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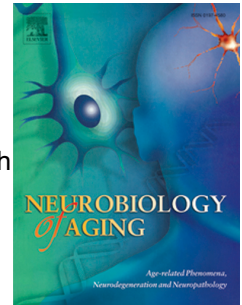
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Is there a specific memory signature associated with A β -PET positivity in patients with amnesic Mild Cognitive Impairment?

Clémence Tomadesso^{1,2}, Julie Gonneaud¹, Stéphanie Egret¹, Audrey Perrotin¹, Alice Pélerin², Robin de Flores¹, Vincent de la Sayette³, Béatrice Desgranges², Gaël Chételat¹, Renaud La Joie^{1,4}

¹ Inserm, Inserm UMR-S U1237, Université de Caen-Normandie, GIP Cyceron, Boulevard H. Becquerel, 14000 Caen

² Normandie Université, UNICAEN, PSL Université Paris, EPHE, Inserm, U1077, CHU de Caen, France

³ CHU de Caen, Service de Neurologie, Caen, France

⁴ Memory & Aging Center, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA

Corresponding author:

Renaud La Joie, PhD

Memory and Aging Center

University of California, San Francisco

+1 415 476-6749

Renaud.LaJoie@ucsf.edu

Highlights

- aMCI patients show medial temporal predominant atrophy, regardless of A β status
- A β - and A β + aMCI patients harbor broadly comparable memory deficits
- A β + aMCI patients show more severe primacy effect deficits than A β - patients

Keywords: Alzheimer's disease; Amnesic mild cognitive impairment; beta-Amyloid; positron emission tomography; hippocampus; memory

Abstract (152/170 words max)

Amnesic Mild cognitive Impairment (aMCI) is a clinical entity with various potential etiologies including but not limited to Alzheimer's disease (AD). We examined whether a positive ([18F]Florbetapir) β -amyloid-PET scan, supporting underlying AD pathophysiology, was associated with specific memory deficits in 48 patients with aMCI (33 β -amyloid-positive, 15 β -amyloid-negative). Memory was evaluated using an autobiographical fluency task and a word-list learning task with two different encoding types (shallow/incidental versus deep/intentional). Compared to 40 β -amyloid-negative controls, both aMCI subgroups demonstrated severe deficits in the global memory score and in most sub-scores of both tasks. Finer-grained analyses of memory tests showed subtle association with β -amyloid status, revealing a stronger impairment of the primacy effect in β -amyloid-positive patients. Structural MRI showed that both aMCI subgroups exhibited comparable atrophy patterns, with similar degrees of medial temporal volume loss compared to controls. Specifically assessing the primacy effect might complement global memory scores in identifying β -amyloid-positive patients with aMCI.

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder defined by the presence of β -amyloid ($A\beta$) plaques and tau-rich neurofibrillary tangles (Braak and Braak, 1991; Hyman et al., 2012; Jellinger, 1990; Masters and Beyreuther, 2005), which are thought to trigger a neurodegenerative cascade leading to cognitive decline and eventually dementia. AD pathophysiology is thought to progress over decades, emphasizing the need to identify individuals at preclinical or early clinical stages for the successful implementation of intervention strategies.

Mild cognitive impairment (MCI) is a clinical term referring to the stage of cognitive decline beyond what is expected for one's age and baseline characteristics. However, the deficits do not interfere with activities of daily living so patients do not fulfill criteria for dementia, even though their risk of future conversion to dementia is elevated (Mitchell and Shiri-Feshki, 2009). Traditionally, memory-predominant MCI (amnesic MCI or aMCI) is considered better able to capture the pre-dementia stage of AD (Morris et al., 2001; Petersen et al., 1999), although it is becoming more widely accepted that AD can present with non-amnesic, or even behavior-predominant, phenotypes (Jack et al., 2018; McKhann et al., 2011; Ossenkoppele et al., 2015b, 2015a). Yet, patients with MCI, or even aMCI, constitute a heterogeneous group with various possible underlying etiologies (Schneider et al., 2009), and not all patients with (a)MCI will progress to dementia.

Currently, biomarkers are available to help identify those patients with MCI who are on the Alzheimer's continuum from those whose clinical syndrome is likely due to other causes, notably positron emission tomography (PET) to detect $A\beta$ deposits (Jack et al., 2018). Indeed, a meta-analysis (Jansen et al., 2015) confirmed that underlying AD pathology is more prevalent in patients with aMCI. 58% of aMCI patients exhibited $A\beta$ -PET positivity, exceeding both age-matched cognitively normal individuals (24%) and patients with non-amnesic MCI (47%).

However, it is important to note that almost half of the patients diagnosed with aMCI are therefore A β -negative, emphasizing the poor specificity of the aMCI syndrome for detecting underlying AD pathology. Given the cost and invasiveness of biomarker testing, there is a need for better clinical measures aimed at identifying those aMCI patients with underlying AD pathology, notably for clinical trial development and screening.

Previous studies correlating A β status with brain injury and cognitive performance in patients with aMCI are not fully consistent but some trends are worth highlighting. At the group level, A β -positive aMCI patients exhibit more AD-like atrophy patterns (including lower hippocampal volume) than their A β -negative counterparts according to most (Hanseeuw et al., 2016a, 2016b; Huijbers et al., 2015; Landau et al., 2016; Petersen et al., 2013; Rowe et al., 2010; Wisse et al., 2015; Ye et al., 2014) but not all (Chételat et al., 2010; La Joie et al., 2013; Tomadesso et al., 2018; Wolk et al., 2009) studies. Regarding cognitive profiles, A β -positive patients with aMCI consistently showed greater episodic memory deficits than A β -negative patients (Jeon et al., 2016; Landau et al., 2016; Tomadesso et al., 2018; Wolk et al., 2009; Ye et al., 2014). Yet, these previous studies have generally considered total memory scores from classic word-learning tests or combined various subtests into a global composite score. To date, no study has examined more subtle differences in the precise memory processes impaired in A β -positive and A β -negative patients with aMCI, although some data suggests that a more process-specific approach could help identify underlying AD.

Specifically, recent research has shown that the primacy effect, classically investigated by probing the first few items of a list (Deese and Kaufman, 1957; Murdock Jr., 1962), is particularly impaired in aMCI and AD dementia (Howieson et al., 2011; Moser et al., 2014). Primacy effect deficits seem to help differentiate AD from late-life depression (Foldi et al., 2003) and provide predictive value for future cognitive decline in both cognitively intact older adults (Bruno et al., 2013) and patients with MCI (Cunha et al., 2012; Egli et al., 2014), indicating

improved specificity and early sensitivity for AD, respectively. Yet, to date, no study has investigated the primacy effect in relation to A β biomarkers. Another unexplored area of research is the relationship between amyloid biomarkers and autobiographical memory, or memory of one's own past. Indeed, the impairment of autobiographical memory is well described in patients with a clinical diagnosis of AD dementia (Addis et al., 2009; Addis and Tippett, 2004; Greene, 1995; Irish et al., 2011; Ivanoiu et al., 2004a; Kopelman et al., 1989; Leyhe et al., 2009; Piolino et al., 2003). Deficits in autobiographical memory, and especially in the ability to retrieve detailed episodic memories, have been described in patients with aMCI (Buckley et al., 2014; Irish et al., 2010; Leyhe et al., 2009; Meléndez et al., 2016; Murphy et al., 2008; Tomadesso et al., 2015). Recent data has even shown that autobiographical memory retrieval was impaired in groups of asymptomatic individuals at genetic risk for AD (Grilli et al., 2018), suggesting that autobiographical memory assessment could be informative in early stages of the disease.

To date, impairment of the primacy effect and autobiographical memory retrieval has been well described in patients with a clinical diagnosis of AD, but little is known about the relationships between these neuropsychological deficits and amyloid biomarkers. The present study aims to explore these fine-grained aspects of memory deficits in patients with a clinical diagnosis of aMCI, and test whether these subtle characteristics of memory impairment are associated with A β -PET. More specifically, we investigated the serial position effects using a word list learning task and autobiographical memory retrieval abilities using an autobiographical memory fluency test. In addition, we analyzed structural magnetic resonance imaging (MRI) data to explore whether cognitive differences between patient subgroups are subtended by differences in brain structure. Based on our focus on memory deficits, we investigated a priori medial temporal regions of interest, in addition to exploratory voxelwise analyses.

2 Methods

2.1 Participants

All participants were included in the *Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce* (IMAP+) study (Caen, France), for which inclusion and exclusion criteria are detailed in previous publications (La Joie et al., 2016, 2013; Tomadesso et al., 2018; Wirth et al., 2018). Patients with aMCI were recruited in memory clinics. The diagnosis of aMCI was made by a team of expert clinicians from the memory clinic that patients had been referred to, and based on classic criteria (Petersen, 2004; Petersen and Morris, 2005). The presence of memory deficits was objectified using standard neuropsychological tests: the French version of the Free and Cued Selective Reminding Test (FCSRT, Grober et al., 2010) and free recall score of the Batterie d'efficience mentale (BEM) figure (Signoret et al., 1991). Only patients with at least one abnormal subscore on these two tests (i.e. <5th percentile based on published normative data (Signoret, 1991; Van der Linden et al., 2004)) were classified as aMCI. Controls were recruited from the community through advertising in local media and word-of-mouth; volunteers had to perform in the normal range on all the tests of a complete neuropsychological battery (including the FCSRT and other tests listed in Table 1) to be further included in the IMAP+ study.

For the present study, controls and aMCI participants were selected if they were older than 55 years (inclusive) and had available MRI and Florbetapir-PET; we included patients with aMCI regardless of PET results, but only considered A β -negative controls. The final sample consisted of 48 patients with aMCI (15 A β -negative and 33 A β -positive) and 40 A β -negative healthy controls (HCs); see 2.3.2 for positivity/negativity classification description.

The IMAP study was approved by a regional ethics committee (Comité de Protection des Personnes Nord-Ouest III) and registered with ClinicalTrial.gov (NCT01638949). All participants gave written informed consent to the study before investigation.

2.2 Neuropsychological procedure

As mentioned above, standard tests (FCSRT and BEM figure) were used as diagnostic and screening tools to confirm or rule out memory deficits in patients with aMCI or healthy controls, respectively. To avoid circularity, the main analyses presented in the current paper relate to two additional tests (described in the following paragraphs) that were administered after inclusion in the study. Yet, FCSRT and BEM results are provided in Table 1 and Figure S1 for the sake of completeness. For all screening and experimental neuropsychological testing, both the patient and the neuropsychologist were blind to Florbetapir-PET scan's results.

2.2.1 Word-list learning task: ESR paradigm

We used the "Encoding, Storage, Retrieval" paradigm from Eustache et al. (2015), to evaluate verbal episodic memory abilities. Briefly, this test consists of two 16-word lists, with both an immediate free recall and a 20-min delayed recognition. The first list was presented to the participants without any instruction to memorize (*incidental* encoding). Words were read aloud one by one, and patients were asked to determine whether the first and last letters of each word were in alphabetical order (*shallow* processing). Immediately after the sixteenth word, participants were asked to recall as many words as possible. No interference task was used and no clues were provided. Patients were then offered the second list of words, and warned that they would be asked to recall them later (*intentional* encoding). Words were read aloud, and participants were asked to generate a brief sentence including the given word (*deep* semantic-based processing) before moving onto the next word. Every two words, an immediate cued recall for the two last words was performed using a semantic cue (e.g. "*What was the fruit I just said? What was the tool?*"). If a participant was not able to recall a word, the experimenter would read the word again and ask the participant to make a full sentence. This process was repeated until the immediate cued recall was successful before moving to the next pair of words (maximum 4 repetitions). After the immediate cued recall of the last pair of words, and without

any interference task, participants were asked to freely recall as many of the 16 words as possible. Twenty minutes later, participants were asked to recognize the 32 words, with each word being presented visually among three distractors.

For both list 1 (incidental and shallow encoding) and list 2 (intentional and deep encoding), the examiner noted whether each word was successfully recalled and recognized. To analyze the effect of words' serial position on recall performance, items were pooled by 4 (items 1-4 enabling to assess the primacy effect, items 5-8, items 9-12, items 13-16 enabling to assess the recency effect, with each of these subscores ranging from 0 to 4). For the sake of being thorough and transparent, response rates for individual items and pairs of items are shown in the Figures S2 and S3, respectively.

2.2.2 Autobiographical fluency test

The other task of interest in this study was an episodic autobiographical memory fluency task, inspired by Dritschel et al. (1992; see also Chételat et al., 2005 and Tomadesso et al., 2015). Before the test, the experimenter explained what an episodic memory was: a specific memory related to a particular life event well located in time and space and containing details about people, activities, conversations, emotions or inner thoughts. Patients were instructed to recall as many episodic memories as possible from three time periods: very recent (corresponding to the last year), recent (the previous 10 years except for the last, i.e. from 10 to 1 years before today) and remote (between ages 20 and 30 years).

The test was administered in 2 parts. The purpose of the first part was to collect as many episodic memories as possible within a time constraint. Participants were given 2 minutes for each time period (starting with remote, then recent, then very recent) to recollect as many episodic memories as possible. For each memory, they mentioned a few key words to the examiner for future elaboration. The specific desired time window, determined by the examiner based on the participant's date of birth (for the remote period) or the examination date (for the

recent and very recent periods), was written down and placed in front of the participant before each 2-minute session. Predefined cues (e.g. a wedding, a birth or a Christmas day) were given to the participants if they stayed silent for 20 seconds. The purpose of the second part was to elaborate on those specific memories to determine episodicity and appropriateness for experimental analysis. The experimenter asked the participant to recollect as many details as possible for each memory mentioned in the first part. Specifically, the rater used a 5-point scale, with one point given for each characteristic of an episodic memory: single event, lasting less than one day, located in time, situated in space, and including at least 2 specific details. Only memories with a full 5-point rating were considered episodic events and included in the global memory count. For example, *"Every Wednesday my grandmother and I cooked cakes that we ate for afternoon snacks"* was a repeated and generic memory and therefore not considered episodic, unlike *"When I was 22 years old, my grandmother and I forgot the cake in the oven. It was burnt and a lot of smoke spread in the house. My grandfather, who was upstairs, detected the burning smell, went off at full speed and tumbled down the stairs"*. The number of episodic events was summed within each life period and the resulting scores were used for statistical analyses.

2.3 Neuroimaging procedures

2.3.1 Data acquisition

All participants were scanned on the same PET and MRI scanners, as previously described (La Joie et al., 2016, 2013; Tomadesso et al., 2018; Wirth et al., 2018). For each participant, a high-resolution T1-weighted anatomical image was acquired with 1mm isotropic resolution on a Philips Achieva 3T scanner. Florbetapir PET scans were acquired on a Discovery RX VCT 64 PET-CT device (General Electric Healthcare). Participants were injected with ~4 MBq/kg of Florbetapir, and a transmission scan was performed for attenuation correction before the PET acquisition (50-70 min post injection).

2.3.2 Data processing

MRI data were segmented and normalized using the Statistical Parametric Mapping 12 software (SPM12; Wellcome Trust Center for Neuroimaging, Institute of Neurology, London, England). Images were then modulated using nonlinear deformations only, allowing us to compare amounts of tissue corrected for individual differences in global head size (Cousijn et al., 2012; Farokhian et al., 2017). Resulting images were smoothed using an 8 mm full-width at half-maximum Gaussian kernel for voxelwise analyses.

In addition, hippocampal volume and entorhinal cortex thickness were estimated for each participant using FreeSurfer 5.1.0 on the raw T1-weighted MRI scan. All segmentations were visually checked (no errors were detected). Right and left estimates were pooled and hippocampal volumes were divided by total intracranial volume (derived from FreeSurfer) to correct for inter-individual variability in head size.

PET data were corrected for partial volume effects (PVE) based on a three-compartment model using PMOD (PMOD Technologies Ltd., Adliswil, Switzerland), coregistered to the corresponding MRI, and normalized to template space using the deformation parameters defined from the MRI. Images then underwent quantitative scaling using the cerebellar grey matter as a reference to obtain standardized uptake value ratio (SUVr) images. PVE-corrected normalized SUVr images were used to extract individual global neocortical Flobetapir-PET SUVr values using a predetermined neocortical mask (see Besson et al., 2015; La Joie et al., 2012). These values were used to classify participants as A β -positive or negative using a threshold of 1.02 derived from an independent group of 41 young individuals aged 21 to 39 years (Besson et al., 2015). Among the 48 aMCI patients, 15 were classified as A β -negative and 33 as A β -positive. For this study, only A β -negative cognitively normal individuals were included in the control group.

2.4 Statistical analyses

2.4.1 Demographic, clinical and neuropsychological data

Continuous data were compared between groups (HC, A β -negative aMCI and A β -positive aMCI) with single-factor (group) analyses of variance, and post hoc comparisons (Fisher's LSD) when the effect of group was significant. Categorical variables were compared using Fisher exact tests.

2.4.2 Word-learning test analyses

2.4.2.1 Full model (group x encoding list x serial position) on free recall performance

A General Linear Model was used to analyze free recall performance. The model included a between-subject factor: group (with 3 levels: HC, A β -negative MCI, and A β -positive aMCI) and two within-subject factors: encoding list (2 levels: shallow and deep) and item serial position (4 levels: items 1-4, 5-8, 9-12, and 13-16). Age and education were entered as covariates as they were related to performance in the control group (data not shown).

Based on the results of this full model indicating a significant three-way interaction (see 3.2.1.), we then created simpler models for each item serial position level (4 models), and only including the two aMCI patient subgroups, i.e. our main contrast of interest. Thus, each model included group as a between-subject factor (2 levels: A β -negative MCI, and A β -positive aMCI) and encoding list as a within-subject factor (2 levels: shallow and deep).

2.4.2.2 Confirmatory (non-parametric) analyses comparing A β -positive and A β -negative aMCI.

In order to confirm that the previous results were not biased by the suboptimal distribution of the dependent variable (for each group of items, scores ranged between 0 and 4 and were therefore ordinal rather than continuous), we repeated the main contrast of interest (effect of A β on recall performance) with three complementary non-parametric tests. First, for each group of items (2 lists * 4 serial position = 8 dependent variables), we used an ordinal logistic regression

to predict each of the number of recalled items (0-4) based on A β status; model fit was assessed using McFadden's pseudo R^2 . Second, we used a non-parametric Receiver Operating Characteristic (ROC) analysis (95% confidence intervals were estimated based on a binomial exact method using Easy-ROC version 1.3, www.biosoft.hacettepe.edu.tr/easyROC/) to test how each recall performance discriminated between A β -negative and A β -positive patients. Third, we assessed correlations between Florbetapir-PET SUVR and the number of recalled items using Spearman's rho, to use the full range of PET values instead of the binary classification into A β -negative/positive.

Lastly, we further investigated the items' serial position that showed free recall differences between A β -negative and A β -positive aMCI patients (see 2.4.2.1.) by assessing performance during recognition; for these items, we used an ordinal logistic regression to predict the number of recognized items (0-4) based on A β status.

2.4.3 Autobiographical fluency task

A General Linear Model was used, specifying a between-subject 'group' factor (3 levels: HC, A β -negative MCI, and A β -positive aMCI) and a within-subject 'time period' factor (very recent, recent and remote period as repeated measures). Age and education were entered as covariates.

2.4.4 Neuroimaging data

Hippocampal volume and entorhinal thickness were compared between groups (HC, A β -negative aMCI and A β -positive aMCI) using ANCOVAs and post-hoc comparisons (Fisher's LSD) when the effect of group was significant; age and education were entered as covariates to parallel the analyses on the cognitive scores, but results were unchanged when ignoring the covariates.

In addition, to characterize global patterns of atrophy within each patient group, we computed W-score maps using the healthy control group as a reference (Chételat et al., 2017; La Joie et al., 2018; Ossenkoppele et al., 2015a). This approach was preferred over the classic two-sample t-test comparison between the control group and each patient group, as it would be biased toward showing more significant patterns in the A β -positive group due to higher statistical power (n=33 versus 15). W-scores are analogous to Z-scores (mean = 0 and SD = 1 in the control group) but they are adjusted for specific covariate(s) (Boccardi et al., 2003; Jack et al., 1997; O'Brien and Dyck, 1995), age and education in the present case. To create W-score maps, voxelwise regressions were first performed in the control group between the gray matter maps and age and education using SPM12. Then, W-score maps were computed using the following formula: $W\text{-score} = [(\text{patient's raw value}) - (\text{predicted value based on the patient's age and education})] / (\text{SD of the residuals in controls})$ in every voxel. Individual W-score maps were averaged across each patient group to provide profiles of whole-brain atrophy, expressed as mean W-scores.

Lastly, a voxelwise two sample t-test was used to directly compare (non W-scored) smoothed, modulated and normalized gray matter maps between A β -negative and A β -positive aMCI patient groups.

3 Results

3.1 Demographic, clinical and neuropsychological data

The three groups (HC, A β -positive aMCI and A β -negative aMCI) were globally matched on demographic variables, although patients tended to be slightly older and less educated than controls (Table 1). As expected based on the literature, the proportion of apolipoprotein ϵ 4 carriers was significantly higher in A β -positive aMCI (61%) compared to HC (10%) and A β -negative aMCI (20%)(Jansen et al., 2015). Both patient groups showed lower performance than

controls on various cognitive tests (global cognition, executive function, verbal fluency, working memory, and episodic memory tests from the screening battery), but none of these tests significantly differentiated A β -positive aMCI from A β -negative aMCI groups (see Table 1 and Figure S1 for the details of episodic tests used for screening).

3.2 Word list learning (ESR) test

3.2.1 *Group x encoding list x serial position interaction on free recall performance*

The full model showed significant main effects of group ($F=55.9$, $p<0.001$, $\eta_p^2=0.57$; HC>A β -negative aMCI, $p<0.001$; HC>A β -positive aMCI, $p<0.001$; A β -negative>A β -positive aMCI, $p=0.02$) and serial position ($F=3.4$, $p=0.02$, $\eta_p^2=0.04$; items 1-4<items 5-8, $p=0.006$; items 1-4<items 9-12, $p<0.001$; items 1-4 <items 13-16, $p<0.001$; items 5-8<items 9-12, $p=0.06$; items 5-8< items 13-16, $p<0.001$; items 9-12<items 13-16, $p<0.001$), but not encoding list ($F=1.3$, $p=0.26$, $\eta_p^2=0.02$). Group interacted with encoding list ($F=5.5$, $p=0.006$, $\eta_p^2=0.118$) but not serial position ($F=0.7$, $p=0.66$, $\eta_p^2=0.016$), and the triple group*encoding list*serial position interaction was significant ($F=3.4$, $p=0.003$, $\eta_p^2=0.08$). Figure 1A shows that group differences were more marked for the second list (deep and intentional encoding), except for the last items. The pattern was globally similar when looking at response rates for individual items (Figure S2), or pairs of items (Figure S3).

3.2.2 *Free recall performance: A β -positive versus A β -negative aMCI*

To better characterize the triple group*encoding list*serial position interaction, smaller two-way models were conducted for each level of the serial position factor, and only including the two aMCI groups to focus on our contrast of interest. For items 1-4 there was a significant effect of encoding list ($F=5.3$, $p=0.026$, $\eta_p^2=0.103$, deep > shallow), a trend for group ($F=3.7$, $p=0.062$, $\eta_p^2=0.074$; A β -negative aMCI > A β -positive aMCI), and a significant group * encoding list interaction ($F=11.0$, $p=0.002$, $\eta_p^2=0.193$). Figure 1B and post hoc analyses indicated that, unlike A β -negative aMCI patients (and HC), the A β -positive aMCI group did not benefit from the deep

and intentional encoding for items 1-4. In contrast, the three other two-way models showed a consistent pattern with mild group differences (Figure 1B; A β -negative aMCI > A β -positive aMCI across items; items 5-8: $p=0.075$, $\eta_p^2=0.068$; items 9-12: $p=0.40$, $\eta_p^2=0.015$; items 13-16: $p=0.044$, $\eta_p^2=0.085$), and no group * encoding list interaction (items 5-8: $p=0.79$, $\eta_p^2=0.002$; items 9-12: $p=0.40$, $\eta_p^2=0.015$; items 13-16: $p=0.53$, $\eta_p^2=0.009$). Breaking down the word-list by items (Figure S2.B) or pairs of items (Figure S3.B) showed the same pattern: while HC and A β -negative aMCI showed a benefit from deep encoding on recall performance (list 2 > list 1) across most items (including the first), this benefit was only apparent in the second half of the list for the A β -positive aMCI group.

Additional analyses were conducted to confirm the relationship between A β and item recall performance in aMCI based on 3 complementary approaches more fitted to ordinal variables: ordinal logistic regression, ROC analysis, and Spearman correlation with Florbetapir SUVR in the whole aMCI group. These tests were applied to each item group (2 lists x 4 serial position: $n=8$) and confirmed previous results (see Table 2 and Figure S4). Indeed, only the first items of the second list (deep and intentional encoding) showed consistent and robust association with A β in patients with aMCI, regardless of the method: $p=0.009$ for ordinal regression, $p=0.0047$ for ROC analyses (surviving stringent Bonferroni correction) and $p=0.01$ for correlation with SUVR.

3.2.3 Recognition performance: A β -positive versus A β -negative aMCI

Based on the aforementioned finding that the first items of the deep and intentional encoding list consistently showed lower free recall performance in A β -positive compared to A β -negative aMCI, we further tested whether patient subgroups also differed in recognition performance for this specific group of items (i.e. the first one). Indeed, A β -positive patients recognized the first items of list 2 (mean \pm sd: 2.9 ± 1.1 items out of 4) less frequently than the A β -negative patients (3.7 ± 0.6 ; ordinal logistic regression $p=0.02$, see Figure S5 for further details and breakdown of each group performance).

3.3 Autobiographical fluency task

As shown in Figure 3, there were significant effects of group ($F=18.2$, $p<0.001$, $\eta_p^2=0.31$; HC>A β -negative aMCI: $p<0.001$, HC>A β -positive aMCI: $p<0.001$, and a trend for A β -negative aMCI> A β -positive aMCI: $p=0.06$) but no significant group * life period interaction ($F=0.9$, $p=0.48$, $\eta_p^2=0.02$) on the recall of autobiographical episodes.

Figure S6 shows the details of participants' responses for each life period. Statistical analyses were used to directly compare A β -negative aMCI and A β -positive aMCI groups using ordinal logistic regression, ROC analyses, and correlation to Florbetapir SUVR, similar to the approach used for the word-list learning task. These complementary statistical tests confirmed a general trend for fewer memories recalled by the A β -positive patients, although the difference was mild and did not reach statistical significance when correcting for multiple comparisons.

3.4 Structural neuroimaging analyses

As shown in Figure 3, analyses of specific medial temporal regions of interest using Freesurfer software showed that both A β -positive and A β -negative aMCI groups had significant bilateral hippocampal atrophy in comparison to HC (16% and 18% smaller average volumes than controls for both $p<0.001$, respectively). Results were comparable for entorhinal thickness, though only the A β -positive group showed a significant decrease compared to controls ($p=0.001$). The difference between controls and A β -negative aMCI did not reach significance ($p=0.10$), likely because of lower statistical power. Direct comparison between the two aMCI groups showed no differential alteration of these medial temporal regions ($p=0.69$ and $p=0.34$, respectively).

Voxelwise analyses of gray matter volume (expressed as mean W-scores maps) showed that both aMCI groups had very similar patterns of atrophy, predominating in the bilateral medial temporal lobe, in contrast to HC. Finally, direct voxelwise comparison of the aMCI groups

showed no significant difference, even at the very liberal threshold of $p < 0.01$ uncorrected and $k = 150$ voxels.

4 Discussion

In this study, we used complementary neuropsychological tests to explore memory deficits in patients with a clinical diagnosis of aMCI, suspecting that patterns of impairment would differ based on the presence of A β pathology as evidenced by PET imaging. The specific tests we investigated were independent from those used to make the diagnosis of aMCI and targeted different components and processes of episodic memory. First, using a word-list learning task that included two encoding conditions (shallow and incidental versus deep and intentional), both A β -positive and A β -negative patients showed severe free recall deficits compared to controls, and both aMCI groups showed limited benefit from intentional and deep semantic encoding. Within aMCI groups, A β -status had limited influence. However, the A β -positive group showed poorer recall (and recognition) performance, especially for the items that were presented at the beginning of the intentionally and deeply encoded list, i.e. a more severely affected primacy effect. Second, on an autobiographical memory fluency task investigating different life periods, both A β -positive and A β -negative patients recalled fewer episodic memories than the controls, regardless of the time period, and A β -positive patients tended to recall slightly fewer memories than their A β -negative counterparts. Finally, the differential pattern observed on the word-list learning test was not subtended by differential structural alterations as the two aMCI patient groups harbored comparable patterns of brain atrophy compared to the control group, with volume loss predominating in the medial temporal lobe.

First of all, it should be noted that the two groups of aMCI patients were more similar than different: regardless of A β status, patients had medial temporal atrophy and severe deficits in most memory and non-memory subscores compared to controls. A β positivity was only associated with mild memory differences, consistent with a recent meta-analysis suggesting that

cognitive scores are only slightly predictive of A β -positivity in healthy controls and patients with MCI (Jansen et al., 2018). This result has implications for clinical trial enrichment strategies aimed at screening patients at high likelihood of being A β -positive: our data suggest that classical cognitive testing and structural MRI have little added value in identifying these cases. In contrast, the apolipoprotein E4 genotype was highly associated with Florbetapir-PET findings (Table 1), in line with existing literature (Jansen et al., 2015).

Similar to most previous studies, A β -positive aMCI patients tended to have lower performance than the A β -negative aMCI group on most memory subscores (Table 1 and Figure S1 for standard tests of episodic memory; Figures 1 and S2-5 for the ESR task; Figure 3 and S6 for autobiographical fluency). Yet, not all memory subscores were equally affected, as evidenced by the significant group*list*serial position interaction observed on the ESR task (section 3.2). Indeed, the A β -associated difference was more pronounced for the first items, where the A β -positive group did not benefit from the deep encoding condition (Figure 1.B.). This effect was independent of retrieval modality, as the group difference was significant for both free recall (Figure 1 and S4) and recognition (Figure S5). These findings are consistent with impaired encoding and early consolidation processes typically described in aMCI (Kasper et al., 2016), reflecting a diminished capacity for transferring new information from short-term to long-term storage (Becker and Morris, 1999). In contrast, the recency effect was preserved in both patient groups, as evidenced by minimal group differences in recall performance for the last items (note that the recency effect observed with the ESR task was particularly salient due to the absence of an interference task before the free recall). The recency effect preservation in both aMCI groups was particularly noticeable in the intentional and deep encoding condition (list 2), illustrating relatively spared short-term memory. This is consistent with the absence of group differences for the forward digit span (Table 1). This differential impairment of primacy and recency effects echoes previous reports in patients with MCI who subsequently converted to

dementia (Cunha et al., 2012; Egli et al., 2015, 2014), and in healthy individuals with a positive family history for AD (La Rue et al., 2008).

It should be noted that the present approach differs from multiple previous and ongoing studies in which episodic memory is evaluated based on a composite score combining scores from multiple (sub)tests, including visual and verbal memory tests, free and cued recall, etc. The latter has indisputable advantages, notably in terms of psychometric properties (e.g. statistical distribution and measurement error), which justifies its use as a cognitive endpoint in clinical trials (Crane et al., 2012; Langbaum et al., 2014). Yet, these composite metrics aim to capture a robust global memory latent variable rather than a specific memory process. Here, we propose that targeting specific aspects of memory deficits (i.e. the primacy effect in the context of an intentional and deeply encoded word-list) may provide additional information to help stratify patients, in spite of limited statistical distributions. Future studies, including replication of this finding on larger and longitudinal cohorts, are needed to evaluate the potential added value of probing the primacy effect in patients with aMCI.

Interestingly, the analysis of the structural MRI data did not provide an anatomical explanation for the more impaired primacy effect in A β -positive aMCI: no volumetric difference was found between the two aMCI groups, even using liberal statistical thresholds. This negative finding raises the possibility that A β pathology might exert a non-hippocampal atrophy-mediated deleterious effect on cognition, as suggested by previous independent studies (Chételat et al., 2011). The cognitive differences associated with the presence of A β pathology could then either be a direct consequence of A β pathology or be mediated by additional mechanisms and pathways that were not measured in the present investigation. For instance, a previous study conducted in patients with aMCI (whose A β status was unknown) showed that the primacy effect was associated with the functional connectivity of the hippocampus, even when controlling for hippocampal volume (Brueggen et al., 2016). Future studies integrating

complementary imaging modalities might help elucidate the neural underpinnings of the cognitive difference associated with A β -PET positivity in our cohort. In contrast, both patient groups had relatively focal medial temporal atrophy, which was consistent with the intact recency effect in both groups. Indeed, previous studies showed that recency effect deficits were associated with degeneration of extra-hippocampal, neocortical areas, usually at more advanced disease stages (Kasper et al., 2016; Staffaroni et al., 2017).

The analysis of the autobiographical fluency task showed reduced recall of episodic memories in patients with aMCI compared to controls. Weaker autobiographical memory abilities have been previously demonstrated in patients with a clinical diagnosis of AD dementia (Addis et al., 2009; Addis and Tippett, 2004; Greene et al., 1995; Ivanoiu et al., 2004; Kopelman et al., 1989; Leyhe et al., 2009; M. Irish et al., 2011; Piolino et al., 2003) or MCI (Irish et al., 2010; Leyhe et al., 2009; Murphy et al., 2008; Tomadesso et al., 2015), and more recently in cognitively normal individuals at genetic risk for AD (Grilli et al., 2018). Yet, the group difference was independent of life period, contrasting with the general idea that AD usually affects the recall of recent more than remote memories (Eustache et al., 2004; Leyhe et al., 2009), though other studies have not demonstrated this temporal gradient (Dall'Ora et al., 1989; Grilli et al., 2018; Ivanoiu et al., 2004; Nestor et al., 2002). In addition, A β -positive patients trended towards greater deficits in recall for all life periods, providing complementary evidence that the presence of A β pathology is associated with stronger episodic memory deficits. However, the relatively small size of our cohort and the absence of existing studies focusing on autobiographical memory and A β biomarkers shows the need for more data to establish this relationship.

Overall, our analyses showed that patients with a clinical diagnosis of aMCI showed severe memory deficits across cognitive tests, with broadly comparable deficits in A β -positive and A β -negative patients. Similarly, patients harbored medial temporal predominant atrophy regardless of A β status. However, subtle differences were found between biomarker-defined subgroups,

with A β -positive patients showing more severely impaired scores, especially on measures that target encoding and early consolidation processes. Future studies are needed to replicate these findings and test the added value of specific neuropsychological measures to identify A β -positive patients in an independent cohort.

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Disclosure Statement

Conflicts of interest: Dr Perrotin currently works for Piramal Imaging Ltd. None of the other authors report any conflict of interest.

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Figure legends

Figure 1. Free recall performance on the word-list learning task.

A. Full three-way model illustrating the free recall performance according to group (between subject, 3 levels), encoding list (within subject, 2 levels) and item serial position (within subject, 4 levels). The model shows a significant triple interaction ($p=0.003$, see section 3.2.1. for more details).

B. Separate two-way models conducted for each level of item serial position and restricted to the two aMCI groups (the control group is shown in light green for reference, as they were not included in the statistical models).

Plots show average number of recalled items and 95% confidence intervals.

Figure 2. Autobiographical fluency tests performance across three life periods.

Plots show average number of recalled episodic memories for each life period (remote: 20-30 years old; recent: last 10 years minus last year; very recent: last year) and 95% confidence intervals. Green: healthy controls; yellow: A β -negative aMCI; red: A β -positive aMCI.

For the details, see Supplementary figure 6.

Figure 3. Comparison of medial temporal lobe structural measures across the three groups.

Top panel shows hippocampal volume (Left + Right, divided by total intracranial volume) and entorhinal thickness (average of left and right) obtained using Freesurfer. Bars show average values and 95% confidence intervals.

Bottom panel shows voxelwise patterns of gray matter atrophy in the A β -negative and A β -positive aMCI respectively, expressed as group-average *W*-score (using the healthy control group as a reference, controlling for age and education) calculated in each voxel.

Table 1. Demographic, clinical and neuropsychological data for the healthy controls (HC) and the patients with amnesic mild cognitive impairment (aMCI) categorized by amyloid status (A β -positive aMCI and A β -negative aMCI).

	HC (n=40)	A β -negative aMCI (n=15)	A β -positive aMCI (n= 33)	Group comparison	A β -neg versus A β -pos aMCI AUROC [95CI]
Age years	70.8 \pm 5.7	71.8 \pm 7.5	73.9 \pm 7.1	$\eta^2=0.047$	
Males N (%)	23 (58%)	8 (53%)	19 (58%)	$p_{\text{fisher}}=1$	
Education years	12.6 \pm 3.8	10.0 \pm 2.7	11.5 \pm 4.1	$\eta^2=0.058^t$	
APOE $\epsilon 4$ carriers n (%)	4 (10%)	3 (20%)	19 (61%)*	$p_{\text{fisher}}<0.001$	
MMSE total score, /30	28.7 \pm 1.1	26.9 \pm 2.0	26.6 \pm 1.8	$\eta^2=0.290^{***}$	0.55 [0.39-0.69]
MADRS total score, /144	142.0 \pm 2.0	134.5 \pm 5.8	132.6 \pm 5.5	$\eta^2=0.523^{***}$	0.60 [0.45-0.74]
Trail Making Test Part A, time	44.2 \pm 12.2	47.3 \pm 17.1	53.0 \pm 18.4	$\eta^2=0.064^t$	0.57 [0.41-0.71]
Trail Making Test B-A, time	51.4 \pm 28.8	83.0 \pm 62.5	86.4 \pm 56.0	$\eta^2=0.122^{**}$	0.53 [0.38-0.68]
Stroop Color naming time	66.2 \pm 9.4	80.5 \pm 14.8	76.4 \pm 18.4	$\eta^2=0.153^{***}$	0.43 [0.28-0.58]
Stroop interference time	124.5 \pm 26.8	150.6 \pm 30.5	177.0 \pm 70.0	$\eta^2=0.205^{***}$	0.60 [0.44-0.74]
Semantic fluency words, 2min	31.63 \pm 6.7	24.1 \pm 7.1	24.0 \pm 6.6	$\eta^2=0.191^{***}$	0.49 [0.34-0.64]
Phonemic fluency words, 2min	22.8 \pm 6.9	16.4 \pm 5.7	18.0 \pm 8.3	$\eta^2=0.126^{**}$	0.45 [0.31-0.60]
Digit Span Forward score	5.98 \pm 1.17	5.93 \pm 0.96	5.63 \pm 1.10	$\eta^2=0.022$	0.58 [0.43-0.73]
Digit Span Backward score	4.60 \pm 1.08	3.67 \pm 0.72	4.09 \pm 1.03	$\eta^2=0.112^{**}$	0.38 [0.24-0.53]
FCSRT free recall Sum of 3 scores	31.6 \pm 5.0	18.0 \pm 6.1	15.4 \pm 5.5	$\eta^2=0.679^{***}$	0.64 [0.41-0.73]
FCSRT total recall Sum of 3 scores	46.3 \pm 2.1	38.2 \pm 5.6	35.4 \pm 7.5	$\eta^2=0.503^{***}$	0.62 [0.45-0.76]
BEM figure recall score	9.5 \pm 1.7	7.13 \pm 1.7	6.3 \pm 2.4	$\eta^2=0.362^{***}$	0.63 [0.48-0.77]

Abbreviations: HC= Healthy controls, aMCI= amnesic Mild Cognitive Impairment; MMSE= Mini Mental State Examination, MADRS= Mattis Dementia Rating Scale; FCSRT= Free & Cued Selective Reminding Test; BEM= Batterie d'Efficiency Mentale; AUROC= Area Under the Receiver Operating Characteristic curve (with binomial exact 95% Confidence interval).

All scores are expressed with mean \pm standard deviation. All three groups were compared using an Analysis of Variance (effect sizes are shown using η^2 , t: $p<0.1$, **: $p<0.01$, ***: $p<0.001$) for continuous variables and Fisher exact p value for categorical variables. Post hoc tests did not reveal any variable with a significant ($p<0.05$) difference between the two aMCI groups. For cognitive measures, Receiver Operating Characteristic analyses were conducted to discriminate the two aMCI groups. AUROC values above 0.5 reflect worse performance in the A β -positive aMCI group whereas values below 0.5 reflect worse performances in the A β -negative aMCI group.

*APOE $\epsilon 4$ genotype data were not available for two patients.

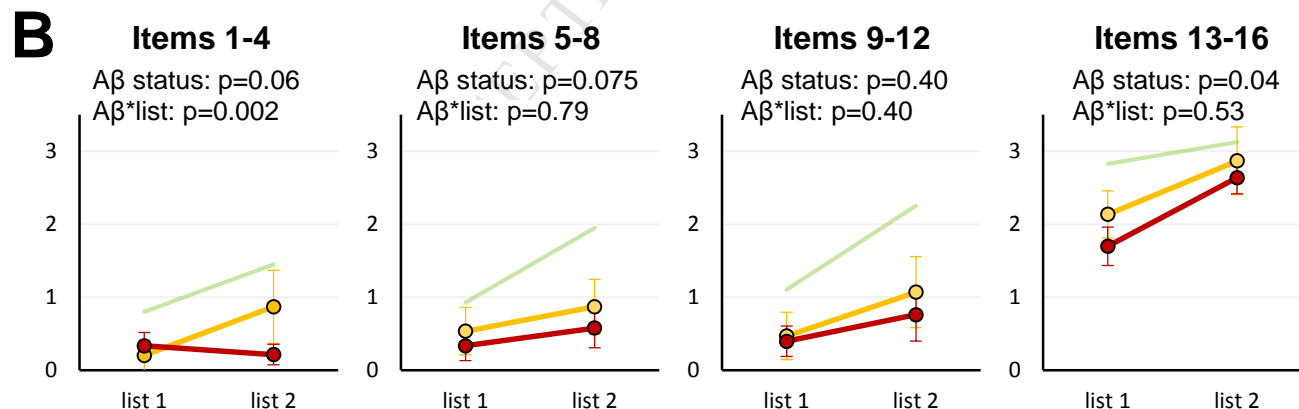
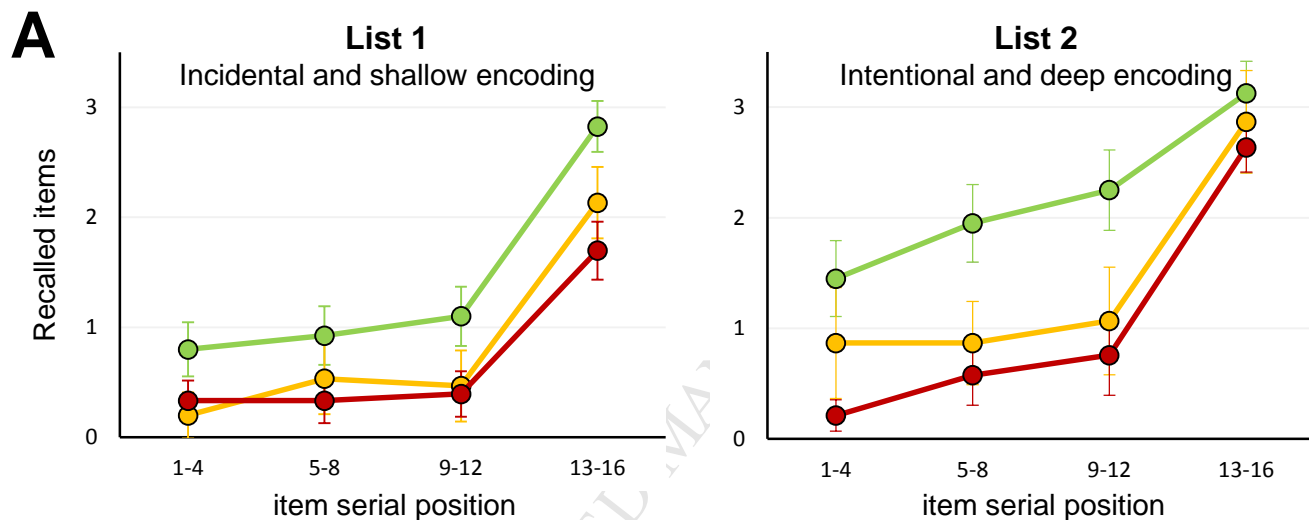
Table 2. Complementary analyses of the association between Florbetapir-PET results and free recall performances for all item groups in patients with aMCI.

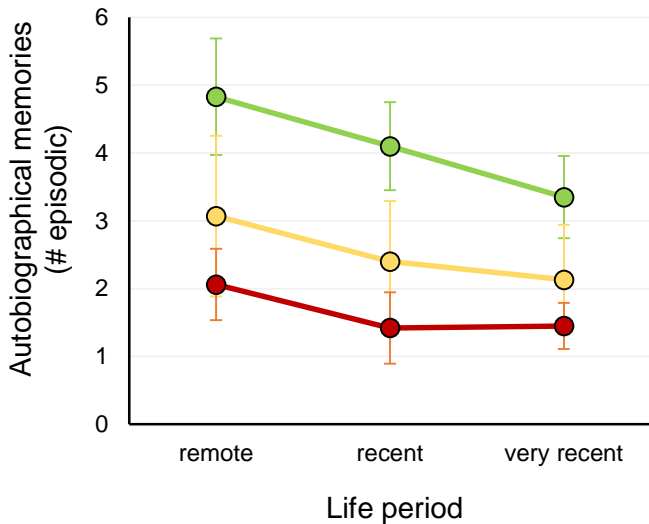
	1. Ordinal logistic regression			2. ROC analysis				3. Correlation analysis	
	R^2_{McF}	χ^2	p	AUC	95%CI	Z	p	Spearman's ρ	p
List 1: incidental and superficial encoding									
Items 1-4	0.010	0.64	0.43	0.45	[0.31-0.60]	-0.76	0.45	0.03	0.87
Items 5-8	0.019	1.47	0.23	0.59	[0.44-0.73]	1.30	0.20	-0.09	0.53
Items 9-12	0.002	0.18	0.67	0.53	[0.38-0.68]	0.45	0.65	-0.04	0.81
Items 13-16	0.034	3.64	0.06	0.66	[0.51-0.79]	2.32	0.02	-0.16	0.27
List 2: intentional and deep encoding									
Items 1-4	0.083	6.74	0.009	0.69	[0.54-0.81]	2.83	0.0047	-0.37	0.01
Items 5-8	0.019	1.88	0.17	0.62	[0.46-0.75]	1.64	0.10	-0.29	0.04
Items 9-12	0.015	1.82	0.18	0.62	[0.46-0.75]	1.65	0.10	-0.07	0.63
Items 13-16	0.012	1.21	0.27	0.59	[0.44-0.73]	1.24	0.22	-0.18	0.21

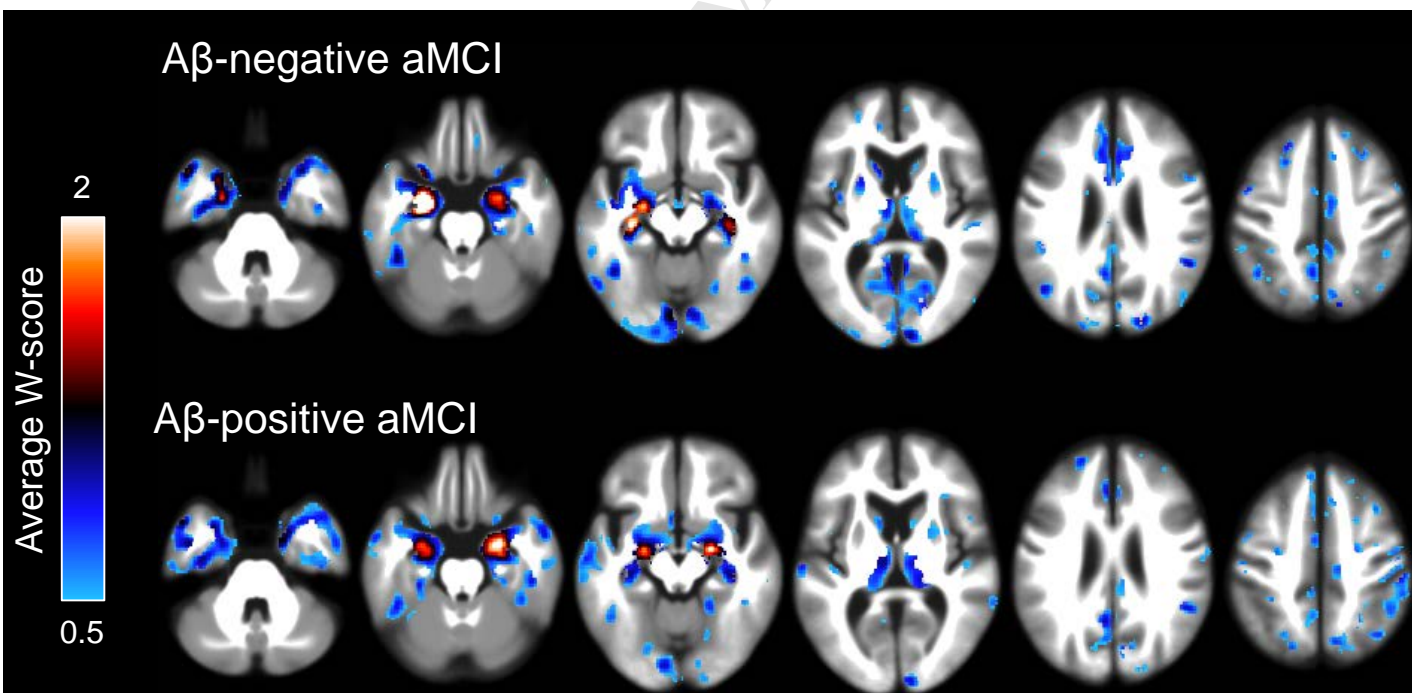
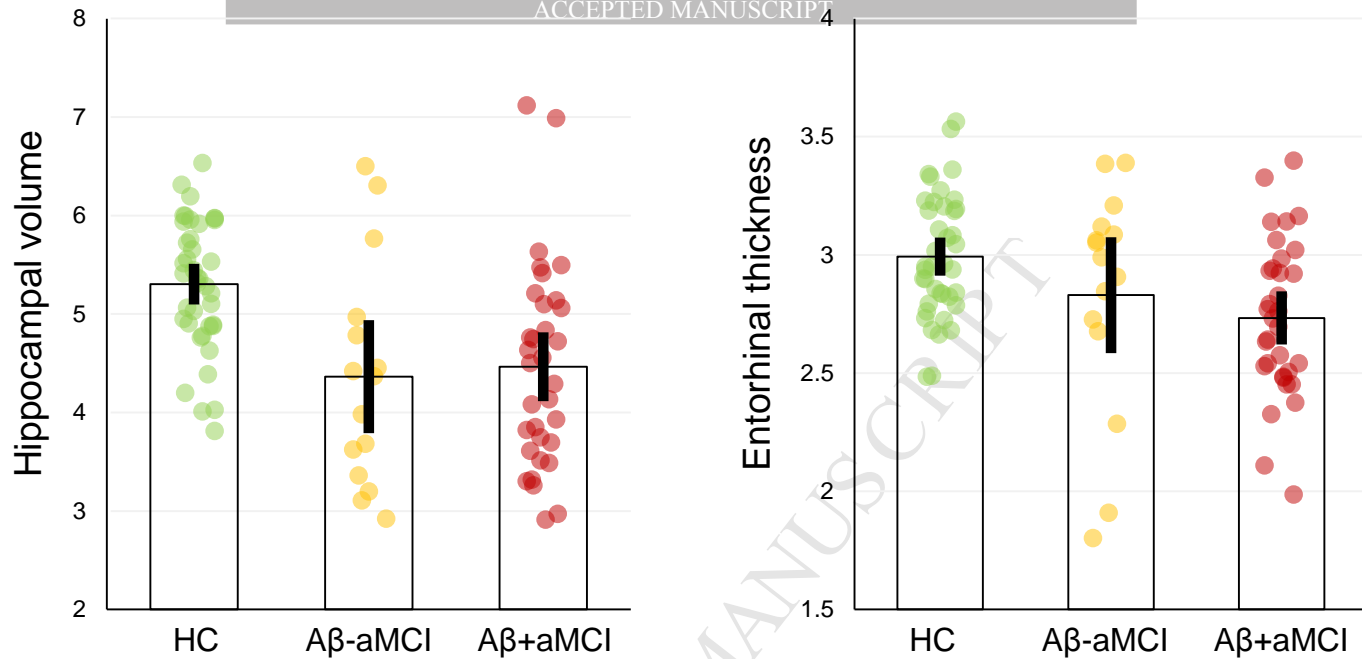
For each group of 4 items, three analyses were conducted: 1) ordinal logistic regression (dependent variable: number of recalled items, predictor: A β status), 2) ROC analysis (comparison between 33 A β -positive and 15 A β -negative aMCI patients), 3) correlation between continuous Florbetapir SUVR and number of recalled items in the 48 patients with aMCI. For the detail of performances, see Supplementary figure 3.

R^2_{McF} : McFadden's pseudo R^2 ; ROC: Receiver Operating Characteristic; AUC: Area Under the Curve; 95CI: binomial exact 95% confidence interval. P values are uncorrected for multiple testing but Bonferroni correction results in $\alpha=0.05/8 = 0.00625$ threshold for each set of analyses.

Controls

A β -negative aMCIA β -positive aMCI





Highlights

- aMCI patients show medial temporal predominant atrophy, regardless of A β status
- A β - and A β + aMCI patients harbor broadly comparable memory deficits
- However, A β + aMCI patients show more severe primacy effect deficits than A β - patients