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# **Building memories on prior knowledge: behavioral and fMRI evidence of impairment in early Alzheimer's disease**

Pierre-Yves Jonin<sup>a,b,c,\*</sup>

Quentin Duché<sup>b</sup>

Elise Banner<sup>b,d</sup>

Isabelle Corouge<sup>b,d</sup>

Jean-Christophe Ferré<sup>b,d</sup>

Serge Belliard<sup>c</sup>

Christian Barillot<sup>b†</sup>

Emmanuel J. Barbeau<sup>a</sup>

*\*corresponding author : pierreyves.jonin@chu-rennes.fr*

*†In Memoriam*

<sup>a</sup>Brain & Cognition Research Center (CerCo), CNRS-University of Toulouse Paul Sabatier, Toulouse, France

<sup>b</sup>Empenn research team, INRIA, Rennes University-CNRS-INSERM-IRISA, Rennes, France

<sup>c</sup>Neurology Department, Rennes University Hospital, Rennes, France

<sup>d</sup>Radiology Department, Rennes University Hospital, Rennes, France

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## **Abstract**

Impaired memory is a hallmark of prodromal Alzheimer's disease (AD). Prior knowledge associated with the memoranda improves memory in healthy individuals. However, little is known about its effect in early AD. We used functional MRI to investigate whether prior knowledge enhances memory encoding in early AD, and whether the nature of this prior knowledge matters. 17 patients with early AD and 19 controls underwent a task-based fMRI experiment where they learned face-scene associations. Famous faces carried pre-experimental knowledge (PEK), while unknown faces with which participants were familiarized prior to learning carried experimental knowledge (EK). As expected, PEK enhanced subsequent memory in healthy controls, but not in patients. Importantly, partly nonoverlapping brain networks supported PEK vs. EK encoding in healthy controls. Patients displayed impaired activation in a right subhippocampal region where activity predicted successful associative memory formation for PEK stimuli. Despite the limited sample sizes, these findings underline how prior knowledge impacts learning and suggest that the extent of associative memory impairment in early AD has hitherto been underestimated.

## **Keywords**

Alzheimer's disease; prior knowledge; source memory; recognition memory; perirhinal cortex; fMRI

## Highlights

- We asked if prior knowledge lessens the learning deficit observed in prodromal AD.
- AD patients did not benefit from pre-experimental knowledge (PEK; famous faces).
- Distinct networks subtended associative encoding of (pre-)experimental knowledge.
- Controls exhibited a memory effect in the perirhinal cortex for PEK associations.
- By using unfamiliar items to probe memory in AD, a deficit may be underestimated

## 1. Introduction

The idea that prior memories influence new learning can be traced back to Hermann Ebbinghaus. He deliberately used meaningless syllables to investigate human learning, as he did not want new learning to be corrupted by things he already knew. Far from Plato's metaphor of the wax tablet (Roediger, 1980), new learning rarely occurs in a vacuum. Instead, it is typically processed in relation to existing knowledge. Years of research have shown that prior knowledge about memoranda has a very powerful effect on memory (e.g., Fernández and Morris, 2018; Umanath and March, 2014), likely to strongly reduce the impact of age on associative memory (e.g. Badham Estes Maylor 2012). For example, it is easier to remember meeting a neighbor in a given setting than to remember an unknown face, even it has been presented repeatedly. Surprisingly little is known about the influence of prior knowledge in Alzheimer's disease (AD). More specifically, it is not yet known whether prior knowledge is as effective at promoting memory in patients as it is in healthy individuals, and whether the neural correlates of this effect are altered in this disease.

In experimental settings, the ability of participants to remember stimuli carrying pre-experimental prior knowledge (PEK), such as famous faces, is often contrasted with their ability to remember either completely unknown items, or stimuli carrying experimental prior knowledge (EK), that is, resulting from repeated exposure to initially unknown stimuli, such as unknown faces (Poppenk et al., 2010a). The reason for contrasting e.g. famous faces to unknown but familiarized faces is the need to isolate the genuine contribution of pre-experimental knowledge. Indeed, by using entirely novel faces as control stimuli, one would confound the benefits of multiple past exposures and those arising from pre-experimental semantic knowledge as discussed in previous studies (Poppenk et al., 2010a, 2010b). Evidence from behavioral studies has robustly supported the role of PEK in enhancing associative learning in healthy adults (Bird et al., 2011; Ellis et al., 1979; Greve et al., 2007; Klatzky and Forrest, 1984; Long and Prat, 2002; Reder et al., 2013), including older individuals (Badham et al., 2015; Badham and Maylor, 2015; McGillivray and Castel, 2010). However, the cognitive processes supporting PEK-related learning remain unclear, with hypotheses putting forward accelerated

consolidation (Van Kesteren et al., 2012), modulation of attentional demands (Castel and Craik, 2003), or increased elaborative processing (Bein et al., 2015).

Similarly, the corresponding neural underpinnings remain elusive so far, albeit the involvement of key structures have been identified. Task-based functional MRI studies in young adults have highlighted the role of the medial temporal lobes and temporal poles, together with the ventromedial and inferior/middle prefrontal cortex (PFC), in PEK-based learning, compared with the learning of either novel or recently learned stimuli (Leveroni et al., 2000; Liu et al., 2016; Van Kesteren et al., 2012). By contrast, EK-based learning has been associated with activity in the parietal regions and posterior hippocampus (Dennis et al., 2015; Poppenk et al., 2010a, 2010b; Poppenk and Norman, 2012).

In the present study, we assessed whether PEK enhances memory of patients in the early stage of AD, and whether the fMRI response differed for PEK- versus EK-based associative memory encoding, both in patients and healthy elderly. Using an event-related fMRI task design, we asked patients with mild cognitive impairment due to Alzheimer's disease (AD-MCI) and matched healthy controls to encode face-scene associations. Prior knowledge about the stimuli was manipulated using either famous faces (PEK condition) or unknown faces with which participants had been familiarized just before the learning phase (EK condition). To identify the brain areas involved in the encoding task, we looked for the neural adaptation effect, that is, modulation of the blood-oxygen-level-dependent (BOLD) fMRI response as a result of stimulus repetition (Grill-Spector et al., 2006).

## **2. Material and methods**

### **2.1. Participants**

The study was approved by a national ethics committee and registered in the Clinical Trials database (EPMR-MA Study 2014-A01123-44). A total of 22 patients who met the NIA-AA criteria for AD-MCI (Albert et al., 2011) and 25 healthy controls were screened to participate in the study. Patients were recruited at the Upper Brittany Memory Clinic of Rennes University Hospital, which has over 20 years

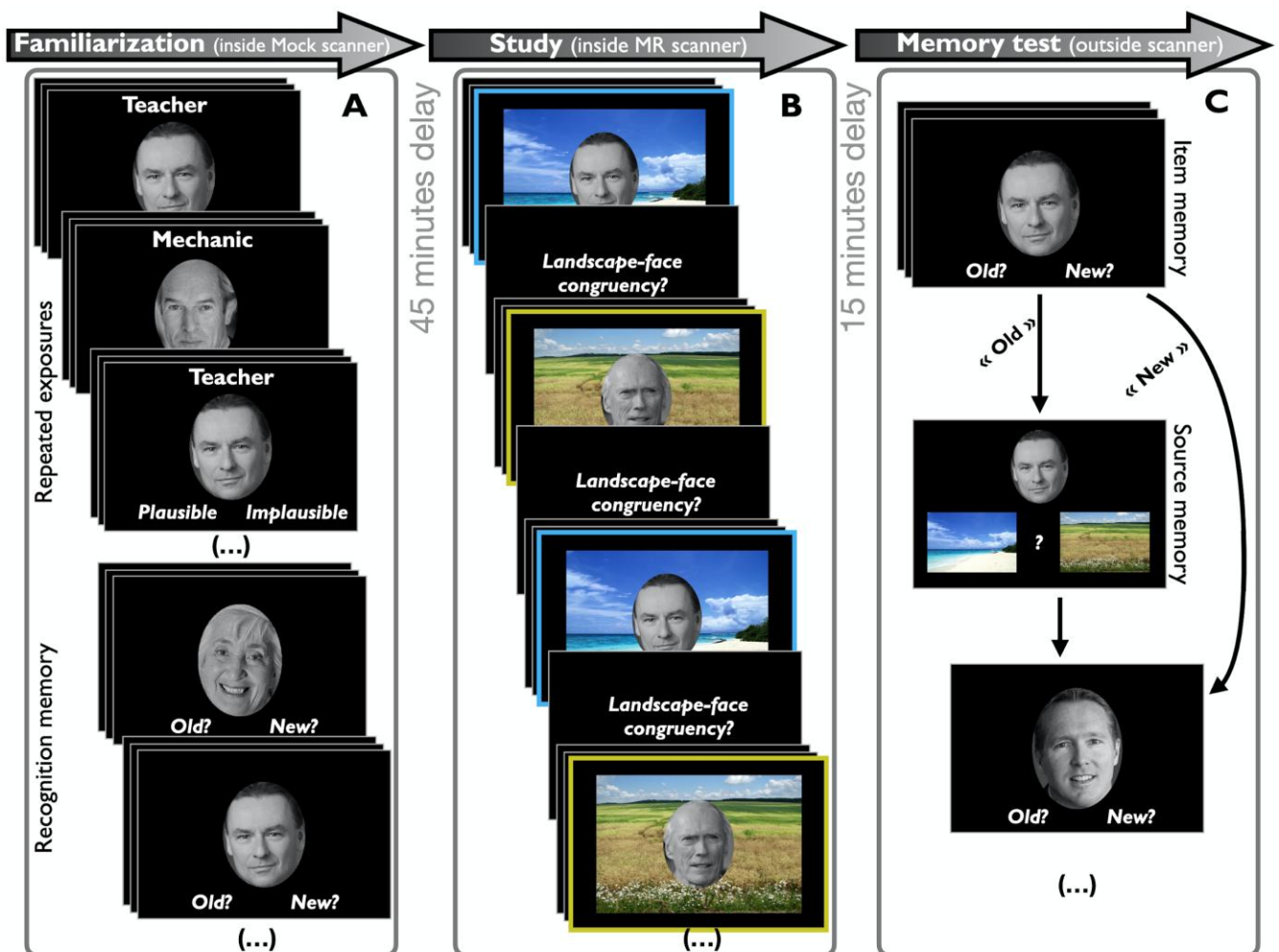
of clinical expertise in the field, after diagnosis by a senior neurologist (SB). Inclusion criteria for patients with AD-MCI were i) well founded concern about a cognitive change, ii) impaired episodic memory confirmed by neuropsychological assessment, iii) fully preserved independence in functional abilities, iv) evidence of hippocampal atrophy, v) evidence of amyloidopathy, either from cerebrospinal fluid (CSF) measures indicating lower A $\beta$ <sub>42</sub> levels or from positron-emission tomography (PET) scans indicating A $\beta$  deposition. Further inclusion criteria were i) age 60-75 years, ii) > 7 years of education; iii) native French speaker, and iv) right-handedness. Exclusion criteria were i) any history of alcoholism, drug abuse, head trauma or psychiatric condition, ii) score > 2 on 7-item modified Hachinski Ischemic Scale (Hachinski et al., 2012), iii) score above available age- and sex-adjusted cut-off on the Beck Depression Inventory (BDI-II; Beck et al., 1996) or the State-Trait Anxiety Inventory (STAI A&B; Spielberger et al., 1983), and iv) dementia (McKhann et al., 2011).

All participants underwent two testing sessions. The first one featured an extensive neuropsychological assessment (see Supplementary Materials for details) that allowed us to (1) rule out any subtle cognitive impairment among healthy controls, (2) rule out severe impairments in AD-MCI that would be incompatible with the second experimental session, and (3) avoid the inclusion of atypical AD profiles such as particular progressive focal degenerative phenotypes in our experimental group (Alladi et al., 2007). The second session included the imaging and behavioral experimental sessions.

Five patients with AD-MCI were excluded from the final sample (two presented with severely impaired cognition that prevented them from undergoing the experiments, one scored above the cut-off on the BDI-II, one voluntarily withdrew during the second session, and one experienced claustrophobia in the scanner). Six healthy controls were also excluded (two owing to technical issues during MRI acquisition, one owing to cognitive scores below the norm, one because of back pain in the scanner, one because of a score above the cut-off on the BDI-II, and one because of the discovery of a pituitary adenoma), resulting in the final inclusion of 19 healthy controls and 17 patients with AD-MCI.

## 2.2. Design & general procedure

After completing the first testing session, participants returned to the lab within 1 month for the second session. The procedure followed in the second session is illustrated in **Figure 1**. It was divided into four sequential phases: 1) familiarization with the MRI environment and with a series of unknown faces in a mock scanner; 2) study phase (i.e., learning) during actual MRI acquisition; 3) recognition memory test outside the scanner; and 4) fame judgment for all items featured in the study phase. Behavioral and imaging data are available from the authors upon request.



**Figure 1.** Experimental design. (A) During the *familiarization phase*, unknown faces were repeatedly presented inside a mock scanner. Participants were instructed to make a congruency judgment for the face-occupation association. They then completed an immediate old/new recognition test. (B) Forty-five



minutes later, **the study phase** inside the MR scanner involved the explicit encoding of face-scene associations of two types: EK trials (outlined in blue here for illustrative purposes) featured faces from the familiarization phase; PEK trials (yellow outline) featured famous faces. Photos of the response collection devices participants used to provide their responses were displayed (not shown) alongside the “Landscape-face congruency?” questions. (C) The **memory test phase** took place outside the scanner after a 15-minute delay. Participants had to make old/new judgments for individual faces. For each hit (i.e., correct “old”) response, participants performed a two-alternative forced-choice test in which they had to recall the correct source (i.e., which scene was associated with the face at study). Finally, after a 5-minute break, a **fame judgment** test (not shown) featured the whole set of famous and unknown faces.

### 2.3. Cognitive tasks

**Stimuli.** During the study phase performed in the MRI scanner, unique associations between a scene (landscape) and a face were used as stimuli (**Fig. 1**). Famous faces were used in the PEK condition, while unknown faces (rendered familiar through repeated presentations before the encoding phase) were used in the EK condition. Face images were converted to grayscale pictures and cropped to a 250 px-wide oval shape. Extensive pretesting of fame judgments in 35 healthy older individuals (aged 55-79 years, not included in the present study) resulted in the selection of one set of famous faces ( $n = 132$ ) and one set of unknown faces ( $n = 184$ ), which were matched as closely as possible for sex ratio, age, ethnicity, hair color, emotional expression, and paraphernalia. We further selected 98 colored landscape images: half represented a beach, and half the countryside. None included humans, animals, or artifacts. They were all normalized to 720 x 484 px. Two sets of famous ( $n = 48$ ) faces and two sets of unknown ( $n = 48$ ) faces were chosen at random, and each face was randomly associated with one of 24 countryside images and one of 24 beach landscapes, resulting in 96 PEK stimuli (i.e., famous face-landscape associations) and 96 EK stimuli (i.e., unknown face-landscape associations). Half were used as targets and half as distractors. An additional set of 26 unknown faces was randomly chosen for use as distractors in the recognition test during the familiarization phase (see below & **Fig. 1**). The order of

presentation, the set of pictures, and the face-scene combinations were fully randomized across participants.

***Familiarization phase (pre-scan).*** Participants were installed in a mock MRI scanner designed to familiarize them with the real MRI scanner environment, including space, noise, light level, grip used to collect responses, and computer screen viewed through a rear-facing mirror. They were shown a series of faces randomly associated with different occupations, and were instructed to make congruency judgments about these associations. Each of the 48 unknown faces was presented three times across six blocks, with face-occupation combinations remaining constant across repetitions. For each participant, we used a pseudorandom order of presentation, so that two identical stimuli were separated by at least three trials. Each stimulus was displayed for 2.5 seconds, followed by a 1.5-second response window. No memorization instruction was given. Immediately after this familiarization phase, participants performed a surprise old/new recognition memory test featuring the 48 target faces, together with 26 new unstudied, unknown distractor faces. The purpose of this testing session was to ensure that each participant had correctly encoded the 48 unknown target faces. Following the recognition test, participants remained in the mock scanner and received the instructions and some practice trials for the actual fMRI study phase.

***Study phase (inside the MRI scanner).*** Forty-five minutes after the familiarization phase, participants underwent the study task, inside the MRI scanner. The critical trials required them to explicitly learn face-scene associations. Each stimulus was displayed for 3.5 seconds, after which participants had 1.5 seconds to decide whether the background scene was congruent or not with the face. The congruency task was designed to ensure that enough attention was paid to both the face and the scene at encoding, and participants were explicitly instructed that they would be further tested for their memory of the associations. The arrow task (Stark and Squire, 2001) was adapted and used as an active baseline, and jittered white fixation crosses appeared between trials. The sequence of events was optimized via Optseq2 (Dale, 1999). Each run started and finished with a 4-second fixation cross and included 44 events: 16 EK, 16 PEK, and 12 arrow. The 48 EK and 48 PEK trials were each repeated once, so each

study event occurred twice across the six runs, but never within a run. The median lag between two identical events was 8 minutes. Lag durations between two occurrences of the same stimulus were similar for PEK and EK events (670 s for EK vs. 630 s for PEK;  $U = 5035$ ,  $p = 0.268$ ). The order in which the runs were presented was counterbalanced across participants.

**Test phase (outside the scanner).** Fifteen minutes after the study phase, participants performed a recognition memory test in a quiet room. Target faces were randomly mixed with distractors, and participants had to make old/new decisions with reference to the study phase. This provided a measure of item memory (i.e., memory for faces only). After a hit response (i.e., “old” response to a target face), the face was presented again with two scenes, one featuring a beach, the other the countryside. Participants were instructed to choose the correct source, namely the scene associated with the face at study. As both scenes were taken from the study phase, absolute familiarity alone could not trigger the correct choice. This provided a behavioral proxy for associative memory accuracy. The order of presentation was fully randomized across participants.

**Fame judgment phase.** Five minutes after the test phase, participants were shown all the faces from the test phase again and asked to make a “famous/unknown” judgment. Any PEK or EK stimulus yielding inaccurate responses at this step was removed from further analyses. This allowed us to contrast truly famous (i.e., items associated with PEK) versus truly unknown (i.e., items associated with EK solely due to the familiarization phase) on an individual basis. The participants provided accurate responses (77-100%). Importantly, the control and patient groups did not differ on fame judgment performances, with similar accuracy across all items ( $U = 132$ ,  $p = 0.357$ ), as well as specifically for PEK faces ( $U = 122$ ,  $p = 0.215$ ).

## **2.4. Behavioral data analysis**

We calculated indices of recognition memory performance (i.e., memory for faces only, hit and false alarm rates) within the signal detection theory framework. In line with Verde et al. (2006), we computed  $A_z$  to estimate sensitivity, namely, how well participants discriminated between targets and distractors, and  $B''$ , a nonparametric metric of bias (Grier, 1971). We preferred these indices to the

parametric  $d'$  and C indices of sensitivity and bias, as they are more robust to underlying assumptions about response distributions (Stanislaw and Todorov, 1999; Verde et al., 2006). The corresponding formulae were implemented using a dedicated Excel workbook (Gaetano, 2017; Signal detection theory calculator 1.2 [Excel workbook downloaded from [https://www.researchgate.net/profile/Justin\\_Gaetano2](https://www.researchgate.net/profile/Justin_Gaetano2)]).

Associative learning performance was estimated through source memory accuracy. *Source memory* refers to the ability to correctly recall the context that was associated with the target item at study. Here, we measured source memory as the conditional probability of a source hit (i.e., correct source response), given an item hit (i.e., correct “old” response to a target face), which is a classic behavioral proxy for associative memory accuracy (Cooper et al., 2017). We ran repeated-measures analyses of variance ANOVAs to explore whether type of prior knowledge (EK vs. PEK) affected sensitivity (item memory), bias, and associative memory (item + context memory), both within and between groups. Parametric statistical testing was used when the assumptions of normality and variance equality were met. Otherwise, nonparametric methods were used. Analyses were performed using JASP version 0.9 software (<https://jasp-stats.org>, JASP Team (2018)).

## **2.5. Structural and functional imaging**

### **2.5.1. Image acquisition**

Participants were scanned using a 3T Verio (Magnetom Siemens, Siemens Healthcare, Erlangen, Germany) system equipped with a 32-channel phased-array coil running VB17. High-resolution (1 mm isotropic) MPRAGE T1-weighted images were acquired (TR/TI/TE = 1900/900/2.26 ms, field of view (FOV) 256 x 256, 176 slabs, parallel imaging (GRAPPA factor 2)) for anatomical visualization and spatial normalization. BOLD functional images were collected using a T2\*-weighted single-shot spin-echo EPI sequence with the following parameters: repetition time = 2000 ms, echo time = 30 ms, 3 x 3 x 3.6 mm<sup>3</sup> voxel size, 192 x 192 mm<sup>2</sup> FOV, 64 x 64 matrix, slice thickness = 3.6 mm, 36 slices, parallel imaging (GRAPPA factor 2), echo-spacing 0.51 ms, bandwidth 2368 Hz/Px, spacing between slices =

0.6 mm. An extensive piloting of our fMRI sequence allowed us to optimize the TE/TR trade-off, notably by increasing the receiver bandwidth, while keeping a positive tilt with an Anterior-Posterior phase encoding direction as well as a reasonable 3 mm in-plane resolution. Second, we used a shim box including both MTL. Third, we finally used a classical field map correction since no obvious gain was observed during pilot acquisitions by use of reverse gradients methods. Our scan parameters were in the end in line with most of the studies in the field using a 3T scanner (e.g. see **Nau, 2019**). Fourth, a careful visual quality check was performed for each participant, looking for ghosting, banding and distortion artefacts. Similarly, an overlay of the coregistered EPI images to the T1 weighted images was systematically made to avoid outliers due to signal dropout on the most anteroventral temporal lobe areas. A total of 840 volumes, divided into six sessions (runs) of 140 volumes each, were acquired for each participant. Each session lasted 4 minutes and 40 seconds. The task was run using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). A rear-facing mirror allowed participants to see the stimuli on an LCD screen placed at the back of the scanner, and they gave their responses using a two-button response collection device (ResponseGrip; NordicNeuroLab, Bergen, Norway).

### **2.5.2. *fMRI data preprocessing***

Image preprocessing was performed using SPM12 (7219, <https://www.fil.ion.ucl.ac.uk/spm/>). For each participant, a subset of BOLD images was randomly selected for visual checking. Functional images were then corrected for slice acquisition delay and spatially realigned to the across-run mean image, to correct for motion. They were then coregistered to the T1-weighted anatomical image and normalized to the Montreal Neurological Institute (MNI) stereotactic space at a 2 x 2 x 2 mm<sup>3</sup> resolution, before being spatially smoothed using an 8 x 8 x 8 mm<sup>3</sup> full width at half maximum Gaussian kernel.

### **2.5.3. *fMRI data analysis***

For each participant, we estimated a voxelwise general linear model (GLM). The experimental design for the individual statistical analysis was modeled with 13 regressors: a 3 x 2 x 2 factorial design, plus a

regressor for the active baseline condition. The regressors of interest referred to prior knowledge status (EK, PEK), repetition (order of event presentation; i.e., first: p1; second: p2), and subsequent memory: source hit (SH), source miss (SM; i.e., item hit followed by incorrect source response), or miss (M; i.e., item miss, where an incorrect “new” response is given to a target face). Events of interest (face-scene associations) were modeled with 3.5-s boxcar functions, and a 3-s boxcar function was used to model the active baseline task, but null events (i.e., jittered fixation) were not modeled (Pernet, 2014; Stark and Squire, 2001). The regressors of interest and the active baseline were convolved with the canonical hemodynamic response function. Head motion (six parameters estimated during the realignment preprocessing step) and magnetic field drift were added as confounding factors. At the group level, contrast images from the participant-level analyses were used to perform a one-sample  $t$  test and evaluate the contrasts of interest group-wise. Two-sample  $t$  tests were also performed to probe differences between groups. An individual voxel threshold of  $p < 0.005$  uncorrected was used with a cluster extent threshold of 57 contiguous voxels to correct for multiple comparisons (familywise error rate, FWE) at  $p < 0.05$  at the cluster level. This cluster size extent was computed using Monte Carlo simulations ( $N = 10\,000$  iterations) (Slotnick, 2017; Slotnick et al., 2003). For a recent example of a similar thresholding approach, see Thakral et al. (2017).

This factorial design setup allowed us to estimate four main contrasts to perform our analyses of interest detailed below. The *encoding* contrast corresponded to all our regressors of interest minus the active baseline, thus reflecting the fMRI response associated with the visual encoding of face-scene associations, according to task instructions, independently of prior knowledge type and subsequent memory status. The *repetition* contrast corresponded to the subtraction of all our regressors of interest at p2 from all our regressors of interest at p1, thus reflecting the modulation of the blood-oxygen-level-dependent (BOLD) fMRI response as a result of stimulus repetition (Grill-Spector et al., 2006). The *prior knowledge* contrast corresponded to the subtraction of EK events of interest from PEK events of interest. Finally, we estimated the Prior Knowledge x Repetition interaction contrast: {PEKp1 – PEKp2

– EKp1 + EKp2}, where PEK and EK each included SH, SM and M regressors. Our analysis workflow thereafter involved the following three steps.

**First**, we investigated whether repetition effects allowed us to identify the brain networks involved in explicit encoding of our stimuli. The repetition of stimuli is known to result in either a decrease (repetition suppression) or an increase (repetition enhancement) in the BOLD signal, in brain areas consistent with the ongoing processing—an observation also referred to as *neural adaptation* (Grill-Spector et al., 2006). Neural adaptation has been successfully used to map functional brain networks, notably memory encoding (Rand-Giovannetti et al., 2006; Reggev et al., 2016), and more especially face encoding (Henson, 2016; Henson et al., 2002). We therefore performed a conjunction analysis between the encoding and repetition contrasts, to further confirm that our repetition design would highlight common activations within the bilateral visual ventral pathways. **Second**, as we expected repetition effects to highlight a visual associative encoding network, we computed the Prior Knowledge x Repetition interaction contrast to test the hypothesis that prior knowledge modulates brain activity specifically related to face-scene associative encoding. Clusters identified through this contrast were further explored with repeated-measures ANOVAs on the extracted beta weights. **Third**, beta weights corresponding to the memory regressors were extracted from the above-defined clusters to further look for subsequent associative memory effects. To this end, repeated-measures ANOVAs were computed with the following four regressors of interest: EK.SHp1, EK.SMp1, PEK.SHp1, and PEK.SMp1. Here, we focused on whether SH and SM differed for EK and PEK. Importantly, only beta weights associated with the first occurrence of the above-mentioned regressors were considered for the subsequent memory analysis, thus avoiding confusion between memory and repetition effects, and keeping the interaction and subsequent memory analyses orthogonal (see Reggev et al., 2016, for a similar approach coupling repetition and subsequent memory effects).

### 3. Results

#### 3.1. Behavioral results

##### 3.1.1. Neuropsychological and AD biomarker findings

Patients with AD-MCI and healthy controls were matched for age, sex, education, and premorbid verbal IQ, but the patients' mean Mini-Mental State Examination (MMSE) score was, as expected, significantly lower (**Table 1**). Participants' neuropsychological and psychological characteristics are provided in **Supplementary Material 1 (Table S.1.)**. Patients with AD-MCI essentially exhibited impairments on recall and recognition memory tests, compared with healthy controls. Measurements of hippocampal volumes in both groups confirmed atrophy in the patient group (Manjón and Coupé, 2016). Biomarker investigations confirmed amyloidopathy in patients ( $A\beta_{42}$  dosage in CSF,  $n = 7$ , or abnormal amyloid retention using 18F-AV-45-PET,  $n = 7$ ; data not available for three patients) (**Table 1**). Our AD-MCI group therefore fulfilled the diagnostic criteria for AD as the cause of their cognitive impairments (Albert et al., 2011).

	Healthy controls	AD-MCI	<i>p</i> values
N	19	17	-
Mean age in years (SD) [range]	68.3 (4.4) [61-75]	69.7 (4.1) [63-76]	0.435
Female:Male ratio	9:10	8:9	0.985
Mean education in years (SD) [range]	12.8 (3.3) [8-19]	11.1 (3.1) [8-18]	0.129
Mean premorbid VIQ (SD) [range]	110 (7.8) [91-119]	105 (8.7) [91-123]	0.083
Mean MMSE (SD) [range]	28.5 (1.3) [26-30]	25.5 (2.0) [23-29]	<0.001
Mean hippocampal volumes, normalized % of TIV (SD) [range]			
Right	0.28 (0.03) [0.20-0.33]	0.24 (0.03) [0.17-0.30]	<0.001
Left	0.27 (0.02) [0.23-0.32]	0.23 (0.03) [0.17-0.28]	<0.001
Total	0.55 (0.04) [0.47-0.65]	0.46 (0.06) [0.34-0.58]	<0.001
Biomarkers of amyloidopathy			
Mean CSF- $A\beta_{42}$ (SD) [range], cut-off = 700 (n = 7)	-	569.3 (128.4) [426-735]	-
Florbetapir-AV45 (n = 7)	-	All positive	-

**Table 1.** Participants' demographic, clinical and AD biomarker characteristics. Note. VIQ: verbal intelligence quotient; MMSE: Mini-Mental State Examination; TIV: total intracranial volume; CSF: cerebrospinal fluid.

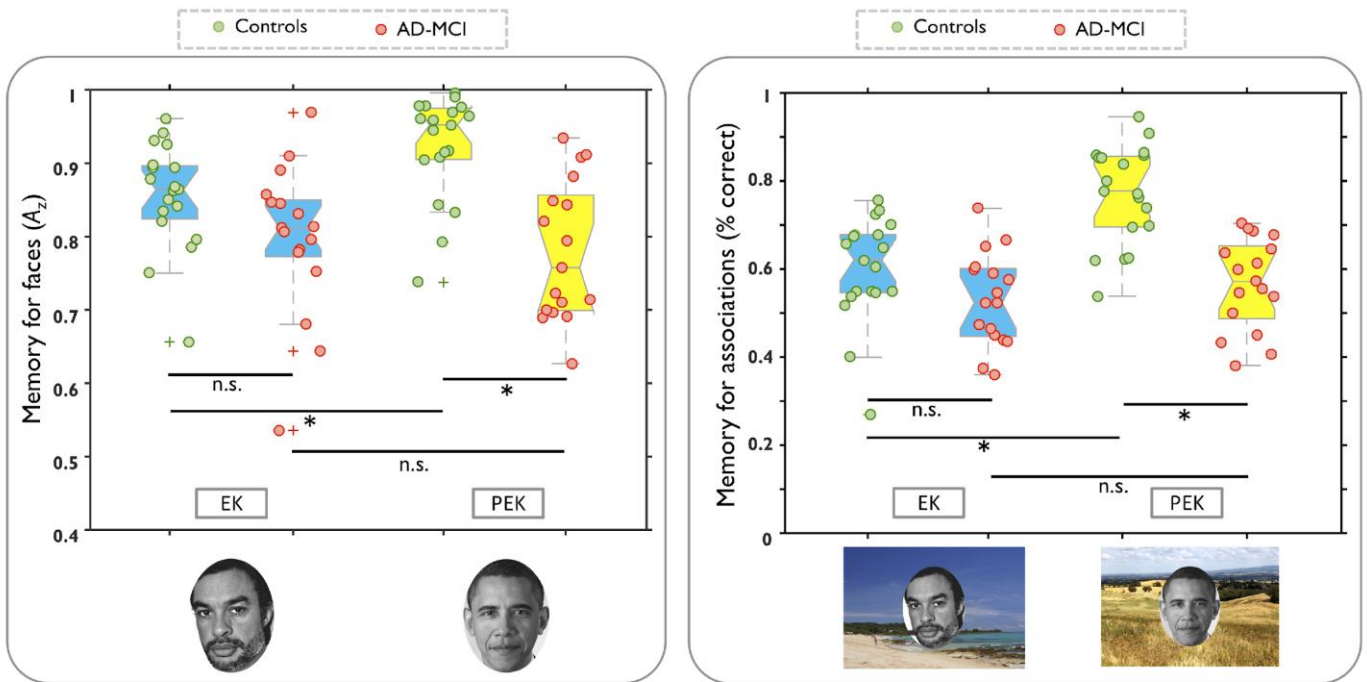


### 3.1.2. *Familiarization and study phases*

Importantly, healthy controls and patients with AD-MCI did not differ on either sensitivity ( $A_z$ ) or omissions (i.e., % misses) at immediate recognition in the familiarization phase ( $A_z$ :  $t = 1.478$ ,  $p = 0.149$ ; % misses:  $t = -0.628$ ,  $p = 0.534$ ). Similarly, the groups did not differ on congruency judgments for either face-occupation combinations in the familiarization phase or face-scene associations in the study phase (familiarization: % “plausible” responses:  $t = 0.836$ ,  $p = 0.409$ ; Study: % “congruent” responses:  $t = 0.176$ ,  $p = 0.862$ ). As expected, faster reaction times were observed with repetition within each group during the study phase in the scanner, despite patients with AD-MCI being slower overall. Importantly, type of prior knowledge modulated response latencies in healthy controls, which were shorter for PEK than for EK, whereas this interaction remained nonsignificant in patients with AD-MCI (see **Supplementary Materials 2** for detailed results and statistics).

### 3.1.3. *Test phase*

Compared with EK stimuli, PEK stimuli led to higher item sensitivity,  $F(1, 18) = 9.017$ ,  $p = 0.008$ ,  $\eta^2 = 0.334$ , and source memory,  $F(1, 18) = 47.071$ ,  $p < 0.001$ ,  $\eta^2 = 0.723$  in healthy controls, but not in patients with AD-MCI (item sensitivity,  $F(1, 16) = 0.644$ ,  $p = 0.434$ ,  $\eta^2 = 0.039$ ; source memory,  $F(1, 16) = 0.446$ ,  $p = 0.514$ ,  $\eta^2 = 0.027$ ), resulting in significant Group x Prior Knowledge interactions (sensitivity,  $F(1, 34) = 5.771$ ,  $p = 0.022$ ,  $\eta^2 = 0.141$ ; source memory,  $F(1, 34) = 13.05$ ,  $p < 0.001$ ,  $\eta^2 = 0.189$ ) (**Fig. 2**). Post hoc analyses using the Holm criterion showed that patients with AD-MCI did not differ from controls on EK stimuli for either sensitivity,  $t = -2.011$ ,  $p = 0.098$ , or source memory,  $t = -1.466$ ,  $p = 0.444$ , but they performed more poorly than controls for PEK stimuli (item sensitivity:  $t = -4.582$ ,  $p < 0.001$ ; source memory:  $t = -5.411$ ,  $p < 0.001$ ) (see **Supplementary Materials 2** for detailed results of the test phase).



**Figure 2.** Performance of healthy controls and patients with AD-MCI in the test phase. Left panel: memory for faces; right panel: memory for face-scene associations. Individual performances (dots) are overlaid on notched boxplots where the notches depict the 95% CI around the median. EK: experimentally familiar stimuli (i.e., unknown but familiarized faces); PEK: pre-experimental familiar stimuli (i.e., famous faces). \*  $p < .05$ .

### 3.2. Imaging results

#### 3.2.1. Repetition and encoding contrasts

A conjunction analysis between repetition and encoding contrasts yielded activations within occipital and occipito-temporal regions, along the visual ventral pathways (illustration in **Supplementary Material 3**) in both groups. Neural adaptation effects thus allowed accurate identification of the functional networks involved in our visual encoding task.

### 3.2.2. *Prior Knowledge x Repetition interaction*

Results of simple contrasts (main effects of prior knowledge, i.e., PEK vs. EK stimulus encoding, and repetition, i.e., neural adaptation for PEK and EK stimulus repetition) are provided in **Supplementary Material 4**, and significant clusters are listed in Table 2.

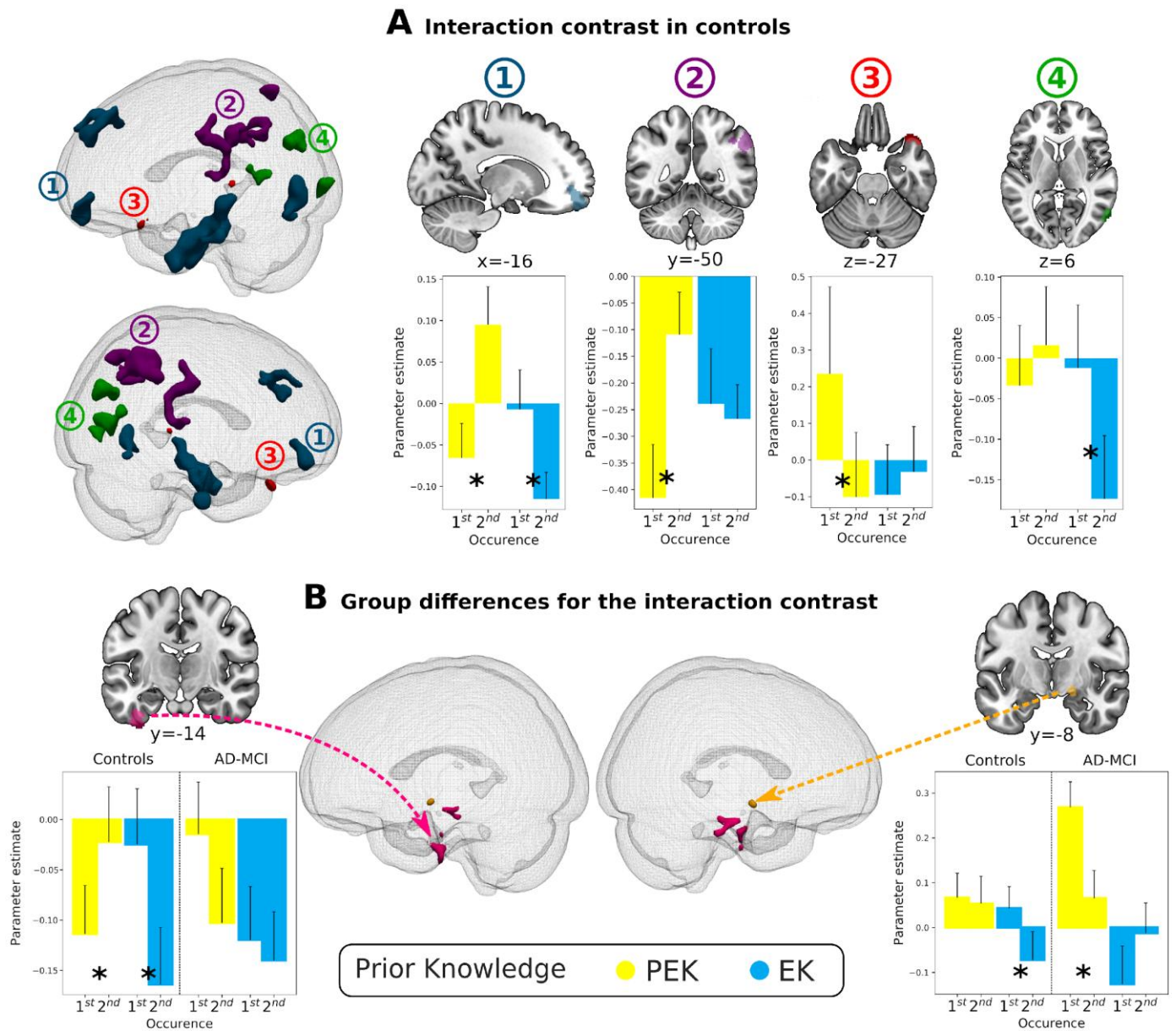
<b>x</b>	<b>y</b>	<b>z</b>	<b>k</b>	<b>T</b>	<b>AAL Label</b>
52	-16	-28	1951	-5.7028	Temporal_Inf_R
14	56	-10	1580	-5.3583	Frontal_Med_Orb_R
-62	-30	-8	1156	-6.4604	Temporal_Mid_L
56	-50	42	604	-5.223	Parietal_Inf_R
0	-30	30	470	-5.4385	Cingulum_Mid_R
-46	40	38	401	-4.9717	Frontal_Mid_L
4	20	26	332	-5.7859	Cingulum_Ant_R
-56	-70	2	274	-5.5446	Occipital_Inf_L
44	18	16	243	-4.2852	Frontal_Inf_Oper_R
40	-6	-8	235	-4.8518	Insula_R
-16	56	-10	234	-4.5027	Frontal_Sup_Orb_L
-16	-74	28	222	-3.6714	Occipital_Sup_L
60	-66	6	134	-4.3637	brodmann area 37
-32	-50	36	118	-4.6134	Angular_L
58	-52	-12	113	-4.0304	Temporal_Inf_R
-12	2	48	112	-4.1928	Supp_Motor_Area_L
-38	-92	2	110	-3.9928	Occipital_Mid_L
12	-52	36	110	-3.8792	Precuneus_R
-52	-24	6	103	-3.884	Temporal_Sup_L
-42	-56	54	95	-3.9865	Parietal_Inf_L
-42	4	36	94	-4.0164	Precentral_L
-56	12	30	85	-4.2438	Precentral_L
10	-14	-4	72	-4.1593	Thalamus_R
-2	42	22	69	-3.8335	Frontal_Sup_Medial_L
4	-2	76	65	-4.2383	Supp_Motor_Area_R
-58	-24	36	60	-3.7917	SupraMarginal_L
-22	14	72	60	-3.91	Frontal_Sup_L
-36	58	12	57	-3.9134	Frontal_Mid_L

**Table 2.** List of suprathreshold clusters for the Prior Knowledge x Repetition interaction contrast in healthy controls. This contrast failed to reveal any significant contrast in AD-MCI patients. MNI ( $x, y, z, mm$ ) peak coordinates are displayed together with clusters extent ( $k$ ) and peak intensities ( $T$ ).

In healthy controls, the Prior Knowledge x Repetition interaction contrast revealed activation within three sets of regions (**Fig. 3A**): bilateral inferior temporal lobes and occipito-temporal cortices, including medial temporal lobe structures, bilateral medial and lateral parietal structures, and left ventromedial and dorsolateral PFCs. Multiple repeated-measures ANOVAs with Repetition and Prior Knowledge as dependent variables revealed four distinct patterns of activation. 1) PEK gave rise to repetition enhancement, and EK to repetition suppression, in a number of clusters in bilateral occipito-temporal regions, extending to the perirhinal cortex in the right hemisphere, as well as in the ventral and dorsal PFCs (**Fig. 3A 1**). 2) Parietal clusters showed repetition enhancement for PEK only (**Fig. 3A 2**), 3) while bilateral occipital regions showed suppression effects for EK only (**Fig. 3A 4**). 4) Lastly, although PEK was generally associated with repetition enhancement, it was associated with repetition suppression in two small clusters in the posterior and anterior temporal lobes (**Fig. 3A 3**). Our results therefore support the proposition that in healthy controls, distinct types of prior knowledge generate opposite neural adaptation in clusters common to PEK and EK, while partly nonoverlapping networks subtend PEK- and EK-based associative encoding.

In sharp contrast to these results for healthy controls, the same analyses in patients with AD-MCI failed to yield any significant cluster. One possible confound here lies in the fact that some unknown faces were not accurately endorsed as ‘Old’ during the short recognition test that followed the familiarization phase (see section 3.1.2.). As a result, one cannot ensure that these faces truly benefited from the extensive familiarization prior to the study phase. We therefore replicated the above analyses after excluding, on an individual basis, every target unknown face that was familiarized but incorrectly endorsed as ‘New’. This was done by adding a novel regressor in the GLM where the corresponding onsets were given a null weight. As shown in Supplementary material 2, the Prior Knowledge x

Repetition interaction contrast computed with this novel modeling resulted in the same pattern of clusters in Controls. Likewise, it did not yield any significant cluster in patients.



**Figure 3.** *fMRI Prior Knowledge x Repetition interaction contrast. (A) Distinct patterns of fMRI responses in healthy controls. For each pattern, a plot illustrates the typical neural adaptation effects found within each cluster (coordinates above each plot). For example, the first plot shows that within the left ventromedial prefrontal cortex, PEK and EK stimuli had opposite neural adaptation effects, resulting in a significant interaction that was similar within all the clusters of the same blue color displayed in the 3D views on the left. See text for a description of the four different patterns. (B) Clusters where significant differences were found between healthy controls and patients with AD-MCI*

*on the interaction contrast. The clusters in pink show significant neural adaptation effects observed in healthy controls but not in patients with AD-MCI. A cluster in the right hippocampus (in orange) shows neural suppression for EK in healthy controls, but for PEK in patients with AD-MCI. \*  $p < 0.05$ , error bars depict standard error of the mean.*

Two-sample  $t$  tests yielded differences between the groups for this interaction contrast within two main clusters located in the bilateral inferior temporal lobes (**Fig. 3B**). Two smaller clusters within the right medial temporal lobe failed to reach our clustering threshold, but proved significant after small volume correction for medial temporal lobe structures (as defined with the AAL template; Tzourio-Mazoyer, 2002;  $p < .05$  FWE-corrected): right hippocampus ( $k = 22$ ; main peak:  $x = 18, y = -8, z = -12$ ) and right lateral perirhinal cortex ( $k = 21$ ; main peak:  $x = 34, y = -16, z = -36$ ). We further aimed at taking into account structural differences (i.e. voxel-wise difference in grey matter density) across groups. Indeed, AD-MCI participants present with decreased grey matter density, in particular but not limited to the medial temporal lobes (see Table 1 and section 2.1.). Yet, anatomical between-group differences can lead to differences in partial volumes effects, in turn affecting the voxel-wise BOLD signal (e.g. increasing the potential contribution of CSF in a given region/voxel displaying grey matter loss, see Rombouts et al., 2007), finally resulting in potential type I error when probing group differences (Dukart & Bertolino, 2014). We therefore re-ran our two-sample  $t$  test meanwhile accounting for grey matter density differences, within a voxel-wise computational framework recently developed for that purpose (VoxelStats, Mathotaarachchi et al., 2016). The resulting t-map confirmed the four clusters described above independently of any local atrophy (detailed results of this analysis are available as **Supplementary Materials 5**). To investigate these group differences, we ran mixed ANOVAs on the mean beta weights extracted from the group difference clusters, with group as a between-participants factor, and prior knowledge and repetition as within-participants factors. These analyses revealed the absence of repetition effects in the AD-MCI group, with the exception of the right hippocampus, where PEK stimuli gave rise to repetition suppression. In healthy controls, EK stimuli triggered repetition suppression in the right hippocampus, right lateral perirhinal cortex, and bilateral

fusiform gyri. By contrast, the last two regions showed repetition enhancement effects for PEK stimuli. Although these results informed us about brain activity related to visual associative encoding of face-scene pairs depending on the kind of prior knowledge, they collapsed across subsequent memory status (i.e. independently of whether accurate source memory could be recalled at test). As such, they did not shed any light on the neural substrates of *successful* associative encoding, namely associative encoding giving rise to successful source memory at test, which we report in the following section. The rationale of the following analyses therefore lies in the question of whether these regions where associative encoding-related activity is modulated by prior knowledge also display subsequent associative memory effects.

### 3.2.3. *Associative memory effects*

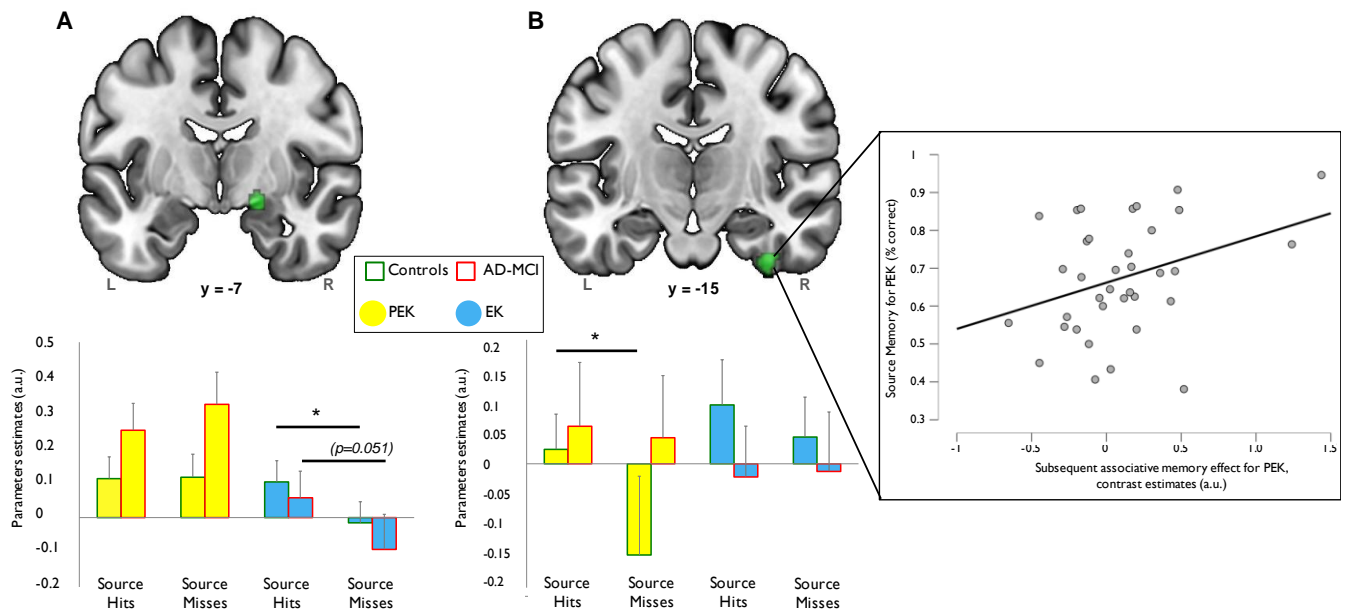
Here, we ran exploratory, post-hoc analyses to investigate whether the above findings held for successful associative encoding (i.e., correct retrieval of face-scene associations). We extracted the beta weights associated with the memory events in the study phase within the data-driven regions of interest (ROIs) highlighted in the previous section (source hits reflecting accurate associative memory, source misses reflecting correct “old” response but inaccurate associative memory, and misses reflecting face forgetfulness; see Materials and Methods section). We then looked for subsequent associative memory effects (i.e., significant differences between source hits and source misses) across a series of paired-samples t-tests. First, we did so within clusters identified in healthy controls. Second, we applied the same approach within clusters in which significant group differences were observed for the interaction contrast (see previous section). These analyses were intended to answer two questions: 1) Did the network involved in associative encoding of PEK versus EK stimuli also play a role in successful associative memory formation in healthy controls? And 2) Did the regions exhibiting between-group differences for the Prior Knowledge x Repetition interaction contrast also display differential subsequent associative memory effects between groups?

In healthy controls, we found subsequent associative memory effects for both PEK and EK stimuli within the left middle occipital and occipito-temporal areas, as well as within the left ventromedial

PFC. A series of regions also showed selective associative memory effects for PEK or EK stimuli (see **Supplementary material 6** for details). Activity in the left dorsolateral PFC and right medial temporal lobe, including the perirhinal cortex, was higher for PEK source hits than for PEK source misses, but there was no such source memory difference for EK stimuli. Conversely, the bilateral precuneus, left fusiform gyrus, left posterior hippocampus, and a right-sided area including the posterior angular gyrus were more activated for EK source hits than for EK source misses. These analyses were not performed for patients with AD-MCI, as none of the clusters reached significance for the Prior Knowledge x Repetition interaction contrast (see previous section).

Finally, subsequent associative memory effects were also found in the regions that responded to the interaction contrast differently in healthy controls and patients with AD-MCI. Healthy controls and patients with AD-MCI showed similar associative memory effects for EK stimuli in the right hippocampus (albeit only reaching  $p = 0.051$  in the patient group; **Fig. 4A**). However, the right perirhinal cortex and fusiform gyrus showed a higher fMRI response for source hits than for source misses (**Fig. 4B**) for PEK stimuli in healthy controls. No such memory effect was observed in patients with AD-MCI. Moreover, we found that the associative memory contrast estimates (i.e., beta weight difference between source hits and source misses) in this region correlated positively with the behavioral source accuracy measure for PEK stimuli across all participants ( $r = 0.344$ ,  $p = 0.02$ ) (see **Fig. 4**).





**Figure 4.** Regions associated with correct face-scene associative memory effects within data-driven ROIs derived from group differences for the *Prior Knowledge x Repetition* interaction contrast. (A) The right hippocampus showed a similar difference between source hits and source misses for both groups, but for EK only. (B) By contrast, the right perirhinal region only showed a difference for PEK in healthy controls. \*  $p < 0.05$ , error bars depict standard error of the mean. The right hand correlation plot shows the association between source memory accuracy for PEK and subsequent associative memory contrast estimates for PEK.

## 4. Discussion

Prior knowledge is recognized as a memory enhancer in healthy individuals, but surprisingly little is known about it in AD. In the present study, patients with AD-MCI and matched healthy controls learned new face-scene associations. At study, faces were associated with two kinds of prior knowledge. Famous faces (i.e., PEK items) carried prior knowledge resulting from long-lasting multiple exposures, while unknown faces (i.e., EK items) carried prior knowledge acquired via repeated presentations immediately prior to study. Memory for faces and for face-scene associations improved for PEK versus EK stimuli in healthy controls, thus showing the expected effect of prior knowledge. In

sharp contrast, patients with AD-MCI did not appear to benefit from pre-experimental prior knowledge.

In healthy controls, the interaction between repetition and prior knowledge effects on the fMRI response revealed large encoding networks recruited for EK and PEK that only partly overlapped. In sharp contrast again, this interaction was absent in patients with AD-MCI. Finally, patients displayed impaired activation in a right subhippocampal region where activity was positively associated to successful associative memory formation for PEK stimuli.

#### **4.1. Explanations for the benefits of prior knowledge**

The memory advantage for PEK stimuli fits in with the levels-of-processing (LOP) framework ( Craik and Lockhart, 1972), in that deeper processing at encoding (i.e., semantic processing of famous faces) enhances long-term memory formation more than shallower encoding does (i.e., resulting from weaker or absent prior knowledge for an unknown face). In healthy controls, the observation of a larger repetition priming effect on response times for PEK versus EK stimuli at study is consistent with this interpretation.

However, while the LOP explains the PEK advantage for item memory, it does not in itself account for the finding of increased accuracy for source memory in healthy controls. Two main accounts have been put forward to explain this *familiarity bonus* for source memory (Poppenk et al., 2010a, 2010b; Poppenk and Norman, 2012). Prior knowledge may reduce the attentional resources required at encoding to build a new association (Castel and Craik, 2003; Naveh-Benjamin and Craik, 1998). However, given that participants were familiar with both PEK and EK stimuli at study, this account seems unlikely. Alternatively, an extension of the LOP suggests that famous faces generate more elaborative processing at encoding, enriching event representations (Bein et al., 2015). In turn, enriched representations become more distinctive and therefore less prone to interference at retrieval. This elaborative processing may take the form of unitization, with unitization strategies at encoding alleviating the associative learning deficit in aging (Bastin et al., 2013; Delhaye and Bastin, 2016). This

is consistent with our finding of substantial associative memory enhancement in our older controls for PEK versus EK stimuli.

#### **4.2. The perirhinal cortex is involved in successful pre-experimental knowledge learning**

The perirhinal cortex may support some forms of declarative learning, with minimal involvement of the hippocampus, as long as pre-existing representations are available and congruent with the memoranda (e.g., Fernández and Morris, 2018; Kan et al., 2009; Van Kesteren et al., 2012). In healthy controls, we found subsequent associative memory effects for PEK (but not EK) stimuli in the right perirhinal area, along with other regions consistently associated with semantic retrieval (e.g., left middle frontal gyrus; Barbeau et al., 2012; Joubert et al., 2010, 2008; Kapur et al., 1994; Martin, 2007; Pineault et al., 2018). Associative memory for PEK, but not EK, stimuli was also positively related to the fMRI response in the right perirhinal cortex across the two groups.

This finding could explain the pattern of performance we observed in both healthy controls and patients with AD-MCI. The role of the perirhinal cortex in the computational requirements of unitization has already been robustly highlighted in healthy individuals (Diana et al., 2010; Haskins et al., 2008). Semantic retrieval in healthy controls when PEK is involved at study may promote unitization strategies, supported by perirhinal cortex processing, thereby facilitating the successful formation of new face-scene associations. By contrast, this mechanism may be impaired in patients with AD-MCI. Consistent with reports of early person knowledge impairment in the course of AD (e.g., Barbeau et al., 2012; Brambati et al., 2012; Joubert et al., 2010, 2008), activation of pre-experimental semantic knowledge during learning was presumably impaired in our sample of patients with early AD, as suggested by our findings of similar repetition priming effects for PEK and EK stimuli in our patient sample during the study phase, but different effects in healthy controls. Knowledge about unique entities like faces has been shown to be impaired at an early stage in AD, owing to tau pathology in subhippocampal structures (entorhinal and perirhinal cortices; Braak and Braak, 1995), thus disrupting semantic retrieval (Didic et al., 2011). This interpretation is also consistent with the finding that

unitization does not alleviate the associative memory deficit in patients with early AD (D'Angelo et al., 2016), on account of perirhinal cortex atrophy (Delhaye et al., 2018, 2019).

### **4.3. Knowledge available at encoding involves different brain networks**

More broadly, the interaction between the fMRI responses to neural adaptation and prior knowledge suggests that encoding networks are sensitive to the nature of pre-existing representations associated with the memoranda. Some brain areas displayed opposite repetition effects, depending on the type of prior knowledge involved. This extends prior evidence that neural adaptation is not an automatic brain response to stimulus repetition (Henson et al., 2002), but instead is associated with either reduced involvement of encoding mechanisms (i.e., repetition suppression), or explicit and/or implicit successful retrieval (i.e., repetition enhancement; Kim, 2017).

The regions identified in our study as being involved in either type of prior knowledge are consistent with other subsequent memory and/or retrieval studies (ventral and dorsal PFCs, bilateral occipito-temporal regions, up to the perirhinal cortex; Kim, 2013, 2011; Maillet and Rajah, 2014; Spaniol et al., 2009). We suggest that in the presence of pre-existing semantic knowledge, enhanced activity is observed in regions involved in memory retrieval, schema detection, and visual encoding. However, when recent, episodic-like, pre-existing representations are available, repetition suppression is observed in a visual encoding network, including regions involved in the detection of prior occurrence, across successive learning trials. For example, we found repetition suppression for EK stimuli along the visual ventral stream, reflecting the reduced engagement of a visual encoding network in the absence of pre-existing semantic knowledge. By contrast, repetition enhancement for PEK stimuli in the same regions may have reflected successful retrieval of pre-existing semantic knowledge, along with the involvement of congruency detection processes, as reflected by the involvement of the ventromedial PFC. This region plays a critical role in the detection of congruency between the processing of incoming perceptual information and pre-existing knowledge, or *schemas* (Bein et al., 2014; Van Kesteren et al., 2012). The observation of repetition enhancement for PEK stimuli within the right angular gyrus, with no repetition effect for EK stimuli, also lends support to this interpretation, as this area forms a hub for

the representation of prior knowledge (Gilboa and Marlatte, 2017; Wagner et al., 2015). Taken together, our findings therefore underline the dynamic nature of new associative encoding in older individuals, which seems to entail distinct mechanisms, but partly nonoverlapping neural networks, depending on the type of prior knowledge involved.

Importantly, this pattern of interactions between prior knowledge and neural adaptation was severely impaired in AD-MCI, and we found essentially absent or aberrant neural adaptation in this group, consistent with prior reports (Pihlajamäki et al., 2011, 2008). Thus, the reduced benefit of PEK in patients with AD-MCI may arise from dysfunctions in both networks and more focal areas (i.e., perirhinal region), that might concur to their poor memory.

#### **4.4. The learning impairment in early AD is probably underestimated**

We provide strong evidence that in healthy aging, knowledge about a face accumulated throughout the lifetime massively enhances associative learning beyond what could be expected owing to multiple exposures (Badham et al., 2015, 2012; Bastin et al., 2013; Umanath and March, 2014). By contrast, our sample of patients with AD-MCI completely failed to take advantage of such prior knowledge. If replicated, this could open up highly promising avenues for better characterizing early memory impairments in AD versus healthy aging, asking whether PEK associative memory is impaired for other types of stimuli and memoranda.

From a practical point of view, these results suggest that memory deficits in patients with early AD are underestimated. When they were repeatedly presented with unfamiliar stimuli in the EK condition, our sample of patients with AD-MCI performed fairly well. This situation closely matches the typical multiple-trial learning tasks used in clinical and research settings, where lists of rather unfamiliar items (e.g., isolated words or pictures) are repeatedly presented across learning trials. However, the inability of our patients to take advantage of pre-experimental knowledge suggests that their ability to do so in everyday routines, where most of the stimuli and events are highly familiar (e.g., neighbors, friends, family members encountered in familiar environments such as shops, streets, etc.), is probably

impaired. In other words, whereas remote prior knowledge increases the likelihood of encoding in healthy aging, it is of no additional value in patients with early AD. Despite this, memory assessments in clinical or research settings usually either do not take prior knowledge into account, or else involve familiarization with initially unfamiliar stimuli. Actual memory impairments in patients with early AD may well, therefore, be underestimated.

#### **4.5. Strengths and limitations**

This study has several limitations. First, our samples of patients and controls are small, so that our findings certainly need replication before one can fully confirm, or reject, our interpretations (e.g. Bossier et al., 2020; Turner et al., 2018). Nonetheless, reaching ad hoc sample sizes (probably over 100 participants, see Turner et al., 2018) in studies involving patients with neurodegenerative conditions such as AD, is highly challenging and probably even more challenging when considering the need to provide biomarkers-based evidence for AD pathology at the MCI stage. The median sample size for MCI patients and matched controls across most of the previous task-based fMRI studies is 15, ranging from 6 to 42 (for a meta-analysis, see Li et al., 2015), most of which did not report either on biomarkers of AD pathology (i.e. amyloidopathy), or on the detailed neuropsychological assessment required to best characterize both patients and controls, as we did here. We thus believe that one strength of the present study is that our samples are well defined. This included biomarkers of AD for patients. It also included MRI and an extensive neuropsychological assessment for both groups, ensuring that our patients sample was rather homogeneous, but also that the healthy participants were free of any cognitive impairment or medial temporal lobe atrophy. Noteworthy, despite the limited sample sizes, our main finding of a significant interaction between Repetition and Prior Knowledge within a large cortical network in Controls could be replicated even after the exclusion of a substantial amount of the EK trials. Second, the study of group differences in brain activation using fMRI, especially when comparing healthy participants to patients with known different structural and functional brain features due to disease also comes with important limitations. Among those, differences in brain morphology between groups can result in baseline differences in fMRI responses (e.g., Rombouts 2007; Dukart &

Bertolino, 2014), which is an important issue barely addressed across prior fMRI studies involving AD patients. Here, we adopted a more radical approach than prior attempts (e.g., Hanseeuw et al., 2011, Gaubert et al., 2017) by using a recently developed voxel-wise computational framework allowing to account for voxel-wise grey matter differences between groups (Mathotaarachchi et al., 2016). Certainly though, future research is warranted to better take into account these and other issues, like the normalization challenges related to the use of custom atlases (Lancaster et al., 2007).

Another potential limitation relates to our study design. Because participants were familiarized across three presentations with the “EK” faces prior to the study phase, these faces differ from the “PEK” faces in terms of the number of *recent* exposures. It could be argued that this difference is responsible for a relative preservation of memory for EK vs. PEK stimuli in our patient sample. While we consider this possibility as very likely, we believe that it is very unlikely to change our main findings, for several reasons. First, while it is impossible to control for the number of recent exposures to PEK faces, it seems reasonable to consider that it was quite similar across groups, so that an effect of the number of pre-experimental exposures to PEK faces is unlikely to explain the memory impairments reported in patients for these stimuli. Second, the difference in the number of pre-experimental exposures between EK and PEK *faces* would hardly account for the better memory for PEK *face-scene associations*. Third, if a higher number of pre-experimental exposures to EK faces improved memory in patients for these faces, it most likely had the same effect in controls. Yet, we reported a clear-cut item- and associative memory superiority for PEK stimuli in controls, while patients did not display any reliable difference for PEK vs. EK stimuli. Therefore, if our findings actually reflected an overall expected decline in memory in early AD, one would also expect at least some advantage of EK over PEK stimuli in this group, due to higher pre-experimental exposure, which we did not find. Finally, two limitations must be discussed with respect to our imaging findings. First, our goal was to assess whether prior knowledge effects during an explicit associative encoding paradigm did hold in healthy older adults and patients with early AD, and relied on overlapping or distinct brain networks. Therefore, the subsequent associative memory analyses were made post-hoc, as exploratory analyses, and must be taken with

caution. Further research is warranted with studies using appropriate subsequent memory paradigms directly assessing whether subsequent memory effects differ depending on the nature of prior knowledge and are impaired in early AD.

Finally, on a related note, we also would like to argue for one important strength of our study considering the main question of interest, namely investigating the role of pre-experimental knowledge specifically. Contrasting memory for e.g. famous faces (as a model of pre-experimental knowledge) with memory for unknown faces could have been a tempting alternative. Yet, in doing so, we would have introduced two strong biases, one related to recognition and the other one to encoding processes. Regarding recognition, this would have led to different discrimination demands during recognition (e.g. see Poppenk et al., 2010): unknown targets at test could have been endorsed as ‘Old’ on the basis of familiarity alone, and similarly lures could have been rejected on the same basis. However, for famous targets to be endorsed as ‘Old’, it requires further source monitoring processes not required for unknown stimuli (i.e. “I feel familiar with this face, but does it pertain to the study phase?”), and similarly for famous lures to be correctly rejected. This would therefore bring confusion as to whether any prior knowledge effect arises from stimuli-related properties or to differential memory demands. Regarding the issue related to encoding, contrasting entirely novel faces to famous faces would have resulted in an absence of any perceptual fluency for novel stimuli at study (i.e. entirely novel face-scene associations would not have generated any familiarity signal, Whittlesea & Williams, 2001). In contrast, it would have been the case for PEK stimuli since they included a famous face. We therefore chose to contrast pre-experimental and experimental knowledge for faces within our face-scene encoding trials (for a similar approach, see Poppenk et al., 2010a, 2010b). This approach does not imply that, at first presentation during study, recognition of famous faces and recognition of familiarized faces are supported by common processes. There are in fact evidences against this view. For example, familiarity signals may arise from distinct sources: while perceptual fluency is likely to occur for PEK and EK faces, conceptual fluency most likely took place for PEK faces only (**Oppenheimer**, 2008). Therefore, our approach allowed to control for potential biases related to unequal perceptual fluency,



while ensuring that any benefit of PEK for further subsequent memory is not simply related to countless exposures to famous faces vs. one single exposure for novel faces.

#### **4.6. Conclusion**

The present findings provide new evidence for a critical difference in the way that patients with early AD and healthy older adults form new memories. Pre-experimental prior knowledge proved beneficial for subsequent memory formation in healthy controls, supported by the perirhinal region and specific neural networks at encoding. By contrast, pre-experimental knowledge was found to be of no benefits in patients, who also displayed abnormal neural adaptation. These results open up new perspectives for our comprehension of the memory difficulties observed in this disease.

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#### **Declaration of interest**

None. The authors declare no conflict of interest.

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