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Functional role of the prefrontal cortex in retrieval of memories: a PET study

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RETRIEVAL of information from episodic memory involves the processes invoked by the attempt to remember (retrieval attempt) as well as processes associated with the successful retrieval of stored information (ecphory). Previous PET studies of memory have shown an activation of the prefrontal cortex in memory retrieval tasks, and we hypothesised that this activation represents retreival attempt, not ecphory. This hypothesis was directly directed using [^{15}O]H_2 PET imaging in 19 healthy subjects who performed three matched tasks which involved different levels of retrieval attempt and ecphory. The results showed that retrieval attempt was associated with activation of the prefrontal cortex, right greater than left, while ecphory involved the posterior cortical regions. These findings illuminate the functional role of the different neuroanatomical regions involved in episodic remembering.

Key words: Episodic; memory; Human; PET; Retrieval; Prefrontal cortex

Introduction

Recent positron emission tomography (PET) studies of human memory show that retrieval of episodically stored information engages a network of brain regions including the right prefrontal cortex together with posterior cortical regions.[1–6] The involvement of the right prefrontal cortex is particularly reliable and has been observed in studies which use different stimuli (verbal and non-verbal) and different modalities (visual, aural, olfactory).[2] However, the specific role played by the prefrontal cortex in the act of remembering has not been addressed in any of these previous studies.[2,6] The main purpose of this study was to specify the functional contribution of the prefrontal cortex in the retrieval of stored memories.

Several authors,[7–11] have suggested that retrieval of information from memory can be subdivided into component processes. While the authors differ in details, all subscribe to a basic distinction between retrieval attempt, the processes involved in the individual's conscious attempt to remember, and ecphory, the processes associated with the successful recovery of stored information. In keeping with this, neuropsychological studies suggest that the prefrontal cortex is involved in strategic processing,[7,8] temporal ordering[12,13] and the organization of search[11] – all functions compatible with the notion of retrieval attempt, as noted above. Based on the foregoing, this study directly tests the hypothesis that the activation of the prefrontal cortex observed in PET studies of episodic retrieval is a reflection of retrieval attempt, not ecphory.

Methods

Nineteen healthy right-handed men, age range 23–34 years, participated in this study approved by the Human Subject Use Committee of the University of Toronto and the Baycrest Centre. We operationalized the retrieval attempt/ecphory distinction for the PET experiment by scanning subjects while they were engaged in three different matched visual tasks. The tasks were identical in their perceptual, attentional and motor output demands, but differed in the requirements for retrieval attempt and ecphory. In each task, a word (concrete nouns, white on a black screen, lower case, centred on a fixation point) appeared on a computer screen, once every 1.5 s and the subjects conveyed a binary decision by pressing the appropriate mouse button. In the first task subjects decided whether each word represented a living or a non-living thing. There were no specific instructions to learn or remember and the task required no recourse to episodic memory. This task involved the perceptual, verbal, attentional and semantic aspects of the episodic memory tasks, and hence served as an appropriate control for the recognition tasks.[3,6,14]

Following two tasks in this condition, some of the words were presented again as targets in two separate recognition tasks. In both recognition tasks subjects were asked to indicate (yes/no decision) if they had seen the words earlier in the experiment. In the high target recognition condition 34 of the 40 words presented during the scan were targets. In the low target condition only six of the 40 words during the scan were targets. Since the instructions were identical and the subjects performed equally well in terms of memory (see results), retrieval attempt was equally engaged in both tasks. However, the high target recognition task, since it contained 85% targets, was associated with high levels of ecphory; while the low target recognition task, since it has only 15% targets, was associated with minimal ecphory. Therefore, the low target minus control (LT–CT) subtraction identifies brain regions differentially active during retrieval attempt and the high target minus low target (HT–LT) condition reflects ecphoric processes. Furthermore, the high target minus control subtraction (HT–CT), which is independent of the above two subtractions, involves both retrieval attempt and ecphory, and hence provides an independent confirmation of the above findings. Consistent with our hypothesis regarding the involvement of the prefrontal cortex in retrieval attempt only, we expected the following: (a) the right prefrontal cortex would be activated in the LT–CT and the HT–CT subtractions, as both these subtractions show the retrieval attempt component; (b) that the high target minus low target (HT–LT) subtraction would show no difference in the prefrontal cortex, since retrieval attempt is equally engaged by the two tasks and therefore cancels out.

PET scans were obtained with a GEMS-Scanditronix PC2048-15B head scanner using a bolus injection of 40 mCi (1.48 GBq) of $[^{15}O]H_2O$ and 60 s data acquisition scans. The PET data were analysed using the new version of the Statistical Parametric Mapping (SPM) technique (using software from the Wellcome Dept. of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc, Sherborn, MA, USA). The analysis involved the following steps: the different images from each subject were realigned to the first image, using a rigid body transformation. These realigned images from each subject were then transformed into a standard space by matching to a reference image that already conforms to the standard space.[15,16] These images were then smoothed using a isotropic Gaussian kernel of FWHM of 15 mm. The effects of the conditions (cognitive tasks) on the regional cerebral blood flow at each voxel were then estimated using a general linear model, wherein the changes in global counts are considered as a covariate.[17] The effects of each comparison are estimated using linear contrasts, which yields a *t*-statistic for the comparison at each voxel. The *t*-statistic is expressed as a standardised Z-score.[18] Since SPM involves multiple comparisons, a few voxels may reach the threshold of significance just by chance. To obviate this, the significance of each region was estimated using distributional approximations from the theory of Gaussian Fields and only those regions in which the probability of observing the peak voxel was less than $p < 0.05$ were considered significant (in this study this corresponded to a Z-score of 4).[18]

Results

For the high target condition the subjects showed an average hit rate (HR) of 80% and a false alarm rate (FA) of 30% resulting a HR–FA of 50% (s.d. = 15). In the low target condition subjects showed a HR of 75%, a FA of 29%, and a HR–FA of 46% (s.d. = 19). The values of HR–FA did not differ significantly (Student's paired $t_{(df=18)} = 1.39$, $p = 0.18$). This result shows that the subjects were equally proficient in discriminating new from old words in the two types of recognition tests (which was the intention of this experiment) and suggests that subjects applied equal levels of retrieval attempt. This conclusion is further bolstered by the fact that debriefing the subjects after the scan showed that none of the subjects had noticed the difference, in the number of targets, between the high-target and the low-target recognition tasks.

The main image comparison of interest is the low target minus control task which isolates the brain

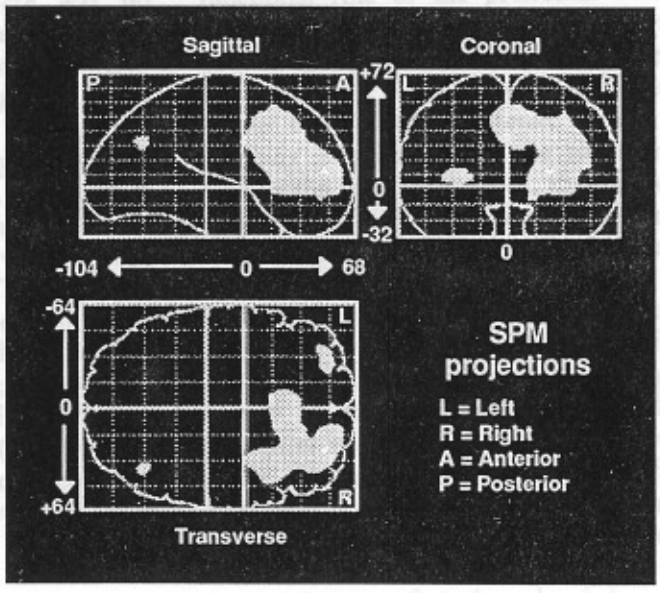

FIG. 1. Brain regions that exhibited an increased rCBF corresponding to retrieval attempt, as obtained in the low-target minus control subtraction. The co-ordinates are listed in Table 1 (LT–CT column). The SPM is displayed in a standard format as a maximum intensity projection viewed from the back, the right hand side and the top of the brain. The anatomical space corresponds to the atlas of Talairach and Tournoux.[15]

Table 1. Regions of the brain which are associated with retrieval attempt

Region (Brodmann Area) Activated in LT–CT subtraction	Coordinates x, y, z in mm.			LT–CT p-value (Z)	HT–CT p-value (Z)	HT–LT p-value
Prefrontal Cortex						
Rt. Frontopolar (10)	20	52	8	$p < 0.001$ (7.1)	$p < 0.001$ (6.7)	$p > 0.5$
Rt. Middle Frontal Gyrus (46)	32	52	16	$p < 0.001$ (5.5)	$p < 0.01$ (4.6)	$p > 0.5$
Rt. Middle Frontal Gyrus (9)	36	18	32	$p < 0.001$ (5.1)	$p < 0.001$ (5.1)	$p > 0.5$
Lt. Frontopolar (10)	−28	52	8	$p < 0.01$ (4.6)	$p < 0.05$ (4.1)	$p > 0.5$
Midline Anterior Cingulate (8/32)	0	26	40	$p < 0.001$ (5.1)	$p < 0.001$ (4.9)	$p > 0.5$
Rt. Temporo-parietal area (39)	36	−62	28	$p < 0.05$ (4.1)	$p < 0.01$ (4.6)	$p > 0.5$

The first column shows each region that showed a significant (corrected for multiple comparisons, $p < 0.05$, corresponding to a $Z > 4$) change in the LT–CT comparison. For each region listed (with its Brodmann's area in brackets) the Talairach co-ordinates of c central voxel are provided in the second column.[15] The complete extent of the regions involved in retrieval attempt is better appreciated with reference to Figure 1. The third column (LT–CT) shows the corrected *p*-values (and the Z-score in brackets) at the voxels listed in the second column, as obtained in the low target minus control comparison. The fourth column (HT–CT) shows the corrected *p*-values (Z-score) for the voxels listed in the second column, as obtained in the high target minus control comparison. The final column, (HT–LT) lists the *p*-values for each of the voxels when the high target condition is compared directly with the low target condition.

regions involved in retrieval attempt. The most prominent activation (Fig. 1) was in the right prefrontal cortex, in a region extending from the right frontopolar (Brodmann's area (BA)10) region, postero-superiorly, along the right middle frontal gyrus (BA 46,9). In addition, activations were also observed in the left frontopolar region (BA 10) and the midline anterior cingulate region (BA 8/32). An isolated region of activity was observed in the right temporo-parietal region. The co-ordinates and statistical significance of these regions are listed in Table 1 (LT–CT). These findings are further supported by the fact that each of the prefrontal regions was also significantly activated in the high target condition (Table 1, HT–CT). Additionally, there was no significant differences in any of the prefrontal regions, even at an uncorrected significance threshold, in the high target minus low target (HT–LT) condition.

The high target condition, since it involved both retrieval attempt and successful retrieval, was expected to involve more regions than the low target condition, and as reasoned above these regions would reflect ecphoric processes. Indeed, the HT–LT subtraction showed a circumscribed activation in the right medial parietal (BA 31) in the region of the precuneus (Talairach co-ordinates 16, −66, 20; $Z = 4.49$, corrected $p < 0.008$). A similar, though more lateral region was identified on the left side (Talairach co-ordinates −38, −56, 36; $Z = 3.67$, uncorrected $p < 0.001$); however this region did not survive correction for multiple comparisons.

Discussion

The major finding of this study is that the activation of the right prefrontal cortex is related to the attempt to retrieve memories — not to their successful retrieval. This interpretation is well supported by three different analyses of the data. First, low target minus the control condition, a subtraction which isolates the retrieval attempt process, showed a predominant activation of the prefrontal cortex, right greater than left (Fig. 1; Table 1, LT–CT). Second, each of these regions was also activated in the high target condition, a comparison which also reflects the retrieval attempt processes (Table 1, HT–CT). Finally, a comparison of the two recognition conditions, which by our design should negate any effects of retrieval attempt, showed no significant changes in any prefrontal region (Table 1, HT–LT).

The present results are consistent with previous published studies, and add to them by specifying the functional role of the prefrontal cortex activation observed in those studies. Activation of the prefrontal cortex, right greater than left, has now been observed in over half a dozen functional imaging studies.[1–5] While these studies differed in the modality of stimulus presentation, in the nature of stimuli, as well as the level of ecphory, they are similar in one respect: they all involved retrieval attempt. Likewise, the studies have one finding in common: the involvement of the prefrontal cortex, right greater than left. The consistency between our results and previously published reports from different centres suggests that the activation of the right prefrontal cortex in studies involving retrieval of episodic memories is a reliable and reproducible finding. Our study further shows that the prefrontal cortex activation is related to the attempt to remember and not to the successful retrieval of memories.[1–5] In fact, in a study currently underway at our centre, we have been able to confirm the role of the right prefrontal cortex in retrieval attempt, using aural as opposed to visually learned words (L. Nyberg, personal communication).

This interpretation of our results is in line with preliminary findings using evoked response potentials

which suggest a role for the frontal regions in the control and monitoring of retrieval.[19] In addition, our claim that the prefontal cortex is associated with retrieval attempt in normal subjects is consistent with neuropsychological evidence suggesting its role in strategic processes,[7,8] temporal ordering[12,13] and the organization of search.[11] The case is made even stronger by recent reports linking transient right prefrontal hypoperfusion and hypometabolism with transient global amnesia[20] and demonstrating right frontal lobe perfusion deficits, in the absence of temporal lobe deficits, in some patients with amnesia.[21]

Two aspects of our experiment that bear on our interpretation should be clarified. First, the study test interval for the episodic memory recognition test was 20–40 min and one may wonder how our findings would generalize to longer delays. A recent PET study by Andreasen and colleagues[22] addressed this issue directly by comparing the brain regions involved in the retrieval of episodic information learned 1 min prior to test versus that learned a week before. Both retrieval tasks engaged the right prefrontal cortex, and did so equally. Based on Andreasen's findings,[22] we think the right prefrontal is involved in retrieval attempt in episodic memory, regardless of study test interval. A second issue concerns the difference between semantic and episodic retrieval attempt. While this study focused on dissecting 'episodic' retrieval into retrieval attempt and ecphory, a similar dissection of 'semantic' retrieval is tenable and potentially testable.[2] In a previous experiment using similar stimuli,[23] we have shown that retrieval and processing of semantic information engages the left prefrontal cortex, to the exclusion of the right; furthermore, this finding is consistent over previous studies.[23] Since these previous studies show that the entire process of retrieval from semantic memory engages only the left and nor the right prefrontal cortex, 'semantic retrieval attempt' (a component of semantic retrieval) must involve only the left prefrontal cortex. Given our present knowledge, then, the right prefrontal activation is best understood as reflecting 'episodic retrieval attempt', although it remains possible that difficult or every effortful retrieval from semantic memory might also engage right frontal regions.

In addition to the prefrontal regions, a circumscribed region of the right temporoparietal area was also engaged by both the high and low target recognition tasks. Following our logic this region should also reflect some component of retrieval attempt. However, we had not hypothesized this finding a priori, and since the spatial extent of the activation is limited (Fig. 1), we consider this finding tentative and await a replication before venturing an explanation.

A secondary finding of the experiment is the activation in the posterior regions, mainly the right cuneus-precuneus (medial parietal) regions in the high target minus low target subtraction; a similar finding was also observed more laterally on the left side but did not survive correction for multiple comparisons. Similar activations, in the precuneus or in the adjoining multimodal association cortex have been reported in previous PET experiments of human memory,[1,3,4] and our experiment shows that these regions are associated with successful retrieval. These areas could be implicated in the memory process in two different ways. First, they could represent reactivation of stored engrams; if so, our results would be consistent with a proposed model of memory function wherein the prefrontal regions drive the retrieval process, which is successful only when this retrieval attempt leads to a reactivation of an engram stored in the posterior multimodal association cortices.[7,8] Second, these regions have previously been activated in studies involving visual imagery.[24] Given that this experiment utilised a visual paradigm, it is plausible that the activation of these regions reflects visual imagery, which may have facilitated or accompanied successful recovery of a stored memory.[3] Further experiments directed at these possibilities will be needed to clarify between these possibilities.

Conclusions

This study has shown that the activation of the right prefrontal cortex is related to the processes underlying the 'attempt' to retrieve an episodic memory, but not to the success or failure of that retrieval attempt. This finding helps in understanding why this region was activated in previous PET studies of memory which differed in their stimuli and modality of presentation. In addition, it lends further credibility to the claims, based on neuropsychological findings, that the prefrontal cortex is involved in strategic processing or search operations. The present results lead us to speculate that on the presentation of a retrieval cue, the prefrontal cortex drives the retrieval attempt. This retrieval attempt, when successful, is accompanied by the activation of the posterior multimodal association cortex, thereby constituting the neural basis for the human experience of remembering.

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General Summary

Psychologists have long differentiated between the mental processes involved in the attempt to remember as opposed to those involved in a successful memory. This study used positron emission tomography, a brain imaging method, to identify the brain regions which underlie these processes. Eighteen healthy subjects were given two types of memory tasks, in one they attempted to remember but failed, in the other they attempted and succeeded. Comparison of the brain scans obtained during these tasks revealed that the right prefrontal cortex region is involved in the attempt to remember regardless of success, and that successful memories are associated with activity in the posterior regions of the brain. This suggests that the human experience of remembering is initiated by the prefrontal regions of the brain, and if it leads to a successful remembering, it is accompanied by activation in the posterior brain regions.