Hippocampal and neocortical activation during repetitive encoding in older persons

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Abstract

Episodic memory function is known to decline in the course of normal aging; however, compensatory techniques can improve performance significantly in older persons. We investigated the effects of the memory enhancing technique of repetition encoding on brain activation using event-related functional magnetic resonance imaging (fMRI). Twelve healthy older adults without cognitive impairment were studied with fMRI during repetitive encoding of face–name pairs. During the first encoding trials of face–name pairs that were subsequently remembered correctly, activation of the hippocampus and multiple neocortical regions, including prefrontal, parietal and fusiform cortices, was observed. The second and third encoding trials resulted in continued activation in neocortical regions, but no task-related response within the hippocampus. Functional imaging of successful memory processes thus permits us to detect regionally specific responses in the aging brain. Our findings suggest that hippocampal function is preserved in normal aging and that repetition-based memory enhancing techniques may engage primarily neocortical attentional networks.
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1. Introduction

Normal aging is known to be associated with a decline in episodic memory performance, which is particularly striking on delayed recall tasks [1,2,20]. Studies comparing young and elderly healthy adults have suggested that age-related alteration in memory is associated with changes in the synaptic function and neurotransmitter levels, rather than neuronal loss in the hippocampus itself [2,4,5,12,47,56,59]. Thus, alterations in the synaptic connections between the medial temporal lobe (MTL) and neocortical regions may underlie the memory deficits seen in normal aging. However, little is known about how these neurophysiological changes impact functional activity within the aging brain when individuals are performing a memory task. Functional magnetic resonance imaging (fMRI) techniques provide one method for examining this issue.

Although converging evidence strongly supports the conclusion that the hippocampus and related structures in the MTL are critical for normal episodic memory [64], recent functional imaging studies suggest that neocortical regions, particularly the prefrontal cortices, also play an important role in episodic memory performance [9,61,68]. Recent findings related to differences between young and elderly subjects in fMRI activity during episodic memory tasks emphasize the importance of both MTL and neocortical regions for normal memory formation [10,11,24]. A number of studies

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have suggested that healthy elderly and young subjects show similar patterns of hippocampal activation during encoding [24,42,55,58,61], but different patterns of cortical activation, primarily in the prefrontal cortex [11,30,39,46,61]. These findings suggest that age-associated impairments in memory may be related to changes in neocortical activation rather than dysfunction within the MTL.

By extension, these findings suggest that experimental methods that improve memory performance in the elderly may do so by altering the integration of cortical and hippocampal activity. Several methods improve episodic memory in the elderly, but only a few techniques have been shown to benefit the elderly to the point where the age-related difference is eliminated. Repetition has been shown to significantly improve memory performance in elderly subjects [34,37]. In some studies, repeated presentation of the to-be-remembered material has improved memory equally for both young and elderly subjects [44], while in others repetition effects have eliminated the age-related difference in memory performance entirely [48,49]. Likewise, cueing at the time of recall can almost eliminate the age-related difference in memory [20,51]. In contrast, increasing presentation time appears to have an equal benefit for both young and elderly subjects [19]. The changes in the brain that underlie these improvements in performance remain unclear.

In the current study, we wanted to determine whether there are regionally specific neural responses to memory enhancement techniques in older individuals, specifically the pattern of fMRI activation in repeated encoding trials. Memory for proper names is one of the most common memory complaints among elderly persons [38,79] and older adults consistently perform worse than young adults on face–name memory tasks [14,21]. We recently developed an event-related "subsequent memory" fMRI paradigm employing face–name pairs to examine the pattern of activation during the successful formation of novel cross-modal associations. Using this paradigm, we demonstrated that young subjects activate the anterior hippocampus bilaterally and the left prefrontal cortex during the encoding of face–name pairs that were subsequently remembered successfully compared to those that were forgotten [62]. For the current study, we adapted the event-related face–name memory task for use in older adults by enhancing the encoding conditions to improve memory performance. To increase the likelihood of recognition success in elderly adults, we increased the amount of time each face–name pair was presented, reduced the total number of stimuli presented, and used three encoding trials to allow subjects enough time to fully learn the faces and names. This technique has been shown to successfully enhance memory performance in healthy elderly adults, and it is important to understand the neural basis for this effect. The paradigm design allowed us to examine the regional responses to each encoding trial for associations that were subsequently remembered correctly. Based on neurophysiological, neuroanatomical and previous fMRI studies in healthy elderly adults, we hypothesized that the response to stimulus repetition might differ across brain regions. Specifically, we wanted to investigate the response of the hippocampus and neocortical regions to repetitive encoding.

2. Methods

2.1. Study subjects

Twelve right-handed, native English-speaking, healthy elderly subjects (seven females, five males; mean age: 72.6 years, range 65–82 years) participated in this study. None of the subjects had any subjective memory complaints or showed objective cognitive impairment (mean MMSE: 29.5 ± 0.7). All subjects were screened for neurological and psychiatric illness, as well as any contraindications to MRI. None of the subjects were taking prescription or over-the-counter drugs with central nervous system effects. All subjects provided written informed consent in accordance with the Human Research Committee at Massachusetts General Hospital, Boston, MA.

2.2. fMRI activation task

During functional image acquisition, subjects viewed face–name pairs, which consisted of digital color photographs of unfamiliar faces paired with fictional first names printed in white text below the photo on a black background. Before scanning subjects were told that they would be asked to view and remember the face–name pairs. The task was a mixed event-related/block design comprised of 10 runs. Each run included one encoding block and one recognition block. During the encoding block, subjects were presented with four novel faces. Each face was presented three times throughout the encoding block for 4.75 s. The presentation of faces was random, intermixed with a white fixation cross. To control for stimulus complexity during the recognition phase, each face was shown with the same name printed below it three times in a row during encoding. Subjects were instructed to press a key, corresponding to one of the name positions, using a three-button box with their right hand. The encoding task did not have correct or incorrect answers as all three names were identical, but this task ensured that the subjects were awake and responding to both the face and the name in a similar manner to what was required during recognition. Recognition for each face–name pair occurred immediately after the encoding block and after a 5-min delay (i.e., in the subsequent run). In the recognition blocks, subjects were shown each of the faces with three names printed underneath (the correct name, one name previously seen paired with a different face and one distractor name not otherwise seen during the experiment). The position (left, middle or right) of the correct name was counterbalanced for each face shown in the recognition block, and subjects were instructed to press the key corresponding to the name that was correctly associated with the face in the previous run. A total of 40 novel face–name

pairs were encoded three times and recognized twice (initial and delayed recognition) over the course of 10 runs. Verbal instructions were given before each run.

The order and timing of the stimuli presentation were determined using OptSeq (http://www.surfer.nmr.mgh.harvard.edu). Stimuli were presented using MacStim 2.5 on a Macintosh computer and projected via a Sharp XG-2000V color LCD projector (Osaka, Japan) through a colliminated lens (Buhl Optical) onto a rear projection screen. Subjects viewed the screen through a mirror attached to the head coil.

2.3. Image acquisition

Subjects were scanned using a Siemens Allegra 3.0 Tesla scanner (Siemens Medical Systems, Iselin, NJ) with a three-axis gradient head coil. Twenty-nine slices (5 mm, skip 1 mm) were acquired in an oblique coronal orientation, perpendicular to the anterior commissure–posterior commissure (AC–PC) line, in order to maximize in-plane resolutions (3.125 mm × 3.125 mm × 6 mm) and reduce susceptibility artifact within the hippocampus. Functional data were acquired using a gradient echo sequence (TR = 2500 ms, TE = 30 ms and Flip angle = 90°). Ten functional runs were acquired for each subject with 75 time points per run.

2.4. Data analysis

Functional MRI data were preprocessed and analyzed using Statistical Parametric Mapping (SPM99) (Wellcome Department of Cognitive Neurology) for Matlab (Mathworks Inc.). Each subject's functional images were realigned using sinc interpolation to correct for motion artifact. The realigned images were then spatially normalized to the standard SPM99 EPI template based on the MNI 1305 stereotactic space and spatially smoothed using an 8 mm full width half maximum isotropic Gaussian kernel.

Data were analyzed according to a mixed-effects general linear model. First, data were analyzed at the single subject-level, treating all 10 runs as a single time series and modeled with the canonical hemodynamic response function and included regressors for the effect of run number. No slice timing correction was applied and no scaling was implemented for global effects. In order to eliminate low frequency noise, data were analyzed using a high pass filter of 320 s. Second, data were averaged together, treating each subject as a random effect. The random effects analysis determined which regions were the most consistently activated across subjects, using a one-sample t-test with a significance level of $p < 0.001$ (uncorrected), with a minimum extent threshold of five contiguous voxels (resampled SPM voxel size: 3 mm × 3 mm × 3 mm). Due to the small sample size and the susceptibility to noise in older subjects, we were not able to correct for multiple comparisons.

Event-related analyses allowed us to specifically examine activation during individual encoding trials based on the subsequent response during recognition. Due to the small number of incorrect responses, we restricted our analysis to trials, in which the subject subsequently correctly identified the name associated with the face at both first and second recognition. Random effects group averaged statistical activation maps were generated comparing first successful encoding with baseline (SE1 versus fixation), and the subsequent successful encoding trials (SE1 versus second successful encoding (SE2); SE1 versus third successful encoding (SE3)). We then performed region of interest (ROI) analyses using functionally defined ROIs that included all significant voxels within a 6 mm radius of a peak voxel from the contrast SE1 versus fixation using the SPM ROI Toolbox (http://www.spm-toolbox.sourceforge.net). Illustrative time courses of MR signal modulation averaged across the ROI during SE1, SE2 and SE3 were generated with data points plotted every 2.5 s.

To investigate the ROI activation over the three encoding trials statistically, we extracted the mean beta weight across the ROI defined from SE1 versus fixation. The mean beta weight for each subject within the ROI was entered into a repeated measures ANOVA using SPSS. F-tests for the 17 ROIs were considered significant at $p < 0.05$ after Bonferroni correction for multiple comparisons. For the four suprathreshold ROIs, linear and quadratic contrasts were examined to determine the pattern of the response within the region. Contrasts were considered significant at $p < 0.05$, Bonferroni corrected for multiple comparisons.

3. Results

3.1. Behavioral analysis

Successful encoding was defined as encoding of face–name pairs that the subject subsequently chose the correct name associated with the face in both immediate and delayed recognition. Subjects correctly identified the name in $94.3 \pm 8.1\%$ of the first recognition trials and $93.2 \pm 5.4\%$ of the second recognition trials, showing no significant loss of information between immediate and delayed recognition ($p = 0.47$). Reaction time for the first recognition trial was 1.70 ± 0.25 s and 1.88 ± 0.42 s in the second trial ($p = 0.53$). Response time for the encoding task did not influence the likelihood of success, nor did the order of the stimulus presentation.

3.2. Activation patterns for successful encoding

We initially examined activation for the first successful encoding trials versus baseline (SE1 versus fixation). This contrast showed a pattern of activation similar to what we have found in previous face–name associative memory studies in both young and elderly subjects. Significant activation was seen bilaterally in the hippocampal formation: right hippocampus (MNI coordinates x, y, z: 9, −27, −6; Z-score = 4.21) and left hippocampus (−21, −30, −9; Z = 3.42;

Table 1
Anatomical regions showing significantly greater activation in first successful encoding than during fixation

Region	x	y	z	z-score	No. of voxels
Left frontal cortex	−39	21	27	4.73	9
	−33	9	27	4.13	30
	−45	36	3	3.67	11
	−42	24	18	3.42	10
Right frontal cortex	36	33	6	3.78	25
	39	15	27	3.55	11
Left thalamus	−12	−21	0	4.04	14
Left hippocampus	−21	−30	−9	3.42	5
Right hippocampus	9	−27	−6	4.21	29
Left parietal cortex	−30	−54	39	5.26	111
	−45	−30	48	4.15	18
Right parietal cortex	36	−72	18	4.37	129
	54	−18	24	3.90	6
	48	−24	33	3.70	6
Left temporal cortex	−33	−81	−6	4.14	684
Right temporal cortex	42	−75	−3	4.81	748
Right occipital cortex	9	−90	−12	3.54	7

x, y, z denotes stereotaxic coordinates (MNI-space). Z limits for single-tailed p-values: $p = 0.001$, uncorrected.

see Table 1). Additionally, significant activation was observed in multiple neocortical regions: bilateral prefrontal, parietal, fusiform and striate cortices. This pattern was similar to the one we have previously observed during novel encoding with a block design in healthy older subjects [61]. Activation maps comparing SE1 to SE2 (see Fig. 1) and SE1 to SE3 demonstrated significant activation ($p < 0.001$, uncorrected) primarily in the hippocampus and fusiform cortices bilaterally.

3.3. Regional responses to repeated stimulus exposure

In order to further examine regional responses to repeated stimulus exposure, we used a region of interest approach, using functionally defined peak areas of activation determined from the SE1 versus fixation contrast. The MR signal time courses were extracted for first, second and third successful encoding trials from these ROIs (see Fig. 2). The left and right hippocampal ROIs demonstrated a marked increase in MR signal above baseline, while the signal for SE2 and SE3 remained at baseline. Several neocortical regions, in particular the left and right fusiform ROIs, showed evidence of a
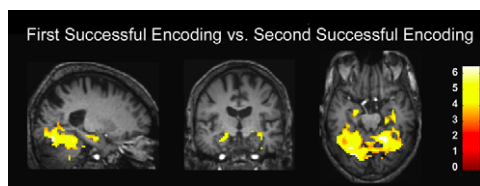

Fig. 1. Statistical parametric map (SPM) of group averaged fMRI activation superimposed on a T1-weighted image of single elderly subject. Activation map for first > second successful encoding trial demonstrates bilateral hippocampal and fusiform activation.

graded response in MR signal over the three encoding trials (see Fig. 2). However, unlike the hippocampus, the MR signal in these neocortical regions showed a signal response above baseline for SE2 and SE3 trials.

In order to determine the degree to which the MR signal response was altered across encoding trials, we extracted the beta weights for each of the ROIs and performed a repeated-measures ANOVA. Polynomial contrasts examining linear and quadratic trends within these ROIs were then generated in order to characterize the response pattern for the beta weights. Four regions demonstrated differences across the three encoding sessions (significant after correction for multiple comparison with Bonferroni procedure, yielding a corrected threshold of $p < 0.0029$): right hippocampus ($F(2,22) = 22.727$; $p < 0.000005$, uncorrected), left fusiform ($F(2,22) = 12.946$; $p < 0.0002$), right inferior parietal ($F(2,22) = 8.621$; $p < 0.0018$) and one left inferior frontal region ($F(2,22) = 9.506$; $p < 0.0018$). The beta weights for the remaining neocortical ROI, including the right prefrontal ROIs, showed a similar response across the three trials. The left fusiform, right parietal, left frontal and right hippocampal ROIs all showed a significant linear contrast ($p < 0.002$), with evidence of a graded decrease in response over the three trials. Only the right hippocampal ROI, however, demonstrated a significant quadratic contrast ($p < 0.002$), with a large positive beta weight value for the initial encoding trial and negligible beta weights for the subsequent trials (see Fig. 3). Although the left hippocampal ROI did not exceed the corrected ANOVA significance threshold overall, it showed a similar pattern of beta weight response to that seen in the right hippocampus, and had a strong trend towards a significant linear contrast ($p < 0.007$) with a weaker trend towards a significant quadratic contrast ($p < 0.097$).

4. Discussion

Our findings indicate that when repetition is used as an encoding enhancement device in healthy older subjects, there is a differential response among the brain regions involved in successful encoding. Specifically, we found that the hippocampal formation activated only during the initial encoding trial, whereas multiple neocortical regions showed continued activation during subsequent stimulus encoding trials. These results, in combination with other recent fMRI studies of older and young adults and our own previous studies using block-design paradigms, suggest that age-related differences in the ability to successfully encode new information may be related to alterations in the neocortical attention network rather than the medial temporal lobe system. Furthermore, this study suggests that techniques that improve memory performance with repeated stimulus exposure may do so by modulating activity in the neocortical attention network.

Our study demonstrated significant activation of the hippocampal formation bilaterally in healthy older adults during
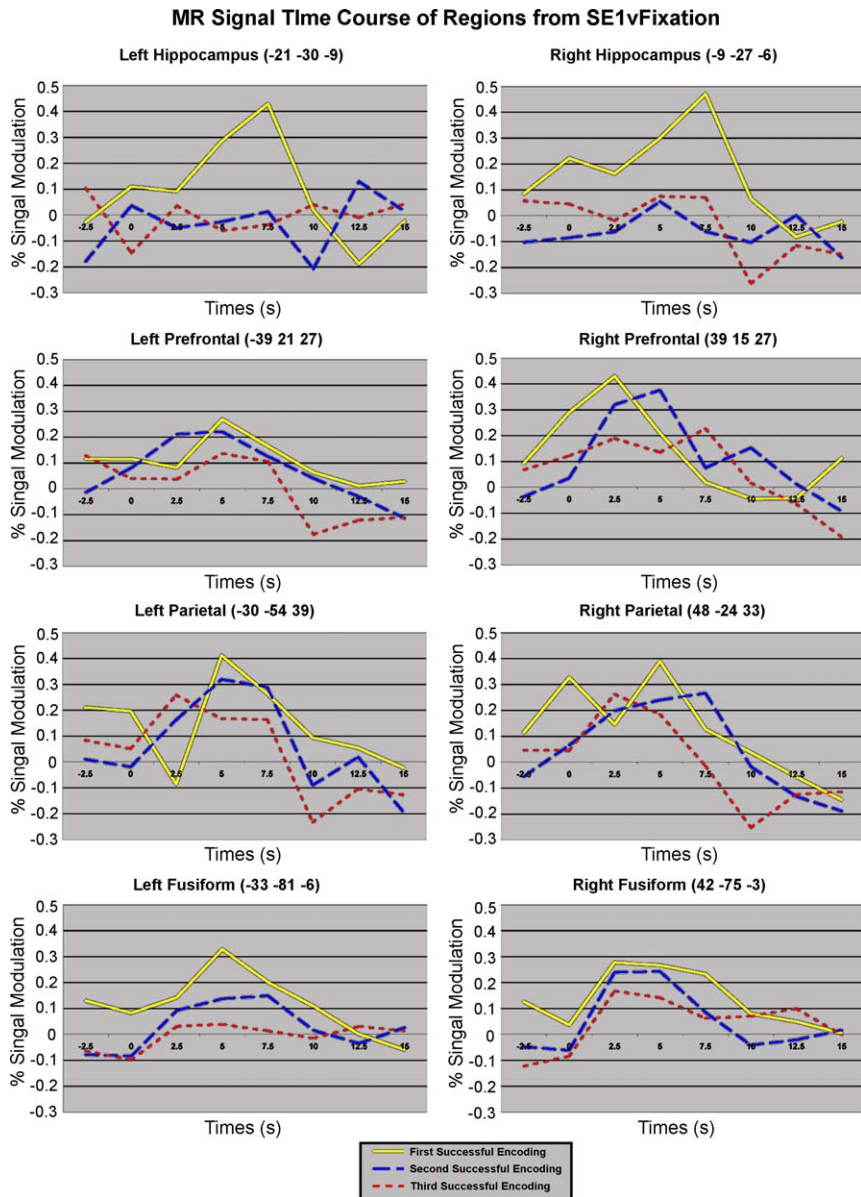
MR Signal TIme Course of Regions from SE1vFixation

Fig. 2. Time courses of MR signal sampled from eight regions of interest (ROIs) selected from activation maps of the first successful encoding trial > fixation. Time course graphs represent percent MR signal modulation for all activated voxels within each region during first, second and third successful encoding trials across time. Hippocampal ROIs showed significant increase in MR signal only for the first successful encoding trial, whereas neocortical ROIs demonstrated increased MR signal above baseline during subsequent stimulus repetition.

the initial encoding trials for face–name pairs that were subsequently successfully remembered. The magnitude and extent of the hippocampal activation is similar to what we have previously reported using a more difficult event-related face–name fMRI paradigm in healthy young subjects [62]. This finding is also consistent with several previous studies suggesting that older subjects show evidence of significant hippocampal activation during encoding of novel stimuli [24,32,55]. A few studies, however, have reported decreased hippocampal activation during encoding in elderly subjects compared to young subjects. A careful review of these studies suggests that the age-related decreases in hippocampal activation may be due to the differences in memory per-

formance between young and elderly adults. A study comparing performance between elderly and young adults on a block-design object and location associative memory task found that in young adults, an area of the left anterior hippocampus was significantly more active in the associative encoding task versus the item encoding condition, but not in older adults [45]. The authors concluded that there was age-related hippocampal dysfunction in working memory for the association of two separate items of information. However, their experiment did not control for successful performance, and older adults had significantly decreased performance on the memory test compared to younger adults.
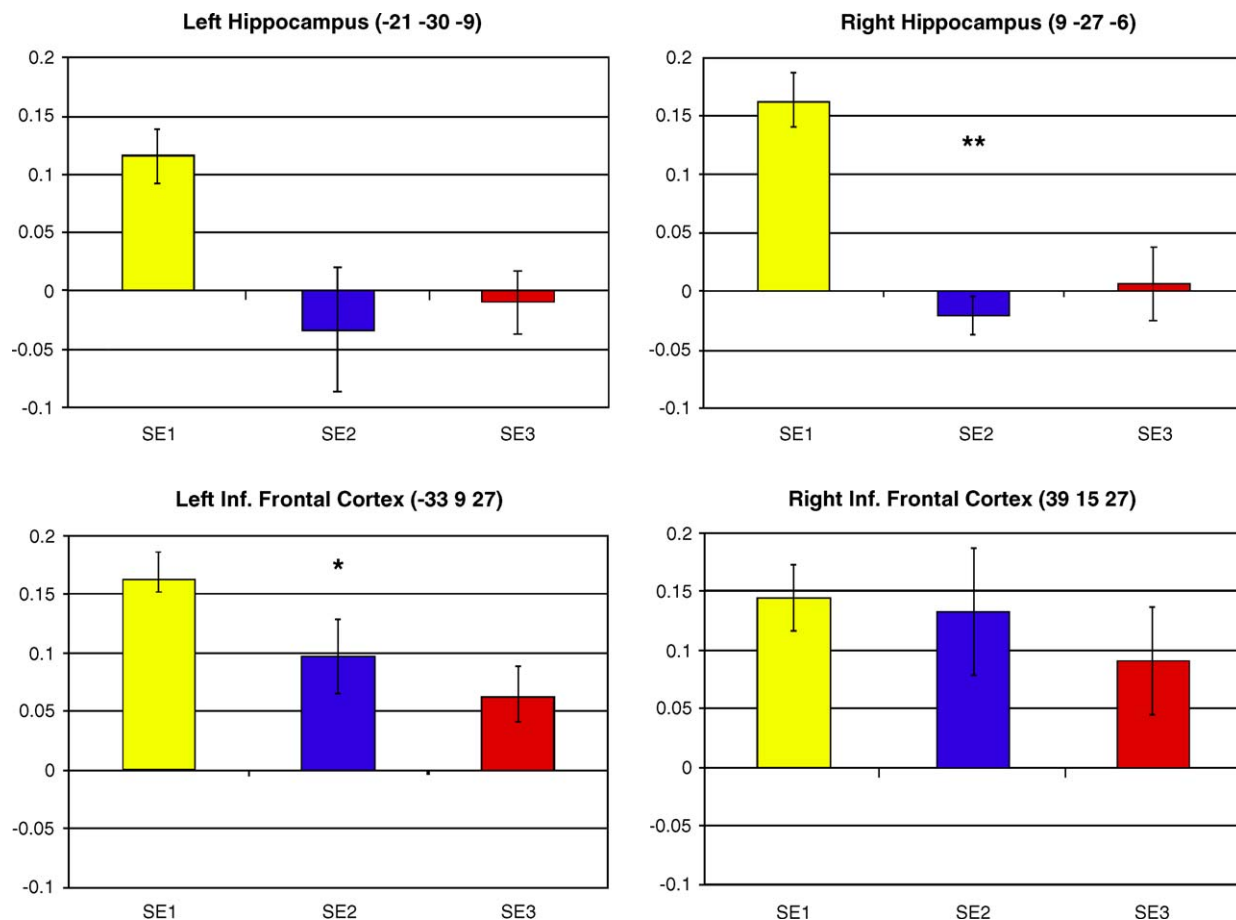
Fig. 3. Bar graphs depicting the beta weights extracted from bilateral hippocampal and selected prefrontal regions of interest (ROIs). Both hippocampi demonstrated evidence of a large positive response during the first successful encoding trial, with negligible response during stimulus repetition. The right hippocampus demonstrated a significant quadratic contrast (marked with (**)) across the three encoding trials. The prefrontal regions demonstrated a similar initial response but continued to show a response to the second and third trials. The left inferior prefrontal region did demonstrate a significant linear contrast (marked with (*)) with a graded decrease over the three encoding trials.

Consistent with the hypothesis that the degree of hippocampal activity is related to task performance rather than pure age effects, a study comparing young and elderly subjects for recall of abstract geometric patterns on a block-design paradigm reported that hippocampal activation was correlated with successful memory performance [32]. This study found that although elderly subjects showed less hippocampal activation than young adults, there was a significant positive correlation between overall hippocampal activation during initial learning blocks and subsequent success rates. Similarly, an event-related fMRI study comparing successfully encoded items to fixation also showed patterns of significant MTL activation for successful encoding in healthy elderly and young subjects [24]. However, elderly subjects with memory deficits showed significantly less activation in the left anterior MTL. This suggests that when controlling for memory performance by comparing healthy older adults who perform comparably to young subjects, there is no evidence of hippocampal impairment in older subjects. In our current study, we restricted the analysis to the encoding trials for face–name pairs that were successfully remembered

both immediately and after a 5-min delay. We demonstrated clear evidence of significant hippocampal activation during the initial encoding trial in our older subjects.

Interestingly, our group of older subjects did not show any evidence of hippocampal activation during repeated stimulus exposure. Our study did not directly compare young and older subjects, as this repetition paradigm was designed specifically to enhance encoding in older subjects, and would have not have been appropriate for use in younger subjects. Thus, we cannot definitively state how the patterns of activation we observed in this experiment would compare with those of young subjects, but we can make inferences based on results from other studies. In our own studies, we have observed similar decreased hippocampal responses to repeated face–name stimuli in our previous block-design paradigms in both young and older subjects [61,63]. A recent study from another research group, also using a block-design face–name encoding task in young subjects, with four repetitions of the same set of face–name pairs, demonstrated significant activation (compared to a fixation baseline) within specific subregions of the hippocampal formation for the first encoding trial

[78]. Similar to our observations in older subjects, the young subjects in that study also showed significantly reduced hippocampal activation on each subsequent encoding trial.

In contrast to the pattern observed in the hippocampus, the older subjects in this study demonstrated continued activation in multiple neocortical regions to repeated stimulus exposure. During the first successful encoding attempt, we observed significant activation in the fusiform and left prefrontal cortices, similar to our previous study in young subjects during successful encoding [62]. Interestingly, in the present study, we also found activation in the right prefrontal and bilateral superior parietal cortices, which are regions that are not as consistently activated in young subjects during encoding. Our results are consistent with multiple studies reporting that normal aging is associated with altered patterns of activation in prefrontal regions compared to young subjects [30,39,54,65]. Studies in young subjects have suggested that activation of the left prefrontal cortex is crucial for episodic memory processes, particularly successful memory formation [46,62,71]. Conversely, research in older subjects on a verbal memory task found that older subjects showed decreased left prefrontal activation compared to young subjects, and this decrease is positively correlated with a decrease in memory ability in older subjects [65]. Furthermore, both PET and fMRI studies comparing high performing older subjects with young subjects show greater bilateral prefrontal activation in older subjects during encoding [10,11,39,46]. Taken together, these studies suggest that increased prefrontal activation, particularly the bilateral recruitment of these regions in older subjects, may represent a compensatory response to maintain memory performance. Although we do not have a direct comparison with a young group on this paradigm, we hypothesize that a similar compensatory mechanism in our older subjects may explain our finding of continued activation in the prefrontal cortex and other neocortical regions on the second and third learning attempt.

Priming studies have demonstrated evidence of decreases in neural activation in neocortical regions for previously seen items. Several studies in young healthy individuals have shown significant activation for initial visual processing of an object and reduced activation for repeated processing of that object in the fusiform and lateral occipital cortices [7,8,31,35,43,57,67], as well as the prefrontal cortices [23,25,26,43,52,69,70]. The majority of the neocortical regions we examined showed no evidence of significant repetition suppression to repeated stimulus exposure. We did see evidence of a linear decrease in activation in a subset of the neocortical regions that were initially activated. However, these regions showed clear evidence of some response above baseline to the second and even third encoding trials. Interestingly, only one of the prefrontal regions, the inferior left prefrontal cortex, showed a statistically significant decrease in activation with stimulus repetition. The location of this left inferior prefrontal region, in our older subjects, was very similar to the left inferior prefrontal region, which predicted the likelihood of successful subsequent memory in our previous

study with young subjects [62] and in several other similar subsequent memory studies [6,68]. Furthermore, our functional connectivity analyses conducted in young subjects suggested that activity in the left inferior prefrontal region was highly correlated with bilateral hippocampal activity [62]. The most striking suppression of activation in our paradigm was observed in the hippocampus, which demonstrated no response above baseline to either the second or third encoding trial. Our finding that specific neocortical regions show continued activation to stimulus repetition suggests that compensatory activation is occurring outside the network subserving successful memory for this paradigm in young subjects.

A recent study of priming effects, which compared young and elderly subjects on a repetitive semantic classification task, reported that both young and healthy elderly subjects demonstrated repetition priming suppression in the prefrontal cortex [40]. At first pass, these findings might seem somewhat contradictory to our results, since we did not find this suppression effect in the right prefrontal cortex, and found evidence of modulation in one left prefrontal subregion. However, the designs of the two studies differ significantly. The priming study [40] utilized an incidental encoding task that required a semantic classification judgment, so specific compensation mechanisms for intentional memory tasks may not have been engaged. Furthermore, in their study, the first three presentations of the "old" words occurred prior to scanning, thus the activation pattern during scanning presented for "old" words began with the fourth presentation of each word. In our study, we scanned only during the first three encoding trials of the face–name associations, and it is possible that if we had examined additional repetitions over a longer time period, then we would have observed more evidence of neocortical suppression in our older subjects. Finally, the priming study [40] did not demonstrate hippocampal activation during presentation of novel or old words, and thus it is unclear whether there were any differences between hippocampal and neocortical responses to repeated stimulus exposure in their study. Further studies directly comparing incidental encoding during priming to stimulus repetition during intentional encoding task may clarify whether additional neural recruitment is related to specific task demands in older populations.

Interestingly, the parietal cortex has also been shown to activate more in elderly subjects than in young subjects on episodic memory tasks [10,61]. Several neuroimaging studies have shown a network of parietal, frontal and often anterior cingulate activation during demanding attentional tasks [3,17,22,41,75,76]. Our own previous work comparing young and older subjects using a block-design face–name paradigm also demonstrated that the greatest age-related alterations in activation were found in prefrontal and parietal cortices [61]. In our current study, regions known to be involved in this attentional network (i.e., bilateral prefrontal and parietal regions) all continue to activate during subsequent encoding trials, while the hippocampus does not. The striking regional specificity of the response to repeated stimulus exposure, taken in combination with other recent fMRI studies in aging

and our own previous studies using block-design paradigms, suggests that age-related differences in the ability to successfully encode new information are related to alterations in the neocortical attentional network, rather than the medial temporal lobe system. Furthermore, this study provides evidence that techniques that improve memory performance with repeated stimulus exposure may do so by virtue of modulating activity in the neocortical regions subserving complex attention.

The regionally specific pattern of functional MRI activation reported here is also consistent with what is known about neuropathological alterations and structural imaging data in aging. Stereological cell-counting studies have shown minimal cell loss in the medial temporal lobe, including the entorhinal cortex and most subfields of the hippocampal formation with the exception of the subiculum [2,28,29,47,72–74]. Recent studies have suggested that age-related atrophy may be primarily related to white matter loss [50,66]. Further research using structural MRI has suggested a relatively small decrease in MTL volume in normal aging [15,27,36] and this loss is not statistically related to memory impairment [77]. However, several structural MRI studies have reported frontal [13,16,18,33,53] and parietal association cortex atrophy in aging [60]. Taken together, these studies suggest alterations in cortical structure and functional connectivity may be responsible for age-related deficits in memory, rather than the minimal alterations in MTL structures.

It is important to acknowledge the limitations of this study. First, we do not have data using the identical paradigm to directly compare young and older subjects. Thus, we can draw only limited inferences regarding the effects of aging, based on comparisons to our previous work with related paradigms and other reports in the literature in young and older adults. Unfortunately, the scanner used for this study underwent a major upgrade after 12 healthy elderly subjects were scanned, and we were unable to subsequently add a young control group or additional older subjects. Secondly, we did not have a sufficient number of face–name pairs that were incorrectly remembered to permit a valid comparison of successful versus failed memory processes in aging, and thus we restricted our analyses only to successfully encoded associations. We are pursuing variants on this paradigm to examine both young and older controls, as well as cognitively impaired older individuals. Finally, although we restricted our analyses to face–name pairs that were subsequently correctly remembered, we did not test memory after each encoding trial. The immediate recognition task may also have contributed to successful delayed recognition, but the comparison between immediate and delayed recognition was important to determine exactly how well the information was encoded and whether it was retained over the delay. Thus, it is difficult to determine how much additional information was encoded on each subsequent trial. Nevertheless, our data did demonstrate an interesting divergence of hippocampal and neocortical responses to repetitive encoding, which may serve to elucidate the neural mechanisms responsible for repetition enhanced memory performance.

In summary, we found that healthy older subjects demonstrate significant hippocampal activation during initial encoding trials, consistent with neuropsychological, neuroanatomical and neuropathological data, suggesting that the MTL memory system is largely preserved in the process of normal aging. We demonstrated a striking difference between hippocampal and neocortical responses to subsequent encoding trials. Consistent with our previous block-design studies, we found that older subjects continued to activate neocortical regions during repeated stimulus exposure, particularly in the bilateral prefrontal and superior parietal cortices, regions that have been implicated in maintaining complex attention. Furthermore, the differential responses of the hippocampus and neocortical regions to subsequent encoding trials suggest that techniques that improve memory performance with repeated stimulus exposure may do so by virtue of modulating activity in neocortical attentional networks.

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