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The role of hippocampus and frontal cortex in age-related memory changes: a PET study

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THE purpose of this study was to examine the neuroanatomical correlates of explicit retrieval of episodic memories in older and young adults. We used an experimental paradigm that allowed us to separate the effort involved in attempting to retrieve a recently studied word from the actual recollection of the item. Both older and younger adults showed hippocampal blood flow increases in association with recollection of a studied word. In contrast, younger but not older adults showed bilateral blood flow increases in anterior prefrontal cortex during retrieval attempts: older adults showed more posterior frontal lobe activations during attempted retrieval. We conclude that the hippocampus activations may reflect a commonality in the way that older and younger adults remember past events, whereas differences in frontal activation may reflect age-related changes in their retrieval strategies.

Key words: Positron emission tomography; Memory; Aging; Hippocampal formation; Frontal lobes

Introduction

Memory for recent episodes tends to decline as people age. It has been proposed that such memory loss is associated with alterations in the hippocampal formation[1,2] and frontal cortex,[3] brain regions that contribute importantly to episodic memory.[4–7] The specific role played by these structures in age-related memory impairments remains an unresolved though central issue. Recent research using positron emission tomography (PET) has revealed diminished hippocampal activation in elderly adults during encoding of episodic information.[8] In this study we examined retrieval of episodic memories in older adults with a paradigm that allowed us to separate the effort involved in retrieving recently studied information from the actual recollection of it. In a previous study we found that prefrontal activation was related primarily to retrieval effort or attempt, whereas hippocampal activation was related to successful recollection of studied words.[8] Here we report equivalent hippocampal activation in older and younger adults during explicit retrieval of recently studied words, together with age-related differences in prefrontal activation.

Materials and Methods

PET images of regional cerebral blood flow were obtained in eight elderly (mean age 67.9 years) and eight young (mean age 20.5 years) healthy volunteers using a General Electric-Scanditronix PC4096 15 slice whole body tomograph. The PET facilities and procedures have been described previously in detail.[10,11] PET data were acquired while volunteers inhaled $[^{15}O]CO_2$ gas, beginning 30 s after initiation of the task and finishing 60 seconds later. Following motion correction and transformation to Talairach space,[12] the mean concentration in each run was normalized to 50 ml/min/100 g, and rescaled and smoothed with a two-dimensional 20 mm (full-width half maximum) Gaussian filter. Pairwise subtractions were then performed, yielding images of mean difference and standard deviation, from which t-values were computed and converted to z-scores to produce statistical parametric maps (SPMs). Each SPM was inspected for regions of activation with z scores >3.00 ($p<0.001$, uncorrected for multiple comparisons) for unplanned comparisons, and $z>2.58$ ($p<0.005$) for planned comparisons involving the hippocampal formation and prefrontal cortex.

A gantry held a computer monitor, with the screen tilted so that it was visible from within the PET camera. During each of eight scans, volunteers viewed three-letter word stems for up to 5 s each (see Table 1 for schematic of experimental design). For the first and eighth scans, participants said the first word that came to mind (baseline condition); during scans two through six, subjects tried to recall words from a study list. By manipulating how subjects studied these words, we created one condition in which subjects remembered many target words (high recall condition) and another in which they remembered few words (low recall condition).

During each of three (non-scanned) study conditions, subjects were presented with 48 different words (40 target plus 8 buffers) and completed one of two different encoding tasks: (1) a perceptual encoding task (counting t-junctions), repeated once for each of 20 targets (low recall words); and (2) a semantic encoding task (counting word meanings), repeated four times for each of the other 20 targets (high recall words). The encoding tasks were followed by two scanned recall conditions in which subjects were instructed to complete three-letter stems with words from the study condition; during one scan, stems could be completed with low recall words and during the other they could be completed with high recall words. The order of scanned conditions within each study-test unit and the items assigned to each condition were completely counterbalanced across subjects.

Table 1. Experimental design

Condition	Scanning status
Practice Trials	Transmission Scan
Baseline	PET Scan 1
Study-test unit 1	
Study (Encoding)	Offline
High Recall	PET Scan 2
Low Recall	PET Scan 3
Study-test unit 2	
Study (Encoding)	Offline
Low Recall	PET Scan 4
High Recall	PET Scan 5
Study-test unit 3	
Study (Encoding)	Offline
High Recall	PET Scan 6
Low Recall	PET Scan 7
Baseline	PET Scan 8

Forty-eight familiar words were presented during each study phase (40 target words plus 8 buffers). High recall words appeared four times during the study phase and subjects made semantic encoding judgments about them; low recall words appeared once and subjects made nonsemantic judgments about them. High recall and low recall words were then tested in separate scans using three-letter word beginnings as cues; subjects were instructed to complete them with words from the study list. During the baseline scans, subjects completed three-letter stems of nonstudied words with the first word that came to mind. The order of high recall and low recall scans, and the assignment of items to the different experimental conditions, was completely counterbalanced across subjects.

Results

Behavioral data confirmed that both old and young subjects remembered significantly ($p < 0.0001$) more words from the high recall condition (old = 0.65, young = 0.79) than from the low recall condition (old = 0.26, young = 0.35); the young recalled more words than the old in both conditions ($p = 0.005$). Baseline levels of performance were comparable in old (0.16) and young (0.19).

Analyses of PET images from the elderly subjects revealed significant blood flow increases in the hippocampal formation in both the high recall minus baseline and high recall minus low recall comparisons, bilaterally in the former comparison and on the right in the latter (Table 2; Fig. 1). In each comparison, younger and older adults showed similar patterns of hippocampal blood flow increases, as reflected in z-score units and location of change. Following the logic of our experimental design, brain regions associated with the effort to recall target words should show blood flow increases in the low recall condition, whereas regions associated with the actual recollection of target words should show blood flow increases in the high recall condition. Accordingly, we conclude that hippocampal blood flow increases reflect some aspect of actual recollection of a target word from the list.

The low recall minus baseline comparison revealed blood flow increases in the frontal lobe, but the pattern of increases differed in old and young (Table 2; Fig. 1). Previous PET studies have consistently documented blood flow increases in anterior regions of the right frontal lobe during episodic retrieval,[10,20,21] which are associated with effortful search of episodic memory.[16,22–24] The low recall minus baseline comparison revealed extensive right anterior frontal lobe blood flow increases in young subjects, centering on Brodman Area 10, but no significant increases in old subjects (maximum pixel for elderly, $z = 2.14$). Young people showed in addition significant increases in the left anterior frontal region, also principally involving BA 10, whereas older adults showed only trends (maximum pixel value, $z = 2.55$). Between-group comparisons revealed significant age effects in both right and left BA 10 in the low recall condition ($p < 0.05$), together with non-significant age differences for the same areas in the baseline condition. By contrast, older adults showed blood flow increases in more posterior frontal regions during low recall minus baseline that were not activated in young people: right area 46, left Broca's area (BA 45), and also the right motor area (BA 4/6; Table 2), although older adults did not show significantly greater activations than younger subjects in these areas when between group comparisons were made. In the low recall minus high recall comparison both older and younger adults showed

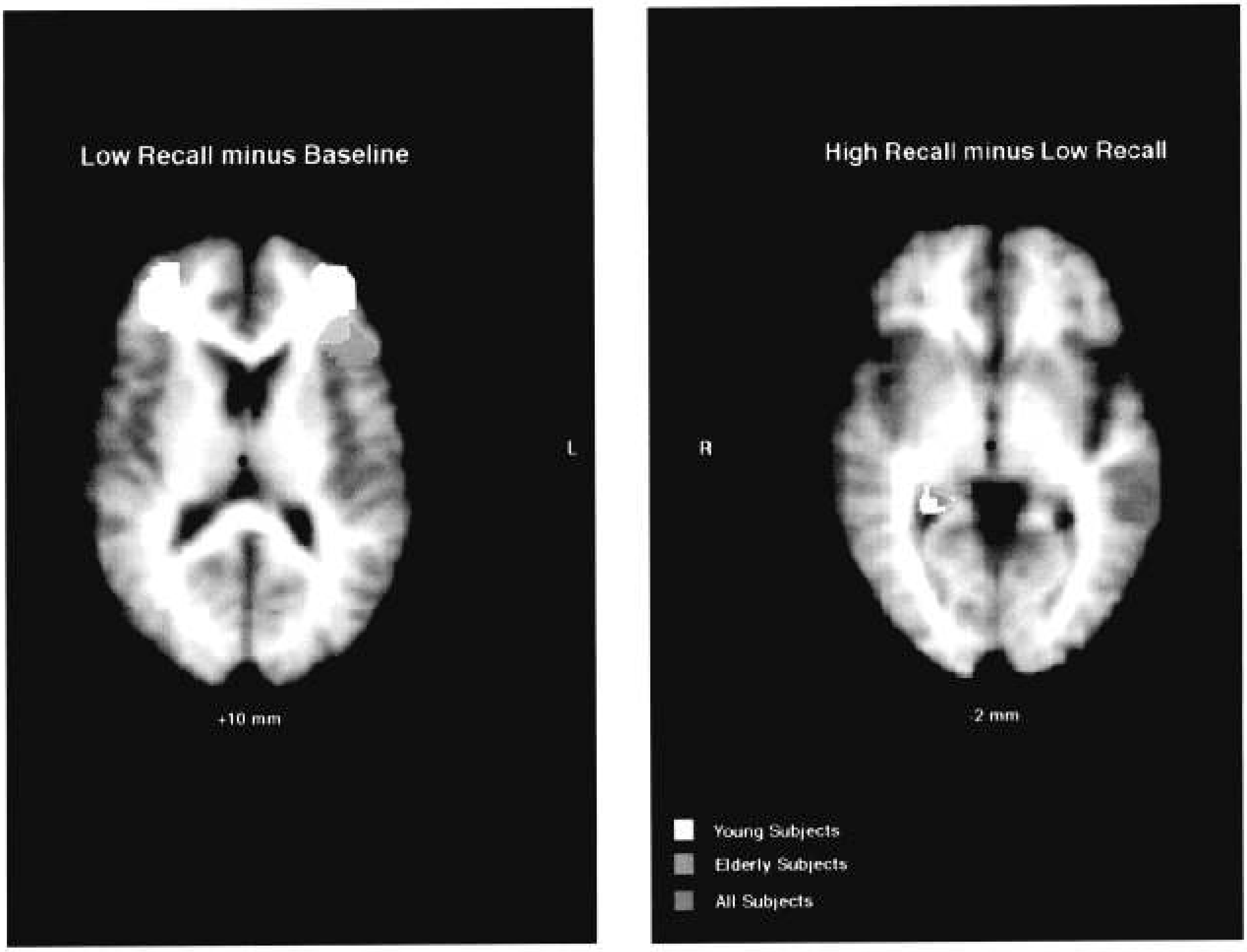

FIG. 1. PET statistical maps showing regions of activation co-registered with an average magnetic resonance image (MRI), transformed to Talairach space.[12] Activations include all pixels with a z-score $\geq$2.00, represented in green for elderly subjects, yellow for young subjects, and red where groups overlap. Images are transverse sections, with coordinates reflecting distance in millimeters from the AC-PC plane. The high recall minus low recall image shows a region of activation associated with high levels of explicit recall in the vicinity of the right hippocampus, present in both groups. The low recall minus baseline images show regions of activation associated with high effort and low explicit recall in bilateral prefrontal cortex (area 10) for young subjects and left area 45 (Broca's area) for elderly subjects. Other regions of significant activation are listed in Table 2.

anterior frontal lobe blood flow increases, primarily on the left. However, older adults again showed a significant increase in Broca's area that was not found in the young.

We also observed additional blood flow increases in young people that are described in another report,[9] and older adults showed the same increases, with some exceptions. For example, in the low recall minus baseline recall comparison, there were blood flow increases in the right anterior cingulate for young but not old subjects, which may be related to such attentional processes as selection of target responses.[13–14] Additional findings with elderly adults will be described in a separate report.

Discussion

Older and younger adults showed equivalent activation of hippocampal regions in association with successful recollection of studied words. As discussed elsewhere, the exact features of recollection that are related to hippocampal activity remain to be elucidated.[9,15] Because older and younger adults showed similar hippocampal blood flow increases in the High Recall condition, the present findings suggest that the features of recollection indexed by hippocampal activity operate similarly in old and young. For example, it has been proposed that the hippocampal formation performs an automatic pattern completion retrieval operation,[2,16–18] and this mechanism may operate similarly in older and younger people. The subjective correlate of this process may be expressed as confidence in a recalled item, which is generally preserved in older adults.[19] The fact that older adults remembered fewer items than younger adults in the high recall condition probably reflects inadequate encoding of target information during the study task.[8] However, once encoded, information is not forgotten at a faster rate in older adults than in the young.[20]

In comparison to the young, older adults showed

Table 2. Primary regions of interest exhibiting significantly increased activation associated with Explicit Recall

Contrast	Region	Z Score*	Coordinates†
Elderly Subjects			
Low Recall – High Recall	L Prefrontal (Area 10)	3.24	–8, 58, 8
	L Area 44 (Broca's Area)	3.25	–54, 14, 16
	R Orbitofrontal (Area 11)	2.89	35, 35, –12
	Anterior Cingulate	3.65	–1, 17, 36
Low Recall – Baseline	R Frontal (Area 46)	4.36	33, 23, 24
	R Motor (Area 4/6)	3.25	55, 2, 16
	L Area 45 (Broca's Area)	3.00	–36, 29, 8
High Recall - Low Recall	R Hippocampal	4.34	22, –31, –8
High Recall - Baseline	L Hippocampal	2.83	–22, –31, –8
	R Hippocampal	3.22	21, –28, –4
Young Subjects‡			
Low Recall – High Recall	L Prefrontal (Area 10/46)	3.81	–31, 43, 8
	L Anterior Cingulate	3.25	–7, 15, 32
	L Precuneus (Area19)	3.70	5, –72, 32
Low Recall - Baseline	R Orbitofrontal (Area 11)	3.25	5, 35, –12
	R Anterior Cingulate	3.77	7, 34, 0
	L Prefrontal (Area 10)	3.47	–35, 54, 8
	R Prefrontal (Area 10)	3.12	30, 46, 8
	R Prefrontal (Area 9)	4.04	12, 47, 28
High Recall - Low Recall	R Hippocampal	2.82	25, –34, 0
High Recall - Baseline	L Hippocampal	3.38	–19, –39,. –4
	R Hippocampal	3.96	15, –37, 0

*Values represent the maximum pixel (z score units) within the region of interest from the statistical parametric map.
†Maximum pixel coordinates in Talairach space (Talairach & Tournoux, 1988), expressed as "x,y,z"; $x>0$ is right of the midsagittal plane, $y>0$ is anterior to the anterior comissure, and $z>0$ is superior to the AC-PC plane.
‡ Data for young subjects have been previously reported and discussed in Schacter *et al* (in press)

markedly different patterns of prefrontal activations during attempts to remember low recall words, most notably bilateral anterior frontal blood flow increases in low recall minus baseline in the young together with a shift toward more posterior frontal activations in the older adults. Both older and young adults showed significant left frontal blood flow increases in the low recall minus high recall comparison, suggesting that the age-related decrease in anterior frontal activation, particularly on the right, reflects a problem in engaging or initiating the episodic retrieval mode.[21,22] We propose that when switching from lexical or semantic retrieval (baseline) to difficult episodic retrieval (low recall), older adults relied on inefficient retrieval strategies. For example, the activation of Broca's area in old but not young in the present study suggests that older adults may rely inappropriately on a phonetic search strategy.[23] Other PET evidence indicates that older adults can show anterior frontal activations relative to a non-memory control condition without additional activation of Broca's area during recognition of faces, which probably involves different kinds of retrieval processes than those examined here.[8]

Consistent with the idea that older adults have selective difficulties switching from lexical to episodic retrieval strategies (i.e. baseline to low recall), in the low recall minus high recall comparison both older and younger adults showed anterior frontal lobe blood flow increases, primarily on the left. Previous research has revealed that elderly adults may show blood flow increases when performing some lexical generation tasks akin to the one used in our baseline condition,[24] raising the possibility that non-significant blood flow increases in older adults in the low recall minus baseline comparison could reflect increased blood flow during baseline in the older subjects. However, when we directly compared estimates of blood flow in old and young during the baseline condition in regions where young showed significant blood flow increases but elderly did not, we found no significant differences, thus making it unlikely that age-related differences in blood flow during the baseline task account for our results.

A recent PET study by Grady *et al*[8] revealed that young people show hippocampal blood flow increases during encoding of unfamiliar faces, consistent with previous evidence of hippocampal activation during encoding of novel information,[25] but older adults did not show such increases. Although there are many differences between the Grady *et al* study and ours, including non-verbal *vs* verbal materials and encoding *vs* retrieval, the combined findings suggest that the hippocampus carries out different functions during encoding and retrieval, with the hippocampal contribution to encoding of novel information being more vulnerable to aging than its contribution to retrieval of well-learned information. Previous conceptions of hippocampal contributions to age-related memory deficits have been broadly stated, and have not distinguished between hippocampal contributions to encoding and retrieval or other specific aspects of memory.[1-2] Our results indicate that the role of the hippocampal formation in age-related memory deficits is more circumscribed than was previously suspected, and thus encourage a conception of aging memory that focuses on selective impairments to specific processing structures.

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General Summary

Numerous studies have revealed that memory tends to decline as people age, but little information is available about the neuroanatomical correlates of age-related memory functions. Here we report a PET study that examines retrieval of episodic memories in older and younger adults with an experimental paradigm that allows us to separate out the effort involved in attempting to retrieve a recently studied word from the actual recollection of the item. Both older and younger adults showed hippocampal blood flow increases in association with the actual recollection of a studied word, thereby providing the first PET evidence of normal hippocampal activation in older adults. In contrast, younger but not older adults showed bilateral blood flow increases in the anterior prefrontal cortex in a condition designed to maximize retrieval effort; older adults showed more posterior frontal lobe activations during this effortful retrieval. We conclude that the hippocampal activations may reflect a commonality in the way that older and younger adults remember past events, whereas differences in frontal activations may reflect age-related changes in retrieval strategies.