69
Sex, *female, n (%)*	26 (90%)		17 (54.8%)	
Ethnicity, *caucasian, n (%)*	29 (100%)		31 (100%)	
Education (years)	15.17 (3.20)	9–25	15.42 (3.00)	9–20
Memory performance				
FCSRT (Delayed free recall: 0–16)	13.66 (1.70)	9–16	13.00 (2.24)	9–16
Logical Memory (items delayed recall: 0–25)	12.64 (3.31)	8–19	12.37 (3.88)	3–21
RM	0.84 (0.08)	0.69–1	0.77 (0.16)	0.18–0.94
BPS	0.20 (0.18)	−0.16 – 0.64	0.21 (0.17)	−0.13–0.58
BPS-1	0.10 (0.14)	−0.17 – 0.42	0.12 (0.13)	−0.17–0.42
BPS-5	0.34 (0.28)	−0.23 – 0.85	0.26 (0.29)	−0.31–0.85
AD biomarkers				
THK-PET in Braak I/II ROIs	2.21 (0.18)	1.86 – 2.59	2.31 (0.23)	1.83–2.77
CL Aβ-PET in Thal I/II ROIs	3.46 (5.00)	−4.74 – 15.49	3.65 (8.43)	−27.06–16.24
Hippocampal volume (mm^3)	5302.09 (537.94)	4541.65–6271.42	5006.29 (474.91)	3671.93–6081.38

SD: standard deviation, FCSRT: Free and Cued Selective Reminding Test, RM: Recognition Memory, BPS: Behavioral Pattern Separation, BPS-1: Behavioral Pattern Separation score for most similar items, BPS-5: Behavioral Pattern Separation score for the most dissimilar items.

"Old" and "Similar" for each trial type at the MST are illustrated in Fig. 1.

The GLMM analysis showed significant associations between MST (RM and BPS-5 scores) and hippocampal volume when age group is explicitly modelled (below and over 60 y.) (Table 4 and Fig. 2). For the two measures, age group was related to memory performance (with a better performance in the younger group; see Table 3) and this effect interacts with hippocampal volume. Post-hoc analyses showed that the association between memory performance and hippocampal volume is observed only in participants above 60 y. [RM younger: t(51) = −0.50, p = 0.62; RM older: t(51) = 2.14, p = 0.019; BPS-5 younger: (t(52) = −0.63, p = 0.53; BPS-5 older: t(52) = 2.68, p = 0.009]. In contrast, recognition memory and pattern separation performance were not related to regional tau/neuroinflammation and Aβ deposits. The group effect and interaction between group and hippocampal volume is nearly significant for the FCSRT [younger: t(52) = −0.86, p = 0.39; older: t(52) = 1.95, p = 0.057], but not related to regional tau/neuroinflammation and Aβ deposits. Finally, the GLMM analysis showed no significant association between AD biomarkers and the Logical Memory scores, and no effect of sex or education was observed on the six memory scores.

The observation of 95% confidence for non-significant results indicated that the possibility that there is no difference between groups should not be ruled out for low statistical power (Levine & Ensom, 2001). Indeed, a low statistical power would explain only the absence of association between hippocampal volume and RM /BPS-5. However, these effects become significant when the interaction with age group is taken into account.

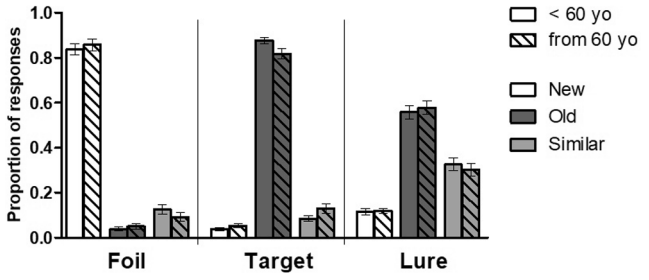

Fig. 1. Performance of participants younger. (n = 29) and older (n = 31) than 60 y at the MST. Graphics illustrate the proportion of response for "Foil", "Target" and "Lure" items, calculated as number of correct responses/ total number of each items category. Data show mean ± SEM.

3.3. Relationship between AD biomarkers and memory performance in younger and older healthy participants (below and over 60 y.) when subjective age is modeled

The last set of analyses was performed on the whole sample by including subjective age instead of chronological age for the models showing an association between memory performance and AD biomarkers. As this variable was not available for all our participants (n = 45), these analyses have an exploratory purpose in order to eventually refine the association previously observed.

We observed first that subjective age is not associated to variables previously investigated (all p > 0.05), excepted for chronological age [F (1.36) = 24.92, p < 0.0001, $R^2_{\beta*}$=0.41]. The GLMM analysis replicated associations between the MST (RM and BPS-5 scores) and age groups, as well as age group in interaction with hippocampal volume, when subjective age is explicitly modelled, with only a trend for BPS-5 (Table 5).

4. Discussion

The main purpose of the present study was to evaluate the associations between the amount of AD-related biomarkers and episodic memory performance in healthy late middle-aged participants and older individuals. To this end, participants completed episodic memory tasks, volumetric MRI for hippocampal atrophy and two PET-scans for tau NFT/neuroinflammation quantification within Braak stage I/II regions (Braak and Braak 1991) and Aβ burden in early Thal stages I/II regions. Contrary to previous studies using a composite score of episodic memory performance (Charlton et al., 2010; Schöll et al., 2016; Maass et al., 2018), we focused on specific aspects of episodic memory by considering separately scores assessing verbal delayed recall, visual recognition and behavioral pattern separation processes. The main finding was that, in participants aged older than 60 y., decreased performance in visual recognition memory (RM) and pattern separation for the most dissimilar items (BPS-5) were associated with a decreased hippocampal volume. By contrast, these associations were not significant when the sample included a larger age range with both middle-aged and older participants (50–69 y.) or in the young group (50–60 y.). Similar results are obtained when subjective age is entered in the model, although at lower p values. Finally, tau NFT/neuroinflammation, Aβ measurements were not associated with memory scores.

Previous meta-analyses and reviews on healthy older individuals reported discrepancies in findings on the association between

Table 4
Statistical outcomes of the GLMMs seeking for associations between AD biomarkers and delayed recall at FCSRT and logical Memory tasks, as well as RM, BPS, BPS-1 and 5 at the MST (dependent variables; each column corresponds to one model) when interaction effects with group age (below and over 60y.) are modelled. For the FCSRT and MST n = 60 ($n = 59$ for RM due to one outlier) and for the Logical memory, n = 55 (5 missing values). Estimate ± SE are presented; 95% confidence intervals are presented in brackets.

	FCSRT	Logical Memory	RM	BPS	BPS-1	BPS-5
Sex	0.32 ± 0.48 $F_{1, 52} = 0.25$ $p = 0.62$ [−0.96 1.59]	0.26 ± 1.24 $F_{1, 47} = 0.05$ $p = 0.83$ [−2.23 2.76]	0.01 ± 0.03 $F_{1, 51} = 0.15$ $p = 0.70$ [−0.05 0.08]	0.52 ± 0.81 $F_{1, 52} = 2.24$ $p = 0.14$ [−0.20 ; 0.030]	0.00 ± 0.05 $F_{1, 52} = 0.01$ $p = 0.94$ [−0.09 ; 0.10]	−0.11 ± 0.09 $F_{1, 52} = 1.62$ $p = 0.21$ [−0.29 0.07]
Group age	**−11.21 ± 5.44** **$F_{1, 52} = 4.25$** **$p = 0.04$** **$R^2_{\beta^*}$=0. 084** **[0.23 22.12]**	−1.57 ± 11.97 $F_{1, 47} = 0.02$ $p = 0.90$ [−22.51 ; 26.65]	**0.62 ± 0.28** **$F_{1, 51} = 5.11$** **$p = 0.03$** **$R^2_{\beta^*}$=0. 010** **[0.07 1.17]**	0.04 ± 0.50 $F_{1, 52} = 0.01$ $p = 0.93$ [−1.04 0.96]	−0.00 ± 0.39 $F_{1, 52} = 0.00$ $p = 0.98$ [−0.78 0.79]	**−1.81 ± 0.76** **$F_{1, 52} = 5.72$** **$p = 0.002$** **$R^2_{\beta^*}$=0. 011** **[0.29 3.34]**
Educational level	0.009 ± 0.09 $F_{1, 52} = 0.01$ $p = 0.92$ [−0.17 0.19]	0.13 ± 0.18 $F_{1, 47} = 0.50$ $p = 0.48$ [−0.23 0.48]	−0.001 ± 0.004 $F_{1, 51} = 0.06$ $p = 0.81$ [−0.01 0.008]	0.01 ± 0.01 $F_{1, 52} = 1.38$ $p = 0.25$ [−0.007 0.026]	0.01 ± 0.01 $F_{1, 52} = 0.84$ $p = 0.36$ [−0.008 0.19]	0.01 ± 0.01 $F_{1, 52} = 1.34$ $p = 0.25$ [−0.01 0.04]
Tau-PET on BraakI/II regions	−1.80 ± 1.30 $F_{1, 52} = 1.90$ $p = 0.17$ [−4.41 0.82]	3.77 ± 2.58 $F_{1,47} = 2.14$ $p = 0.15$ [−1.42 8.96]	−0.03 ± 0.065 $F_{1, 51} = 0.22$ $p = 0.64$ [−0.16 0.10]	−0.08 ± 0.12 $F_{1, 52} = 0.41$ $p = 0.52$ [−0.32 0.16]	−0.02 ± 0.09 $F_{1, 52} = 0.04$ $p = 0.84$ [−0.21 0.17]	0.005 ± 0.18 $F_{1, 52} = 0.00$ $p = 0.97$ [−0.36 0.36]
CL Aβ-PET on ThalI/II regions	−0.004 ± 0.04 $F_{1, 52} = 0.01$ $p = 0.91$ [−0.08 0.07]	−0.27 ± 0.79 $F_{1, 47} = 0.11$ $p = 0.74$ [−0.18 0.13]	−0.00 ± 0.00 $F_{1, 51} = 0.44$ $p = 0.51$ [−0.005 0.003]	0.00 ± 0.00 $F_{1, 52} = 0.55$ $p = 0.46$ [−0.004 0.010]	0.00 ± 0.00 $F_{1, 52} = 0.06$ $p = 0.81$ [−0.005 0.006]	−0.00 ± 0.01 $F_{1, 52} = 0.43$ $p = 0.51$ [−0.014 0.007]
Hippocampal volume (mm^3)	−0.00 ± 0.00 $F_{1, 52} = 0.84$ $p = 0.36$ [−1E−4 3E−03]	−0.000 ± 0.001 $F_{1, 47} = 0.39$ $p = 0.54$ [−0.005 0.003]	−0.00 ± 0.00 $F_{1, 51} = 0.25$ $p = 0.62$ [1.5E−5 1.72E−4]	0.00 ± 0.00 $F_{1, 52} = 0.09$ $p = 0.77$ [−1.2E−4 1.6E−4]	−0.00 ± 0.00 $F_{1, 52} = 0.44$ $p = 0.51$ [-1.4^{E}−3 8.1^{E}−5]	−0.00 ± 0.00 $F_{1, 52} = 0.39$ $p = 0.53$ [7.2^{E}−5 5^{E}−4]
Group*Hippocampal volume (mm^3)	0.003 ± 001 $F_{1, 52} = 3.96$ $p = 0.052$ $R^2_{\beta^*}$=0. 078 [−0.005 2E−5]	0.000 ± 0.002 $F_{1, 47} = 0.00$ $p = 0.96$ [−0.005 0.005]	**0.000 ± 000** **$F_{1, 51} = 4.51$** **$p = 0.039$** **$R^2_{\beta^*}$=0. 09** **[−2.2E−4 −6E−6]**	0.000 ± 0.000 $F_{1, 52} = 0.00$ $p = 0.99$ [−1.9E−4 1.9E−4]	0.000 ± 0.000 $F_{1, 52} = 0.00$ $p = 0.96$ [−1.6E−4 1.5E−4]	**0.001 ± 000** **$F_{1, 52} = 5.75$** **$p = 0.020$** **$R^2_{\beta^*}$=0. 11** **[−6.4E−4 −6E−5]**

FCSRT: Free and Cued Selective Reminding Test, RM: Recognition Memory, BPS: Behavioral Pattern Separation, BPS-1: Behavioral Pattern Separation score for most similar items, BPS-5: Behavioral Pattern Separation score for the most dissimilar items.

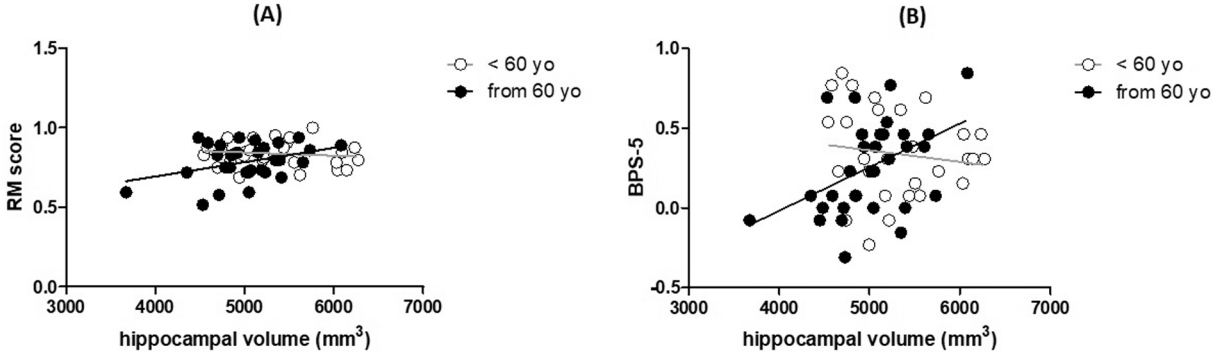

Fig. 2. Scatter plot visualizing in participants under and over 60 y. associations of the hippocampal volume with (*A*) the recognition memory score (RM) and (*B*) the behavioral pattern separation score for the most dissimilar items (BPS-5). Regressions were used for visual display only, and not as a substitute for the GLMM statistics presented in Table 4.

hippocampal volume and episodic memory among healthy older adults that may be due to methodological differences (Van Petten, 2004; Kaup et al., 2011). However, very specific patterns of associations were observed when processes associated to the MST were related to hippocampal subfields. Indeed, recognition memory and pattern separation scores in the MST were respectively associated with CA3 and dentate gyrus (DG) volumes (Dillon et al. 2017). In addition, lure discrimination is associated with age-related fMRI hyperactivation of CA3/DG subfields and fMRI hypoactivation of the anterolateral part of enthorinal cortex (alErC) (Reagh et al. 2018). We observed here that BPS for the most dissimilar items (BPS-5) is associated with age-related decrease in hippocampal volume in the older group, while this relationship is not observed for global BPS and BPS-1 (most similar items). The BPS-5 score was reported as the one that best differentiated older from younger adults (Yassa et al. 2010). In healthy aging, recognition memory is typically found to be better preserved than recall (Craik and McDowd 1987). The current finding that visual recognition memory and discrimination of lures that are not too similar to targets (i.e., the easiest form of discrimination) decreases in individuals with smaller hippocampal volume may suggest that such scores could be candidate markers

Table 5
Statistical outcomes of the GLMMs seeking for associations between AD biomarkers and the MST (RM and BPS-5) (dependent variables; each column corresponds to one model) when subjective age is added in the model in addition to group age (below and over 60y., $n = 45$). Estimate ± SE are presented.

	RM	BPS-5
Sex	0.05 ± 0.04	−0.01 ± 0.12
	$F_{1, 35} = 1.52$	$F_{1, 36} = 0.02$
	$p = 0.23$	$p = 0.90$
Subjective age	0.002 ± 0.003	−0.007 ± 0.008
	$F_{1, 35} = 0.74$	$F_{1, 36} = 0.76$
	$p = 0.39$	$p = 0.39$
Objective age (group)	**0.85 ± 0.35**	**1.18 ± 0.57**
	$\boldsymbol{F_{1, 35} = 5.83}$	$\boldsymbol{F_{1, 36} = 4.24}$
	$\boldsymbol{p = 0.005}$	$\boldsymbol{p = 0.047}$
	$\boldsymbol{R^2_{\beta^*}}$**=0.14**	$\boldsymbol{R^2_{\beta^*}}$**=0.11**
Educational level	−0.003 ± 0.005	0.01 ± 0.01
	$F_{1, 35} = 0.48$	$F_{1, 36} = 0.39$
	$p = 0.50$	$p = 0.549$
Tau-PET on BraakI/II regions	−0.003 ± 0.003	−0.104 ± 0.24
	$F_{1,35} = 1.28$	$F_{1, 36} = 0.17$
	$p = 0.27$	$p = 0.68$
CL Aβ-PET on ThalI/II regions	−0.09 ± 0.09	−0.003 ± 0.007
	$F_{1, 35} = 1.19$	$F_{1, 36} = 0.18$
	$p = 0.28$	$p = 0.67$
Hippocampal volume (mm^3)	0.00 ± 0.00	−0.00 ± 0.00
	$F_{1, 35} = 2.74$	$F_{1, 36} = 1.47$
	$p = 0.11$	$p = 0.23$
Group*Hippocampal volume (mm^3)	**−0.000 ± 000**	**−0.00 ± 000**
	$\boldsymbol{F_{1, 35} = 4.88}$	$\boldsymbol{F_{1, 36} = 3.46}$
	$\boldsymbol{p = 0.03}$	$\boldsymbol{p = 0.07}$
	$\boldsymbol{R^2_{\beta^*}}$**=0.12**	$\boldsymbol{R^2_{\beta^*}}$**=0.09**

RM: Recognition Memory, BPS-5: Behavioral Pattern Separation score for the most dissimilar items.

of very early memory decline. However, other data seem to indicate that age-related declines on the MST in healthy older adults are explained not only by decrements in mnemonic discrimination associated to the hippocampus, but could also interact with executive functioning (Foster & Giovanello, 2020), perceptual discrimination processes (Davidson et al. 2018), or even general cognitive functioning (Pikashbadian et al., 2020). These hypotheses should be tested in longitudinal studies assessing cognitive decline in order to assess whether BPS-5 could help to distinguish healthy from pathological aging using confirmed cases of preclinical AD.

The fact that the association we observed between memory scores at the MST and hippocampal volume was detected only in participants aged above 60 y. echoes with the literature showing stronger correlation of brain size with cognitive performance in older than in younger (18–50 y.) individuals (Kaup et al. 2011). In more direct relation with the present study, episodic memory decline was previously associated with reduced hippocampal volume in older individuals aged between 65 and 80, but not between 55 and 60 years (Gorbach et al. 2017). A likely explanation is that both hippocampal atrophy and cognitive measures show more pronounced age-related changes after the age of 60–65 years (Albert, 1997; Rönnlund et al., 2005; Gorbach et al., 2017). Even if the hippocampus undergoes some degree of atrophy at earlier ages, cognitive reserve (Stern, 2002; Brickman and Stern, 2009) might attenuate the impact of hippocampal atrophy on memory performance in middle age (before 60 y.). Indeed, an association between hippocampal volume and the learning component of an episodic memory task was observed in midlife only among individuals with lower levels of cognitive reserve, measured by general cognitive ability at age 20 (Vuoksimaa et al. 2013). Given our strict inclusion criteria encompassing health risk factors (BMI, alcohol consuming, hypertension, diabete, sleep breathing disorders…) for cognitive decline and brain integrity at middle age (Neth et al. 2020), high cognitive reserve in our sample may lead either to preserved integrity of brain structures in middle-aged participants or to the use of alternative brain networks to compensate for hippocampal atrophy.

With regard to Aβ deposits, we did not observe any significant relationship between the amount of Aβ deposits and memory performance, even in the older subgroup of participants. Actually, a link between Aβ burden and decline in episodic memory performance is observed in some studies (Clark et al., 2016; Farrell et al., 2017), but not systematically (Okonkwo et al., 2014; Mielke et al., 2016). There is an ongoing debate in the literature concerning the influence of Aβ on memory performance in healthy aging, as effects are small and seem to account for less than 2% of the total variance in cognitive performance (Hedden et al. 2013). Cross-sectional studies showing an association between episodic memory measures and Aβ deposits included both patients (MCI and AD) and cognitively normal participants with or without above-threshold amyloid accumulation ($A\beta^{\pm}$ and $A\beta^{-}$) (*i.e.*, Mormino et al., 2009; Pereira et al., 2019). This association was not systematically observed when only healthy $A\beta^{+}$ participants were included (Johnson et al., 2014; Song et al., 2015), and not observed in healthy older participants without reported Aβ positivity (i.e., Mormino et al., 2009; 2011). Therefore, the fact that all participants included in our analyses were $A\beta^{-}$ may be one reason for the lack of a significant relationship between amyloid-tracer uptake and memory. Moreover, it seems that the effect of amyloid-beta is more important for memory change over time, and this effect is often triggered and reinforced by the presence of tau burden (Leal et al. 2018).

As for the tau/neuroinflammation biomarker, we did not observe any significant associations between [^{18}F]THK5351 uptake and episodic memory performance. This contrasts with previous studies that demonstrated such a relationship with composite and specific recall measures (Schöll et al., 2016; Aschenbrenner et al., 2018; Maass et al., 2018; Pereira et al., 2019; Terrera et al., 2020). Some of them also showed a specificity of this association, with early tau staging on the Braak I/II regions predicting cross sectional memory performance (Schöll et al., 2016; Maass et al., 2017, 2018) and retrospective longitudinal memory decline (Schöll et al. 2016). However, it is important to mention that in most of these studies, the radiotracer used is AV-1451 with a lower off-target binding than [^{18}F]THK5351 (Jang et al. 2018). An association between tau and memory performance is also observed with measures of CSF tau in middle-aged with verbal memory and by using a longitudinal design (Racine et al. 2016). In healthy older participants, higher CSF tau is associated with decreased object pattern separation score and increased fMRI hippocampal activity (Berron et al. 2019). This suggests that for PET studies, more specific radiotracers of tau protein are needed to better identify relationships between specific memory scores and regional tau in the medial temporal lobe.

To sum up, memory performance is associated to decreased hippocampal volumes, but not to Aβ and tau/neuroinflammation biomarkers. However, one limitation of this study is the use of a cross-sectional design. Indeed, biomarkers could be a better predictor for memory change over time than for explaining memory performance *per se*. Moreover, biomarkers have their specific time-course (see Jack et al., 2010; 2013), with complex interactions on cognitive decline that can be assessed only in longitudinal studies. For example, Hanseeuw et al. (2019) showed in older adults with normal cognition at baseline that higher initial beta-amyloid level was associated with subsequent tau accumulation in inferior temporal cortex, and this sequence of event was strongly associated with cognitive decline. Moreover, tau increase was faster in those individuals with increasing beta-amyloid, supporting the idea that tau changes are more related to beta-amyloid changes than to beta-amyloid level. They have also pointed out that cognitive decline was most closely associated with tau change over time, and beyond baseline beta-amyloid and tau. Also using a longitudinal setting, Leal et al. (2018) showed that Aβ measures predict tau deposition well before memory decline. Moreover, they also showed that initial Aβ level is the strongest predictor of memory decline when baseline beta-amyloid levels are high while for low or intermediate baseline levels, beta-amyloid accumulation across time becomes the strongest predictor

In conclusion, our results indicated an association between selective

memory processes (visual recognition and pattern separation) and hippocampal volume in healthy adults aged from 60 to 69 y. By contrast, no significant relationship was found between memory scores and Aβ and tau/neuroinflammation PET tracers in any decade in our participants, that we partly attribute to their negative status for Aβ biomarker. Future longitudinal studies should assess the possibility that visual recognition memory and pattern separation of relatively dissimilar stimuli could be an early cognitive marker specific to Alzheimer's disease, by testing whether poorer performers show accelerate cognitive decline or start to harbor above-threshold AD biomarkers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

E.S., P.M., G.V., C.B. and F.C. designed the experiment. L.R., J.N., M. V.E, D.C., G.B., M.B., E.S., P.M., G.V., C.B., and F.C. helped in data acquisition, analysis, and interpretation. M.A.B, E.S., and P.M. provided administrative, technical, or material support. L.R., C.B., and F.C. wrote the manuscript. L.R., J.N., M.V.E, D.C., G.B., M.B., M.A.B., E.S., P.M., G. V., C.B. and F.C. contributed to manuscript revising.

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