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Abnormal fMRI response in sub-hippocampal structures: how prior knowledge impairs memory in AD

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Introduction

Early AD typically impairs associative learning abilities, up to 18 years before dementia (Rajan et al. 2018). Importantly, patient concerns refer to their daily routine and thus impairment of associative memory for highly familiar stimuli. Since, most of the tests involve less familiar stimuli (e.g. isolated words). It follows that we ignore whether prior knowledge about memoranda alters memory formation and its neural correlates in Alzheimer's Disease. Neural adaptation refers to the decrease (suppression) or increase (enhancement) of the neural signal with repeated presentations of identical stimuli (Grill-Spector et al., 2006), and it has been successfully used to functionally map encoding networks. Here, we aimed at manipulating prior knowledge available at encoding and repetition to investigate whether prior knowledge could alter the neural underpinnings of associative encoding, in a way sensitive to early AD.

Methods

17 patients with Mild Cognitive Impairment due to AD (Albert et al., 2011) and 19 controls underwent BOLD fMRI. They were asked to learn face-scene associations. Each association was presented twice across runs. Pre-experimental knowledge (PEK) trials involved famous faces while Experimental Knowledge (EK) trials involved unknown faces that were repeatedly presented prior to the scanned encoding session. A recognition memory test was performed after the scan, allowing to back sort the study

events at study along 3 categories: Source hits (correct face-scene memory); Source misses (correct face memory, incorrect face-scene memory); Misses (forgetting). The participants were scanned using a 3T Siemens Verio System equipped with a 32-channel phased-array coil. An MPRAGE sequence provided structural data while functional data was obtained with a T2*-weighted single-shot spin-echo EPI sequence (TR=2000ms, TE=30ms, 36 axial slices, in-plane matrix size 64x64, resolution=3x3mm2, slice thickness=3.6mm). Images were processed using SPM12. At the first level, the BOLD signal was modeled using a 3x2x2 factorial design within the general linear model framework. The factors were subsequent memory (source hit (SH), source miss (SM), miss (M)), prior knowledge (EK, PEK) and occurrence of the stimulus (first, second). Corresponding events were modeled with a boxcar function convolved with the canonical hemodynamic response function. To test whether encoding networks could be altered by prior knowledge status, we computed the interaction contrast between repetition and prior knowledge. In the resulting clusters, within- and between groups ANOVAs were used to investigate subsequent memory effects, namely differences between parameter estimates for SH and SM.

Results

PEK trials led to a 28% increase in associative memory by comparison with EK trials. In AD-MCI however, no memory improvement was observed. Significant [Prior knowledge x Repetition] interactions were found within core regions pertaining to the retrieval and encoding networks in Controls, but aberrant or absent neural adaptation were observed in patients. For EK associative memory, subsequent memory analysis provided evidence for the involvement of the right hippocampus in both groups. For PEK associative memory however, only controls showed a memory effect within right subhippocampal structures.

Conclusion

The present study calls for a thorough consideration of the prior knowledge associated with the memoranda in future studies. Distinct forms of prior knowledge may drive partly non-overlapping brain networks at encoding, and in turn these regions differentially contributes to successful memory formation. In AD, tau pathology starts within the anterior sub-hippocampal region (entorhinal, perirhinal cortices, Braak & Braak, 1995). Thus, our finding that sub-hippocampal, not hippocampal, activation underlie the inability of the patients to benefit remote prior knowledge in new learning opens perspectives for further diagnostic and prognostic markers development.

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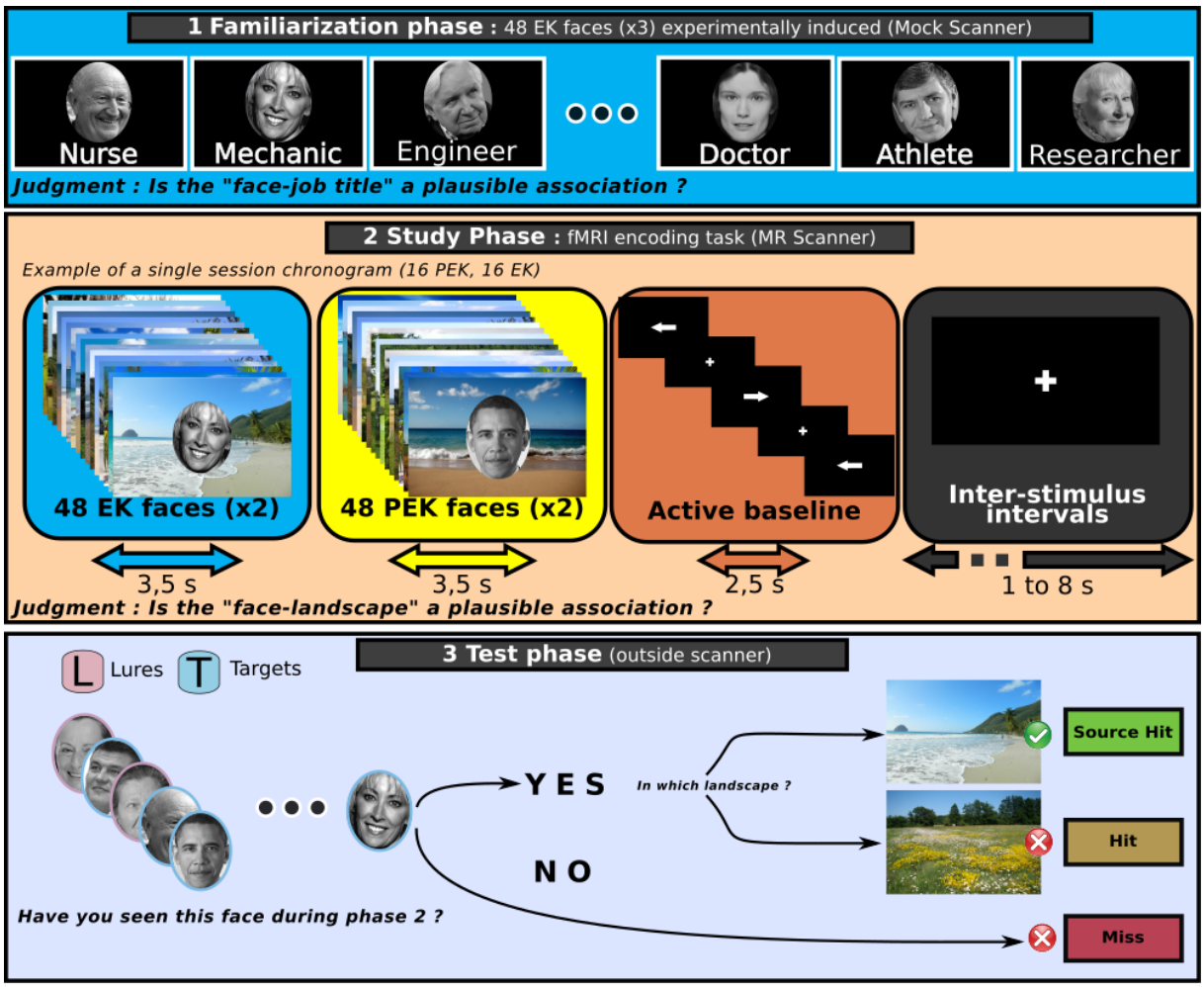

Figure 1. Experimental design & procedure. During **Familiarization**, a series of 48 unknown faces were repeatedly presented and participants were instructed to make a congruency judgment for the face-occupation association. An immediate Old/New recognition test was administered (not shown). 45 minutes later, **Study phase** inside the scanner involved the explicit encoding of face-scene associations of two types: for EK trials, a face from the familiarization phase was displayed; for PEK trials, a famous face was used. After a 15 minutes delay, the **Test phase** took place outside scanner. Participants had to make Old/New judgement for individual faces, then to rate their confidence. For each Hit (i.e. true positive) response, a two-alternate forced choice test asked subjects to recall the correct source (i.e. which scene was associated with the face at study?), then they rated their confidence level for that response. Finally, after a 5 minutes delay, a Fame judgment test (not shown) involved the whole set of faces (i.e. targets and distractors).

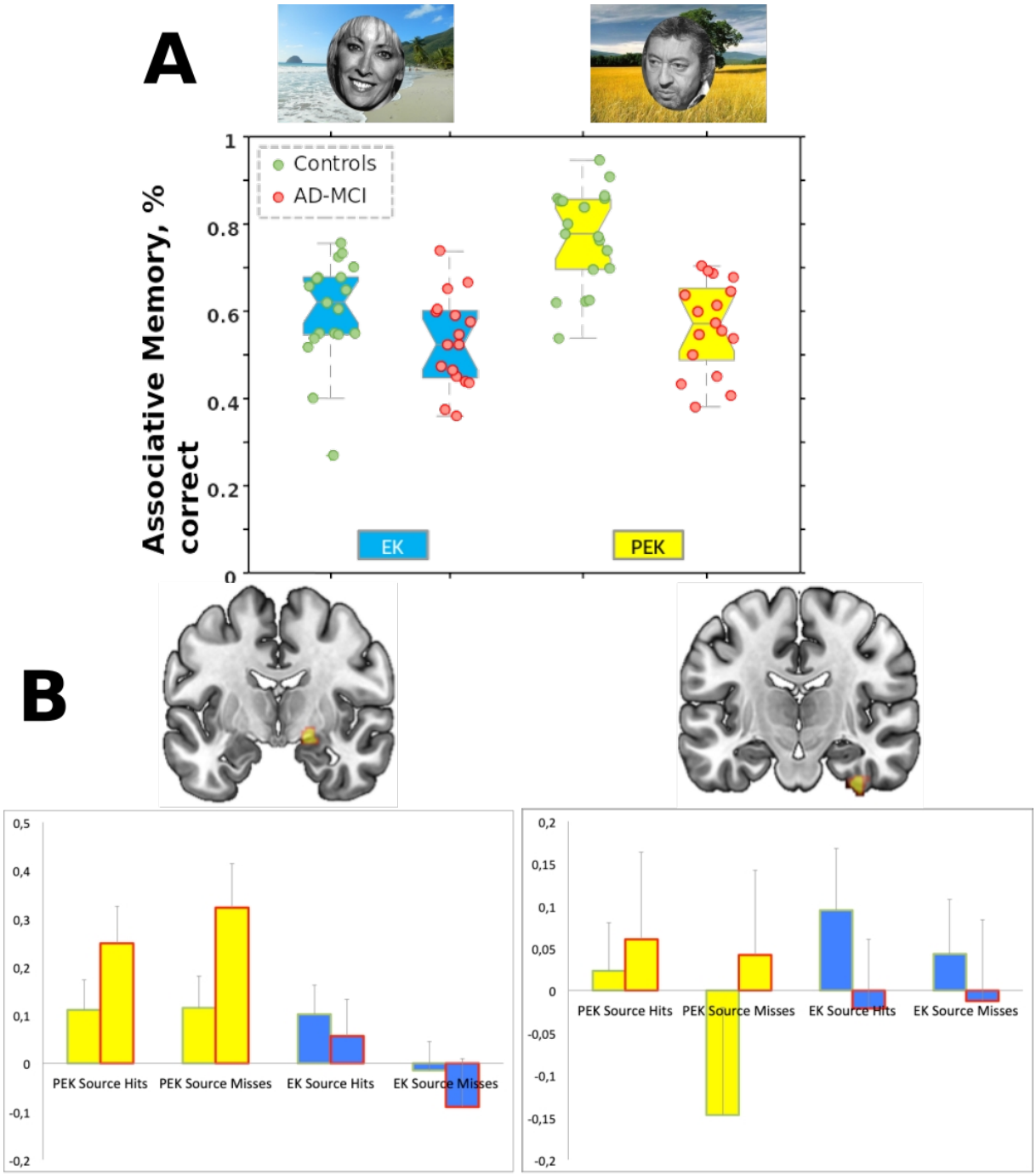

Figure 2. A Behavioral results demonstrate that memory for face-scene associations was improved for PEK stimuli in healthy controls but not in AD-MCI. **B** Subsequent associative memory effects within data-driven ROIs resulting from group differences for the Prior Knowledge x Repetition interaction contrast.