

Deep processing activates the medial temporal lobe in young but not in old adults

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Abstract

Age-related impairments in episodic memory have been related to a deficiency in semantic processing, based on the finding that elderly adults typically benefit less than young adults from deep, semantic as opposed to shallow, nonsemantic processing of study items. In the present study, we tested the hypothesis that elderly adults are not able to perform certain cognitive operations under deep processing conditions. We further hypothesised that this inability does not involve regions commonly associated with lexical/semantic retrieval processes, but rather involves a dysfunction of the medial temporal lobe (MTL) memory system. To this end, we used functional MRI on rather extensive groups of young and elderly adults to compare brain activity patterns obtained during a deep (living/nonliving) and a shallow (uppercase/lowercase) classification task. Common activity in relation to semantic classification was observed in regions that have been previously related to semantic retrieval, including mainly left-lateralised activity in the inferior prefrontal, middle temporal, and middle frontal/anterior cingulate gyrus. Although the young adults showed more activity in some of these areas, the finding of mainly overlapping activation patterns during semantic classification supports the idea that lexical/semantic retrieval processes are still intact in elderly adults. This received further support by the finding that both groups showed similar behavioural performances as well on the deep and shallow classification tasks. Importantly, though, the young revealed significantly more activity than the elderly adults in the left anterior hippocampus during deep relative to shallow classification. This finding is in line with the idea that age-related impairments in episodic encoding are, at least partly, due to an under-recruitment of the medial temporal lobe memory system.

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1. Introduction

One of the most prominent hypotheses that have been put forward to account for age-related impairments in episodic memory is an extension of the levels-of-processing framework proposed by Craik and Lockhart [6]. This framework is based on the view that a memory trace can be characterised as a record of processes that have initially been executed upon a stimulus in order to perceive and interpret that stimulus. It is further asserted that deeper, more meaningful analyses result in stronger memory traces than shallow,

superficial analyses regarding the appearance or sound of a stimulus.

Following this hypothesis, it has been suggested that age-related memory impairments are the result of a deficiency in deep, semantic processing. Two different extensions of the levels-of-processing hypothesis have been proposed. The production deficiency hypothesis states that elderly adults do not employ deep processing strategies spontaneously, but they are able to make use of them when forced to do so [1,7]. The alternative version, the processing deficiency hypothesis, asserts that older adults are not able to perform certain deep semantic processing actions [1,14]. Evidence for the latter hypothesis comes from studies in which recall of young and old subjects was compared

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after performing semantic and nonsemantic processing tasks. In line with the levels-of-processing framework, memory performance was best for semantic tasks and poorest for nonsemantic tasks in each group, but semantic relative to nonsemantic processing of study items improved memory performance more in young than in old adults [13,14,22].

Neuroimaging studies that compared deep and shallow processing tasks in young subjects generally reported increased activity in areas commonly assumed to subservise lexical/semantic retrieval processes, involving the left inferior prefrontal cortex and lateral temporal regions [8,19–21,24,25], and also in the medial temporal lobe (MTL), a region known to be involved in episodic memory function [8,21,24,25]. The greater involvement of the MTL in deep relative to shallow processing can be explained by a relational account of MTL function in memory [10,12,17,18]. It has been suggested that the MTL operates by establishing associations between sensory inputs, cognitive processes, and emotions that together form a memory episode. Consequently, more associations will be formed during a complex event, such as interpreting the meaning of a stimulus, than during a less complex event, such as processing the physical properties of a stimulus. Evidently, memory retrieval will be easier for events with many associations (deep processing) than for events with few associations (shallow processing). Accordingly, it is possible that age-related reductions in the depth-of-processing effect are not due to an inability to process the meaning of a stimulus, as indicated by the finding that young and elderly subjects generally perform similarly on the semantic orienting tasks that have been used in studies on this topic [20,23], but are rather due to reduced efficiency in the establishment of memory associations as a consequence of age-related MTL dysfunction.

In the present study, we used functional MRI to examine brain activity patterns in young and elderly subjects during a deep and a shallow classification task. We tested the prediction, based on the processing deficiency hypothesis, that ageing is accompanied by an under-recruitment of the medial temporal lobe memory system under deep processing conditions. Furthermore, we tested the hypothesis that lexical/semantic retrieval functions are still intact in elderly adults, so that brain regions commonly associated with semantic retrieval will be similarly activated in young and elderly adults resulting in similar behavioural performances.

2. Methods

2.1. Subjects

Twenty-six right-handed males between the ages of 30 and 35 and 39 right-handed males between the ages of 63 and 71 participated. They were recruited by means of advertisements in local newspapers. None of the subjects were

Table 1
Demographic data and self-rated health

	Young (<i>N</i> = 26) [S.D.]	Elderly (<i>N</i> = 39) [S.D.]
Age	32.4 [1.8]	66.3 [2.0]
Education (7-point scale)	5.9 [1.0]	5.5 [0.8]
Self-rated physical health (1 = bad, 5 = excellent)	4.0 [0.6]	4.0 [0.6]
Self-rated psychological health (1 = bad, 5 = excellent)	4.1 [0.7]	4.3 [0.6]

taking psychoactive medication and they did not report any neurological or psychiatric impairment on a general health questionnaire. All elderly subjects scored 25 (out of 30) or higher (mean = 27.8, S.D. = 1.48) on the Mini Mental Status Examination (MMSE), a common test for evaluating cognitive competence [15]. In addition, structural MR images, which were acquired previous to this study, did not contain indications for anatomical aberrations atypical for age. The subjects' informed consent was obtained according to the declaration of Helsinki and approved by the ethical committee of the "Vrije Universiteit" Medical Center. Demographic data and self-rated health measures are shown in Table 1 for the different groups.

2.2. Magnetic resonance procedures

Imaging was performed on a 1.5 T Siemens Sonata (Siemens, Erlangen, Germany) scanner using a standard circularly polarised 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 subject'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 immobilised using foam pads to reduce motion artifact and ear plugs were used to reduce scanner noise. For each subject, a series of echo planar images (EPI) was obtained sensitive to BOLD contrast, involving a T2*-weighted gradient echo sequence (Repetition Time = 2.1 s, Echo Time = 50 ms, flip angle = 90°) consisting of transversal whole-brain acquisitions (20 slices, 3 mm² × 3 mm² in-plane resolution, 5 mm slice thickness, 1 mm interslice gap).

The structural scan that was made previous to this study consisted of an axial inversion recovery prepared three-dimensional gradient echo, T1-weighted sequence (MPRAGE: inversion time: 300 ms; Repetition Time: 15 ms; Echo Time: 7 ms; flip angle: 8°).

2.3. Classification task

The classification task included two conditions, a deep (D) and a shallow (S) classification condition. During D, subjects were instructed to indicate whether a word represented

a living (left-hand press) or a nonliving object (right-hand press) using their index fingers. During S, subjects had to indicate whether the word was presented in lowercase (left-hand press) or uppercase font (right-hand press). Stimuli consisted of two sets of 100 nouns that were drawn from a standard Dutch dictionary with word lengths ranging from 4 to 11 letters. One set of nouns represented living objects (e.g. “chicken”), the other set referred to nonliving objects (e.g. “pencil”). These nouns were randomly assigned to 10 alternating blocks (i.e. D–S–D–S–D–S–D–S–D–S) of 20 trials each, yielding different stimulus sets for each individual subject. The blocks were separated by a 5-s instruction screen (i.e. “LIVING/NONLIVING”; “LOWERCASE/UPPERCASE”).

Stimuli were presented in a self-paced fashion, although a time limit of 5 s was maintained in case of nonresponses. On each trial, response options were indicated at the bottom of the screen by two cursors pointing to the left (“living”; “lowercase”) and right (“nonliving”; “uppercase”). Scores were only registered when the subject responded within the 5-s time limit. After the time limit had passed or the response was made, a 1-s response-stimulus interval started. During this interval, the word “NEXT . . .” appeared at the bottom of the screen. The task duration was fixed at 6;07 min, corresponding to 175 functional scans; consequently, the number of trials completed varied across subjects.

2.4. Analysis

Data were analysed using SPM99 (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 using sinc interpolation. Next, the EPI volumes were spatially normalised into approximate Talairach and Tournoux space (1988) defined by the SPM EPI template, and resliced to 3 mm × 3 mm × 3 mm voxels. Data were smoothed using a Gaussian kernel of 8 mm.

Evoked hemodynamic responses to stimulus blocks were modeled as boxcar functions convolved with a synthetic hemodynamic response function in the context of the general linear model. Individual blocks were modeled as separate conditions in order to account for different lengths of the blocks due to the self-paced design. Specific effects were tested by applying appropriate contrasts to the parameter estimates for each stimulus block, resulting in a *t*-statistic for every voxel. Group averages were calculated by employing a random-effects analysis.

For both groups, the contrasts D versus S, and S versus D were tested for significance. The activated regions that are reported below consisted of clusters of at least 10 adjacent voxels that survived a threshold of $P < 0.05$ using a False Discovery Rate-correction [16]. These areas were subsequently defined as regions of interest for assessing group interactions, which were thresholded at $P < 0.001$, uncorrected, minimal cluster size = 10.

Table 2

Behavioral data

	Percent of correct D [S.D.]	Percent of correct S [S.D.]	RT D (ms) [S.D.]	RT S (ms) [S.D.]
Young	96.2 [2.7]	97.7 [2.6]	954 [189]	799 [237]
Elderly	94.7 [4.6]	96.3 [5.7]	980 [239]	848 [162]

3. Results

3.1. Behavioural data

As shown in Table 2, the young and elderly groups performed similarly on the deep and shallow processing tasks. On all trials, subjects responded within the 5-s time limit. A group × condition ANOVA with condition as repeated measure and response times as dependent variable revealed a significant main effect for condition ($F(1, 63) = 69.6$; $P < 0.001$). However, no significant effects were found for group ($F(1, 63) = 0.874$; $P = 0.353$) and the group × condition interaction ($F(1, 63) = 0.447$; $P = 0.506$), reflecting similar response times for the two groups. A repeated measures (condition) ANOVA with percentage correct responses as dependent variable revealed a significant effect for condition ($F(1, 63) = 5.66$; $P = 0.020$), but not for group ($F(1, 63) = 2.64$; $P = 0.109$) and the group × condition interaction ($F(1, 63) = 0.15$; $P = 0.703$), indicating similar degrees of accuracy for the two groups as well. Overall, these results indicate similar behavioural performances on the classification tasks for the young and old adults.

3.2. Imaging results

As indicated in Tables 3 and 4, both groups showed an increase in activity in the middle frontal gyrus, the posterior cingulate gyrus, and parietal regions comparing S versus D. The opposite comparison, D versus S, revealed common activity in the left inferior prefrontal cortex, the right inferior prefrontal cortex, the middle frontal gyrus extending into the anterior cingulate, left and right lateral temporal regions, and visual areas. However, the young group revealed a significant increase in activity in the left hippocampus as well, whereas the elderly group did not. This difference was found to be significant as determined by a direct group comparison (Fig. 1, Table 5). Other group differences comparing young to old subjects were observed in right prefrontal, left middle temporal, and visual regions. The opposite comparison, S versus D, revealed a significant difference in the posterior cingulate gyrus, a region that was activated in both groups for this comparison. Consequently, this difference was considered again to reflect increased activity for the young relative to the old adults; this time, for the opposite comparison, S versus D.

Table 3

Maxima of regions showing significant BOLD signal increases ($P < 0.05$, FDR-corrected; extent threshold = 10) during deep (D) vs. shallow (S) encoding for the group of young adults

Region of activation	Left/right	Brodman area	Talairach coordinates x, y, z {mm}			Z value
D > S						
Medial frontal gyrus	L	6/32	-6	17	46	6.04
	R	6	12	-21	48	3.66
Inferior frontal gyrus	L	47	-48	29	-4	5.68
	R	47	42	20	-11	4.98
Hippocampus	L	28/35	-30	-16	-19	3.72
Thalamus	R	-	12	-17	4	3.34
Middle temporal gyrus	L	21	-48	-3	-10	3.90
	R	21	39	-27	-11	3.59
Superior temporal gyrus	L	37	-48	-70	3	3.37
	L	38	-48	13	-31	3.35
	R	42	45	-11	14	3.07
Precentral gyrus	L	6	-21	-12	42	3.00
Postcentral gyrus	L	43	-53	-8	17	3.52
Posterior cingulate gyrus	R	31	21	-28	32	3.23
Inferior parietal lobe	L	40	-48	-22	29	3.37
Cuneus	L	18	-6	-89	21	4.06
Precuneus	L	7	-24	-54	33	3.60
Cerebellum	R	-	12	-80	-24	4.26
S > D						
Middle frontal gyrus	R	8	30	29	46	4.43
Posterior cingulate gyrus	R	30	6	-40	16	5.24
	L	31	3	-24	40	4.66
Superior parietal lobe	R	7	6	-64	56	5.03
Inferior parietal lobe	R	40	59	-33	43	4.92
	R	40	33	-68	42	4.63
	L	40	-56	-33	46	4.49
	L	40	-48	-56	42	3.67

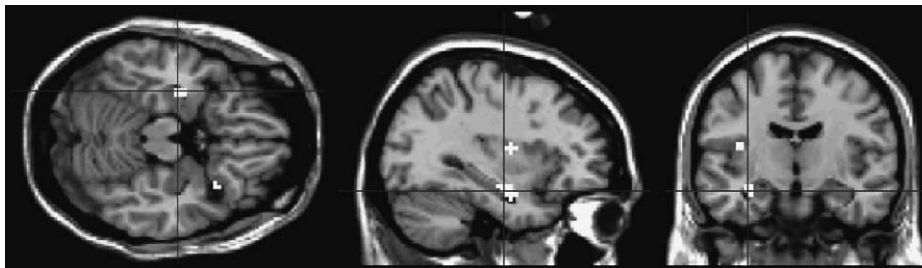


Fig. 1. Statistical parametric map (SPM) overlaying a normalised T1-image, showing increased activity in the left hippocampus during deep (D) relative to shallow (S) processing in young compared to elderly adults ($P < 0.001$, cluster = 10).

4. Discussion

In this study, we tested the processing deficiency hypothesis regarding age-related reductions in the depth-of-processing effect, stating that elderly relative to younger adults under-recruit certain cognitive operations when deep, semantic processing conditions are provided to them [1,5,14]. We further hypothesised that this under-recruitment does not involve brain regions that are commonly assumed to subservise lexical/semantic retrieval processes, as indicated by the general finding that behavioural performances on semantic classification tasks are comparable for young and old

adults [20,23], but rather involves the medial temporal lobe memory system. To this end, we used fMRI to compare brain activity patterns obtained during a deep (living/nonliving) and a shallow (uppercase/lowercase) encoding task across rather extensive groups of young and old adults.

The deep versus shallow comparison revealed common activity in elderly and young adults in a variety of regions that have commonly been related to semantic retrieval processes, including largely left-lateralised activity in the inferior prefrontal cortex (BA 47), the middle temporal gyrus (BA 21), the visual cortex, and the medial frontal gyrus extending into the anterior cingulate (BA 6/23)

Table 4

Maxima of regions showing significant BOLD signal increases ($P < 0.05$, FDR-corrected; extent threshold = 10) during deep (D) vs. shallow (S) processing for the group of elderly adults

Region of activation	Left/right	Brodman area	Talairach coordinates x, y, z {mm}			Z value
D > S						
Middle frontal gyrus	R	9	33	5	41	3.78
Medial frontal gyrus	L	6	-6	6	58	4.69
Inferior frontal gyrus	L	45/46	-48	24	7	6.53
	L	47	-36	28	-14	5.80
	R	44/45	39	18	7	4.92
	R	47	36	31	-12	3.76
Insula	R	-	30	-19	23	3.81
Middle temporal gyrus	L	21	-27	-61	9	4.02
	R	21	53	-61	9	4.02
	R	21	48	-29	-4	3.75
	L	39	-42	-63	14	3.74
	L	21	-50	-47	0	3.64
Inferior temporal gyrus	L	20	-59	-13	-20	3.95
Precentral gyrus	L	6	-50	-4	39	3.89
Cuneus	R	18	12	-92	21	4.53
	R	17	3	-70	6	3.75
Precuneus	L	7	-15	-53	50	3.89
S > D						
Middle frontal gyrus	R	10	33	55	0	4.22
Superior frontal gyrus	R	8	27	23	51	3.82
Inferior frontal gyrus	R	44	48	41	1	3.72
Superior temporal gyrus	L	42	-56	-20	7	3.55
Inferior temporal gyrus	R	37	53	-50	-5	3.39
Anterior cingulate gyrus	L	32	-3	32	-9	3.67
Posterior cingulate gyrus	R	31	6	-27	40	4.61
Inferior parietal lobe	R	7	33	-65	47	5.19
	L	40	-39	-47	55	3.82
Central parietal lobe	R	5	3	-41	60	3.49
Precuneus	R	7	12	-62	36	5.97
Cerebellum	R	-	6	49	-2	3.43

[11,14,19–21,24,25]. Although the young adults showed significantly more activity in some of these areas, including the left middle temporal gyrus, and right inferior frontal cortex, the finding of mainly overlapping activity in regions that have been previously related to semantic processing is in line with the suggestion that lexical/semantic retrieval processes are still intact in elderly adults. This received further support by the finding that the elderly and young sub-

jects showed similar behavioural performances on both the semantic and nonsemantic classification tasks. The shallow versus deep comparison also revealed comparable group activity, including the right middle frontal gyrus (BA 10), the posterior cingulate gyrus (BA 23), and left and right parietal regions (BA 7/40). The only group difference that was found in relation to this comparison was somewhat more activity in the posterior cingulate gyrus for the young subjects.

Table 5

Maxima of regions showing significant BOLD signal increases ($P < 0.001$, uncorrected; extent threshold = 10) during deep (D) vs. shallow (S) processing in comparison of young and elderly adults

Region of activation	Left/right	Brodman area	Talairach coordinates x, y, z {mm}			Z value
Young–elderly: D > S						
Inferior frontal gyrus		47	39	14	-11	3.61
Middle frontal gyrus	R	10	36	55	0	3.96
Hippocampus	L	28/35	-30	-9	-15	3.50
Middle temporal gyrus	L	21	-36	-9	-10	4.02
	L	21	-42	-18	-7	3.67
Cuneus	R	18	9	-81	21	3.75
Young–elderly: S > D						
Posterior cingulate gyrus	-	31	0	-58	55	3.77

An additional group difference that was found comparing the deep versus the shallow encoding task was observed in the left hippocampus, which was significantly activated in the young, but not in the elderly adults. This finding is in line with the processing deficiency hypothesis and in support of the idea that ageing is accompanied by an under-recruitment of the MTL memory system with the result that memory associations are formed less efficiently even when study items are processed deeply. Hence, our data seem to be in contradiction to the production deficiency hypothesis, stating that age-related memory impairments are the result of a less spontaneous utilisation of deep processing strategies by elderly adults instead of an inability to recruit certain deep processing operations [1,7]. In this respect, our results could be used as an argument against therapeutic intervention methods that are based on such strategic memory differences between young and old adults. However, our findings are not necessarily in disagreement with the production deficiency hypothesis. It is quite possible that under intentional learning conditions, without a specific task to constrain depth of processing, elderly adults are indeed less likely to employ deep processing strategies than young adult do. In support of this, a small number of studies have reported somewhat larger benefits from the employment of deep processing versus intentional learning conditions comparing old to young adults [5,7,20]. Hence, these findings, in conjunction with the solid finding that age-related differences are never dissolved under deep processing conditions, suggest that age-related impairments in episodic memory encoding are due to a combination of both production and processing deficiencies.

Although the focus of this study was on the MTL, as mentioned previously, age-related reductions in other regions of the brain were found as well. In particular, the finding of a significant age-related activity reduction in the right inferior prefrontal cortex, but comparable activity in the left inferior prefrontal cortex is interesting. A number of imaging studies have reported more bilateral frontal activity during encoding and retrieval in old relative to young adults [2,4,20,23]. This pattern of results has been conceptualised in the HAROLD model (Hemispheric Asymmetry Reduction in Old Adults) stating that elderly subjects show more bilateral activity than young subjects do when carrying out the same cognitive task, presumably to compensate for reduced efficiency of other regions of the brain [3]. An explanation for the discrepancy between our findings and, particularly, those obtained in two previous fMRI studies that observed age-related frontal asymmetry reductions during deep encoding [20,23] may reside in the age of the elderly sample that was used. Logan et al. [20] distinguished between a “young–old” group (mean age = 67), comparable to our elderly sample (mean age = 66), and an “old–old” group (mean age = 80), and only found the HAROLD pattern for the latter group. Stebbins et al. [23] similarly found reduced frontal asymmetry in an older group (mean age = 76) than the one we used in our study. These findings do not imply that reduced asymmetry is only apparent in advanced old age, since

asymmetry reductions have been observed in “young–old” subjects as well during a variety of different tasks [2,3]. Assuming that reduced asymmetry of brain activity during task performance reflects a compensatory mechanism, its presence will be determined both by the age of the subject and the difficulty of the task, and accordingly, the classification tasks that we used may have been too undemanding to necessitate any compensation in our elderly sample.

Finally, as a limitation of the present study, it should be noted that we did not specifically test for subsequent memory performance. However, in a recent follow-up study, we have replicated the finding of age-related under-recruitment of the MTL during deep incidental encoding, and found that it was indeed related to impaired memory performance as assessed by a subsequent recognition test [9].

Resuming, we found largely comparable brain activity patterns and behavioural performances on the deep and shallow classification tasks, indicating that lexical/semantic retrieval functions are still intact in elderly adults. The finding that increased activity was observed in the left hippocampus only for the young subjects in the deep versus shallow comparison, supports the idea that age-related impairments in episodic memory encoding are, at least partly, due to an under-recruitment of the MTL memory system.

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