

Parahippocampal Activation during Successful Recognition of Words: A Self-Paced Event-Related fMRI Study

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In this study, we investigated retrieval from verbal episodic memory using a self-paced event-related fMRI paradigm, similar to the designs typically used in behavioral studies of memory function. We tested the hypothesis that the medial temporal lobe (MTL) is involved in the actual recovery of verbal information (retrieval success) rather than in the attempt to retrieve information (retrieval attempt). To this end, we used a verbal recognition task, distinguishing correctly recognized words, correctly rejected words, and a low-level baseline condition. Directly contrasting correct recognition with correct rejection of words, we found activation in the left fusiform/parahippocampal gyrus, indicating that this region has a distinct role in the successful retrieval of verbal information. Furthermore, our results were in agreement with those of previous imaging studies that compared a fixed-paced verbal recognition task to a baseline condition, showing activation in bilateral inferior frontal cortex, left dorsolateral prefrontal cortex, left anterior insular cortex, and anterior cingulate. This demonstrates the applicability of a self-paced event-related design within imaging studies of memory function.

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INTRODUCTION

Functional MRI (fMRI) has greatly advanced the research on neuroanatomical correlates of human memory function. At present, the areas involved in episodic retrieval are well defined and, in line with findings from neuropsychological studies (Shallice, 1988; Milner *et al.*, 1991; Teng and Squire, 1999), the frontal and medial temporal lobes have been pointed out as important sites for episodic retrieval processes (e.g., Nyberg *et al.*, 1996; Buckner *et al.*, 1995, 1996a,b; Schacter *et al.*, 1996a,b, 1997a,b). Research is now beginning to focus on the involvement of specific brain areas in selective subcomponents of episodic retrieval.

A basic distinction is that between processes associated with the attempt to retrieve information and processes supporting the actual recovery of information. The first set of processes has been referred to as retrieval mode (Lepage *et al.*, 2000; Tulving, 1983) or retrieval attempt (Kapur *et al.*, 1995), whereas the latter has been termed retrieval success (Buckner *et al.*, 1998a,b) or ecphory (Tulving, 1983; Kapur *et al.*, 1995).

Several imaging studies have indicated that the medial temporal lobe (MTL) is specifically involved in retrieval success. These studies manipulated success rate either by using an encoding manipulation (deep vs shallow encoding) or by varying the percentages of studied and novel items over the conditions (Schacter *et al.*, 1996b; Nyberg *et al.*, 1996; Rugg *et al.*, 1997; Heckers *et al.*, 1998). However, other studies using similar designs did not report activation in the MTL (Kapur *et al.*, 1995; Buckner *et al.*, 1998a; Rugg *et al.*, 1996, 1998; Wagner *et al.*, 1998a).

A possible methodological problem in these studies is the use of block designs: items of the same type are presented in blocks of trials. In this way, subjects may be prompted to change their strategy depending on whether they are faced with a block with a high chance of success or with a low-success block. Furthermore, even when performance scores are used as a covariate, such epoch designs do not permit full separation between retrieval success and retrieval attempt, because the blocks representing retrieval attempt will be contaminated with successful responses and the success blocks with errors.

Event-related fMRI, a method to study activation patterns on a trial-by-trial basis (Buckner *et al.*, 1996a; Boynton *et al.*, 1996; Josephs *et al.*, 1997), offers a more straightforward way of separating these retrieval components by permitting a direct comparison of successfully recognized words (retrieval success) to correctly rejected words (retrieval attempt). However, earlier event-related studies that made such a comparison did

not find activation in the MTL. It must be noted, though, that these studies used long intervals between trials varying from 8 to 16 s to prevent individual hemodynamic responses from overlapping (Schacter *et al.*, 1997a; Buckner *et al.*, 1998b; Henson *et al.*, 1999). Such unusually long interstimulus intervals may interfere with processes associated with retrieval success, e.g., by inducing attentional lapses.

In the present study, we investigated the hypothesis that the MTL is specifically involved in successful recognition of words. We used an event-related fMRI paradigm with a rapid, random presentation of trials to directly compare recognition of studied words (retrieval success) against rejection of novel words (retrieval attempt), based on earlier reports indicating linear summation of successive hemodynamic responses in such a design (Dale and Buckner, 1997; Buckner *et al.*, 1998c). Furthermore, we applied a self-paced paradigm that allowed us to investigate brain activation under similar conditions as typically employed in behavioral and clinical tests of memory function. Moreover, such a design reduces the effective interval between trials to a minimum, and additionally gives automatic jitter of stimulus presentation relative to scan onset, increasing the number of sampling points across peristimulus time (Dale, 1999).

MATERIALS AND METHODS

Thirteen healthy volunteers (7 male, 6 female) between the ages of 20 and 30 (mean 23.8 ± 2.5) participated. They had no known history of any neurological or psychiatric impairment. All subjects gave their written informed consent.

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 = 60 ms, flip angle = 90°) consisting of transversal whole-brain acquisitions (20 slices, $3 \times 3\text{-mm}^2$ in-plane resolution, 6-mm slice thickness, 1-mm interslice gap).

Behavioral Procedures

The verbal recognition task consisted of a study and a retrieval phase, separated by an 8-min retention interval. A list of 133 abstract and concrete nouns was drawn from a standard Dutch dictionary with word lengths ranging from 3 to 12 letters. Ten of these words were used as filler words and three as dummy trials (see below). The remaining 120 words from the list were randomly assigned to conditions within the experiment, yielding different stimulus sets for each individual subject.

At study, subjects were presented with 70 nouns: 60 study words and 10 filler words. Five filler words were presented at the beginning and five at the end of the list in order to prevent primacy and recency effects (Graf *et al.*, 1984). The subjects were instructed to memorize these words for subsequent testing. The words were presented for a maximum duration of 5 s, but subjects were free to continue with the next word by pressing a button.

During the retention interval, subjects were instructed to do some simple addition sums by choosing between two alternative answers with a left- or right-hand response (for example: $256 + 324 = 580$ or 590). We included this interference task to increase uniformity of test performance by preventing rehearsal strategies during the retention interval.

During retrieval, fMRI data were obtained. Three different trial types were distinguished: 60 targets (study words), 60 distracters (novel words), and 60 baseline items consisting of the instruction "do not press." The baseline condition was included to permit the comparison of our results to those of previous fixed-paced imaging studies that applied a low-level reference condition within a verbal recognition task. Prior to each experiment, the trials were randomly intermixed into 20 blocks of 9 stimuli (Fig. 1). The baseline items were presented on the screen for two seconds, followed by a 2-s interstimulus interval (ISI), taken from stimulus offset to the onset of the next stimulus. The length of this interval was considered to be optimal based on previous reports of hemodynamic saturation effects at intervals shorter than 2 s (Friston *et al.*, 1998). During the ISI the word "NEXT. . ." appeared at the bottom of the screen.

Presentation of the words was self-paced, although a time limit of three seconds was maintained in case of nonresponses. The duration of this time limit was based on pilot experiments that showed that the vast majority of responses fell well within this 3-s period. Subjects were instructed to indicate whether they had previously seen the word (left-handed press) or not (right-handed press) using their index fingers. Scores were only registered when the subject responded within the 3-s time limit. After the response was made or the time limit had passed, the ISI started. The trials

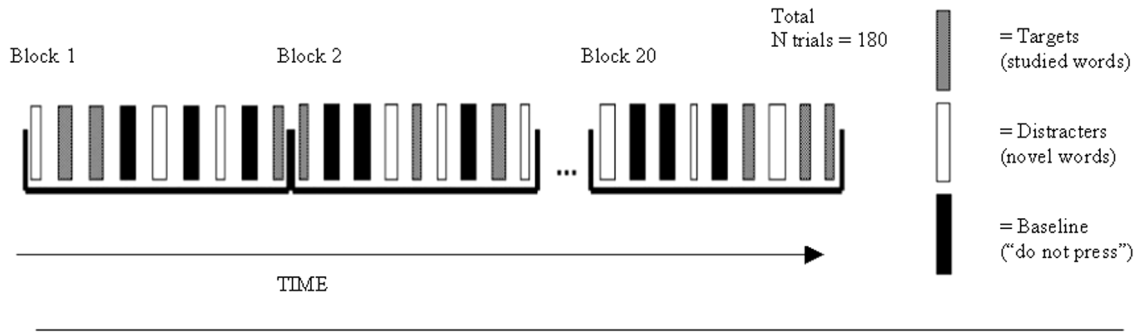


FIG. 1. Stimulation paradigm: Trial types were randomly presented in 20 blocks of nine items, consisting of three targets, three distracters, and three baseline items. In this way, a condition could be presented maximally six times in succession. This ensured that any variance resulting from drifts in the MR signal would be spread equally over the different trial types. Every 2.27 s a new scan was made. The words were displayed until button-press for a maximum duration of 3 s. The interstimulus interval and the presentation of the baseline items were fixed to 2 s. Total number of trials was 180 (60 targets, 60 distracters, 60 baseline items).

were preceded by five dummy trials 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.

Analysis

Data were analyzed using SPM99 (Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>). After discarding the first 2 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 to $3 \times 3 \times 3$ mm voxels. Data were spatially smoothed using a Gaussian kernel of 8 mm.

The event-related fMRI analysis was based upon the assumption that individual hemodynamic responses summate in a practically linear fashion over time (Dale and Buckner, 1997; Buckner *et al.*, 1998c). Evoked hemodynamic responses to event-types were modeled as delta functions convolved with a synthetic hemodynamic 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). In the first step, the number of scans per session (ranging from 270 to 313) was graded to the fastest session, i.e., sessions were truncated to 270 scans, in order to meet the equal variance assumption implicit in random effects analyses. Next, specific effects were tested by applying appropriate contrasts to the parameter estimates for each event, resulting in a *t* statistic for every voxel. In this way, SPMs (Statistical Parametric Maps; Friston *et al.*, 1995) were determined for each individual subject. In the second step, we carried out a one-sample *t* test upon the resulting contrast images. For the retrieval trials, only correct responses were included to either studied (retrieval success, RS), or novel words (retrieval attempt, RA).

The contrasts retrieval (RS + RA) vs baseline (B), RS vs RA, and RA vs RS were tested for significance. Since our analysis was mainly hypothesis driven, focusing on areas reported in earlier studies (e.g., Buckner *et al.*, 1995, 1996, 1998a,b; Schacter *et al.*, 1996a,b, 1997a,b) and the MTL, we applied an uncorrected threshold of $P < 0.0005$ with a minimum cluster size of five voxels.

RESULTS

Behavioral Data

Subjects correctly recognized 74 (SD = 13)% of the studied items and correctly rejected 80 (SD = 13)% of the new items, giving a hit-false alarm index of $0.74 - 0.20 = 0.54$, indicating good discrimination between the trial types. The rate of nonresponses was 2 (SD = 2)% for the studied items and 2 (SD = 4)% for the new items. No significant differences were found in mean reaction times (1.11 (SD = 0.19) s for correctly recognized and 1.18 (SD = 0.21) s for correctly rejected items).

Imaging Data

Retrieval vs baseline. Regions showing increased BOLD signal in comparison of retrieval (RS + RA) and baseline (B) (Table 1A and Fig. 2A) were left primary motor/somatosensory cortex, left dorsolateral prefrontal cortex (BA 9/44), left anterior insular cortex including the putamen, extending into the left inferior frontal cortex (BA 47), right putamen, right inferior frontal cortex (BA 47), the SMA (BA 6), and the anterior cingulate (BA 32/8).

Retrieval success vs attempt. Directly comparing RS to RA (Table 1B and Fig. 2B) revealed increased signal in right primary motor/somatosensory cortex (following a left-hand response), left inferior parietal cortex (BA 40), left middle temporal gyrus (BA 21), and left fusiform/parahippocampal gyrus (Fig. 2C).

The opposite comparison RA vs RS yielded a signal

TABLE 1A

Maxima of Regions Showing Significant ($P < .0005$, Uncorrected; Cluster Size > 5) BOLD Signal Rises in Comparison of Retrieval (RS + RA) and Baseline (B)

Region of activation	Left/Right	Brodmann area	Talairach coordinates x, y, z {mm}			Z value
Primary motor/somatosensory cortex	L	4	-57	-21	45	3.85
Supplementary motor area	R	6	9	-6	54	4.03
Anterior cingulate	R	32/8	6	33	42	3.53
	L	32/8	-9	33	39	3.53
Middle frontal gyrus	L	9/44	-36	15	33	3.63
Inferior frontal gyrus	L	47	-36	27	-9	4.74
	R	47	33	27	-9	3.82
Putamen	R	—	24	9	-12	3.77
Cerebellum	R	—	—	—	—	4.47
Prestriate cortex	L	18	-9	-87	-6	4.19

increase in left primary motor/somatosensory cortex (following a right-hand response).

DISCUSSION

The main findings of this study are that (1) the left fusiform/parahippocampal gyrus was activated when comparing retrieval success against retrieval attempt and that (2) our self-paced event-related design yielded activations that were in good agreement with previous fixed-paced imaging studies that compared a verbal recognition task to a low-level reference condition, in-

cluding the left inferior frontal cortex (Petrides *et al.*, 1995; Henson *et al.*, 1999; Buckner *et al.*, 1995; Schacter *et al.*, 1997a), right inferior frontal cortex (Buckner *et al.*, 1998a,b; Schacter *et al.*, 1997a; Henson *et al.*, 1999; Shallice *et al.*, 1994), left dorsolateral prefrontal cortex (Busatto *et al.*, 1997; Petrides *et al.*, 1995; Nolde *et al.*, 1998; Buckner *et al.*, 1995, Buckner *et al.*, 1998b), left anterior insular cortex (Buckner *et al.*, 1998a,b), and the anterior cingulate (Buckner *et al.*, 1998a, Kapur *et al.*, 1995; DallaBarba *et al.*, 1998).

Our finding that the left parahippocampal gyrus was more active during correct recognition than during cor-

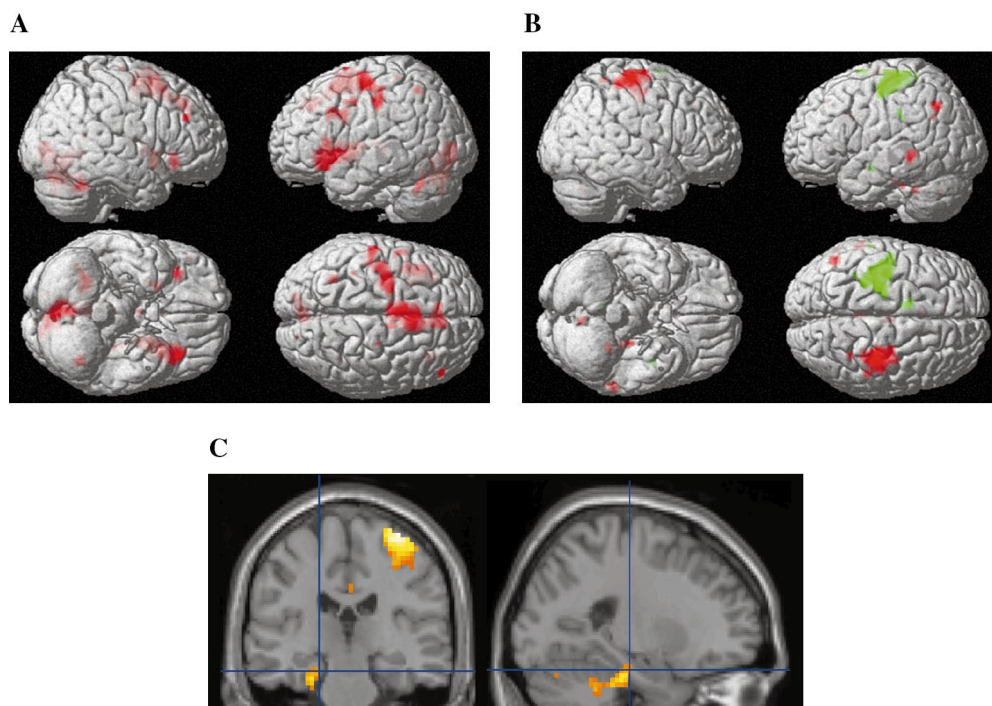


FIG. 2. (A–C) For the purpose of illustration the thresholds were set slightly lower than for Tables 1A and 1B. (A) Areas showing BOLD increases in comparison of retrieval (RA + RS) and B ($P < .001$). (B) Areas showing BOLD increases in comparison of RS (red) and RA (green) ($P < .001$). (C) Statistical Parametric map [SPM] overlaying a normalized T1 image, showing increased activation in the left fusiform/parahippocampal gyrus in comparison of RS and RA ($P < .005$).

TABLE 1B

Maxima of Regions Showing Significant ($P < .0005$, Uncorrected; Cluster Size > 5) BOLD Signal Rises in Comparison of Retrieval Success (RS) and Retrieval Attempt (RA)

Region of activation	Left/Right	Brodmann area	Talairach coordinates x, y, z {mm}			Z value
Increases during RS						
Primary motor/somatosensory cortex	R	4	36	-27	69	4.44
Fusiform/Parahippocampal gyrus	L	36	-24	-27	-27	3.80
Middle temporal gyrus	L	21	-63	-39	-3	3.53
Inferior parietal lobe	L	40	-48	-63	39	3.90
Increases during RA						
Primary motor/somatosensory cortex	L	4	-39	-27	66	4.44

rect rejection combined with the fact that no activation was seen in the MTL comparing retrieval against baseline, is consistent with the hypothesis proposed by Nyberg and colleagues (1996) that the MTL is involved in the actual recovery of information (retrieval success), but not in the general attempt to retrieve information (retrieval attempt).

Regarding the role of the MTL in the actual recovery of information, it has been suggested that the MTL is called for during the retrieval of relatively new information, as is typically required during clinical tests of memory function (Squire, 1992; Teng and Squire, 1999). Accordingly, it has been proposed that the MTL is involved in a gradual process of consolidation, operating as a temporal memory store for the immediate storage of new data, while the neocortex serves as a permanent memory store (Alvarez and Squire, 1994). The role of the parahippocampal region in this process has been suggested to pertain to the persistence of memory traces through direct and reciprocal interconnections with the neocortex (Eichenbaum *et al.*, 1996).

Our results are not consistent with the suggestion that the MTL is involved in novelty detection, because in that case this region would be more activated during novel relative to familiar items (Stern *et al.*, 1996; Gabrieli *et al.*, 1997; Rombouts *et al.*, 1997). However, it is possible that the function of the MTL switches along with the nature of the memory task: encoding instructions may induce processes related to novelty detection, which are not invoked under retrieval instructions.

An interesting aspect with regard to the verbal nature of the task is that, compared to studies investigating retrieval of spatial or figural material, many imaging studies that used verbal stimuli failed to provide evidence of MTL activation (e.g., Rugg *et al.*, 1996, 1998; Kapur *et al.*, 1995; Buckner *et al.*, 1998a,b). A possible explanation for this is that the MTL operates by establishing associations between sensory inputs, thoughts, and emotions that together constitute an episode in memory (Alvarez and Squire, 1994; Eichenbaum, 1996; Henke *et al.*, 1997). Hence, the less com-

plex an episode is, the fewer associations are required to encode or retrieve it, and as a result, the less MTL activation can be expected. Accordingly, it can be expected that it will be more difficult to activate the MTL with verbal stimuli than with more complex stimuli such as pictures and spatial scenes. Several imaging studies have found support for this relational account of MTL function in human memory (Henke *et al.*, 1997, 1999; Nyberg *et al.*, 2000).

The left-sided activation we found is in agreement with a study by Kelley *et al.* (1998) that showed material-dependent lateralization of the MTL during encoding: the left MTL was activated during the encoding of words, whereas the right was activated during the encoding of unfamiliar faces. These findings support the evidence from lesion studies for the dependence of verbal memory on the left MTL (Milner, 1966). We did not find support for a functional dissociation within the MTL implicating the posterior part with encoding processes and the anterior part with retrieval (for a review see Schacter and Wagner, 1999), since the site of activation was located in the middle of the MTL.

In order to evaluate the use of our self-paced event-related design, we compared our results to those of previous fixed-paced studies that compared a recognition task to a low-level reference condition. The fact that our results are in good agreement with these earlier findings indicates that a self-paced design can be applied in imaging studies of memory function. This might have implications for future cognitive research. First, it provides us with the opportunity to investigate brain activation under similar conditions as typically used in behavioral and clinical studies of memory. Second, it may facilitate the application of functional imaging studies to less accessible groups (e.g., elderly and cognitively impaired subjects), because it allows a flexible speed of responding. And third, it may increase the comparability across populations because the same task can be used for different experimental or clinical groups.

In addition to the MTL, we found increased activation in the left inferior parietal cortex and left middle

temporal gyrus comparing correct recognition to correct rejection of words. Lateral parietal and temporal areas have been previously implicated with retrieval success. However, the specific roles of these areas are still subject of debate (Nyberg *et al.*, 2000; Henson *et al.*, 1999; Kapur *et al.*, 1995; Konishi *et al.*, 2000).

One recent study by Konishi *et al.* that showed similar left parietal activation to our study in relation to retrieval success also used rapid-presentation event-related fMRI. However, this study did not report activation in the MTL. A possible source for this inconsistency may come from the fact that in this study data acquisition was synchronized to trial presentation, resulting in a biased sampling of the peristimulus time. Previous reports have shown that, particularly when using short intertrial intervals, measurement efficiency greatly increases when stimulus presentation and data acquisition are desynchronized (Dale, 1999; Burock *et al.*, 1998). In our study, this feature was automatically incorporated by using a self-paced design.

Although activation was found in bilateral inferior frontal and left dorsolateral prefrontal cortex when contrasting retrieval and baseline, no differential activation was seen in frontal areas comparing correct recognition to correct rejection. This finding provides support for the idea that frontal areas are involved in the attempt to retrieve information, but not in the actual recovery of information. These results are in line with a recent multistudy analysis by Lepage *et al.* (2000) that also identified the left and right inferior frontal cortex as regions that support retrieval attempt independent of the level of retrieval success. However, our data should be interpreted with some caution, since the debate on frontal lobe involvement in attempt vs success mainly focused on a right anterior prefrontal area (e.g., Kapur *et al.*, 1995; Rugg *et al.*, 1996, 1998; Buckner *et al.*, 1998a,b) that was not found to be activated in any of the comparisons made in our study. In two previous event-related studies on verbal recognition, this activation component was found to be delayed for several seconds after stimulus presentation (Buckner *et al.*, 1998b; Schacter *et al.*, 1997a). However, we were unable to replicate this finding even when incorporating delays of up to 8 s in our analysis, which may have been due to methodological differences such as in length of the ISI.

We did not find support for the hemispheric encoding retrieval asymmetry (HERA) model, which states that the right frontal cortex is more involved in retrieval processes, whereas the left frontal cortex is called upon during encoding into episodic memory (Tulving, 1994). However, our results are in line with studies that showed a material-dependent lateralization of the frontal lobes, similar to that seen in the MTL (Wagner *et al.*, 1998; Kelley *et al.*, 1998; McDermott *et al.*, 2000).

Finally, it should be mentioned that some caution in interpreting our data would be appropriate, since we did not explicitly control for motor responses. Consequently, some of our results could also be attributed to activation resulting from a left- or right-handed button-press. However, areas involved in motor activity have been well documented and do not seem to involve the regions that were highlighted in this discussion (Schubotz *et al.*, 2000; Lotze *et al.*, 1999; Lee *et al.*, 1999; Hendler *et al.*, 1999).

In summary, we demonstrated the involvement of the MTL in retrieval from verbal episodic memory. The fact that the left fusiform/parahippocampal gyrus was found to be more active during retrieval success than during retrieval attempt suggests that this region has a distinct role in the actual recovery of verbal information. Furthermore, our results were largely concordant with the results of previous imaging studies comparing a verbal retrieval task to a low-level reference task. Our data therefore indicate that it is feasible to implement a self-paced event-related design within fMRI experiments studying higher cognitive processes. This might have implications for future cognitive studies, permitting investigations of brain activation under similar conditions as generally employed in behavioral and clinical studies of cognition.

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