

# Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects

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## Summary

Lesion studies have shown convincingly that the medial temporal lobes (MTL) and frontal lobes are critical to episodic memory. Ageing generally has been found to have a generally negative effect on episodic memory performance, which might relate to neurofunctional changes in the frontal and medial temporal brain regions. In the present study, we used functional MRI (fMRI) to investigate separately the contributions of encoding and retrieval to the age-related decline in memory. To this end, we compared brain activity patterns obtained during incidental encoding (pleasant/unpleasant judgements about nouns) and subsequent retrieval (recognition) in three groups: a group of young subjects, a group of elderly subjects showing reduced memory performance (ELD-RED), and a group of elderly subjects who still performed in the normal range (ELD-NORM). This allowed us to differentiate between age-related changes in brain activity that affect memory function and those that do not have an apparent effect on memory function, because they are found in both elderly groups. Contrary to previous imaging studies on this topic, we used (self-paced) event-related fMRI to control for differences in per-

formance level across groups by including correct responses only. Comparing the encoding of successfully remembered items with baseline (press left/press right), the young subjects showed a significant increase in brain activation in the left anterior MTL compared with the ELD-RED but not the ELD-NORM subjects. Comparing correctly rejected items (retrieval attempt) with baseline, the ELD-RED group showed much increased overall activity throughout the brain compared with the other groups. However, when correctly recognized items (retrieval attempt + success) were compared directly with correctly rejected items (retrieval attempt), these differences were greatly reduced, revealing common activity in the left parietal, retrosplenial and left anterior prefrontal regions. Therefore, we conclude that the reduced performance in the ELD-RED group is likely to be due to MTL dysfunction during encoding. The differences observed during retrieval attempts may reflect strategic differences. The lack of differences observed in relation to retrieval success suggests that ageing does not affect the processes that support the actual recovery of information.

**Keywords:** functional MRI; ageing; encoding; retrieval; medial temporal lobe

**Abbreviations:** CREC = correctly recognized words; CREJ = correctly rejected words; ELD-RED = elderly subjects with reduced memory performance; ELD-NORM = elderly subjects with normal memory performance; fMRI = functional MRI; MMSE = Mini-Mental State Examination; MTL = medial temporal lobes; SPM = Statistical Parametric Map

## Introduction

It has generally been found that performance on episodic memory tasks declines with increasing age. This decline seems to be a result of anatomical and physiological degradation of the brain as a consequence of the ageing process (Coleman and Flood, 1987). Behavioural studies indicate that ageing impairs both episodic encoding and retrieval processes. The involvement of encoding in age-

related memory decline has been indicated by studies showing that young subjects benefit more than elderly subjects from the level of processing of words to be remembered ( Craik and Lockhart, 1972; Burke and Light, 1981). This finding indicates, as one source of age-related memory difficulties, that elderly people encode the meaning of new information less thoroughly. A role for retrieval is

indicated by the finding that, although an age-related deficit can be observed during both recall and recognition tasks, the deficit is generally larger for recall. This difference has been attributed to fewer memory search requirements in recognition tasks (Burke and Light, 1981; Craik and McDowd, 1987). However, isolating encoding from retrieval processes in a behavioural setting is problematic, because a reduced test score reflects the contribution of both episodic encoding and retrieval. This problem is greatly reduced when neuroimaging techniques such as functional MRI (fMRI) are used, because measures of brain activity can then be obtained during both episodic encoding and retrieval.

Neuroimaging studies in young subjects have by now revealed important information on the functional neuroanatomy of human memory function. In line with findings from lesion studies, the medial temporal lobes (MTL) and the frontal lobes have been pointed out as important sites for both episodic encoding (e.g. Stern *et al.*, 1996; Gabrieli *et al.*, 1997; Rombouts *et al.*, 1997) and retrieval processes (e.g. Buckner *et al.*, 1995, 1996; Nyberg *et al.*, 1996). In addition, different activity patterns have been observed in relation to episodic encoding and retrieval. Regarding the frontal lobes, these findings have been integrated in the HERA (hemispheric encoding and retrieval asymmetry) model, which states that the left prefrontal cortex is more involved in episodic encoding, whereas the right prefrontal cortex is called upon specifically during the retrieval of episodic information (Tulving *et al.*, 1994). However, there are also indications of material-dependent lateralization of the frontal lobes. Mainly left-lateralized frontal activity has been observed for verbal stimuli, whereas more right-lateralized frontal activity has been found for non-verbal study material during both episodic encoding and retrieval (e.g. Kelley *et al.*, 1998; Wagner *et al.*, 1998a; Golby *et al.*, 2001).

The findings concerning the MTL are less consistent. One aspect is that the MTL is more reliably activated during encoding than during retrieval (Schacter and Wagner, 1999). Furthermore, indications have been provided that the anterior part of the MTL is more involved in retrieval, whereas the posterior part is associated with encoding processes (Gabrieli *et al.*, 1997; Schacter and Wagner, 1999; Rombouts *et al.*, 2001).

Some neuroimaging studies have also begun to identify changes in functional neuroanatomy that may underlie age-related decline in episodic memory function. However, these studies have provided mixed results. With respect to episodic encoding, Grady and colleagues (Grady *et al.*, 1995) found reduced activity in the MTL and frontal areas for elderly compared with young subjects using faces as study items. Cabeza and colleagues (Cabeza *et al.*, 1997) also found reduced activity in the left prefrontal cortex and occipitotemporal regions during encoding of word pairs. However, Madden and colleagues (Madden *et al.*, 1999) reported generally increased activity during encoding of words in old compared with young subjects.

The findings concerning retrieval have centred mainly on the prefrontal cortex. Contrary to their findings for the encoding of faces, Grady and colleagues did not observe age differences in brain activity during face recognition. However, several other studies did report age-related retrieval differences. Schacter and colleagues (Schacter *et al.*, 1996) found that frontal activity during recall of word pairs was located more posteriorly in older subjects compared with young subjects. A number of other studies (Cabeza *et al.*, 1997, 2001; Madden *et al.*, 1999) found more bilateral retrieval-related frontal activity for old compared with young subjects. The findings of reduced left prefrontal activity during encoding and more bilateral retrieval-related frontal activity during retrieval for old compared with young adults have been integrated in the HAROLD (hemispheric asymmetry reduction in old adults) model, which states that young subjects, in line with the HERA model, engage the left frontal cortex more heavily during encoding and the right frontal lobes during retrieval, whereas elderly subjects show more bilateral frontal activity during encoding and retrieval, presumably reflecting compensatory mechanisms (Cabeza *et al.*, 2001).

Apart from differences in experimental design, a possible source of the inconsistent findings mentioned above is that these previous studies, except for the study by Cabeza and colleagues (Cabeza *et al.*, 1997), did not control for the differences in performance level that were found between the groups of elderly and young adults. Since items that have resulted in an incorrect response are very likely to have been processed differently by the brain compared with items that are followed by a correct response, it is conceivable that the differences in brain activity observed in these previous studies were due merely to differences in error rates between the groups. Event-related fMRI, a method of studying item-specific activity patterns (Buckner *et al.*, 1996; Josephs *et al.*, 1997), provides a means to deal with performance differences by selecting only brain activity patterns that are specifically associated with correct responses.

Another methodological problem in these previous studies is that they do not distinguish age-related changes in brain activity that affect memory function from changes that do not have an effect on memory performance. Therefore, more insight would be obtained if three different groups were compared: a group of young subjects, a group of elderly subjects with reduced memory function, and a group of elderly subjects whose memory performance is still intact. Age-related changes in brain activity are less likely to reflect reduced memory function when they are observed in both elderly groups compared with the young group.

In the present study, we used event-related fMRI to investigate the extent to which encoding and retrieval contribute to age-related memory decline by comparing a group of young subjects, a group of elderly subjects with reduced memory performance (ELD-RED) and a group of elderly subjects whose memory performance was still in the normal range, as determined by a verbal recognition task

**Table 1** Demographic data and self-rated health

	Young (n = 17)	ELD-NORM (n = 19)	ELD-RED (n = 21)
Age (years)	32.7 (1.8)	66.4 (2.0)	66.2 (2.0)
Education (7-point scale)	5.9 (1.0)	5.6 (0.8)	5.3 (0.7)
Self-rated physical health (1 = bad, 5 = excellent)	4.0 (0.7)	4.0 (0.6)	3.9 (0.6)
Self-rated psychological health (1 = bad, 5 = excellent)	4.0 (0.8)	4.3 (0.5)	4.1 (0.8)

Data are mean (SD).

(ELD-NORM). In addition, we tested the hypothesis, conceptualized in the HAROLD model, that young subjects engage the left frontal cortex more heavily during encoding and the right frontal lobes during retrieval, whereas elderly subjects show more bilateral frontal activity during encoding and retrieval (Cabeza *et al.*, 2001). Furthermore, we distinguished between retrieval processes associated with the attempt to retrieve information (retrieval attempt) and processes involved in the actual recovery of information (retrieval success), by distinguishing between correct rejection of novel items (retrieval attempt) and correct recognition of studied items (retrieval attempt + success). This enabled us to investigate separately the effects of ageing on these subcomponents of episodic retrieval. Finally, since groups of elderly are usually characterized by large inter-individual variability in response characteristics (Woodruff-Pak, 1997), we applied a self-paced event-related design similar to the one we used in a previous study on episodic memory (Daselaar *et al.*, 2001).

## Material and methods

### Subjects

Twenty right-handed males between the ages of 30 and 35 years and 40 right-handed males between the ages of 63 and 71 years participated. They were recruited by means of advertisements in local newspapers. None of the subjects was taking psychoactive medication and they did not report any neurological or psychiatric impairment on a general health questionnaire. All elderly subjects scored 25 or higher (out of 30) on the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975), a widely used test for the assessment of cognitive competence. In addition, the structural MRI images acquired from each subject (see below) should not have contained evidence for anatomical abnormalities atypical for age. The subjects' informed consent was obtained according to the Declaration of Helsinki and the study was approved by the ethics committee of the Vrije Universiteit Medical Center.

On the basis of the young subjects' test scores [(% correctly recognized items + % correctly rejected items)/2] on the episodic memory task described below, a normal score was determined with a standard normal deviation of  $-1$ . We used

this score (= 86.6% correct) as a cut-off in order to obtain three groups: a group of 17 young subjects with normal memory performance, a group of 19 elderly subjects with normal memory performance (ELD-NORM) and a group of 21 elderly subjects with reduced memory performance (ELD-RED). No significant differences were found between the ELD-RED and ELD-NORM groups in MMSE score [27.6 (SD 1.5) and 28.2 (1.4) respectively], self-rated health and the demographic data shown in Table 1.

### Procedures

For the purpose of this study, subjects visited the out-patient clinic twice. During the first visit, the tasks that were to be completed during the experiment were practised (with different words), and the MMSE was administered. During the second visit, within the following week, the subjects performed an episodic memory task while fMRI data were obtained. Subjects practised the encoding task in the MRI scanner before the scanning took place. The memory task consisted of an encoding phase, a 10 min retention interval and a retrieval phase (see below).

### MRI

Imaging was done on a 1.5 T Siemens Sonata (Siemens, Erlangen, Germany) scanner using a standard circularly polarized head coil. Stimuli were generated by a Pentium PC and projected on a screen at the back end of the scanner table. The projected image was seen through a mirror mounted above the participant's head. Two magnet-compatible four-key response boxes were used to record the subject's performance and reaction times. The subject's head was immobilized using foam pads to reduce motion artefact and earplugs were used to reduce scanner noise.

For each subject, a series of EPI (echo-planar images) was obtained that were sensitive to BOLD (blood oxygenation level-dependent) contrast, entailing a  $T_2^*$ -weighted gradient echo sequence [repetition time (RT) = 2.1 s, echo time (ET) = 60 ms, flip angle =  $90^\circ$ ] consisting of transverse whole-brain acquisitions (20 slices,  $3 \times 3 \text{ mm}^2$  in-plane resolution, 5 mm slice thickness, 1 mm interslice gap).

## Materials

Stimuli consisted of 233 abstract and concrete nouns ranging from three to 12 letters that were taken from a standard Dutch dictionary; 71 of these words were used as dummy trials. The remaining 162 words were assigned randomly to be used either as targets or distractors, yielding different stimulus sets for each individual subject (see below).

## Task procedures

During the encoding phase, we implemented an incidental-learning paradigm in which, at study, no reference was made to the test phase. Subjects were instructed to indicate whether a noun presented on the screen gave them a pleasant feeling, by pressing a left-hand button, or an unpleasant feeling, by pressing a right-hand button. Whenever a word was considered to be emotionally neutral, they were instructed to make associations with that word until either a pleasant or an unpleasant feeling had been invoked. We chose this paradigm on the basis of earlier studies that had reported high rates of recollection for items that were processed either semantically ( Craik and Lockhart, 1972) or emotionally (Hamann, 2001), in order to obtain as many correct responses as possible so as to maximize statistical power.

Two trial types were distinguished: 81 study words and 54 baseline items. During the presentation of baseline items, subjects were instructed to press left when '<<< left' was presented on the screen (50% of the cases) and right when 'right >>>' was presented on the screen. The stimulation paradigm was similar to the one we used in a previous study on episodic memory (Daselaar *et al.*, 2001). Prior to each experiment, the trials were intermixed randomly into 27 blocks, each consisting of three study words and two baseline items. In this way, the encoding trials could be presented a maximum of six times in succession and the baseline items a maximum of four times in succession. This was done in order to ensure that the experimental frequency was high enough to minimize contributions from low-frequency drifts in the MRI signal. Presentation of the stimuli was self-paced, although a time limit of 5 s was maintained for non-responses. The response–stimulus interval was set to 2 s. The number of functional scans was fixed at 245 in order to meet the assumption of equal variance that is implicit in random effects analyses. For this reason, whenever the subject had completed the encoding trials, the remaining scan time was filled up with additional baseline items and dummy trials.

During the retention interval, a structural scan was made involving a coronal inversion recovery prepared 3D gradient echo, T<sub>1</sub>-weighted sequence [MPRAGE (magnetization-prepared, rapid gradient echo): inversion time = 300 ms, TR = 15 ms, ET = 7 ms, flip angle = 8°].

The retrieval phase (verbal recognition) consisted of three trial types: 81 targets (study words), 81 distractors (novel words) and 54 baseline items (press left/press right). For the retrieval trials, subjects were instructed to indicate whether

they had seen the word previously during the encoding task (left-hand press) or not (right-hand press). The stimulation paradigm was analogous to the encoding task. Trials were randomly presented in a self-paced fashion in 27 stimulus blocks, each consisting of three targets, three distractors and two baseline items. The trials were preceded by five dummy trials, each consisting of three words and two baseline items, because pilot experiments had shown that many errors were made in the first few trials of the task. The duration of the recognition task was fixed at 285 functional scans; consequently, the number of recognition trials completed varied across subjects.

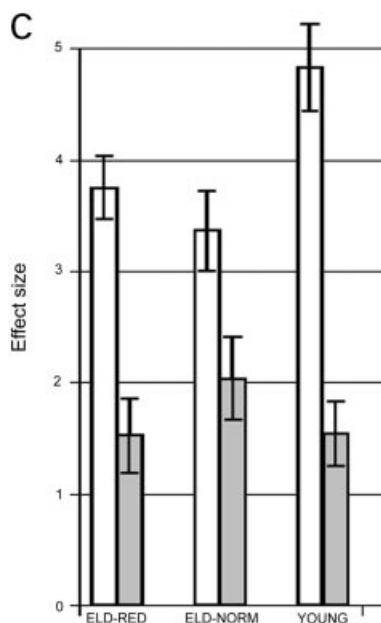
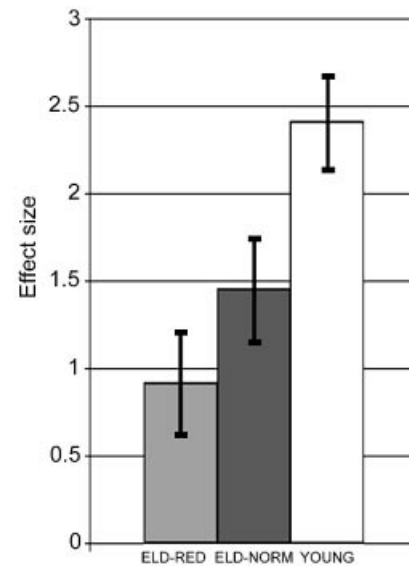
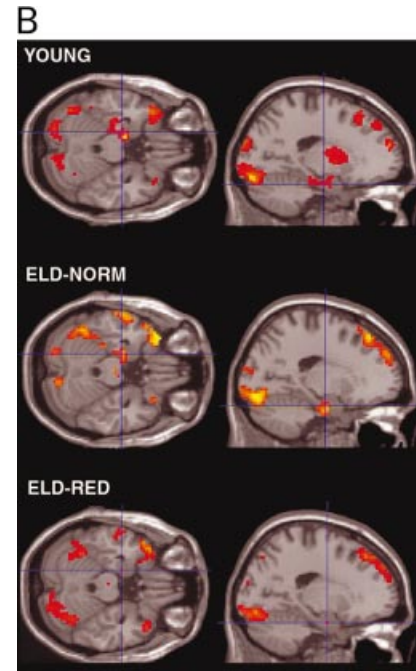
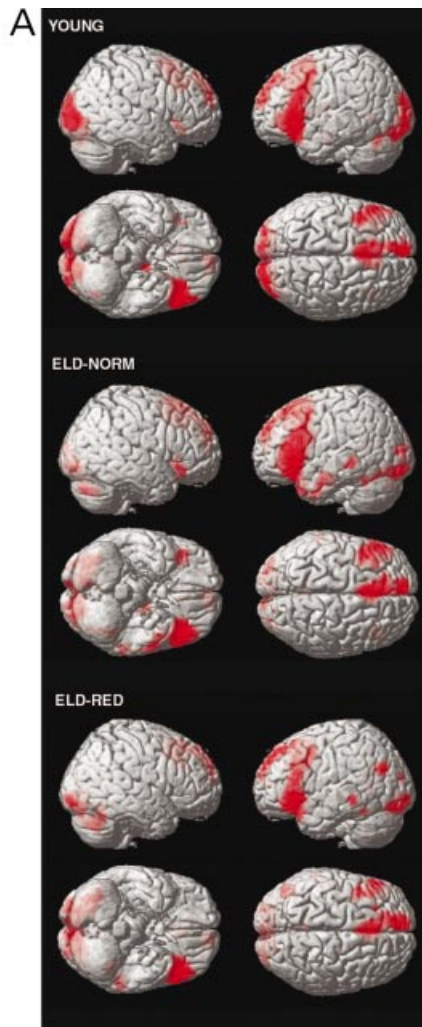
## Analysis

Data were analysed using SPM99 (Statistical Parametric Map; SPM99 from Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>). After discarding the first three volumes, time-series were corrected for differences in slice acquisition times, and realigned. Next, the EPI volumes were spatially normalized into approximate Talairach and Tournoux space (Talairach and Tournoux, 1988) defined by a standard SPM EPI template and resliced to a resolution of 3 × 3 × 3 mm voxels. Data were spatially smoothed using a Gaussian kernel of 8 mm and normalized for global effects using proportional scaling.

The event-related fMRI analysis was based upon the assumption that individual haemodynamic responses summate in a practically linear fashion over time (Dale and Buckner, 1997; Buckner *et al.*, 1998). Evoked haemodynamic responses to event types were modelled as delta functions convolved with a synthetic haemodynamic response function in the context of the general linear model (Josephs *et al.*, 1997).

We assessed average activations across subjects by carrying out a two-step random effects analysis (Woods, 1996). Because this type of analysis assumes approximately equal within-subject variances, the number of scans, and therefore the number of degrees of freedom, was held equal across subjects. As a first step, specific effects were tested by applying appropriate contrasts to the parameter estimates for each event, giving a *t* statistic for every voxel. In this way, SPMs (Statistical Parametric Maps, Friston *et al.*, 1995) were determined for each individual subject. During the second step, we carried out a one-sample *t* test or, in the case of group comparisons, a two-sample *t* test upon the resulting contrast images.

For the encoding task, we contrasted successfully encoded items (i.e. those that were correctly recognized afterwards) with baseline items in our analysis. In view of a lack of sufficient statistical power, it was not possible to examine unsuccessfully encoded items because there were not enough misses on the recognition task. For the retrieval task, we distinguished between correctly recognized words (CREC), correctly rejected words (CREJ) and baseline items. For each group, we contrasted CREJ with baseline (retrieval attempt), CREC with CREJ (retrieval success) and CREJ with CREC.



**Fig. 1** (A) Signal areas showing BOLD (blood oxygenation level-dependent) increases for the comparison of successful encoding and baseline for each group ( $P < 0.001$  uncorrected; cluster size  $\geq 15$ ). (B) (Top) SPM overlaying a normalized  $T_1$  image, showing increased activity in the left perirhinal/parahippocampal region for the comparison of successfully encoded items with baseline for each group (for the purpose of illustration;  $P < 0.005$  uncorrected). (Bottom) Graph of effect sizes (percentage signal change) for this comparison in the left perirhinal/parahippocampal region for each group [Talairach coordinates ( $x, y, z$ ) of local maxima: ELD-RED,  $-18, -7, -20$ ; ELD-NORM,  $-18, -10, -22$ ; young,  $-12, -10, -20$ ]. Standard errors are indicated by the black bars. (C) Graph of effect sizes (percentage signal change) in the left (white bars) and right (grey bars) inferior prefrontal cortex for each group for the comparison of successful encoding with baseline [Talairach coordinates ( $x, y, z$ ) of local maxima: ELD-RED,  $-45, 29, -9$ ;  $39, 20, -11$ ; ELD-NORM,  $-39, 33, -14$ ;  $42, 20, -11$ ; young,  $-50, 26, 1$ ;  $36, 31, -12$ ]. Standard errors are indicated by the black bars.

**Table 2** Behavioural data

Group	% correct targets	% correct distractors	RT targets(s)	RT distractors(s)	RT baseline(s)	RT encoding(s)
Young	91.3 (4.7)	94.3 (3.6)	1.15 (0.32)	1.29 (0.33)	0.57 (0.10)	1.45 (0.44)
ELD-NORM	92.5 (4.2)	93.0 (4.6)	1.10 (0.17)	1.17 (0.20)	0.68 (0.11)	1.36 (0.28)
ELD-RED	75.1 (12.6)	82.1 (10.2)	1.14 (0.25)	1.14 (0.25)	0.66 (0.10)	1.31 (0.35)

Data are mean (SD).

Furthermore, each group was compared directly with the other groups on all contrasts mentioned above.

We applied a threshold of  $P < 0.05$  (corrected for multiple comparisons) for the assessment of group averages. The regions that survived this threshold in either one of these groups were identified subsequently as regions of interest for assessing group interactions and main effects in the other groups, which were all thresholded at  $P < 0.001$  uncorrected, with cluster size  $\geq 15$ . In addition, focusing on areas reported in previous studies (e.g. Henson *et al.*, 1999; Habib and Lepage, 2000; Konishi *et al.*, 2000), this lower threshold was also used to distinguish between retrieval success (CREC) and retrieval attempt (CREJ).

## Results

### Behavioural data

As shown in Table 2, both the young and the ELD-NORM group performed well on the episodic memory task, with accuracy scores well above 90%. Although the subjects from the ELD-RED group performed considerably worse, their hit–false alarm index ( $0.75 - 0.18 = 0.57$ ) was still acceptable, indicating good discrimination between trial types.

The response times for each group were characterized by large inter-subject variability, particularly for the encoding trials. Significant within-group differences in mean reaction time were found for the young participants (17 subjects), who took less time [ $t(16) = 2.55$ ,  $P = 0.02$ ] to decide that they had seen a target (CREC) than to decide that they had not seen a distractor (CREJ). There was a trend for such an effect in the ELD-NORM group [ $t(18) = 1.71$ ,  $P = 0.10$ ] as well, but it was completely lacking in the ELD-RED group.

No significant between-group differences were found in mean reaction times for the recognition and encoding trials. However, there was a significant difference in response times for the baseline items that were presented during the recognition task comparing the young subjects with the ELD-RED [ $t(36) = 4.4$ ;  $P = 0.00$ ] and the ELD-NORM [ $t(34) = 4.3$ ,  $P = 0.00$ ] groups, indicating age-related slowing of motor responses.

No significant correlation was found between response times on the encoding trials and test score.

### Imaging data

Due to technical difficulties (scanner failure and data transport problems), imaging data from two subjects were

partly lacking: encoding phase data from a subject in the young group and retrieval phase data from a subject in the ELD-NORM group.

### Encoding – baseline

In Fig. 1A, normalized 3D renderings are depicted for the three groups, showing areas that were more active during the encoding task than during baseline (see also Table 3). At first glance, each group appears to use, on average, the same neuroanatomical system in order to complete the encoding task: a large area in the left prefrontal cortex covering the inferior and middle frontal gyri, the superior frontal gyrus, the medial frontal gyrus extending into the anterior cingulate, and several occipital regions. However, there was one notable difference across groups: a cluster of activity with its focus in the perirhinal/parahippocampal region extending into the hippocampus proper was observed in the young group but not in the elderly groups. At a slightly lower threshold (Table 3), the ELD-NORM group revealed a considerable cluster of activity in this region as well, whereas the ELD-RED group showed only two active voxels at  $P < 0.005$  uncorrected (Fig. 1B). When the groups were compared directly, the young subjects revealed significantly more activity than the ELD-RED group in this area, but not compared with the ELD-NORM group. The other group comparisons did not reveal significant differences.

In order to examine further the possible age-related differences in prefrontal lateralization, we plotted the effect sizes for the local maxima in the left and right inferior prefrontal cortex (Fig. 1C). The results indicated a clearly left-lateralized prefrontal activity pattern for each group, although there was a slight trend for diminished lateralization in the ELD-NORM group.

### Retrieval – baseline

From Fig. 2A and Table 4, in which areas are presented that were more active during retrieval attempt (CREJ) than during baseline, it can be seen that there were considerable differences in the general level of activity during attempted retrieval. The ELD-NORM group showed the least overall activity and the ELD-RED group by far the most activity.

Common activity across groups was seen in the left and right inferior frontal lobes, indicating that these regions are particularly important to the retrieval process. Regionally specific differences became apparent as well when the groups

**Table 3** Maxima of regions showing significant increases in BOLD signal for the encoding – baseline comparison

Region of activation	Left/right	Brodmann area	Talairach coordinates (mm)			Z
			x	y	z	
<b>Young</b>						
Inferior frontal gyrus	L	45/47	-50	26	1	5.94
Medial frontal gyrus	L	9/10	-3	56	19	6.24
Parahippocampal region	L	28	-12	-10	-20	5.20
Lingual gyrus	L	18	-21	-88	-11	5.90
<b>ELD-NORM</b>						
Inferior frontal gyrus	L	47/11	-39	33	-14	5.58
Superior frontal gyrus	L	8	-3	26	48	5.13
Parahippocampal region	L	28	-18	-10	-22	3.83*
Lingual gyrus	L	18	-9	-85	-8	4.94
<b>ELD-RED</b>						
Inferior frontal gyrus	L	47	-45	29	-9	6.71
Medial frontal gyrus	L	8	-6	22	38	5.58
Lingual gyrus	L	18	-6	-90	-3	5.75
<b>Young – ELD-RED</b>						
Parahippocampal region	L	28	-12	-12	-15	4.53*

$P < 0.05$  corrected; \* $P < 0.001$  uncorrected; cluster size = 15.

were compared directly. First, the ELD-RED group revealed more activity compared with the ELD-NORM group in the left insular cortex, right middle temporal gyrus, left supramarginal gyrus, cerebellum, and occipital regions (Table 4). At a slightly lower threshold ( $P < 0.005$  uncorrected), corresponding regional differences were found between ELD-RED and the young group. When comparing ELD-NORM with the young group, increased activation was observed in the left inferior frontal gyrus. This difference was also found in a direct comparison of the ELD-NORM with the ELD-RED group when the threshold was lowered to  $P < 0.005$  uncorrected. No significant differences were found in any of the other group comparisons. In Fig. 2B, effect sizes are shown for the left and right inferior prefrontal cortex, and indicate a nearly bilateral prefrontal activity pattern for each group, with a small trend in favour of the left side for the ELD-NORM group.

### CREC – CREJ

As shown in Fig. 3 and Table 5, the large group differences observed during retrieval became much smaller when contrasting CREC and CREJ. Besides primary motor activity related to button-pressing, common activity was seen in the left anterior prefrontal cortex (Brodmann area 9/10), the retrosplenial/posterior cingulate cortex (Brodmann area 23) and the left inferior/superior parietal cortex (Brodmann area 7/40). The only significant group difference for the contrast CREC – CREJ was found in the left inferior prefrontal cortex, the ELD-RED group showing somewhat more activity than the young subjects.

The opposite comparison (CREJ – CREC) revealed activity in the left anterior transverse temporal gyrus

(Brodmann area 41) for both the young and the ELD-NORM group.

## Discussion

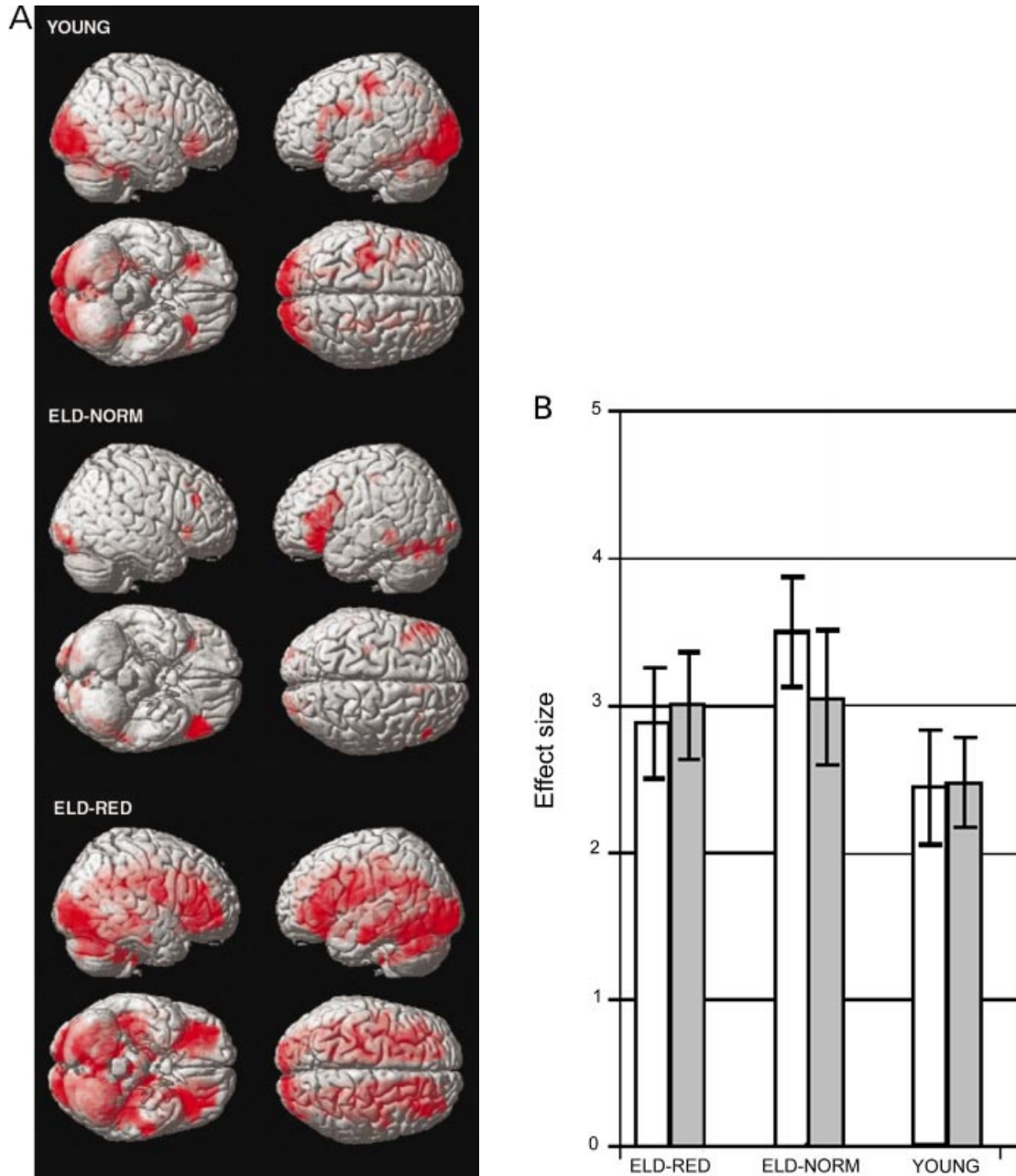
The main finding of this study is that age-related memory decline was associated with decreased activity in the MTL during encoding. Furthermore, we found considerable group differences during attempted retrieval but not in relation to the actual recovery of information.

In the present study, fMRI was used to compare regional brain activity in young and old adults during performance of an episodic encoding and retrieval task. However, contrary to previous imaging studies on this topic (e.g. Grady *et al.*, 1995; Schacter *et al.*, 1996; Cabeza *et al.*, 1997; Madden *et al.*, 1999), we used event-related fMRI to control for differences in performance level across groups by including only correct responses in our analysis. Furthermore, we divided the elderly subjects into a group that showed reduced memory performance (ELD-RED) and a group that still performed in the normal range (ELD-NORM). This enabled us to distinguish between changes that affected memory performance and changes that did not have an apparent effect on memory performance.

### Episodic encoding

During encoding, subjects made pleasant versus unpleasant judgements about nouns without any expectation of a memory test. We chose this paradigm in order to optimize the rate of recollection to obtain greater statistical power, and to increase the uniformity of encoding strategies.





**Fig. 2** (A) Areas showing BOLD (blood oxygenation level-dependent) signal increases for the comparison of CREJ with baseline for each group ( $P < 0.001$  uncorrected; cluster size  $\geq 15$ ). (B) Graph of effect sizes (percentage signal change) in the left (white bars) and right (grey bars) inferior prefrontal cortex for each group for the comparison of CREJ with baseline [Talairach coordinates of local maxima ( $x, y, z$ ): ELD-RED,  $-30, 43, -5$ ;  $36, 30, 10$ ; ELD-NORM,  $-45, 28, -14$ ;  $33, 23, -1$ ; young,  $-30, 26, -14$ ;  $33, 29, -12$ ]. Standard errors are indicated by the black bars.

The different groups revealed highly similar activity patterns in relation to successful encoding, including the left dorsolateral and inferior prefrontal cortex, the medial frontal gyrus extending into the anterior cingulate, and several occipital regions. Activity in the left dorsolateral and inferior prefrontal cortex has been reported frequently both during intentional memorization (e.g. Fletcher *et al.*, 1995; Kapur *et al.*, 1996) and during (semantic) tasks that incidentally enhance memory encoding (e.g. Kapur *et al.*,

1994; Gabrieli *et al.*, 1996). Furthermore, activity in this region has been found to predict subsequent memory performance (Wagner *et al.*, 1998b).

The young group and, to a lesser extent, the ELD-NORM group revealed additional activity in the left anterior MTL, covering the perirhinal/parahippocampal region and hippocampus proper, whereas such activity was almost absent in the ELD-RED group. Given earlier evidence for the dependence of verbal memory on the left MTL (Milner, 1966), and



**Table 4** Maxima of regions showing significant increases in BOLD signal for the CREJ – baseline comparison

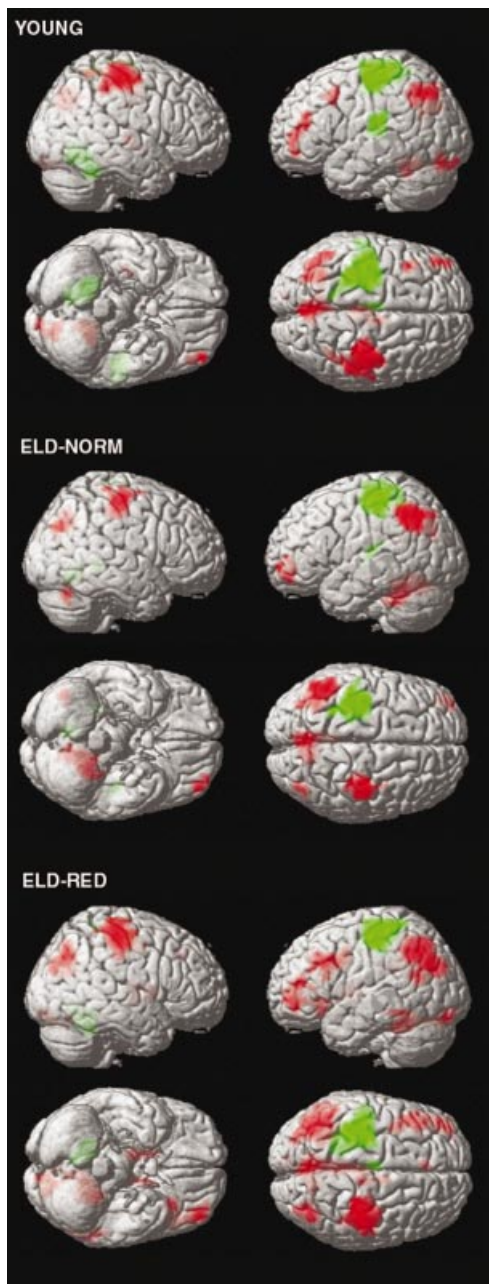
Region of activation	Left/right	Brodmann area	Talairach coordinates (mm)			Z
			x	y	z	
<b>Young</b>						
Inferior frontal gyrus	R	47	33	29	-12	5.02
	L	47	-30	26	-14	4.46*
Precentral gyrus	L	4	-30	-15	45	5.22
Inferior occipital gyrus	R	18	39	-88	-3	6.09
Middle occipital gyrus	L	18	-30	-93	13	5.71
Cuneus	R	17/18	9	-93	13	5.46
	L	17/18	-9	-93	13	5.33
<b>ELD-NORM</b>						
Inferior frontal gyrus	L	47	-45	28	-14	5.42
	R	47	33	23	-1	4.60*
Middle frontal gyrus	R	46	53	33	23	4.44*
Precentral gyrus	L	4	-33	-18	45	3.54*
Lingual gyrus	R	18	27	-85	-8	4.32*
	L	18	-27	-85	-13	3.84*
<b>ELD-RED</b>						
Inferior frontal gyrus	L	47	-30	43	-5	5.44
	R	45/46	36	30	10	5.52
	L	45/46	-33	27	18	5.27
Middle frontal gyrus	R	10	24	44	-2	5.35
Insular cortex	L	-	-30	-25	21	5.09
Precentral gyrus	L	4	-33	-27	46	4.16*
Middle temporal gyrus	L	39	-36	-60	28	5.24
	R	21	42	-27	-6	5.01
Inferior temporal gyrus	L	37	-48	-53	-12	5.12
Posterior cingulate gyrus	L	31	-12	-42	27	5.39
Fusiform gyrus	R	37	39	-47	-13	5.19
Lingual gyrus	L	19	-21	-70	-4	5.21
	L	18	-18	-90	-1	5.36
Inferior occipital gyrus	R	18	42	-76	-1	5.34
Cerebellum	R	-	24	-74	-19	5.61
	R	-	3	-53	-15	5.30
<b>ELD-NORM – young</b>						
Inferior frontal gyrus	L	47	-48	26	-11	3.99*
<b>ELD-RED – ELD-NORM</b>						
Insular cortex	L	-	-24	21	7	3.48*
Middle temporal gyrus	R	21	39	-27	-6	3.48*
Supramarginal gyrus	L	39	-45	-51	30	3.66*
Middle occipital gyrus	R	19	33	-70	-4	3.63*
Cerebellum	L	-	-12	-45	-16	4.36*
	R	-	30	-62	-20	4.10*

$P < 0.05$  corrected; \* $P < 0.001$  uncorrected; cluster size = 15.

given the fact that the perirhinal/hippocampal area has been related to successful encoding (Fernandez *et al.*, 1999; Strange *et al.*, 2002), this finding supports the notion that the age-related decline in episodic memory is due, at least partly, to an encoding deficit.

It might seem counterintuitive that reduced activity in the MTL was observed in relation to the encoding of words that were subsequently remembered. It has been suggested, though, that the MTL operates by forming associations between sensory, cognitive and emotional processes that make up an episode in memory (Alvarez and Squire, 1994; Eichenbaum, 1996). Accordingly, it has been suggested that

there is a relation between the amount of MTL activity and the number of associations that are formed during encoding of study material (Henke *et al.*, 1997, 1999). Given the presence of MTL activity during encoding, this would imply that the ELD-RED group merely formed fewer memory associations. Although recognition judgements are likely to be made with much more ease and confidence when many memory associations have been established during encoding, it is conceivable that, apart from lucky guessing, successful recognition may also occur with less confidence on the basis of only a few associations. In view of this, it would be a methodological improvement for future ageing studies on



**Fig. 3** Areas showing BOLD (blood oxygenation level-dependent) signal increases for the comparison of CREC (red) with CREJ (green) for each group ( $P < 0.001$  uncorrected; cluster size  $\geq 15$ ).

episodic memory to distinguish between trials that have resulted in a stronger recollective experience (remember trials) and trials with a weaker recollective experience (know trials). Furthermore, measures of episodic recall in combination with recognition measures may also yield more insight into age-related differences in episodic encoding.

The fact that we did not observe any differential activity in frontal regions when we compared the groups indicates similar degrees of prefrontal lateralization during encoding. This is not in line with the HAROLD model, which states that

elderly subjects show more bilateral frontal activity than young subjects during encoding and retrieval (Cabeza *et al.*, 2001). However, there was a small trend in this direction in the ELD-NORM group, as indicated by the effect sizes for these regions.

The finding of similar left prefrontal activity is in agreement with the results obtained in a recent study by Buckner and colleagues (Logan *et al.*, 2002). In this study, elderly adults showed less prefrontal activity compared with young adults under intentional learning instructions, but, as in our study, this difference was not observed when a semantic orienting task was used to support episodic encoding. In another recent study, Stebbins and colleagues (Stebbins *et al.*, 2002) also applied an incidental learning paradigm to young and older subjects, but reported reduced left prefrontal activity for elderly subjects. However, they based their conclusions on another critical measure, i.e. the spatial extent of prefrontal activity, and no group differences were reported in peak activation. Given the clear indications for the involvement of the left prefrontal cortex in semantic processing (e.g. Kapur *et al.*, 1994; Gabrieli *et al.*, 1996), our findings, together with the findings reported by Buckner and colleagues (Logan *et al.*, 2002), are in agreement with a production deficiency account of age-related impairments in episodic encoding which states that elderly adults do not employ semantic elaboration strategies spontaneously but are able to make use of them when forced to do so (Burke and Light, 1981). However, in our study, we did observe reduced activity for the ELD-RED group in the MTL memory system under incidental learning instructions. Together, these findings suggest that age-related impairments in episodic encoding are a combination of both strategic encoding differences and MTL dysfunction.

It must be noted, though, that some of the regions isolated by the comparison between successful encoding and the baseline condition may reflect non-mnemonic processes specific to the pleasantness or baseline task, rather than encoding processes. However, this issue is not likely to pertain to the group difference that we found in the MTL memory system.

### **Recognition memory performance**

Both the young subjects and the ELD-NORM group performed excellently during the recognition task, which may have been due to the encoding paradigm employed in this study. Though the performance of the ELD-RED group was considerably worse, they still demonstrated good discrimination between studied and novel items. Contrary to the finding of many previous studies, the responses of the elderly in our sample were not slower than those of the young subjects on the encoding and recognition trials (Cabeza *et al.*, 1997; Madden *et al.*, 1999). However, we did see somewhat increased reaction times on the baseline items (press left/press right) for the elderly groups compared with the young

**Table 5** Maxima of regions showing significant increases in BOLD signal for the CREC – CREJ comparison

Region of activation	Left/right	Brodmann area	Talairach coordinates (mm)			Z
			x	y	z	
Young: CREC – CREJ						
Inferior frontal gyrus	L	46	-42	38	12	4.84
Middle frontal gyrus	L	9/10	-39	16	38	4.42
Insular cortex	R	-	36	-17	4	4.01
Precentral gyrus	R	4	45	-9	50	4.47
Posterior cingulate gyrus	-	23	0	-19	29	4.58
Inferior parietal lobe	L	7/40	-33	-59	44	3.93
Precuneus	L	7	-3	-59	39	4.78
Cerebellum	L	-	-15	-59	-12	4.52
	L	-	-15	-76	-11	4.20
Young: CREJ – CREC						
Precentral gyrus	L	4	-45	-23	56	5.29*
Anterior cingulate gyrus	L	24	-6	-7	42	3.95
Transverse temporal gyrus	L	41	-48	-23	12	4.64
Cerebellum	R	-	12	-56	-10	4.87
ELD-NORM: CREC – CREJ						
Middle frontal gyrus	L	10	-33	58	-8	4.15
Precentral gyrus	R	4	36	-15	48	4.92*
Posterior cingulate gyrus	L	23	-3	-46	22	3.52
Angular gyrus	R	39	42	-71	34	4.18
Inferior parietal lobe	L	40	-48	-50	47	5.27*
Cuneus	L	19	-6	-74	31	4.53
Cerebellum	L	-	-21	-48	-20	5.39*
	R	-	42	-68	-19	4.48
ELD-NORM: CREJ – CREC						
Precentral gyrus	L	4	-27	-44	55	4.97*
Hippocampal gyrus	R	35	30	-41	0	3.96
Transverse temporal gyrus	L	41	-39	-20	12	3.93
Cerebellum	R	-	9	-61	-4	4.68
ELD-RED: CREC – CREJ						
Inferior frontal gyrus	L	47	-30	23	-6	4.06
Middle frontal gyrus	L	10	-45	41	12	5.12*
	L	9/46	-42	22	29	4.80
Medial frontal gyrus	L	8	-6	31	34	3.85
Cingulate gyrus	R	23/24	9	-4	42	4.94*
Precentral gyrus	R	4	33	-24	54	5.54*
Globus pallidus	R	-	12	-3	-2	4.35
	L	-	-9	-3	0	4.01
Inferior parietal lobe	L	7	-27	-56	39	4.66
	R	7	36	-65	42	4.64
Cerebellum	L	-	-24	-48	-18	5.20*
ELD-RED: CREJ – CREC						
Precentral gyrus	L	4	-36	-23	62	6.36*
Cerebellum	L	-	-6	-17	-42	5.25*
	R	-	12	-50	-10	4.28
ELD-RED – young						
Inferior frontal gyrus	L	47	-39	21	18	3.78

$P < 0.001$  uncorrected; cluster size  $\geq 15$ ; \* $P < 0.5$  corrected.

group, indicating age-related slowing of motor responses. Given similar response times on the recognition trials for the different groups, this finding implies that the young subjects actually took more time to decide that they had seen or not seen a word than the elderly subjects. A reason for this might be that, contrary to our expectations, the young subjects tried to benefit more than the elderly subjects from the self-paced nature of the task.

Significant within-group differences in mean reaction times were found for the young subjects, who took less time to decide that they had seen a target (CREC) than to decide that they had not seen a distractor (CREJ). This is a common finding in memory research, and it is likely to be due to the fact that in the first case the search process will be stopped when the word presented is matched to the word in one's memory store, whereas in the last case such a stop

signal is lacking, causing the search process to be continued a little longer. There was a trend for such an effect in the ELD-NORM group as well, but it was completely absent in the ELD-RED group.

### **Retrieval attempt**

The fact that differential activity was observed in the MTL memory system during encoding has implications for the interpretation of our findings in the retrieval task. Given the fact that we only included correct responses and that the ELD-RED group was clearly capable of successful retrieval, any differential activity seen during attempted retrieval (CREJ – baseline) for this group might actually reflect compensation of the encoding deficit.

In this study, we found large differences in overall activity in relation to retrieval attempt, the ELD-RED group showing by far the greatest activity and the ELD-NORM group showing the least overall activity. Hence, in agreement with the suggestion made above, the ELD-RED group may have tried to compensate for the encoding deficit by putting in more effort during the recognition task, although this was not reflected in slowing of the response times. Common activity across groups was seen in the left and right inferior frontal lobes, suggesting that these regions are particularly important to episodic retrieval.

Directly comparing the groups also revealed regionally specific differences. First, the ELD-RED group revealed more activity compared with the ELD-NORM group in the left insular cortex, right middle temporal gyrus, left supramarginal gyrus, cerebellum and occipital regions, and, at a slightly lower threshold, corresponding differences were found between the ELD-RED and the young group. When comparing the ELD-NORM subjects with the young group, increased activation was observed in the left inferior frontal gyrus. Again, at a slightly lower threshold, this difference was also found when we directly compared the ELD-NORM with the ELD-RED group. The more left-lateralized prefrontal activity in the ELD-NORM group compared with the other groups suggests that these elderly subjects relied more heavily on semantic strategies in order to sustain the retrieval process, e.g. by making associations with the words in order to obtain additional retrieval cues.

Our results were not in agreement with the HAROLD model, which predicts reduced prefrontal asymmetry for elderly compared with young adults during retrieval, since the young and the ELD-RED group revealed similar left and right inferior prefrontal activity during retrieval attempts, whereas the ELD-NORM group revealed a greater extent of frontal lateralization in favour of the left side. An explanation for the discrepancy between our results and those of imaging studies that are in line with the HAROLD model (e.g. Cabeza *et al.*, 1997, 2001; Logan *et al.*, 2002) may reside in differences in methodology and statistical analysis that were employed in

this study. For example, we included only correct responses, isolated retrieval attempts from success, and distinguished between elderly subjects with reduced and normal memory performance.

Considerable differences were found in relation to retrieval attempt; the ELD-NORM group showed more left-lateralized frontal activity than the other groups, whereas the ELD-RED group revealed a more global increase in activity, involving several regions. These differences may reflect differences in retrieval strategy or, in the case of the ELD-RED group, compensation of the encoding deficit.

### **Retrieval success**

In order to isolate the processes associated with the actual recovery of information (retrieval success) from the processes involved in retrieval attempt, we directly compared correctly recognized (retrieval attempt + success) and correctly rejected items (retrieval attempt).

Few differences were seen in relation to retrieval success between the groups, which showed common activity in the left anterior prefrontal cortex, the retrosplenial/posterior cingulate cortex and the left inferior/superior parietal cortex. This set of areas has been implicated previously in retrieval success (Henson *et al.*, 1999; Habib and Lepage, 2000; Konishi *et al.*, 2000).

The anterior prefrontal cortex has been related to executive control functions at the highest level and has been activated during complex cognitive tasks requiring the maintenance of an overall goal while periodically updating subgoals (Fletcher and Henson, 2001). Accordingly, the role of the left anterior frontal cortex in retrieval success might involve evaluative processes regarding one's own memory performance in progress. The retrosplenial cortex has been found to be closely connected to the MTL memory system, and has been implicated recently in a network of regions associated with episodic memory function (Aggleton and Pearce, 2001; Vogt *et al.*, 2001). Activity within the lateral parietal lobe even seems to be modulated by the degree of retrieval success. Henson and colleagues (Henson *et al.*, 1999), using a 'remember versus know' paradigm, found a greater response in the left parietal cortex on remember trials (stronger recollective experience) than on know trials (weaker recollective experience). However, the exact role of these regions in successful retrieval is still elusive and remains a question for future studies.

The opposite comparison (CREJ – CREC) revealed activity in the left anterior transverse temporal gyrus (Brodmann area 41) for both the young and the ELD-NORM group. Since both groups took somewhat more time for CREJ than for CREC items, presumably to try to match the items presented to the ones stored in memory, this activity may reflect additional retrieval effort.

## Conclusions

The finding of reduced activity in the left anterior MTL during incidental encoding for the ELD-RED group compared with the young subjects and the ELD-NORM group is in line with the idea, based on behavioural findings, that age-related memory decline is at least partly due to an encoding deficit. Furthermore, this finding indicates that age-related problems in episodic encoding remain when encoding conditions are held equal across groups thereby eliminating strategic encoding differences.

Considerable differences were observed across groups in relation to retrieval attempts. In particular, much increased overall activity was seen in the ELD-RED group. These differences may reflect differences in retrieval strategy and, in the case of the ELD-RED group, compensation for the encoding deficit. Common activity was seen in bilateral inferior frontal regions, suggesting that these areas are particularly important to the retrieval process. The lack of differences observed in relation to retrieval success suggests that ageing does not affect the processes that support the actual recovery of information.

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