Prefrontal Selection and Medial Temporal Lobe Reactivation in Retrieval of Short-term Verbal Information

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Both the prefrontal cortex (PFC) and medial temporal lobe (MTL) are involved in memory retrieval. Here we distinguish between their roles by manipulating demand for interference resolution and reaction of maintained information. Subjects were tested on a letter working memory task with distractors. When the memory delay was interrupted with letter distractors, there was higher activity in the middle frontal gyrus at retrieval compared to when the delay was interrupted by number distractors, suggesting the role of the PFC in interference resolution. By contrast, activity in the parahippocampal gyrus did not differ between the two conditions. The two structures were then compared using the dataset of our previous study on memory reactivation, where subjects performed a letter working memory task with arithmetic distractors or non-distractors. The activity in the parahippocampal gyrus at retrieval was higher when distractors interrupted rehearsal than when the intervening task was non-distracting and subjects continued to rehearse, suggesting the role of the MTL in reactivating the stored information. By contrast, the activity in the middle frontal gyrus did not differ between the two conditions. Taking these results together, we have shown the double dissociation between the PFC and MTL in memory retrieval.

Keywords: functional MRI, interference, parahippocampal gyrus, prefrontal cortex, working memory

Introduction

The prefrontal cortex (PFC) and medial temporal lobe (MTL) are two key structures for memory processing (Buckner and Wheeler, 2001). The present study is aimed at distinguishing between their roles in memory retrieval. An early hypothesis was that the PFC is involved in short-term or working memory whereas the MTL is involved in long-term memory. However, recent studies have shown that the two structures are involved in both types of memory (Cabeza et al., 2002; Ranganath et al., 2003). Thus time is not the factor to distinguish between the two structures.

One factor that can distinguish between the PFC and MTL is interference resolution. The mechanisms of interference resolution have been examined by creating a situation where the subjects have to select information relevant to the present task and to suppress irrelevant information. The demand for interference resolution has been manipulated by presenting items that had been used in the previous trials but are no longer relevant in the present trials (Smith et al., 1995; Bunge et al., 2001; Henson et al., 2002; Thompson-Schill et al., 2002) or presenting distractor items similar to the target items (Wickens et al., 1963; Incisa della Rocchetta and Milner, 1995). In highly interfering situations, activity in the PFC is shown to increase at retrieval from long-term memory (Henson et al., 2002) as well as from short-term, working memory (Bunge et al., 2001). Lesions in the PFC cause increased susceptibility to interference in long-term memory retrieval (Incisa della Rocchetta and Milner, 1993; Shimamura, 1995) as well as in short-term memory retrieval (Thompson-Schill et al., 2002). By contrast, patients with lesions in the MTL are less affected by interference (Incisa della Rocchetta and Milner, 1993; Smith et al., 1995) and its activity at retrieval is not affected significantly by the amount of interference (Bunge et al., 2001; Henson et al., 2002). Thus compared to the MTL, the PFC may play a more significant role in interference resolution at memory retrieval.

Another factor that can distinguish between the PFC and MTL is the reactivation of maintained information. Here reactivation is defined as the process of bringing the off-line, stored information back to the on-line state (Sakai, 2003). Physiological mechanism of reactivation has been examined first by single unit recording from monkeys trained on an object paired association task (Sakai and Miyashita, 1991; Naya et al., 1996). It has been shown that neurons in the inferior temporal cortex that are active at the presentation of a particular object also become active upon demand of retrieval of that object. Subsequently neuroimaging studies on human subjects have confirmed the reactivation of brain areas that had been involved in the initial processing of the to-be-retrieved information (Nyberg et al., 2000, 2001; Wheeler et al., 2000). By contrast, in working memory, areas that are involved in the processing of information show sustained activity during the on-line maintenance of that information (Fuster, 1990; Chafee and Goldman-Rakic, 1998). However, when on-line maintenance is interrupted by distractors, the information can no longer be maintained on-line in the posterior association areas (Miller et al., 1993, 1996; Constantinidis and Steinmetz, 1996). When the remembered item is presented again for recognition judgement, the neurons become active again, that is these neurons are reactivated. Thus a similar reactivation process has been observed in posterior association areas at retrieval from long-term memory and from short-term, working memory after interruption of on-line maintenance. By contrast, there is no need to reactivate the information at retrieval from working memory when information is maintained on-line. The MTL has been thought to play a role in this reactivation process (Nyberg et al., 1996). This area has been shown to be active at retrieval from long-term memory (Schacter and Wagner, 1999) and from working memory when on-line maintenance is interrupted (Sakai et al., 2002). Moreover, activity in the MTL has been shown to accompany reactivation in the posterior association areas (Nyberg et al., 2000). The MTL is also shown to be active at retrieval from working memory even though there is no interruption of on-line maintenance (Ranganath and D’Esposito, 2001) but the activity is significantly smaller compared to when on-line maintenance is interrupted (Sakai et al., 2002).
al., 2002). Thus the primary role of the MTL seems to be to reactivate the information maintained offline. By contrast, the PFC activity at retrieval is not affected by the demand of reactivation. The PFC is active at retrieval from working memory (when there is no need to reactivate the information) as well as retrieval from long-term memory (when there is demand to reactivate the information) (Buckner and Wheeler, 2001). Activity in the PFC is observed when subjects attempt to recall off-line information even though the memory reactivation has been failed (Maril et al., 2001; Kikyo et al., 2002). The PFC is also active at retrieval of short-term memory regardless of whether there is interruption of on-line maintenance or not (Sakai et al., 2002). Thus the PFC seems to be insensitive to the demand for reactivation.

Thus the PFC and MTL can be distinguished by the two factors, the demand for interference resolution and reactivation of remembered information (Sakai, 2003). However, studies to date have not examined the two factors together. The absence of effects of a single factor on one structure (e.g. absence of interference effect in the MTL) could be due to insufficient sensitivity to detect the changes in brain activity or in behavior. Thus a strong argument for the distinction between the two structures requires the demonstration of a double dissociation between the effects of two factors.

Here we show a double dissociation between the roles of the PFC and MTL in retrieval of short-term memory. We used a short-term working memory task for letters with distractor task inserted at the end of the memory delay. The advantage of this paradigm is that by changing the nature of the distractor task we can manipulate the amount of interference and the demand for reactivation without changing the nature of the main memory task.

We first examined the effect of interference on the activity at retrieval of letters. We have inserted either a 5 s letter distractor or number distractor task at the end of the memory delay. The letter distractor causes a higher degree of interference than number distractor task because of the phonological similarity with the letters to be retrieved. On the other hand, on-line maintenance is not possible during the distractor tasks for either condition. Thus the two conditions require the reactivation process to a similar degree. This situation differs from the previous studies on interference resolution in that the distractor item is presented after presentation of the to-be-remembered items. In the previous studies, the distractor items have been presented before presentation of the to-be-remembered items (Smith et al., 1995; Bunge et al., 2001; Henson et al., 2002; Thompson-Schill et al., 2002). None the less, the basic mechanism of interference resolution, selection of task-relevant information, is similarly required in the letter distractor condition of the present study and in the previous studies.

We then examined the effect of the demand of reactivation on the activity in the PFC and MTL using the data set of our previous study (Sakai et al., 2002). In that study, we have inserted a 5 s arithmetic task, serial addition of the five numbers, at the end of the memory delay of a letter working memory task. We tested two conditions. In the distractor condition we have used numbers chosen from 3 to 9 and in the non-distractor condition we have used five ‘0’s. The distractor condition interrupted the rehearsal of to-be-remembered letters and required reactivation of information at retrieval. Thus, although the memory is tested within a short-term period, this situation is similar to retrieval from long-term memory. We have used the term ‘short-term memory task’ only to indicate that the memory was tested within a short-term period. By contrast, in the non-distractor condition where the answer to the arithmetic task was predictable, the subjects were able to continue the rehearsal during this period and therefore there was no need to reactivate the remembered information at retrieval.

Thus one study manipulated the demand for interference without changing the demand for reactivation and the other study manipulated the demand for reactivation without changing the demand for interference.

Materials and Methods

Subjects

Twelve normal, right-handed volunteers (seven men, five women, aged 19–37 years) participated in the study of interference. Written informed consent was obtained from all subjects. The study was approved by the joint ethics committee of the Institute of Neurology and University College London Hospital, London, UK. For the study of reactivation, we used a data set of our previous study (Sakai et al., 2002) where another set of 12 subjects participated (five men, seven women, aged 22–35 years).

Behavioural Procedures

In the study of interference, the subjects saw a sequence of five consonant letters and rehearsed subvocally for an 8–16 s unfilled delay period (Fig. 1). Then subjects performed a distractor task for 5 s. In the distractor task, subjects saw either a sequence of five letters that were different from the memory items or a sequence of five numbers. Subsequently a distractor probe with two letters or numbers was presented and subjects pressed one of the two buttons depending on whether the probe showed the correct order of the five distractor items. After the distractor task, subjects were then asked to recall the five-letter sequence that they had remembered at the start of the trial. A memory probe with two letters and an arrow was presented and subjects pressed one of the two buttons depending on whether the probe showed the correct order of the five memory items. The two

Figure 1. Behavioural paradigm for the interference study. A sequence of five consonant letters was presented on a screen, each for 750 ms separated by 250 ms interval. Subjects rehearsed the letters during an unfilled delay period ranging from 8 to 16 s. Subsequently, five letters or five numbers were presented as distractors, each for 600 ms separated by 200 ms interval. Then, after 200 ms, a distractor probe with two letters or numbers was presented for 600 ms, which the subjects had to confirm or disagree with by pressing a ‘yes’ or ‘no’ button. Then, after 1 s, a memory probe followed, in which two letters were presented. The subjects judged whether the order of the two letters was the same as or different from the remembered sequence, and responded by pressing the ‘yes’ or ‘no’ button. For the reactivation study (not shown), the time line was essentially the same and we presented five numbers from 3 to 9 or five ‘0’s as distractors. The subjects were asked to add the five numbers and respond to the arithmetic probe (for details, see Sakai et al., 2002).
letters in the memory probe was taken from the five memory items, not from the distractor items. The letter distractor task was chosen so as to cause greater interference at retrieval of letter sequence than the number distractor task. Subjects also performed control trials where five 'x's were presented as memory items, which were followed by a letter distractor task or a number distractor task as in the memory trials. Thus, there were four conditions, ‘Memory_Letter Distractor’ (high interference), ‘Memory_Number Distractor’ (low interference), ‘Control_Letter Distractor’, ‘Control_Number Distractor’. After practice of the behavioural paradigm for 20 min, imaging was started. The four conditions were intermixed pseudo-randomly and 15 trials of each condition were presented in a pseudo-random order with inter-trial intervals of variable length, 8–16 s, varied in steps of 2 s.

Of note is that the time line of the task paradigm is the same as in our previous study on reactivation (Sakai et al., 2002), where we used 4 s encoding period, 8–16 s rehearsal period, 5 s distractor period, 3 s retrieval period and 8–16 s inter-trial interval. The only difference is the nature of distractors: in the previous study on reactivation we used a distracting arithmetic task, adding five numbers chosen from three to nine, and a non-distracting task, in which only '0's were presented as arithmetic items. Thus in that study there were four conditions, ‘Memory_Distractor’, ‘Memory_Number_distractor’, ‘Control_Distractor’, ‘Control_Number_distractor’ and 15 trials of each condition were presented in a pseudorandom order.

**Imaging Procedures**

Imaging was performed using a 2 T Siemens Vision scanner. The functional images sensitive to blood-oxygen level dependent (BOLD) changes were acquired with a T1-weighted echo planar imaging (TE = 4.5 s, T1 = 40 ms, 525 sequential whole brain volume acquisitions, 48 axial slices, slice thickness = 2 mm, slice gap = 1 mm, 64 x 64 in-plane resolution with FOV of 192 mm). The onset of each task trial relative to the preceding image acquisition was jittered in steps of 0.5 s within 1 T1 (4.5 s). High-resolution structural T1-weighted MPRAGE images (TE = 9.5 s, TR = 4 ms, TI = 600 ms, voxel size 1 x 1 x 1.5 mm, 108 axial slices) were also acquired on all subjects. These parameters were used for both studies on interference and reactivation.

**FMRI Data Analysis**

Image processing and analysis were performed using SPM99 (http://www.fil.ion.ucl.ac.uk). The first five volumes of images were discarded to allow for T1 equilibration. The remaining 520 image volumes were realigned spatially to the first image and the time-series for voxels within each slice was realigned temporally to acquisition of the middle slice. The resulting volumes were normalized to a standard EPI template based on the Montreal Neurological Institute reference brain. The data were spatially smoothed with a Gaussian kernel of full width half-maximum at 10 mm.

Statistical parametric maps of t-statistics were calculated for condition-specific effects within a general linear model. For the study on interference, the model included separate covariates for transient activation in response to the presentation of each memory item (Memory and Control), distractor item (Letter and Number), distractor probe (Letter and Number) and memory probe (‘Memory_Letter Distractor’, ‘Memory_Number Distractor’, ‘Control_Letter Distractor’, ‘Control_Number Distractor’). We also modelled sustained activation during the memory-delay (Memory and Control) as an epoch with its onset time-locked to the start of the memory delay and with its duration matched to the length of the memory delay. Since the subjects were unable to predict the type of distractors (Letter or Number distractor), we have jointly modelled the memory delay preceding the letter distractor and number distractor. All the 12 subjects made at least 11 correct responses among the 15 trials in each condition. To equate the weighting of each subject contributing to the second-level analysis, we chose 15 acquired trials in each condition for each subject. Other correct trials and error trials were modelled separately. All events and epochs were convolved with a canonical hemodynamic response function. The data were high-pass filtered with a frequency cut-off at 90 s.

For the study on reactivation, the data were analysed in the same manner. We have modelled transient activation in response to the presentation of each memory item (Memory and Control), arithmetic item (Distractor and Non-distractor), arithmetic probe (Distractor and Non-distractor) and memory probe (‘Memory_Distractor’, ‘Memory_Number Distractor’, ‘Control_Distractor’, ‘Control_Number Distractor’). We also modelled sustained activation during the memory-delay (Memory and Control).

**Testing the Effect of Interference**

Using the dataset in the study of interference, we identified areas related to memory retrieval, that are the areas that showed larger phasic activation in response to the memory probe in Memory conditions than in Control conditions (main effect of Memory). Images of parameter estimates for the contrast of interest were created for each subject (first-level analysis) and were then entered into a second-level analysis using one-sample t-test across the 12 subjects, thresholded at $P < 0.001$, uncorrected ($q > 4.02$). Areas were identified if the number of supra-threshold voxels exceeded 10. Then, using the retrieval-related areas thus identified as an inclusive mask, we tested the effect of interference on memory retrieval (Letter Distractor versus Number Distractor) in a random-effects model and identified areas that were more active on high interference condition (Letter Distractors) than on low interference condition (Number Distractors).

We then calculated the parameter estimates for the peaks of the activity in the PFC and MTL. These peaks were identified as showing significant activity at memory retrieval compared to control irrespective of the effect of interference. The parameter estimates, that is the effect sizes of the task conditions, were calculated for the four conditions, ‘Memory_Letter Distractor’, ‘Memory_Number Distractor’, ‘Control_Distractor’, ‘Control_Number Distractor’.

**Testing the Effect of Reactivation**

We next examined the effect of reactivation on the activity in the PFC and MTL using the data set of our previous study on reactivation (Sakai et al., 2002). In that study, we presented a distracting arithmetic task or non-distracting task at the end of the memory delay. These did or did not require reactivation of remembered letter sequence at the time of retrieval. We tested the effect of demand for reactivation (Distractors versus Non-distractors) on the retrieval activity for the peak in the PFC and MTL identified in the present study on interference. For these peaks we calculated the parameter estimates for the four conditions, ‘Memory_Distractor’, ‘Memory_Number_distractor’, ‘Control_Distractor’, ‘Control_Number_Distractor’.

**Testing the Double Dissociation**

We then calculated the difference in the parameter estimates between ‘Memory_Letter Distractor’ and ‘Memory_Number Distractor’ conditions for each of those subjects who participated in the study on interference. We also calculated this difference in the parameter estimates between ‘Memory_Distractor’ and ‘Memory_Number_distractor’ conditions for each of those subjects who participated in the study on reactivation. These contrasts of parameter estimates were entered into a two-factor ANOVA. One factor is the manipulation of the demand (interference resolution and reactivation), which is modelled as a between-subject factor because we used different subjects for the two studies. The other factor is the region (PFC and MTL), which is modelled as a within-subject factor because the two regions were compared within each of the subjects. The aim of the analysis is to test whether there is a double dissociation between the PFC and MTL by looking for the cross-over interaction between the manipulation of the demand and region.

**Results**

For the study on interference, the accuracy of the retrieval response was 82, 94, 98 and 100% for the ‘Memory_Letter Distractor’, ‘Memory_Number Distractor’, ‘Control_Letter Distractor’ and ‘Control_Number Distractor’ conditions, respectively.

There were significant main effects of memory (Memory and Control), $F(1,11) = 14.6$, $P < 0.001$ and of types of distractors (Letter and Number Distractors), $F(1,11) = 50.2$, $P < 0.01$. There was also a significant interaction between memory and
types of distractors on the accuracy of retrieval performance \( F(1, 11) = 13.0, P < 0.01 \). Post hoc testing has shown that the performance in 'Memory_Letter Distractor' was significantly worse than any other conditions (\( P < 0.01 \)).

For the study on reactivation, the accuracy of performance was 79, 97, 100 and 100\% for 'Memory_Distractor', 'Memory_Nondistractor', 'Control_Distractor', 'Control_Nondistractor' conditions, respectively. There were significant main effect of memory [Memory and Control; \( F(1, 11) = 73.7, P < 0.01 \)] and main effect of distraction [Distractor and Nondistractor; \( F(1, 11) = 87.3, P < 0.01 \)] on the accuracy of retrieval performance. There was also a significant interaction between memory and distraction \( F(1, 11) = 87.3, P < 0.01 \) and the performance in 'Memory_Distractor' was significantly worse than in any other conditions (\( P < 0.01 \)).

As for the brain activation in the study on interference, we found a significant main effect of Memory on the activity at retrieval in the PFC and MTL: the activity in these areas was significantly higher in 'Memory' conditions than in 'Control' conditions (Table 1). The peak of the PFC activation was located within the inferior part of the middle frontal gyrus (area 46) and the significant activity extended to the inferior frontal sulcus but not to the convexity of the inferior frontal gyrus (Fig. 2a). The peak of the MTL activation was located in the parahippocampal cortex close to the junction between the fusiform gyrus and parahippocampal cortex (Fig. 2b). Among these regions we found that the left PFC showed significantly higher activity at retrieval in the 'Letter Distractor' condition than in the 'Number Distractor' condition. By contrast, activity in the MTL did not differ between the two conditions. For the peak in the left PFC, the parameter estimate was significantly larger in the Letter Distractor condition than in the Number Distractor condition. By contrast, the parameter estimates in the MTL did not differ significantly between the Letter and Number Distractor conditions (Fig. 3).

### Table 1

Areas showing significant activity at memory retrieval: (‘Memory_Letter Distractor’ + ‘Memory_Number Distractor’) – (‘Control_Letter Distractor’ + ‘Control_Number Distractor’)

<table>
<thead>
<tr>
<th>Region</th>
<th>Location</th>
<th>Parameter Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal cortex L</td>
<td>[-42, 44, 26]</td>
<td>9.79</td>
</tr>
<tr>
<td>Parahippocampal cortex R</td>
<td>[-28, -32, -10]</td>
<td>5.91</td>
</tr>
<tr>
<td>Prefrontal cortex R</td>
<td>[38, 54, 22]</td>
<td>7.18</td>
</tr>
<tr>
<td>Broca’s area L</td>
<td>[-48, 18, 6]</td>
<td>5.83</td>
</tr>
<tr>
<td>Presupplementary motor area R</td>
<td>[0, 14, 50]</td>
<td>5.31</td>
</tr>
<tr>
<td>Anterior cingulated cortex L</td>
<td>[-2, 30, 34]</td>
<td>5.76</td>
</tr>
<tr>
<td>Inferior temporal cortex L</td>
<td>[-66, -26, -20]</td>
<td>10.35</td>
</tr>
<tr>
<td>Superior parietal lobe L</td>
<td>[-22, -64, 84]</td>
<td>13.57</td>
</tr>
<tr>
<td>Inferior parietal lobe L</td>
<td>[-52, -32, 32]</td>
<td>6.21</td>
</tr>
<tr>
<td>Parieto-occipital sulcus L</td>
<td>[22, -64, 34]</td>
<td>9.67</td>
</tr>
<tr>
<td>Cerebellum L</td>
<td>[-28, -72, -30]</td>
<td>9.74</td>
</tr>
<tr>
<td>Cerebellum R</td>
<td>[32, -54, -34]</td>
<td>7.55</td>
</tr>
</tbody>
</table>

For these coordinates in the PFC and MTL thus identified in the study on interference, we tested the effect of the demand of reactivation. Using the data set of our previous study (Sakai et al., 2002), we have calculated the parameter estimates for the retrieval-related activity in the PFC and MTL. The parameter estimates for the PFC did not differ between the Distractor and Non-distractor conditions, whereas the parameter estimate for the MTL was significantly larger in the Distractor than in Non-distractor conditions (Fig. 3). Collectively Figure 3 shows a double dissociation between activity related to retrieval in the PFC and MTL. We formally tested the double dissociation using ANOVA with factors of manipulation of demand (interference resolution and reactivation) and region (PFC and MTL). We found significant interactions between the manipulation of demand and regions on the contrasts of parameters estimates \( F(1, 122) = 5.23, P < 0.05 \). This indicates that the two manipulations on retrieval demand, interference resolution and reactivation, had different effects on the activity of the PFC and MTL.

### Discussion

We have used a letter working memory task with distractor task at the end of the memory delay. By using different types of distractor task, we were able to test the effect of interference and reactivation on retrieval without changing the nature of the main memory task. We have used two imaging data sets collected from different group of subjects. Since the results of each study were based on random-effects model and therefore can be generalized to population, we were able to combine the results for the two studies and make inference about the double dissociation between effects of interference and reactivation on the PFC and MTL.

**PFC and Interference Resolution**

For the study on interference, the performance of the subjects on retrieval of letters was significantly worse in the letter distractor condition than in number distractor condition. We interpret the results as due to item non-specific interference. The letter distractor task caused higher interference on retrieval of letter sequence than the number distractor task even though the letters used in the distractor task were different from the letters used as memory items and memory probe. Such domain-specific, item non-specific interference effects have been shown earlier by Wickens et al. (1963). In that study the subjects remembered consonant letters for the first several trials and then switched to remembering numbers. There was progressive decline of the memory performance when subjects continued the letter memory trials, but immediately after the switch to the number memory trials, performance reverted to being almost perfect. The results were taken to reflect release from domain-specific interference. Thus, interference effects could be observed even when the memory probe was different from the distractor items. In the present study, there is an increased demand to select taskrelevant letters among distracting letters. The selection process is less demanding when choosing letters from distracting numbers. It should be noted, however, that the interference effect could still exist in the number distractor condition because the distractor numbers were presented just before the retrieval of letters and subjects had to suppress the phonological or visual code used to process the distractors. The effect is likely to be
due to a greater similarity in sound between letters and other letters than between letters and numbers.

We found that the highly interfering situation at retrieval is associated with an increase of activity in the PFC. The peak activity was observed in the middle frontal gyrus (–42, 46, 26) although it was close to the inferior frontal sulcus. This contrasts with the finding by Jonides et al. (1998) and D’Esposito et al. (1999), in which they found a peak in the inferior frontal gyrus (area 45, coordinates: –48, 21, 9). D’Esposito et al. (1999) has also shown that activity in the middle frontal gyrus (area 46/9) is not affected by interference. Consistent with those results, Thompson-Schill et al. (2002) reported a patient with lesion in the left inferior frontal gyrus who showed impairments in interference resolution. It is possible that the activity in the inferior frontal gyrus reflects inhibition of prepotent responses. In those studies, subjects performed successive trials of a working memory task for four letters and on high interference trials the probe was the same as one of the stimulus sets of the previous, but not the present, trials. On those trials, subjects need to inhibit the increasing tendency to press the Match button. The inferior frontal gyrus has also been shown to be active on no-go trials in a go/no-go task (Konishi et al., 1998a). Konishi et al. (1998b) have also found phasic activity in the inferior frontal gyrus when subjects had to change the response guiding rule in Wisconsin Card Sorting Task. It remains open whether the inhibition occurred at a response stage or at a rule selection stage. By contrast, in our paradigm there was no prepotent motor response. What has been inhibited at retrieval in the present study is the representation of distractor letters, not a prepotent motor response. In this sense our results may suggest that the middle frontal gyrus plays a role in inhibition at a representational level. In fact, others have proposed a role of the middle frontal gyrus in interference resolution. Bunge et al. (2001) have found an effect of interference in the right middle frontal gyrus in addition to the left inferior frontal gyrus. MacDonald et al. (2000) have found activity in the middle frontal gyrus when subjects are preparing to resolve the upcoming interference. The middle and inferior frontal gyri may play roles in interference resolution at different levels, representational and response level, respectively. Consistent with the idea, Konishi et al. (2003) has recently reported activity in the middle frontal gyrus in a modified Wisconsin Card Sorting Task where subjects had to reconfigure the response guiding rule but did not necessarily have to inhibit the prepotent motor response. However, the hypothesis of a distinction between the middle and inferior frontal gyri in interference resolution remains speculative. This issue needs to be addressed in further studies. It could also be significant that while the present study tested item non-specific interference caused by a distractor task within the memory trial, the studies by Jonides et al. (1998) and D’Esposito et al.
(1999) tested item-specific interference caused by preceding trials.

Interference can occur at several stages of memory processing. Brush et al. (2002) have shown modulation of activity during the memory delay of working memory task. In that study, accumulation of proactive interference as subjects go through the trials of working memory has been shown to be associated with an increase of activity in the inferior frontal gyrus during the memory delay. In the present study, across-trial interference effects have reached a ceiling after the training of subjects for >50 trials before starting the fMRI experiment. Also, at encoding or during the delay in the present study, subjects were unable to adopt different strategies for high and low interference conditions because of the unpredictable nature of our event-related design. We have confirmed this by separately modelling the activity during delay period for Letter Distractor and Number Distractor conditions and comparing the activity between the two conditions. We found no significant difference in activity in any part of the brain (P > 0.05 uncorrected). It is possible that interference resolution took place during the distractor task. However, the difference in the type of distraction did not affect the amount of activity in the PFC during the distractor task; the activity did not differ significantly during the letter and number distractor tasks (P > 0.05 uncorrected). Therefore the findings suggest that interference resolution came into play at retrieval, though this argument applies only to the present task paradigms. Memory retrieval in a highly interfering situation requires selection of task-relevant information among distracting information. Our result suggests that the PFC plays a primary role in this selection process.

PFC versus MTL

By contrast, we found that the activity in the MTL was insensitive to the changes in the degree of interference. The MTL were active to a similar degree at retrieval in the interference study. It should be noted that since the distractor task, either with letters or numbers, interrupted the rehearsal of memory letters, the retrieval required reactivation of the memory letters. We predict that if we had applied the present paradigm to patients with MTL lesions, we would have observed significant impairments in retrieval performance. The absence of interference effect is consistent with the previous imaging and patient studies (Incisa della Rocchetta and Milner, 1993; Smith et al., 1995; Jonides et al., 1998; Henson et al., 2002). However we can not make a strong claim based on the negative results: the absence of the interference effect in the MTL can be due to insufficient power to detect the small changes of activity that may exist. In fact, in Henson et al. (2002) the activity in the MTL was higher in interference condition than in non-interfering condition although the difference did not reach significance. Strong support for the distinction between the PFC and MTL can only be obtained by showing a double dissociation.

Here we have shown that the same region of the PFC and MTL behaved in the opposite direction by changing the demand of reactivation. We compared the retrieval activity in these regions between the condition where on-line maintenance was interrupted by distracting arithmetic task and the condition where on-line maintenance was allowed to continue. We found that the activity in the PFC was insensitive to the demand of reactivation: The activity did not differ between the distractor and non-distractor conditions. By contrast the activity in the MTL was affected by the demand of reactivation: It increased in the condition where there was need to reactivate the remembered letter sequence after interruption of its maintenance. The coordinates in the MTL on which we tested the effect of reactivation in the present study (–28, –32, –10) were close to the peak of activity associated with memory reactivation reported in the previous study (–20, –30, –10; Sakai et al., 2002). Thus the role of the MTL may be to trigger the reactivation. Though the memory was tested after a short delay of <20 s in this study, the situation is similar to retrieval from long-term memory in the sense that it requires reactivation of the acquired information. In fact, similar MTL regions have been shown to be active in long-term memory retrieval (Nyberg et al., 1996; Schacter and Wagner, 1999; Nyberg et al., 2000).

Thus the distractor task deteriorated the behavioral performance in both studies, but caused an increase of activation in different brain structures, the PFC in the study of interference and the MTL in the study of reactivation. We interpret the finding as due to the difference in the nature of the distractor task. The distractor task in the study of interference (in ‘Memory_Letter Distractor’ condition) caused an increase of interference as a result of phonological similarity between distractors and memory items, whereas the distractor task in the study of reactivation (in ‘Memory_Distractor’ condition) caused increased demand of memory reactivation as a result of interruption of on-line maintenance by arithmetic operation.

Collectively, our results suggest that the PFC and MTL differ in terms of the effect of two factors. The first factor is interference, which affects the activity in the PFC but not the activity in the MTL. The second factor is reactivation, which affects the activity in the MTL but not the activity in the PFC. The double dissociation also counters the argument that the activity in the PFC or MTL reflects task difficulty. Although the high interference condition in the present study and reactivation condition in the previous study are more difficult as shown by an increase in the number of errors, the two conditions showed differential effects on the activity in the PFC and MTL. It should be noted, however, that a strong argument for the double dissociation can be made only by testing both interference and reactivation within a single scanning session. As we have used datasets from two studies on different subjects, there could be an effect of different experimental contexts. Also there exists a possibility of subtle anatomical difference between subjects from the two studies, especially in the MTL.

Our results are consistent with a theoretical proposal made by O’Reilly et al. (1999) that suggests that the PFC and MTL play roles in biasing and binding of information, respectively. In the high interference condition, there is an increasing need to bias the retrieval processes toward the task relevant information, that is the letters that were remembered at the beginning of the trial rather than the letters in the distractor task. The binding of letters in the remembered sequence is necessary to a similar degree in the high and low interference conditions, but is especially required when the information is not maintained on-line, that is, the information needs to be reactivated. This distinction in memory retrieval processes can be extended to memory encoding processes. In encoding of a long-term association memory, Dolan and Fletcher (1997) have found a double dissociation of activity in the PFC and MTL. The encoding activity in the PFC increased when subjects learned pairs of old and new items, that is when they need to discard the learned association and establish a new association.
Subjects need to counter the interference effects from the now irrelevant associations and bias toward the newly learned associations. By contrast, the encoding activity in the MTL increased when subjects learned pairs of new items, that is when they need to bind a pair of new information.

There can be another factor that distinguishes between the PFC and MTL. While the MTL may be involved in automatic process associated with reactivation, the PFC may be involved in intentional process. In experimental animals, the MTL-induced reactivation process has been observed not only during conscious memory retrieval but also during sleep. In rats, it has been shown that neural representations of the past experience are reactivated during sleep (Kudrimoti et al., 1999; Sutherland and McNaughton, 2000; Louie and Wilson, 2001). The MTL is involved in a repeated cycle of sending and receiving signals to and from the posterior association areas and by so doing consolidates the memory. By contrast, the PFC-induced reactivation seems to occur only under conscious control. In monkeys, the PFC does not show any sign of involvement in reactivation processes during sleep (Hoffman and McNaughton, 2002). Involvement of the PFC in retrieval attempt in human subjects also suggests that the PFC is associated with conscious control processes (Duzel et al., 1999; Maril et al., 2001; Kikyo et al., 2002).

The PFC and MTL are the two structures that are connected with almost all parts of the posterior association areas in the parietal and temporal lobes (Van Hoesen, 1982; Cavada and Goldman-Rakic, 1989; Petrides and Pandya, 1999; Lavene et al., 2002). Both structures have been shown to send signals to posterior association areas during memory retrieval (Tomita et al., 1999; Naya et al., 2001). Here we have shown that the signals from the two structures may act in different manners. We suggest that signals from the MTL trigger reactivation of the information stored off-line, whereas signals from the PFC select the task-relevant information and resolve interference from distractors.

Notes
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