

Research report

# Medial temporal lobe activity during semantic classification using a flexible fMRI design

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## Abstract

In this study, we evaluated the use of a self-paced fMRI design, to allow a flexible speed of responding with only four alternating stimulus blocks to minimize the influence of task switching on a group of young subjects. This was done in view of our intention to use such a design on groups of elderly and demented subjects in the near future. In addition, the hypothesis was tested that the medial temporal lobe is involved in semantic memory similar to episodic memory using a semantic retrieval task. In line with previous imaging studies that compared a semantic (living/nonliving) to a perceptual (alphabetically ascending/descending) classification condition, activity was seen in lateral temporal and inferior frontal regions, indicating the applicability of our design. Additional activity was seen in the right, and, at a slightly lower threshold, also in the left MTL, providing support for the involvement of the MTL in retrieval from semantic memory.

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## 1. Introduction

Semantic memory and episodic memory constitute two types of declarative memory [1]. Semantic memory refers to the store of facts and general knowledge that includes the meaning of words and concepts, whereas episodic memory refers to memory for past events in an individual's life. The contents of semantic memory are explicitly known and accessible for recall, but, in contrast to episodic memory, they do not refer to particular events in a person's past. The difference between these two types of memory has also been

referred to as knowing the past versus remembering the past [2,3].

Performance on semantic memory tasks has been shown to be negatively affected by pathological conditions, such as Alzheimer's dementia [4], and semantic dementia [5], but also by healthy ageing [6]. At present, there is an increasing interest in delineating the neurophysiological changes that underlie these semantic deficits using neuroimaging techniques such as functional MRI (fMRI), a noninvasive technique that can safely be repeated and that provides high spatial resolution. The present study, is part of a larger study on the effects of ageing on different components of memory including semantic memory.

Currently, several fMRI studies have been carried out on semantic memory. These studies predominantly found activity in left lateral temporal areas and the left inferior frontal cortex comparing a semantic condition

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to a nonsemantic control condition [7–9]. However, the designs used in these studies are not very suitable to apply with elderly or demented subjects. A first difficulty is that these studies used very short intertrial intervals with little time to respond. Since ageing and dementia are associated with a general slowing of cognitive functioning [10], elderly or demented subjects are expected to require more time to complete a trial than the young subjects tested in these previous studies. On the other hand, young subjects that are to be used as a comparison group might experience difficulties maintaining their concentration when a slower presentation schedule is used. Another problem, intrinsic to fMRI experiments, is that conditions need to alternate continuously during a scanning session to generate a time-dependent activation sufficiently high to minimize contributions from low-frequency drifts in the MR signal. However, since ageing and dementia tend to correlate with a decline in executive functioning as well, such task switching paradigms may induce additional problems for these subjects [10]. In view of these difficulties, we devised a self-paced semantic retrieval task that allows a flexible speed of responding. Furthermore, at the cost of increased susceptibility to low-frequency noise, only four, rather extensive, blocks of trials were alternated in order to reduce the influence of task switching to a minimum.

Regarding the organization of semantic memory in the brain, there has been a debate whether semantic memory is dependent on the integrity of the medial temporal lobe (MTL) similar to episodic memory [11,12], or whether semantic memory is preserved relative to episodic memory after damage to the MTL [13]. This latter view is based on the finding that retrieval of semantic knowledge seems to be relatively intact in MTL-damaged patients. This notwithstanding, several findings have provided support for a role of the MTL in semantic retrieval. First, although the deficits seen in MTL-damaged patients lie mainly in the episodic domain, these patients tend to perform somewhat worse than healthy controls on semantic retrieval tasks [11,12]. And second, the results of a small number of imaging studies have also indicated the involvement of the MTL in semantic retrieval. Apart from lateral temporal and inferior frontal regions, these studies found activity in the MTL either comparing a semantic classification task [7,14] or a semantic generation task [15] to a nonsemantic control condition. However, these findings have not been very consistent, since a number of other imaging studies that applied similar tasks using both PET [16,17,19] and fMRI [8,9,18,20] did not report activity in the MTL. An illustration of this lack of consistency is that Mummery and colleagues [15] found similar frontal and temporal activity trying to replicate a study by Vandenberghe et al [13], but this time no activation was seen in the MTL.

Several reasons can be put forward to explain these inconsistent results regarding the involvement of the MTL in semantic retrieval. First, in some studies, the MTL was outside the scope of the region of interest defined in their statistical analysis [8,9]. Second, in a number of PET studies the data may have been smoothed to such an extent (15–16 mm) that it has become difficult to detect signal changes in a small structure like the MTL [16,17,20]. And finally, some studies lacked sufficient statistical power. These studies, either employed low sampling rates owing to long repetition times [18], assigned too little scan time to the many conditions in their study [20], or took a very small sample size in view of the scan modality used [14,16]. Hence, the aims of the present study were twofold. First, we evaluated the applicability of a self-paced semantic retrieval task with only four alternations on a group of young subjects by comparing our results to those obtained using fixed-paced fMRI designs as in previous studies. And second, we examined the involvement of the MTL in retrieval from semantic memory using a fMRI design with a short repetition time and moderate smoothing, following two prior studies that found activity in the MTL in relation to semantic retrieval [7,15].

## 2. Methods

### 2.1. Subjects

Six healthy young volunteers (4 male, 2 female) between the ages of 17 and 24 participated. They had no known history of any neurological or psychiatric impairment. All subjects gave their written informed consent.

### 2.2. Magnetic Resonance Procedures.

Imaging was performed on a 1.5 T Siemens Vision (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 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 immobilized using foam pads to reduce motion artifact.

For each subject, a series of echo planar images (EPI) was obtained sensitive to BOLD contrast, entailing a T2\*-weighted gradient echo sequence (Repetition Time = 2.27 s, Echo Time = 50 ms, flip angle = 90°) consisting of transversal whole-brain acquisitions (20 slices, 3 x 3 mm<sup>2</sup> in-plane resolution, 6 mm slice thickness, 1 mm interslice gap).

### 2.3. Behavioural Procedures

The semantic retrieval task encompassed two conditions, a semantic (S) and a perceptual (P) classification condition. During S, subjects were instructed to indicate whether a word represented a living (left-handed press) or a nonliving object (right-handed press) using their index fingers. During P, subjects had to indicate whether the last letter of a presented noun was alphabetically ascending with respect to the first letter (e.g. ‘chicken’, because ‘c’ comes before ‘n’ alphabetically) or descending (e.g. ‘pencil’, because ‘p’ comes after ‘l’ alphabetically).

Stimuli consisted of two sets of 64 familiar Dutch nouns that were drawn from a standard dictionary with word lengths ranging from 5 to 9 letters. One set of nouns represented animate objects (e.g. ‘chicken’), the other set referred to inanimate objects (e.g. ‘pencil’). In addition, half the words in each set were alphabetically ascending, the other half descending. These nouns were randomly assigned to four alternating blocks (i.e. S-P-S-P) of 32 trials, yielding different stimulus sets for each individual subject. The blocks were separated by a 5-second instruction screen (i.e. ‘LIVING/NONLIVING’; ‘ASCENDING/DESCENDING’).

Stimuli were presented in a self-paced fashion, although a time limit of three seconds was maintained in case of non-responses. On each trial, response options were indicated at the bottom of the screen by two cursors pointing to the left (‘living’; ‘descending’) and right (‘nonliving’; ‘ascending’). Scores were only registered when the subject responded within the 3-second time limit. After the time limit had passed or the response was made, a 2-second interstimulus interval (ISI) started, taken from stimulus offset to the onset of the next stimulus. During the ISI, the word ‘NEXT...’ appeared at the bottom of the screen.

### 2.4. Analysis

Data were analyzed using SPM99 (Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>). After discarding the first two volumes, time-series were corrected for differences in slice acquisition times, and realigned using sinc interpolation. Next, the EPI volumes were spatially normalized into approximate Talairach and Tournoux space (1988) defined by the SPM EPI template, and resliced to  $3 \times 3 \times 3$  mm<sup>3</sup> voxels. Data were smoothed using a Gaussian kernel of 8 mm.

Evoked hemodynamic responses to stimulus blocks were modeled as box car 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. After high-pass filtering using a 210-sec cutoff period, 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 fixed-effects analysis.

The contrasts S vs. P, and P vs. S were tested for significance. The activated areas that are reported consisted of clusters of at least five adjacent voxels that survived a corrected threshold of  $P < 0.05$ .

## 3. Results

### 3.1. Behavioural data

On all trials, subjects responded within the 3-second time limit. They correctly classified 96% ( $\pm 3$ ) of the words presented during the semantic condition and 88% ( $\pm 5$ ) during the perceptual condition. Mean reaction times differed significantly between conditions (0.74 ( $\pm 0.06$ ) sec for S and 1.48 ( $\pm 0.12$ ) sec for P;  $F(1,10) = 31.1$ ;  $P < 0.001$ ), indicating that the perceptual task was more difficult.

### 3.2. Imaging data

Increased activity during S compared to P (Table 1; Fig. 1a), was seen in bilateral superior temporal gyrus (BA 12/22/41), left and right temporal pole (BA 38), left inferior/middle frontal cortex (BA 47/11), left uncus, left cerebellum, and in the right anterior MTL, including the entorhinal cortex. However, at a slightly lower threshold ( $P < 0.0005$ , uncorrected; cluster size = 10), two foci of activity were also observed in the left MTL (Fig. 1b).

The opposite comparison (P-S; Table 1; Fig. 1a) yielded activity bilaterally in inferior/superior parietal cortex, superior frontal cortex, occipital cortex, and precentral gyrus.

## 4. Discussion

Our main findings are that (1) our self-paced design with only four alternating blocks of trials produced results that were in good agreement with previous fixed-paced fMRI studies that compared a semantic classification to a nonsemantic control condition, yielding activations in bilateral temporal [7], and left inferior/middle frontal regions [7–9], and that (2) the MTL was activated in relation to semantic retrieval.

In order to evaluate the use of our self-paced design with only four alternations, we compared our results to those of previous fixed-paced fMRI studies that compared a semantic classification task to a nonsemantic control condition. In spite of increased susceptibility to

Table 1

Maxima of regions showing significant ( $P < 0.05$ , corrected; cluster size  $> 5$ ) BOLD signal rises in comparison of Semantic (S) and Perceptual (P) Classification

Region of activation	Left/Right	Brodmann area	Talairach coordinates $x, y, z$ (mm)			Z value
<i>Increases during S</i>						
Middle frontal gyrus	L	10/32	-6	48	-6	6.10
	L	11	-33	42	-15	4.95
Superior temporal gyrus	L	41	-57	-21	12	6.51
	L	38	-36	21	-36	5.15
	R	12/38	57	9	-9	5.54
	R	22	60	-3	6	5.56
Entorhinal cortex	R	20/38	30	-12	-27	4.83
Entorhinal cortex/Uncus/Amygdala	L	28/36	-18	6	-27	5.97
Postcentral gyrus	R	40	51	-21	12	5.58
Cerebellum	L		-	-	-	5.20
<i>Increases during P</i>						
Superior frontal gyrus	R	8	30	21	51	7.13
	L	8	-27	12	48	5.95
Superior parietal cortex	L	40	-36	-51	51	7.14
Inferior parietal cortex	R	40	45	-45	57	6.91
Precentral gyrus	L	6	-27	6	63	6.45
	L	6	-45	12	33	6.25
Cuneus	L	19	-30	-78	36	5.74
Middle temporal gyrus	R	39	39	-81	24	4.66

low-frequency noise due to the extensiveness of the stimulus blocks, our results are in good agreement with these earlier findings, indicating that such a design can be applied in imaging studies of higher cognitive functioning. This may facilitate the application of functional imaging studies to less accessible groups such as elderly and cognitively impaired subjects by allowing a flexible speed of responding and minimizing the influence of task switching.

Our finding that the right, and at a slightly lower threshold also the left, MTL was more active during semantic than during perceptual classification is consistent with the hypothesis that the MTL is involved in retrieval from semantic memory [11,12]. In view of earlier evidence for the dependence of episodic memory on the integrity of the MTL, this finding is in agreement with the proposition of one MTL-dependent declarative memory system that encompasses both semantic and episodic memory [1]. It must be noted, though, that there is an alternative explanation for the finding of medial temporal lobe involvement in semantic retrieval. It has been generally found that semantically processed items (deep processing) are better remembered than items that are processed on a more perceptual basis (shallow processing) [21]. The greater involvement of the medial temporal lobe in semantic than in perceptual classification could, therefore, be due to this difference in episodic encoding rather than to differences in semantic retrieval.

In addition to the MTL, we found activity in bilateral temporal regions, including the left temporal pole (BA 38). This is in accordance with clinical findings on

patients with semantic dementia that show most prominent atrophy in lateral temporal areas, and the left temporal pole in particular [13]. Interestingly, the temporal poles have scarcely been activated in previous imaging studies [22]. One obvious reason for this may be that in many studies this region was not included in the brain volume scanned, because of its extreme anterior/inferior location. Furthermore, due to susceptibility artifacts, fMRI data for this region are characterized by very low signal-to-noise ratio. However, close inspection of our own data did not reveal any particular signal loss in this area.

As in the majority of imaging studies that used tasks requiring some form of semantic processing, activity was found in the left frontal lobe, covering the inferior (BA 47) and middle frontal (BA 11) gyri [9,7,14]. In view of these earlier findings, this region has been put forward as a candidate site for semantic memory [23]. However, the role of the left frontal cortex in semantic processing has been subject of debate. It has been suggested that this region is more involved in the strategic control or selection of semantic material than in semantic processing, based on the fact that there is no evidence for semantic deficits in patients with damage restricted to frontal regions and that patients with semantic impairment often have no damage to frontal structures [16,20]. The perceptual classification task yielded activations in superior parietal and frontal cortex, areas typically associated with attention and working memory [24]. This may have been due to the fact that the perceptual task was more difficult than the semantic task as reflected in longer reaction times and lower accuracy

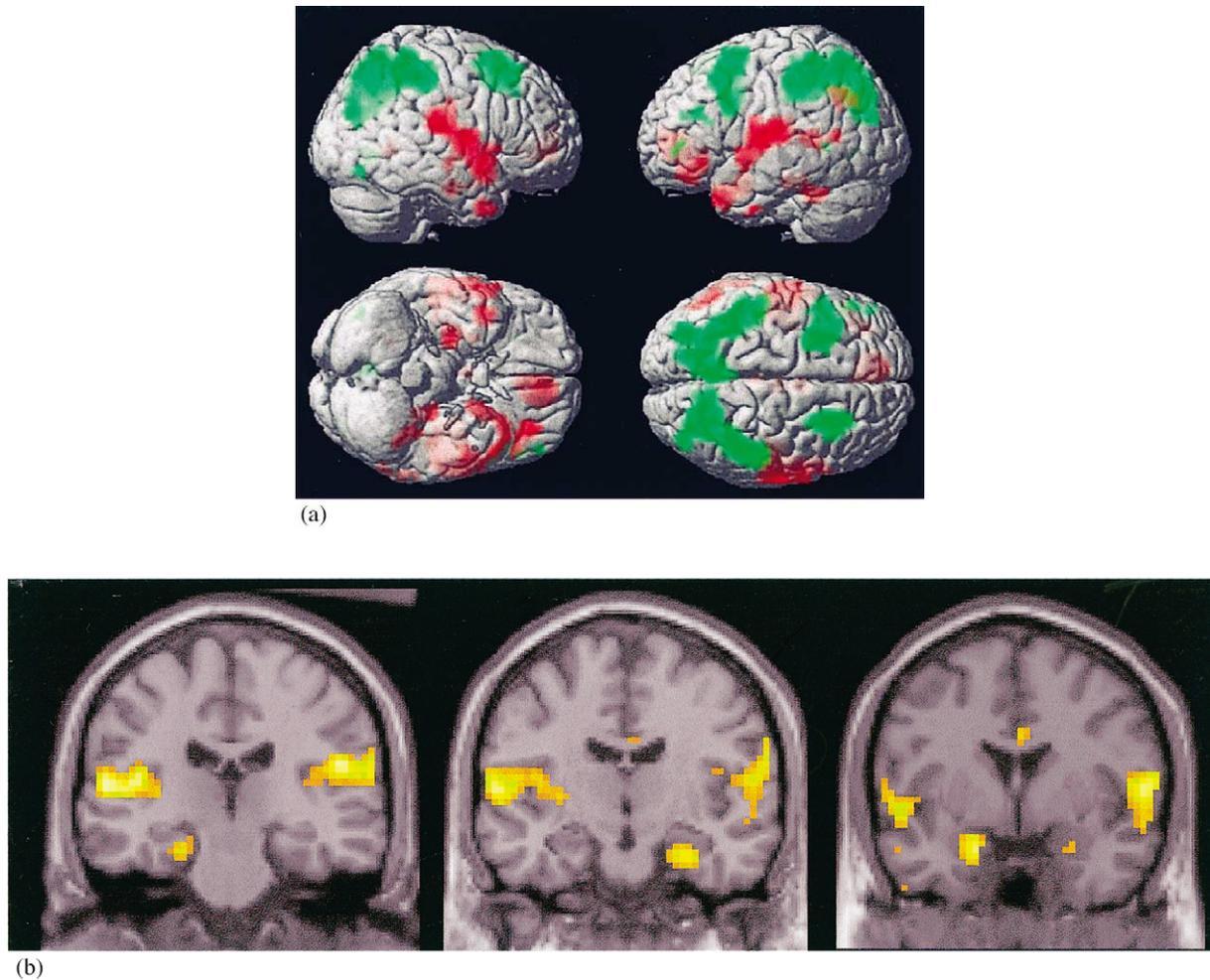


Fig. 1. For the purpose of illustration the thresholds were set slightly lower than for Table 1. (A) Areas showing BOLD increases in comparison of semantic and perceptual classification and B ( $P < 0.0005$ , uncorrected). (B) Statistical Parametric map [SPM] overlaying a normalized T1 image, showing increased activation in the left and right medial temporal lobe in comparison of semantic and perceptual classification. ( $P < 0.0005$ , uncorrected). The focus shown on the left involves the left parahippocampal gyrus, the focus in the middle includes the right entorhinal cortex, and the focus on the right covers the anterior part of the left entorhinal cortex, the uncus, and the amygdala.

scores, which may have instigated subjects to allocate more effort to the perceptual than to the semantic condition. Hence, although our results are in good agreement with previous imaging studies on semantic retrieval, we cannot exclude the possibility that this aspect in some way has influenced our results. Another methodological issue concerns the possibility that activity differences in the MTL reflected a decrease in activity during the perceptual classification task instead of an increase during the semantic task. However, in view of previous indications for the involvement of the MTL in deep processing tasks, this is not very likely.

In conclusion, we found activity in the MTL during semantic classification. Given earlier evidence for the dependence of episodic memory on the integrity of the MTL, this suggests that the MTL is involved both in episodic and semantic memory processes, supporting the proposition of one MTL-dependent declarative memory system that covers both types of memory. Furthermore,

our results were largely concordant with the results of previous imaging studies comparing a semantic retrieval task to a nonsemantic reference task. Our data therefore indicate that it is feasible to implement a self-paced design with only a small number of alternating blocks of trials within fMRI experiments studying higher cognitive processes. This might have implications for future cognitive studies, smoothing the progress of applying fMRI to less accessible groups such as elderly and cognitively impaired subjects.

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