Published in final edited form as:

Brain Imaging Behav. 2011 March ; 5(1): 36–44. doi:10.1007/s11682-010-9110-3.

Failure of repetition suppression and memory encoding in aging and Alzheimer's disease

Maija Pihlajamäki,

Unit of Neurology, Institute of Clinical Medicine, University of Eastern Finland, POB 1627, 70211 Finland, Finland. Department of Neurology, Kuopio University Hospital, POB 1777, 70211 Finland, Finland. Memory Disorders Unit, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA

Kelly O'Keefe,

Department of Psychiatry, Massachusetts General Hospital, 149 13th Street, Boston, MA 02129, USA

Jackie O'Brien,

Department of Psychiatry, Massachusetts General Hospital, 149 13th Street, Boston, MA 02129, USA

Deborah Blacker, and

Department of Psychiatry, Massachusetts General Hospital, 149 13th Street, Boston, MA 02129, USA

Reisa A. Sperling

Memory Disorders Unit, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA. Department of Psychiatry, Massachusetts General Hospital, 149 13th Street, Boston, MA 02129, USA. Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, 149 13th Street, Boston, MA 02129, USA

Maija Pihlajamäki: Maija.Pihlajamaki@uef.fi

Abstract

The suppression of neural activity in the medial temporal lobe (MTL) has been suggested as a marker of successful recognition of familiarity in healthy subjects, but to be impaired in patients with Alzheimer's disease (AD). In this study, we investigated whether the ability to suppress MTL activity during repeated exposure to face-name pairs was related to the ability to successfully encode novel associations in 90 individuals ranging from healthy young and older subjects to mildly impaired elderly and AD patients. Activity in the anterior MTL during Repeated stimuli was inversely related to performance in post-scan associative recognition for the Novel face-name pairs. In a subset ($n=60$) of subjects undergoing more detailed neuropsychological testing, greater MTL Repeated activity was correlated with worse word-list delayed recall performance. Failure of response suppression to familiar information may be a sensitive marker of MTL dysfunction and memory impairment in aging and prodromal AD.

Correspondence to: Maija Pihlajamäki, Maija.Pihlajamaki@uef.fi.

Disclosure Statement The authors have no actual or potential conflicts of interest related to this work.

Keywords

Aging; Alzheimer's disease; Functional magnetic resonance imaging; Medial temporal lobe; Memory; Repetition suppression

Introduction

The ability of the medial temporal lobe (MTL) structures to rapidly discriminate between familiar versus novel stimuli has been demonstrated in several electrophysiological, immediate-early-gene *fos* imaging and lesion studies in rodents and non-human primates (Brown and Aggleton 2001; Eichenbaum et al. 2007; Murray et al. 2007; Squire et al. 2007). Reduction in the anterior MTL neuronal firing rate (i.e., individual neurons or populations of neurons) to repeated stimuli, sometimes termed repetition suppression (Desimone 1996), is also thought to be one of the key mechanisms underlying recognition memory in humans. Functional magnetic resonance imaging (fMRI) studies in healthy young subjects, as well as in healthy elderly individuals, in vivo have demonstrated suppression of the blood-oxygen-level-dependent (BOLD) signal to repeatedly presented (familiar) stimuli in the anterior hippocampal and parahippocampal as well as in the inferior temporo-occipital regions (Brozinsky et al. 2005; Henson et al. 2000; Henson et al. 2003; Johnson et al. 2008; Rand-Giovannetti et al. 2006). In the context of this paper, the term repetition suppression is used to refer to reduction of neural/BOLD fMRI activity with stimulus repetition—a specific phenomenon, which previously has been primarily linked to behavioral measures such as priming and familiarity-based recognition memory.

A recent multimodal imaging study, which combined fMRI with magnetoencephalography (MEG), provided convincing evidence in healthy young subjects that suppression of MTL activity is, indeed, an accompaniment of successful recognition of familiarity of previously learned items (Gonsalves et al. 2005). Similarly, there is recent evidence that MTL response suppression to repeated stimuli is impaired in patients with Alzheimer's disease (AD) and in individuals with amnesic mild cognitive impairment (MCI), who characteristically have significant MTL pathology and difficulty learning and retaining new information (Golby et al. 2005; Johnson et al. 2004; Pihlajamäki et al. 2008). The relationship between the MTL response suppression to repeated information and the ability to successfully form new episodic memories remains, however, to be fully explored. Most former studies on repetition suppression have utilized item stimuli in relatively small groups of subjects. In this study, we used cross-modal associative stimuli to investigate the neural response to repeated stimuli across a large sample of subjects ranging from healthy young to healthy elderly, MCI, and patients with mild AD. Furthermore, we investigated whether the ability to suppress MTL activity to repeatedly presented stimuli was related not only to familiarity-based recognition but also more broadly to episodic memory performance. To this aim, subjects were imaged while processing novel and repeated face-name stimuli alternating with visual fixation, and memory performance was assessed using two independent measures: a post-scan associative name recognition test on the face-name pairs encoded during scanning and a standard neuropsychological word-list delayed recall test.

Successful associative memory formation has previously been shown to require increased anterior MTL activity during the encoding of novel paired stimuli (Chua et al. 2007; Pihlajamäki et al. 2003; Sperling et al. 2003a). We theorized that the ability to successfully encode novel stimuli would also be associated with greater suppression of anterior MTL activity to repeated stimuli. Thus, we hypothesized that cognitively intact young and older subjects would demonstrate preserved repetition suppression in the anterior MTL, whereas we expected the cognitively impaired elderly subjects, and the AD patients in particular, to

demonstrate impaired suppression of fMRI activity. Furthermore, we expected that the degree of repetition suppression in these anterior MTL regions would predict performance on episodic memory measures acquired in the separate neuropsychological assessment. In other words, we hypothesized that MTL repetition suppression over the course of the fMRI experiment would differ across the groups of subjects, and that the degree of repetition suppression would correlate with memory performance. A key question in AD is whether the memory impairment results from failure of encoding, consolidation, or retrieval mechanisms. Previous work has shown that late MCI and AD patients demonstrate significantly impaired MTL activity during novel encoding. In this study, we investigate whether failure of repetition suppression is another key factor underlying the fMRI differences between cognitively impaired vs. intact subjects using comparisons between novel vs. repeated stimuli, and thus a sensitive indicator of the functional integrity of the MTL in advanced aging and early AD.

Material and methods

Study subjects

Ninety individuals participated in the study (Table 1): i) 15 young control subjects; ii) 30 elderly cognitively normal subjects with a Clinical Dementia Rating (CDR) score of 0 (Morris 1997); iii) 30 elderly cognitively mildly impaired subjects with CDR 0.5 (questionable dementia); iv) 15 elderly subjects with CDR 1.0 (mild dementia) meeting NINCDS-ADRDA criteria for probable AD (McKhann et al. 1984). Subjects were classified into the three study groups on the basis of their CDR score, the CDR 0.5 subjects also met the following criteria for MCI: 1) a memory complaint corroborated by an informant, 2) normal general cognitive function, 3) normal activities of daily living, and 4) not demented. The CDR=0.5 subjects did not meet the commonly used Petersen criteria for MCI, and therefore we are also not calling them as “MCI”. The CDR =0.5 subjects of this study were cognitively milder impaired than (amnesic) MCI subjects in most other studies, but likely would meet the new Alzheimer’s disease Neuroimaging Initiative (ADNI) “early MCI” criteria. The purpose of this study was to investigate the whole cognitive range of subjects from young healthy to clinical AD patients, and the CDR=0.5 subjects present an intermediate cognitive state between cognitively intact elderly and patients with dementia of AD type.

The young and elderly CDR 0 subjects were free from psychiatric and neurological illness. None of the subjects were taking medications with known central nervous system effects at the time of scanning. AD patients had either been off cholinesterase inhibitors for at least 30 days prior to scanning or had never taken these medications. The elderly CDR 0 and 0.5 participants ($n=60$) were recruited from a longitudinal study examining preclinical predictors of AD, and underwent additional neuropsychological testing. Age- and education-adjusted Z-scores for the Rey Auditory Verbal Learning Test (RAVLT) delayed recall measures were calculated based on a large group of normal older subjects in our community (Dickerson et al. 2007). Five of the AD patients were recruited from the longitudinal study. The remaining 10 AD patients were recruited from a memory disorder clinic; the RAVLT data was not available for these patients. All subjects provided informed written consent in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and with the Human Research Committee guidelines of the Massachusetts General Hospital and Brigham and Women’s Hospital (Boston, MA, USA). Subsets of these 90 subjects have been previously reported in a study of novel encoding using anatomically defined regions of interest limited to the medial temporal lobe ($n=29$) (Dickerson et al. 2005); a study of memory networks using independent component analysis ($n=52$) (Celone et al. 2006); and in a study focusing on the relationship between the MTL activation and

posteromedial task-induced deactivation findings in AD versus elderly controls ($n=44$) (Pihlajamäki et al. 2008).

fMRI activation paradigm and post-scan memory test

The fMRI activation paradigm consisted of blocks of visually complex cross-modal associative stimuli, that is Novel and Repeated face-name pairs alternating with visual Fixation, for details see (Sperling et al. 2001). For the Novel and Repeated activation conditions, the participants were instructed to try to remember the name associated with each face, and to make a subjective decision as to whether or not they thought the name “fit” the face as indicated with a button press. During the Fixation baseline, they were instructed to focus their attention to a white cross-hair (+) presented on the black background. Each of the six fMRI runs consisted of two Novel blocks presenting faces previously unfamiliar to the subjects paired with contextually novel first names (7 face-name pairs per block, each shown for 5 s) and two Repeated blocks of identical timing, separated by 25 s periods of Fixation. During the Repeated blocks, two randomly alternating face-name pairs (i.e., one male and one female face-name pair) were presented repeatedly. Each repeated face-name pair was viewed during the pre-scan training session to fully familiarize these stimuli prior to scanning, and were viewed an additional 42 times over the course of the fMRI experiment. Perceptually, the face-name stimuli comprised of complex high-resolution color photographs of faces, which were centered on a black background and paired with fictional common English names printed in white font below the face. Visual stimuli were presented using MacStim 2.5 software (WhiteAnt Occasional Publishing, West Melbourne, Australia). Images were projected through a collimating lens onto a screen attached to the head coil. Responses were collected using a fiber-optic response box held in the right hand.

After the scanning session subjects underwent a two-forced-choice associative name recognition memory test, during which a set of twelve Novel faces seen during the experiment and the two Repeated faces were presented. Each face was shown with two names printed underneath: the correct name and one incorrect name that was previously paired with a different face during scanning. The subjects were instructed to indicate the correct name by pointing to it on the computer monitor.

fMRI data acquisition

Subjects were scanned using a Siemens Trio 3.0 T scanner (Siemens Medical Systems, Iselin, NJ) equipped for echo-planar imaging (EPI) with a 3-axis gradient head coil. High-resolution structural images were acquired using a T_1 -weighted 3D MP-RAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) sequence with the following parameters: repetition time (TR)=2,530 ms, echo time (TE)=3.45 ms, inversion time (TI)=1,100 ms, flip angle (FA)=7°, field of view (FOV)=256 mm, matrix=192×256, slice thickness=1.33 mm, 128 sagittal slices. Second, in order to improve co-registration of the structural and functional images we also acquired structural images using a T_1 -weighted EPI sequence and the same slice positioning than for the functional images: TR=30,000 ms, TE=39 ms, TI=1,200 ms, FOV=200 mm, matrix=64×64. Third, BOLD fMRI data were acquired using a T_2^* -weighted gradient-echo EPI sequence with the following parameters: TR=2,500 ms, TE=30 ms, FA =90°, FOV=200 mm, matrix=64×64, resulting in an in-plane resolution of 3.125×3.125 mm². Twenty-eight oblique coronal slices with a thickness of 5.0 mm and an interslice gap of 1.0 mm were acquired, oriented perpendicular to the anterior-posterior commissural line. Scanning time for each functional run was 4 min 15 s and consisted of 102 whole-brain acquisitions; the first 4 functional volumes (Fixation) were later discarded from the data analysis to allow for T_1 -stabilization. Total functional scanning time of six fMRI runs was 25 min 30 s.

fMRI data analysis

fMRI data analysis was carried out using FEAT (FMRI Expert Analysis Tool) 5.63, part of FSL (www.fmrib.ox.ac.uk/fsl). The following pre-statistical processing was applied: motion correction, removal of non-brain structures, spatial smoothing using a Gaussian kernel of full width at half maximum of 5 mm, mean-based intensity normalization of all volumes by the same factor, and high-pass temporal filtering with a frequency cutoff point of 140.0 s. Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction. FMRI images were registered to high resolution structural images and to the Montreal Neurological Institute (MNI) standard brain via the "initial" structural images (the T₁-weighted EPI images) using FLIRT (FMRIB's Linear Image Registration Tool) and 12 parameter affine registration. Registration success was visually checked in each subject using the registration report output of the FSL first-level data analysis.

Subjects were scanned while processing Repeated (R) and Novel (N) face-name stimuli alternating with visual Fixation (F). Processing of Repeated and Novel face-name pairs was separately contrasted to Fixation (contrasts RvF and NvF, respectively). MTL activity during Novel stimuli compared to Fixation (NvF) was examined in addition to RvF in order to investigate suppression of MTL activity during processing Repeated relative to Novel stimuli. Higher-level correlational analyses were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects). The covariance of the brain RvF activity with the post-scan name recognition performance across all 90 subjects and with the RAVLT delayed recall performance across the 60 elderly subjects was examined using corresponding test scores as covariates of interest (entering age, education and gender as covariates of no interest). The resulting Z statistic images were corrected for multiple comparisons using cluster thresholding: the voxelwise Z statistic threshold was set to $Z > 2.3$ and the cluster probability threshold to $p < 0.05$. Data analysis was restricted to the MTL structures by using standard anatomical criteria (Insausti et al. 1998; Pruessner et al. 2002).

Within those MTL regions that demonstrated significant correlation between RvF activity and post-scan recognition memory performance, we performed a ROI analysis by positioning the center of a sphere with 5 voxels' diameter into the peak MNI coordinate of significant MTL clusters. The correct location of the ROIs within the MTL was visually inspected. The mean percent RvF and NvF signal change within each ROI was extracted using FSL Featquery. The ROI analyses were performed to complement the FSL map-level data analyses, i.e., to investigate the magnitude and directionality of the BOLD signal and also to provide some insight into the inter-individual variability of the fMRI response across the study groups.

Demographic and cognitive data analysis

Statistical analysis of demographic, cognitive, fMRI behavioral and ROI data was conducted with SPSS 14.0 (SPSS Inc., Chicago, IL, USA). The level of statistically significant differences was set at $p < 0.05$.

Results

Demographic, cognitive and fMRI behavioral results

As presented in detail in Table 1, there were statistically significant differences in age, education and gender distribution between the study groups and therefore these parameters were entered as covariates in the FSL data analysis. There were also differences between the groups in Mini-Mental State Examination, RAVLT and post-scan name recognition performance. Mean reaction times for both the Novel and Repeated stimuli were slower in

the cognitively impaired elderly subjects' and AD patients' groups (Table 1). All subjects showed a faster reaction time in response to Repeated face-name pairs compared to Novel, consistent with priming to familiar stimuli. Interestingly, this Novel-Repeated reaction time difference was preserved even in the AD patients suggesting that some degree of priming was preserved, although the priming effect appears somewhat diminished in the AD patients relative to the other elderly study groups.

fMRI correlations with post-scan associative recognition memory

In the FSL correlational analyses across all 90 study subjects (Fig. 1, left column), we found three MTL areas to demonstrate significant ($p < 0.05$, cluster-corrected for multiple comparisons) negative correlation between the RvF activity and post-scan face-name recognition memory test scores (peak MNI coordinates, Z-scores and corresponding uncorrected p-values are given in the parentheses): 1) the left anterior hippocampus together with the neighboring perirhinal cortical and amygdala regions (MNI=-18, -8, -20; $Z = 3.12$; $p = 0.0009$); 2) the left middle hippocampus and parahippocampal cortex (-24, -24, -18; $Z = 2.82$; $p = 0.002$); 3) the left posterior hippocampus and parahippocampal cortex (-30, -36, -10; $Z = 2.56$; $p = 0.005$). We found no areas of positive correlation between RvF activity and recognition memory performance.

Region-of-interest (ROI) analysis of RvF signal magnitude within the anterior, middle and posterior MTL clusters of significant correlation (Fig. 1, scatter plots) elucidated the findings of the FSL map-level data analysis that greater MTL fMRI signal during processing Repeated stimuli was correlated with worse recognition memory performance (anterior MTL: $r = -0.62$, $p < 0.001$, Pearson's correlation; middle MTL: $r = -0.31$, $p = 0.003$; posterior MTL: $r = -0.34$, $p = 0.001$). Corresponding correlation analyses between the post-scan recognition memory performance and RvF fMRI signal were also performed within the study groups. Significant correlations similar to the findings across all 90 subjects were observed within the study groups in the anterior MTL, but not in the middle or posterior MTL regions suggesting that the anterior MTL results were not driven by group effects (anterior MTL, within young controls: $r = -0.64$, $p = 0.01$; elderly CDR 0.0 subjects: $r = -0.66$, $p < 0.001$; elderly CDR 0.5 subjects: $r = -0.61$, $p < 0.001$; elderly CDR 1.0 subjects: $r = -0.72$, $p = 0.002$; within the elderly CDR 0.0 and CDR 0.5 elderly $r = -0.59$, $p < 0.001$).

Finally, to illustrate the relation between the RvF repetition suppression and MTL activity during processing Novel stimuli, we also examined the NvF activity in each of the anterior, middle and posterior MTL ROIs (Fig. 1, bar graphs). In the cognitively intact subject groups the anterior, and also the middle, MTL demonstrated suppression of activity during processing Repeated relative to Novel stimuli (young subjects: $p < 0.001$, paired-samples *T*-test), whereas there was no significant difference between NvF and RvF anterior MTL activity in the group of AD patients ($p = 0.8$). The cognitively intact and mildly impaired elderly groups showed levels of repetition suppression intermediate to healthy young subjects and AD patients.

fMRI correlations with word-list delayed recall

In the FSL analysis within the group of 60 elderly CDR 0 and 0.5 subjects with additional neuropsychological testing available, the anterior MTL RvF activity demonstrated significant negative correlation with word-list delayed recall scores (MNI=-16, -4, -30; $Z = 3.29$; $p = 0.0005$) resembling the correlation results between RvF activity and associative recognition memory performance. Anatomically, the anterior MTL cluster covered areas in the hippocampus and in the neighboring entorhinal, perirhinal and amygdala regions, and also extended to the middle parts of the MTL.

The significance of the inverse relation between greater RvF activity and worse word-list delayed recall was illustrated with the ROI analysis ($r=-0.61$, $p<0.001$). Similar to the results with recognition scores as a covariate, word-list delayed recall performance also correlated negatively with posterior hippocampal and parahippocampal RvF activity in the FSL analysis (-30 , -34 , -6 ; $Z=3.51$; $p=0.0002$) as well as in the ROI analysis ($r=-0.44$, $p<0.001$). We found no areas of positive correlation between the RvF fMRI activity and word-list delayed recall scores (Fig. 2).

Discussion

This study found that failure of the MTL activity to discriminate familiar from novel information at encoding was related to poor associative recognition memory test performance as well as poor performance in neuropsychological tests of episodic memory across a range of age and cognitive impairment. Cognitively normal young and elderly subjects show preserved suppression of MTL activity to stimulus repetition, whereas cognitively impaired elderly and patients with Alzheimer's disease show reduced suppression of MTL activity. These results support the hypothesis that intact MTL repetition suppression may be a marker of successful memory encoding, early consolidation, and subsequent memory test performance.

We found the strongest correlation between the impaired repetition suppression and poor memory performance in the anterior MTL regions, which on one hand are known to be sensitive to encoding novel associative stimuli (Chua et al. 2007; Daselaar et al. 2006; Henson et al. 2003; Pihlajamäki et al. 2003; Sperling et al. 2003a; Sperling et al. 2001) and on the other to suppress neural and BOLD fMRI activity to repeated stimuli (Brozinsky et al. 2005; Johnson et al. 2008; Rand-Giovannetti et al. 2006). Involvement of the anterior rhinal cortical regions in repetition suppression, as found in this study along the hippocampus, is consistent with the findings in previous electrophysiological recording studies which demonstrated that a key property of the perirhinal cortical neurons is to discriminate between novelty and familiarity (Brown and Aggleton 2001; Murray et al. 2007), whereas there is less evidence in animal studies of the importance of the anterior hippocampus in repetition suppression. It is worth noting that in this human fMRI study we utilized cross-modal associative stimuli and tested for declarative memory formation using delayed associative measures—factors which may contribute to the significant involvement of the hippocampus in addition to the parahippocampal cortices. It is also important to remember that fMRI measures activity in a large population of neurons and therefore direct comparisons between techniques such as single cell recordings in animals and human fMRI are challenging (Grill-Spector et al. 2006). The results regarding the middle and posterior parts of the MTL were statistically less significant than findings in the anterior MTL. We hope to investigate the less conclusive middle-posterior MTL findings and their implications in more detail with future event-related studies.

Our findings that the anterior hippocampal and parahippocampal regions demonstrate the strongest evidence of repetition suppression are in agreement with results of former fMRI studies in young healthy subjects (Brozinsky et al. 2005; Gonsalves et al. 2005; Henson et al. 2003). The previous fMRI studies typically utilized event-related recognition memory paradigms presenting old and new items, whereas in the present block-design study we imaged the subjects during intentional associative encoding of visually complex cross-modal face-name stimuli. Thus, the repetition suppression effect observed in this study is not influenced by the conscious new/old decision making on each stimulus. Importantly, in this study memory formation was tested using delayed associative measures (whether recognition or free recall) of the ability to form long-term memories. This set-up brings the results between MTL response suppression during stimulus processing and successful

memory formation beyond the continuous “on-line” recognition memory tasks used in most previous studies. Interestingly, in the present study, the subjects were also not able to solve the post-scan associative name recognition memory test based on familiarity with the name only as both names printed underneath the face had been presented during the fMRI experiment. In addition to the present results from a block-design fMRI study, future event-related fMRI studies specifically designed to investigate the relationship between repetition suppression and success of long-term memory formation in cognitively intact and impaired subjects are, however, warranted.

In normal subjects, memory strength is thought to be signaled rapidly by the MTL cortex through repetition suppression (i.e., activation reduction) providing a basis for the quick subjective perception of stimulus familiarity or novelty (Gonsalves et al. 2005). This very rapid signaling is suggestive of changes in the synaptic strength in the feedforward connections from the sensory cortices to the MTL structures (Grill-Spector et al. 2006). It is plausible that during the intact learning process in young and elderly healthy controls, neuronal selectivity to repeated stimuli increases (Yanike et al. 2004) which may then be reflected as reduced BOLD fMRI activity. According to the “novelty-encoding view”, one key function of declarative memory is to support discrimination of stimuli that were previously encountered from those that are novel (Ranganath and Rainer 2003; Tulving et al. 1996). This is consistent with the idea that changes in synaptic strength, which support discrimination of novelty and familiarity are essential initial steps in early memory consolidation. The pronounced initial activation to novel stimuli followed by response suppression to highly familiar stimuli may indirectly indicate enhanced synaptic strength and neuronal selectivity related to effective memory encoding and consolidation.

It is worth noting, however, that the theoretical link between the repetition suppression phenomenon and its potential role in long-term memory formation is not well understood and also cannot be fully explicated by the current fMRI data. In previous studies, the anterior MTL repetition suppression has been most strongly linked to familiarity or item-based memory (Brown and Aggleton 2001). Based on the results of this study, we have speculated that the repetition effects may not only be related to familiarity-based recognition memory, but also more broadly to episodic memory performance. We cannot, however, fully rule out an alternative interpretation of the data, that is the possibility that the repetition effects seen during encoding novel/repeated face-name pairs simply reflect the same kind of item familiarity as reported in prior studies. In other words, the familiarity of the previously observed faces and/or names may drive the finding of reduced MTL activity rather than the actual linking and subsequent associative encoding of these items. Thus, it remains a possibility that the lack of MTL repetition suppression reflects impaired item-based memory, which may then serve as a marker for more extensive MTL dysfunction given the proximity of the neural substrates and MTL substructures as well as the diverse pathological changes already in the earliest changes of AD (Braak and Braak 1991; Gomez Isla et al. 1997; Hyman et al. 1984; Kordower et al. 2001; Scheff et al. 2006). Future event-related studies that can separately investigate the effects of item vs. associative stimuli on regionally specific MTL repetition suppression are needed.

In line with previous studies (Golby et al. 2005; Johnson et al. 2004; Pihlajamäki et al. 2008), this study suggests that in the cognitively impaired elderly subjects the anterior MTL may have lost its inherent sensitivity to recognize familiar information, or—vice versa—sensitivity to novel encoding. Our finding of reduced fMRI response suppression in the cognitively impaired elderly and AD patients suggests that the important initial steps of memory formation are altered already in cognitively mildly impaired subjects at potential risk for AD. The characteristic cognitive deficit in incipient AD is the inability to form and retain new memories due to neuropathological changes (i.e., neurofibrillary tangles as well

as loss of neurons and synapses) often concentrated in the anterior MTL structures in the early stages of the disease (Braak and Braak 1991; Gomez Isla et al. 1997; Hyman et al. 1984; Kordower et al. 2001; Scheff et al. 2006). Results of this study suggest that AD patients, affected by the MTL pathology, and also to a lesser degree the cognitively impaired elderly subjects, are not able to form new stimulus representations and the stimuli do not necessarily become familiarized to the subjects, even when highly repetitive.

Previous fMRI studies in AD patients, compared to healthy elderly individuals, have reported decreased or absent MTL activity during processing of novel versus repeated information (Dickerson et al. 2005; Golby et al. 2005; Rombouts et al. 2000; Sperling et al. 2003b). The present study, together with several other recent studies, provides evidence of increased MTL activity in AD during processing of repeatedly presented stimuli (Golby et al. 2005; Pihlajamäki et al. 2008). Similar to our findings in cognitively impaired elderly individuals, impaired adaptation of the MTL response to repeated stimuli has also been reported in subjects with amnesic MCI (Johnson et al. 2004). Thus, findings of decreased MTL activity comparing novel to repeated stimuli in AD or MCI patients in the fMRI contrast are likely to be explained to a large degree by failure of MTL repetition suppression, in addition to alterations in novel encoding. Furthermore, we found that greater MTL activity to repeated face-name stimuli was inversely correlated with memory performance on a standard verbal memory neuropsychological test. These results provide evidence that episodic memory impairment typically seen in mild AD may not only manifest as decreased but also as increased activation of the MTL memory structures.

In conclusion, this study shows that anterior MTL response suppression to previously encountered associative information is related to successful memory formation as measured by delayed recognition and free recall measures. These results suggest that intact MTL response suppression to stimulus repetition may be a marker of successful memory encoding and early consolidation. The failure of the anterior MTL to discriminate familiar from novel information may be a sensitive indicator of MTL dysfunction early in the course of AD. The results of this study and future multimodality imaging studies, including PET amyloid imaging, should serve to advance our understanding of the pathophysiological substrates of memory impairment in early AD.

Acknowledgments

This study was supported by Academy of Finland grants #108188 and #214050, Kuopio University Hospital EVO grants, as well as National Institute of Aging grants AG027435, AG04953 and AG00513421. We thank the staff of the Massachusetts General Hospital Gerontology Research Unit and Brigham and Women's Hospital Memory Disorders Unit Clinical Research for assistance with subject recruitment, evaluation, and data management, as well as Mary Foley, Larry White, and the Athinoula A. Martinos Center staff for assistance with MRI data collection. We express special gratitude to the subjects who participated in this study.

References

- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol (Berl)* 1991;82:239–259. [PubMed: 1759558]
- Brown MW, Aggleton JP. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat Rev Neurosci* 2001;2:51–61. [PubMed: 11253359]
- Brozinsky CJ, Yonelinas AP, Kroll NE, Ranganath C. Lag-sensitive repetition suppression effects in the anterior parahippocampal gyrus. *Hippocampus* 2005;15:557–561. [PubMed: 15889401]
- Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, et al. Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. *J Neurosci* 2006;26:10222–10231. [PubMed: 17021177]

- Chua EF, Schacter DL, Rand-Giovannetti E, Sperling RA. Evidence for a specific role of the anterior hippocampal region in successful associative encoding. *Hippocampus* 2007;17:1071–1080. [PubMed: 17604351]
- Daselaar SM, Fleck MS, Cabeza R. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. *J Neurophysiol* 2006;96:1902–1911. [PubMed: 16738210]
- Desimone R. Neural mechanisms for visual memory and their role in attention. *Proc Natl Acad Sci USA* 1996;93:13494–13499. [PubMed: 8942962]
- Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, et al. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology* 2005;65:404–411. [PubMed: 16087905]
- Dickerson BC, Sperling RA, Hyman BT, Albert MS, Blacker D. Clinical prediction of Alzheimer disease dementia across the spectrum of mild cognitive impairment. *Arch Gen Psychiatry* 2007;64:1443–1450. [PubMed: 18056553]
- Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. *Annu Rev Neurosci* 2007;30:123–152. [PubMed: 17417939]
- Golby A, Silverberg G, Race E, Gabrieli S, O'Shea J, Knierim K, et al. Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. *Brain* 2005;128:773–787. [PubMed: 15705615]
- Gomez Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, et al. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann Neurol* 1997;41:17–24. [PubMed: 9005861]
- Gonsalves BD, Kahn I, Curran T, Norman KA, Wagner AD. Memory strength and repetition suppression: multimodal imaging of medial temporal cortical contributions to recognition. *Neuron* 2005;47:751–761. [PubMed: 16129403]
- Grill-Spector K, Henson R, Martin A. Repetition and the brain: neural models of stimulus-specific effects. *Trends Cogn Sci* 2006;10:14–23. [PubMed: 16321563]
- Henson R, Shallice T, Dolan R. Neuroimaging evidence for dissociable forms of repetition priming. *Science* 2000;287:1269–1272. [PubMed: 10678834]
- Henson RN, Cansino S, Herron JE, Robb WG, Rugg MD. A familiarity signal in human anterior medial temporal cortex? *Hippocampus* 2003;13:301–304. [PubMed: 12699337]
- Hyman BT, Van Hoesen GW, Damasio AR, Barnes CL. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. *Science* 1984;225:1168–1170. [PubMed: 6474172]
- Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, et al. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *AJNR Am J Neuroradiol* 1998;19:659–671. [PubMed: 9576651]
- Johnson SC, Baxter LC, Susskind-Wilder L, Connor DJ, Sabbagh MN, Caselli RJ. Hippocampal adaptation to face repetition in healthy elderly and mild cognitive impairment. *Neuropsychologia* 2004;42:980–989. [PubMed: 14998712]
- Johnson JD, Muftuler LT, Rugg MD. Multiple repetitions reveal functionally and anatomically distinct patterns of hippocampal activity during continuous recognition memory. *Hippocampus* 2008;18:975–980. [PubMed: 18548578]
- Kordower JH, Chu Y, Stebbins GT, DeKosky ST, Cochran EJ, Bennett D, et al. Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment. *Ann Neurol* 2001;49:202–213. [PubMed: 11220740]
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology* 1984;34:939–944. [PubMed: 6610841]
- Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr* 1997;9(Suppl 1):173–176. [PubMed: 9447441]
- Murray EA, Bussey TJ, Saksida LM. Visual perception and memory: a new view of medial temporal lobe function in primates and rodents. *Annu Rev Neurosci* 2007;30:99–122. [PubMed: 17417938]

- Pihlajamäki M, Tanila H, Hänninen T, Könönen M, Mikkonen M, Jalkanen V, et al. Encoding of novel picture pairs activates the perirhinal cortex: an fMRI study. *Hippocampus* 2003;13:67–80. [PubMed: 12625459]
- Pihlajamäki M, Depeau KM, Blacker D, Sperling RA. Impaired medial temporal repetition suppression is related to failure of parietal deactivation in Alzheimer disease. *Am J Geriatr Psychiatry* 2008;16:283–292. [PubMed: 18378553]
- Pruessner JC, Kohler S, Crane J, Pruessner M, Lord C, Byrne A, et al. Volumetry of temporopolar, perirhinal, entorhinal and parahippocampal cortex from high-resolution MR images: considering the variability of the collateral sulcus. *Cereb Cortex* 2002;12:1342–1353. [PubMed: 12427684]
- Rand-Giovannetti E, Chua EF, Driscoll AE, Schacter DL, Albert MS, Sperling RA. Hippocampal and neocortical activation during repetitive encoding in older persons. *Neurobiol Aging* 2006;27:173–182. [PubMed: 16298252]
- Ranganath C, Rainer G. Neural mechanisms for detecting and remembering novel events. *Nat Rev Neurosci* 2003;4:193–202. [PubMed: 12612632]
- Rombouts SA, Barkhof F, Veltman DJ, Machielsen WC, Witter MP, Bierlaagh MA, et al. Functional MR imaging in Alzheimer's disease during memory encoding. *AJNR Am J Neuroradiol* 2000;21:1869–1875. [PubMed: 11110539]
- Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging* 2006;27:1372–1384. [PubMed: 16289476]
- Sperling RA, Bates JF, Cocchiarella AJ, Schacter DL, Rosen BR, Albert MS. Encoding novel face-name associations: a functional MRI study. *Hum Brain Mapp* 2001;14:129–139. [PubMed: 11559958]
- Sperling R, Chua E, Cocchiarella A, Rand-Giovannetti E, Poldrack R, Schacter DL, et al. Putting names to faces: successful encoding of associative memories activates the anterior hippocampal formation. *Neuroimage* 2003a;20:1400–1410. [PubMed: 14568509]
- Sperling RA, Bates JF, Chua EF, Cocchiarella AJ, Rentz DM, Rosen BR, et al. FMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2003b;74:44–50. [PubMed: 12486265]
- Squire LR, Wixted JT, Clark RE. Recognition memory and the medial temporal lobe: a new perspective. *Nat Rev Neurosci* 2007;8:872–883. [PubMed: 17948032]
- Tulving E, Markowitsch HJ, Craik FE, Habib R, Houle S. Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cereb Cortex* 1996;6:71–79. [PubMed: 8670640]
- Yanike M, Wirth S, Suzuki WA. Representation of well-learned information in the monkey hippocampus. *Neuron* 2004;42:477–487. [PubMed: 15134643]

Fig. 1.

The relation between the medial temporal lobe (MTL) repetition suppression and recognition memory performance. **a** In the FSL analyses, left (L) anterior MTL activity during processing Repeated face-name pairs versus Fixation (RvF) was negatively correlated with the post-scan name recognition memory test performance ($p < 0.05$, cluster-corrected). As shown in the scatter plot, significance of the correlation between impaired repetition suppression and poor memory performance was illustrated using a region-of-interest (ROI) analysis of fMRI signal magnitude across the 90 study subjects ($r = -0.62$, $p < 0.001$, Pearson correlation). The bar graph demonstrates increasing RvF activity (black bars, mean $\pm$ SEM) across the study groups. fMRI activity during processing Novel face-name pairs versus Fixation (NvF, gray bars) is presented to illustrate the diminished suppression of RvF activity relative to NvF activity in the cognitively impaired subject groups (* indicates significantly different NvF versus RvF activity, paired samples T test). The middle and posterior MTL areas of negative correlation between the RvF activity and recognition memory are shown in panels (b) and (c), correspondingly. Different from the anterior MTL, in the posterior MTL difference between the NvF and RvF activity was not significant in the cognitively intact study groups (i.e., young and CDR 0 subjects). MNI-coordinates of the crosshairs, which also are the center coordinates of the spherical ROIs, are given for each panel. CDR Clinical Dementia Rating

Fig. 2.

The relation between the medial temporal lobe (MTL) repetition suppression and free recall performance. In the FSL analyses, fMRI activity of the left (L) anterior and middle hippocampus and neighboring rhinal and parahippocampal cortices during processing Repeated face-name pairs versus Fixation (RvF) demonstrated significant negative correlation with the Rey Auditory Verbal Learning Test (RAVLT) delayed recall performance ($p < 0.05$, cluster-corrected). As presented in the scatter plot, the association of impaired repetition suppression with poor delayed recall performance was elucidated using a region-of-interest (ROI) analysis of fMRI signal magnitude across the 60 cognitively normal (Clinical Dementia Rating, CDR, 0) and mildly impaired (CDR 0.5) elderly individuals ($r = -0.61$, $p < 0.001$, Pearson correlation). The bar graph suggests greater RvF activity (*black bars*, mean $\pm$ SEM) in the CDR 0.5 than in the CDR 0 group. fMRI activity during processing Novel face-name pairs versus Fixation (NvF, *gray bars*) is presented to illustrate the diminished, although still significant, suppression of RvF activity relative to NvF activity in the CDR 0.5 group (* indicates a significant difference in NvF versus RvF activity, paired samples *T* test). MNI-coordinate of the crosshair, which also is the center coordinate of the spherical ROI, is given in the left upper corner

Table 1

Characteristics of the subject groups

	Young	Elderly		
	N=15	CDR=0.0	CDR=0.5	CDR=1.0
		N=30	N=30	N=15
Demographics				
Age, yrs	22.5±1.6	74.0±5.5 ^a	76.7±5.3 ^{a,b}	78.3±6.9 ^{a,b}
Education, yrs	17.1±1.8	15.6±2.6	15.8±3.2	13.3±3.2 ^{a,b,c}
Female/male	12/3	19/11	19/11	8/7
Cognition				
MMSE	–	29.6±0.5	29.1±1.1 ^b	23.3±4.2 ^{b,c}
RAVLT delayed recall ^d	–	0.2±0.8	–0.5±1.4	–
fMRI behavioral data				
Name recognition,%	91.5±7.7	87.3±9.7	84.1±13.0 ^a	65.7±11.7 ^{a,b,c}
RT Novel, ms	1,775±438	1,956±532	2,256±654	2,464±581 ^{a,b,c}
RT Repeated, ms	843±168	792±210	812±191	1,454±693 ^{a,b}
RT Difference Novel–Repeated, ms	932±411	1,164±515	1,444±556 ^a	1,009±449

Mean ± standard deviation. *CDR* Clinical Dementia Rating; *MMSE* Mini-Mental State Examination; *RAVLT* Rey Auditory Verbal Learning Test; *RT* Reaction Time. Significant differences between groups ($p < 0.05$, Mann–Whitney U):

^a vs. Young;

^b vs. CDR 0.0;

^c vs. CDR 0.5.

^d For the RAVLT, age-and education adjusted Z-scores are reported