Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval

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Summary

Six subjects underwent PET scans while they performed three versions of a recognition memory test for words and three versions of a control task. In each memory condition, the subjects discriminated between words presented in a pre-scan study list and words new to the experiment. During the 30 s scanning interval, the ratio of old and new words was 0:20, 4:16 or 16:4, depending on the experimental condition. Outside this interval, the ratio was 50:50 in all three conditions. The requirement in the control task was to discriminate between two character strings, the ratios of which were also manipulated during the 30 s scanning interval. Employing the control task as a covariate, analysis with statistical parametric mapping revealed that regional cerebral blood flow (rCBF) covaried with increasing density of old items in three regions of prefrontal cortex: right dorsolateral [Brodmann area (BA) 9/46], right medial (BA 32/8) and bilateral frontopolar cortex (BA 10). It is concluded that the prefrontal cortex, especially in the right hemisphere, is more active when a retrieval attempt succeeds than when it fails. This finding is consistent with the idea that the prefrontal cortex supports processes that operate selectively on the products of memory retrieval.

Keywords: episodic memory; memory retrieval; prefrontal cortex; recognition memory

Abbreviations: BA = Brodmann area; ERP = event-related potential; rCBF = regional cerebral blood flow

Introduction

Neuropsychological evidence indicates that episodic memory— the conscious recollection of past events—depends upon an extensive network of brain structures, including regions of the medial temporal lobe, the diencephalon and the prefrontal cortex (Mayes, 1988). Whereas lesions to the first two of these structures lead to impaired performance on all memory tests tapping episodic memory, studies of the effects of frontal lobe lesions suggest that the contribution of the prefrontal cortex is more task-dependent. Patients with prefrontal lesions show normal, or only mildly impaired, performance on tests such as recognition memory and cued recall (Janowsky *et al.*, 1989; Swick and Knight, 1996). They are more severely impaired on tests of memory for temporal order, or for contextual details of a study episode (Shimamura and Squire, 1987; Janowsky *et al.*, 1989; McAndrews and Milner, 1991; Milner *et al.*, 1991; Kesner *et al.*, 1994; for a review *see* Stuss *et al.*, 1994). One characterization of this pattern of deficits is that, among its other mnemonic functions,

the prefrontal cortex is necessary for the integration of retrieved information about a specific test item with information about the context in which it was experienced (Squire *et al.*, 1993).

Recent functional neuroimaging experiments using PET to measure rCBF also suggest that the prefrontal cortex plays an important role in memory retrieval. In contrast to lesion studies, however, the PET studies suggest that the frontal lobes are engaged in a wide range of memory tasks, including tasks that do not require retrieved information to be discriminated on the basis of contextual attributes. These studies [for reviews *see* Buckner and Tulving (1995) and McCarthy (1995)] have consistently found that the performance of tasks that require information to be retrieved explicitly from memory is accompanied by activation of dorsolateral prefrontal cortex (BA 9/46), and that this activation is markedly stronger in the right hemisphere. Relative to a variety of different control conditions, this

pattern of results has been found in tasks as diverse as word-stem cued recall (Buckner *et al.*, 1995; Schacter *et al.*, 1996), recognition memory for sentences and single words (Tulving *et al.*, 1994; Kapur *et al.*, 1995), retrieval of paired associates (Fletcher *et al.*, 1995) and forced-choice recognition memory for faces (Grady *et al.*, 1995).

In view of the consistency with which prefrontal activation has been found in episodic retrieval tasks, the question of its functional significance is of considerable interest. In this regard it is noteworthy that with few exceptions (discussed below), the above-mentioned studies employed experimental designs that did not separate the effects of retrieval effort from those of retrieval success. Retrieval effort refers to processes engaged by an attempt to retrieve information from memory in response to a retrieval cue, such as a test word in a recognition memory task. Retrieval success refers to processes that are selectively engaged when a retrieval attempt is successful. In standard tests of memory retrieval, these two sets of processes are confounded, hence the ambiguity surrounding the interpretation of the findings from most of the aforementioned studies with PET.

Three previous studies, all from the same research group, have specifically addressed the question of whether rCBF in the prefrontal cortex is sensitive to retrieval success. Tulving *et al.* (1994) contrasted two tests of recognition memory for auditorily presented sentences. In one condition, all of the sentences presented during the scanning epoch were old, while in the other condition they were all new. The subtraction of the latter condition from the former revealed extensive right prefrontal activation, consistent with the idea that such activation is associated with retrieval success. Interpretation of this finding is, however, complicated by the fact that subjects were informed in advance whether there would be a high or a low density of old items in the test list (raising the possibility that they adopted different retrieval strategies in the two tasks), and because the task was to count the occurrence of the more infrequent sentence type (confounding type of list with the class of item designated as 'targets'). In a second study by the same group (Kapur *et al.*, 1995), subjects first performed a semantic classification task, and then performed two tests of recognition memory; in both tasks the old items were drawn from those presented in the classification task. The proportion of old and new words was 15:85 in one of the test lists and 85:15 in the other. When compared with the initial classification task, prefrontal activation was observed in the condition in which only 15% of items were old, but no additional activation was observed when 85% of the test words were old. Kapur *et al.* (1995) concluded that activation of prefrontal cortex is associated with retrieval effort, rather than with retrieval success.

A final study by the Toronto group (Nyberg *et al.*, 1995) measured rCBF during the performance of two recognition memory tasks in which all items were old, as well as during a recognition task in which the items were all new and during a silent reading control task. When compared with the control task, rCBF in the right dorsolateral prefrontal cortex was elevated in each of the memory tasks. Little additional activation was found, however, when the all-new recognition task was compared with the all-old tasks. Nyberg *et al.* (1995) therefore concluded that right prefrontal activation was associated solely with the adoption of a 'retrieval mode', and not with operations carried out on the products of successful retrieval. This conclusion may be premature, however, as subjects' memory performance in this study was very poor. The miss rate in the recognition tasks containing the critical sequences of all-old items was 42% in one of the tasks and 70% in the other, while the false positive rate in the 'all new' condition was 17%. It is therefore arguable that the study lacked the power to detect rCBF differences between the different recognition tasks.

The present study also addresses the question of whether activation of prefrontal cortex in recognition memory tasks varies according to whether test items elicit successful memory retrieval. The study utilizes a design similar to that of Kapur *et al.* (1995) but with the following differences. (i) Manipulation of the proportions of old and new test items was confined to a short sequence embedded within a longer list, so as to minimize the probability that subjects would adopt condition-specific retrieval or decision strategies. (ii) In addition to critical sequences containing high and low densities of old items, a sequence in which no old items occurred at all was employed. (iii) A non-memory control task was employed, in which the relative probability of 'target' and 'non-target' items (henceforth, 'target density') was manipulated in a manner analogous to that employed for the memory task. The importance of this control condition lies in the fact that it is well established from studies with event-related potentials (ERPs) that the neural activity elicited even by very simple stimuli, such as tones or single visual characters, varies according to their probability and target status (Coles and Rugg, 1995). Because of this, any changes in rCBF associated with the manipulation of target density in the memory task could not be unambiguously attributed to mnemonic factors; they might merely reflect brain activity sensitive to the relative probabilities with which target and non-target stimuli appear in a sequence. The employment of the control task obviates this problem, by allowing the effects of changes in target density in the recognition memory task that are specific to changes in the probability of retrieval success to be separated from other, non-specific effects.

Methods
Subjects
Six healthy, right-handed young adult male subjects took part in the study, which had received approval from the local hospital ethics committee. All subjects gave informed, written consent and were fit, healthy and free of any significant previous or current medical or neurological illness. The study involved the administration of 7.2 mSv effective dose equivalent per subject, and was approved

by the Administration of Radioactive Substances Advisory Committee of the Department of Health of the UK.

PET scanning

Scans were obtained using a CTI model 953B PET Scanner (CTI/Siemens, Knoxville, Tenn., USA) with collimating septa retracted. For each scan, subjects received a 20 s intravenous bolus of $H_2^{15}O$ through a forearm cannula at a concentration of 55 MBq ml^{-1} and a flow rate of 10 ml min^{-1}. With this method, each scan provides an image of rCBF integrated over a period of 90 s from when the tracer first enters the cerebral circulation. The first 30 s of this period is concurrent with the rise of radioactivity in the head, and forms the window in which the experimental manipulation modifies the distribution of CBF (Silbersweig *et al.*, 1993).

Data analysis

The PET scans from each subject were realigned using the first scan as a reference. The six parameters of this rigid body transformation were estimated using a least squares approach (Woods *et al.*, 1992). Following realignment, all images were transformed into a standard space (Talairach and Tournoux, 1988) by matching each scan to a reference template image that already conformed to the space (Friston *et al.*, 1989). As a final pre-processing step, the images were smoothed using an isotropic Gaussian kernel. Condition, subject and covariate effects were estimated for each voxel according to the general linear model, as implemented by the method of statistical parametric mapping (SPM 95, Wellcome Department of Cognitive Neurology, London, UK). The specific contrasts employed to analyse the data from the present experiment are described in the results section below.

Stimuli and experimental design

Memory items were selected from a pool of 500 four- to nine-letter English words, with a mean frequency of occurrence (Kucera and Francis, 1967) of ~50 per million. Six study lists were contructed, each containing a different set of 31 items. For each study list, a set of three corresponding test lists was formed. These lists were each of 50 items, and contained different ratios of study and new words. For all three lists of each test set, the first 20 and the last 10 items consisted of equal numbers of study and new words, randomly ordered. The critical intervening series of 20 items varied across the three lists, and consisted of (i) all new words (zero target condition), (ii) a random ordering of four study and 16 new words (low target density condition) and (iii) a random ordering of 16 study and four new words (high target density condition). No words repeated across the six sets of study/test lists, and each set of test lists employed a different ordering of old and new items.

The items in the control task consisted of the character strings XXX and OOO. Six sets of lists were constructed
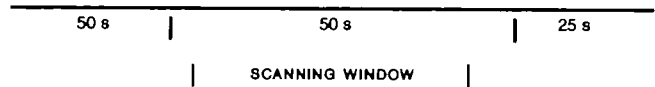
MEMORY TASKS

CONTROL TASKS

Fig. 1 Schematic illustration of the sequence of events in the memory and control tasks.

using these items. Each set corresponded to one of the six sets of test lists employed for the memory task, the XXX string substituting for each new word and the OOO string replacing each study word. Thus, each memory test list had an exactly corresponding control list.

Each subject performed six memory tasks and six control tasks in the course of the study, two scans being conducted at each of the three target/non-target ratios. The tasks were adminstered in an ABCDEFFEDCBA design, three subjects beginning with a memory task and three with a control task. For the memory tasks, each run employed a study list, and a corresponding test list, from a different study-test set. Likewise, for the control task, each run employed a list selected from a different set. For both tasks, the ordering of the conditions (zero, low and high target density) and the mapping of conditions to lists were different for every subject.

Procedure

After installation in the scanner, subjects were informed of the requirements for each task and were given practice runs with lists additional to those employed in the experiment proper. They were not informed that the relative proportions of targets and non-targets would vary across lists. As explained below and illustrated in Fig. 1, the presentation of the memory test and the control lists was co-ordinated with the onset of the scanning interval to ensure that the rCBF was measured only within the 50 s interval in which the target/non-target ratio varied (between the 20th and the 39th item of each list).

Memory task

The first item of the relevant study list was presented 5 min before the beginning of each scan. Presentation was self-paced thereafter, and subjects were required to incorporate each word into a short spoken sentence before moving on to the next item. The words were presented visually for 1 s on a Macintosh LCII monitor suspended on a cradle 45 cm from the subject. The interval between completion of the study

task and the onset of the test list was filled to prevent rehearsal by the requirement to count back aloud in threes from an arbitrary four figure number. Presentation of the corresponding test list began 50 s before scanning commenced. The items were presented on the same monitor as that employed for the study task for a duration of 1 s and with a stimulus onset asychrony of 2.5 s. Subjects were required to give a prompt verbal response following the onset of each item, 'no' whenever they saw a new (non-target) item and 'yes' when they detected an old (target) word.

Control task

The control stimuli were presented in the same manner as the memory test items, and with the same presentation parameters (*see* Fig. 1). Subjects were required to respond verbally to each item, 'No' whenever the XXX string appeared ('non-target') and 'Yes' to each 'OOO' string ('target').

Results

Performance data

Performance in the memory task, as measured by the discrimination index *phit–pFalse alarm* did not differ significantly across the three target density conditions (values of 0.72, 0.77 and 0.66 for the zero, low and high density conditions, respectively). The false positive rate averaged over the critical sections of the two zero-target-density sequences, when no old words were presented, was 6%. Performance was at or near ceiling in all three conditions of the control task.

PET data

Analysis strategy

The principal questions addressed by this study are (i) whether the cerebral regions that are activated differentially by the memory and control tasks include regions identified in previous PET studies as memory-sensitive and (ii) whether rCBF in these regions increases as the density of memory targets increases. To address the first question, areas sensitive to the task manipulation were identified in an initial analysis in which all scans obtained in the control tasks were contrasted with all of those obtained during the memory tests (irrespective of target density in both cases). This contrast identified the regions associated with the different processing demands of the two tasks while eliminating any contribution of the differing response requirements associated with variation in target density.

The regions in which this contrast gave rise to significant increases in rCBF in the memory task relative to the control
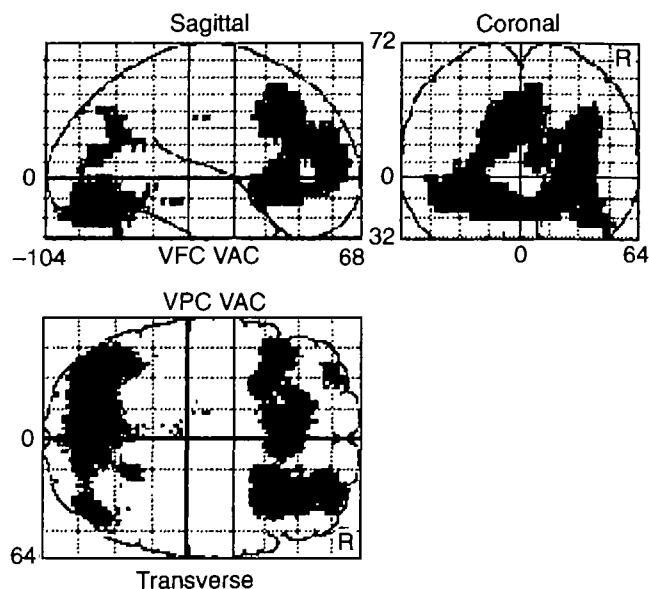

Fig. 2 Cerebral regions showing increased blood flow ($P < 0\,01$, uncorrected for multiple comparisons) in the memory task relative to the control task, with equal weights assigned to each of the three target density conditions. The same set of contrasts provided the mask for the within-condition contrasts illustrated in Figs 3 and 4.

task are illustrated in Fig. 2. The activated regions include several that have been previously reported to be engaged by memory tasks, including the right prefrontal cortex and the pre-cuneus/cuneus. The contrasts also revealed activation of inferior occipital regions, regions likely to be sensitive to the very different perceptual demands of the two tasks (reading versus simple pattern recognition).

The areas identified by the foregoing contrast were employed as a 'mask' with which to constrain subsequent hypothesis-driven contrasts that tested whether rCBF and target density covaried in the memory task. This approach combines the outcomes of two orthogonal sets of contrasts (the masking contrasts and the contrast(s) of experimental interest) to yield a statistical parametric map in which the statistical significance represents the joint probability of a type I error for the two sets of contrasts. The procedure provides an hypothesis-driven alternative to methods that control type I error with respect to an entire population of voxels (Friston *et al.*, 1991). In the present case, the masking and experimental contrasts were each thresholded at $P < 0.05$, and regions containing voxels in which rCBF increases occurred at a conjoint significance level of $P < 0.0005$ were considered to have been reliably activated. Using this procedure, the following contrasts of experimental interest were performed:

(1) *Effects of increasing target density in the memory task.* This comparison tested for a positive relationship between rCBF and the density of recognition memory targets during the scanning period. This was achieved by an orthogonal contrast of the zero, low and high density

Table 1 *Peak rCBF increases associated with increasing target density in the memory tasks*

Peak location (x, y, z)			P-value at peak	Cortical region	Brodmann area
Memory task					
40,	50,	8	< 0.00005	Right lateral frontal pole	10
38,	40,	20	< 0.0005	Right dorsolateral frontal	46
−32,	52,	0	< 0.0005	Left lateral frontal pole	10
10,	24,	40	< 0.0005	Right medial frontal	32
18,	−80,	12	< 0.0005	Right cuneus	17/18
−12,	−76,	36	< 0.0005	Left cuneus/parieto-occipital sulcus	19/7
Memory task analysed with control as covariate					
38,	48,	8	< 0.00001	Right lateral frontal pole	10/46
42,	22,	28	< 0.0005	Right dorsolateral frontal	46/9
−30,	46,	−4	< 0.00005	Left lateral frontal pole	10
4,	20,	48	< 0.0005	Right medial frontal	32/8

The *x*, *y* and *z* coordinates are those of the Talairach and Tournoux (1988) system.

conditions, with weights for the three conditions of −1, 0.25 and 0.75, respectively. As can be seen in Table 1, rCBF increased reliably as a function of increasing target density in the dorsolateral perfrontal cortex, bilateral frontopolar cortex, right medial frontal cortex and medial posterior cortex in the vicinity of the cuneus/pre-cuneus.

(2) *Target effects specific to the memory task.* This comparison was a replication of (1) above, but with the effects of increasing target density in the control task included as a covariate. This set of contrasts removes any covariance between rCBF and target density that is common to the two tasks, allowing the identification of target-related changes in rCBF that are specific to the memory task. As shown in Fig. 3 and Table 1, this comparison, as with its predecessor, indicated that rCBF covaried with increasing memory target density in an extensive region of the right dorsolateral prefrontal cortex, as well as in right medial frontal cortex and in frontopolar cortex bilaterally.

In light of the finding that rCBF is sensitive to the density of memory targets, pairwise contrasts were conducted to determine the pattern of differences between the three conditions. As with the foregoing global contrast, these pairwise comparisons used the relevant control conditions as covariates to remove density effects common to both tasks. The outcomes of these contrasts are illustrated in Fig. 4, where it can be seen that the contrasts between the low and zero target density conditions (Fig. 4A) and the high and zero target density conditions (Fig. 4B) each revealed activation of the same prefrontal regions that were identified in the global analysis. In the high minus low density comparison, no rCBF differences were evident in these prefrontal regions at the P < 0.0005 significance level, the only region to show any effect being a small area in the vicinity of the right parieto-occipital sulcus (BA 23/31). When, however, the criterion for significance was reduced to P < 0.001, the high minus low density contrast revealed an additional region of increased rCBF, which was localized to the anterior part of the right

inferior frontal gyrus (BA 10/46). This effect can be seen in Fig. 4C.

Unmasked contrasts to detect rCBF decreases

These comparisons tested for evidence of an inverse relationship between rCBF and target density. As they were not motivated by the pre-experimental hypothesis, the comparisons were performed unmasked. The significance level for these comparisons was set at P < 0.05 after correction for multiple non-independent comparisons (Friston *et al.*, 1991).

For the memory task, significant rCBF reductions were found in two regions: the left posterior cingulate cortex (peak at x, y, z = −16,−18,40; BA 24/31; Z = 4.92, P(corrected) < 0.005) and the right ventral occipito–temporal cortex (peak at x, y, z = 26,−54,−4; BA 19/37; Z = 4.38, P(corrected) < 0.025). These effects are illustrated in Fig. 5. The analogous contrast for the control task revealed no significant effects.

Discussion

When compared with the zero target condition, test sequences containing memory targets gave rise to reliable rCBF increases in bilateral frontopolar, right dorsolateral and right medial prefrontal cortex. The pattern of findings was unchanged when the data from the control task were employed to covary out the effects of varying the probability of target detection and responding. Thus, these findings further strengthen the link between activation of right dorsolateral prefrontal cortex and episodic memory retrieval. It should be noted, however, that prefrontal activation was not confined to the right hemisphere. In keeping with the findings of Kapur *et al.* (1995) for recognition memory, and of Buckner *et al.* (1995) for cued recall, the frontopolar cortex (the anterior part of area 10) was activated bilaterally.

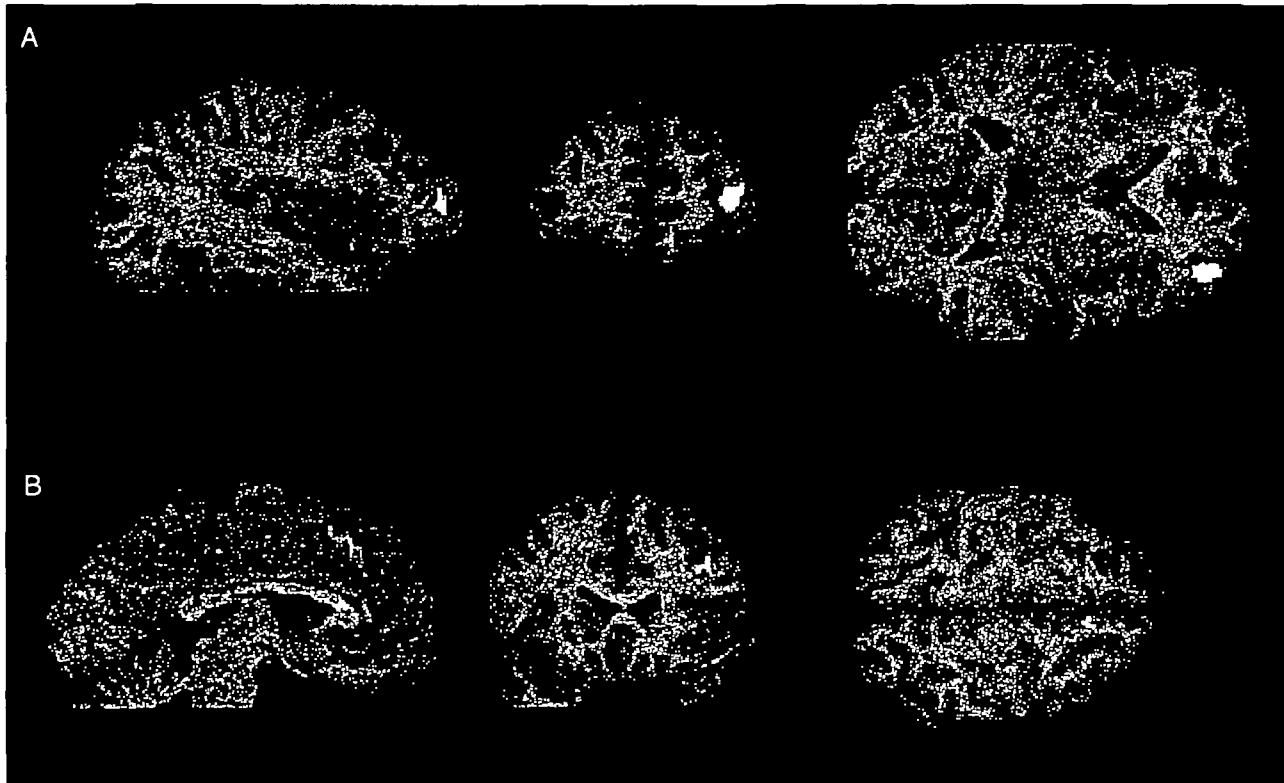The pattern of prefrontal activation found in the present

Fig. 3 Statistical parametric maps superimposed onto MRI images which have been transformed into standard stereotactic space. The maps illustrate regions in which blood flow increased with increasing target density in the memory task. They are based on the outcome of the orthogonal contrast of the zero, low and high target density conditions (weights of -1, 0.25 and 0.75, respectively), employing the corresponding control conditions as a covariate, with the between-task contrast illustrated in Fig. 2 as a mask. The maps are thresholded at $P < 0.001$. (A) Saggital, coronal and transverse sections in the planes $x = 38$, $y = 48$ and $z = 8$, illustrating activation of the right dorsolateral and left polar prefrontal cortex. (B) Sections in the planes $x = 4$, $y = 20$ and $z = 48$, illustrating activation of right medial prefrontal cortex.

study corresponded closely to that described by Kapur *et al.* (1995), but the contrasts used here were quite different from those employed in that study. Whereas Kapur *et al.* (1995) contrasted a recognition memory task with a non-memory control task (semantic classification), the contrasts in the present study were between different conditions of the same task, the only difference between the conditions being the proportion of memory targets in the critical part of the test sequence. Thus the present findings suggest that, during recognition memory, neural activity in the prefrontal cortex varies with whether a test item elicits memory retrieval.

The idea that neural activity in the prefrontal cortex varies with successful retrieval is supported by the results of recent ERP studies of source memory (Wilding and Rugg, 1996) and recognition memory (Allan and Rugg, 1996). In both studies, ERPs elicited by correctly classified test items differed according to whether the items were old or new. At electrode sites overlying the prefrontal cortex, these differences were first seen at ~400 ms post-stimulus, were larger over the right than the left hemisphere and persisted until the end of the recording epoch [1400 ms in Wilding and Rugg (1996); 1900 ms in Allan and Rugg (1996)]. These ERP findings converge with the results of the present study to support the view that stimulus-locked neural activity in

the prefrontal cortex, especially in the right hemisphere, depends on whether a test item elicits retrieval of information from episodic memory.

The high versus low density contrast

One aspect of the present results complicates their interpretation. Broadly similar patterns of activation were seen when separate comparisons were made between the zero density condition and the conditions containing either a low or a high density of old words. But the comparison of the low and the high density conditions yielded evidence of greater prefrontal activation in the latter condition only when the significance threshold was lowered to $P < 0.001$, and then in only a restricted region of right prefrontal cortex. This pattern of findings indicates that the relationship between memory target density and prefrontal rCBF was non-linear, with target-related increases in rCBF reaching near asymptotic levels in the low density condition.

One possible explanation for the non-linear relationship between target density and prefrontal rCBF is that the rCBF differences do not reflect the consequences of successful memory retrieval, but reflect instead the adoption of different retrieval strategies according to whether memory targets were
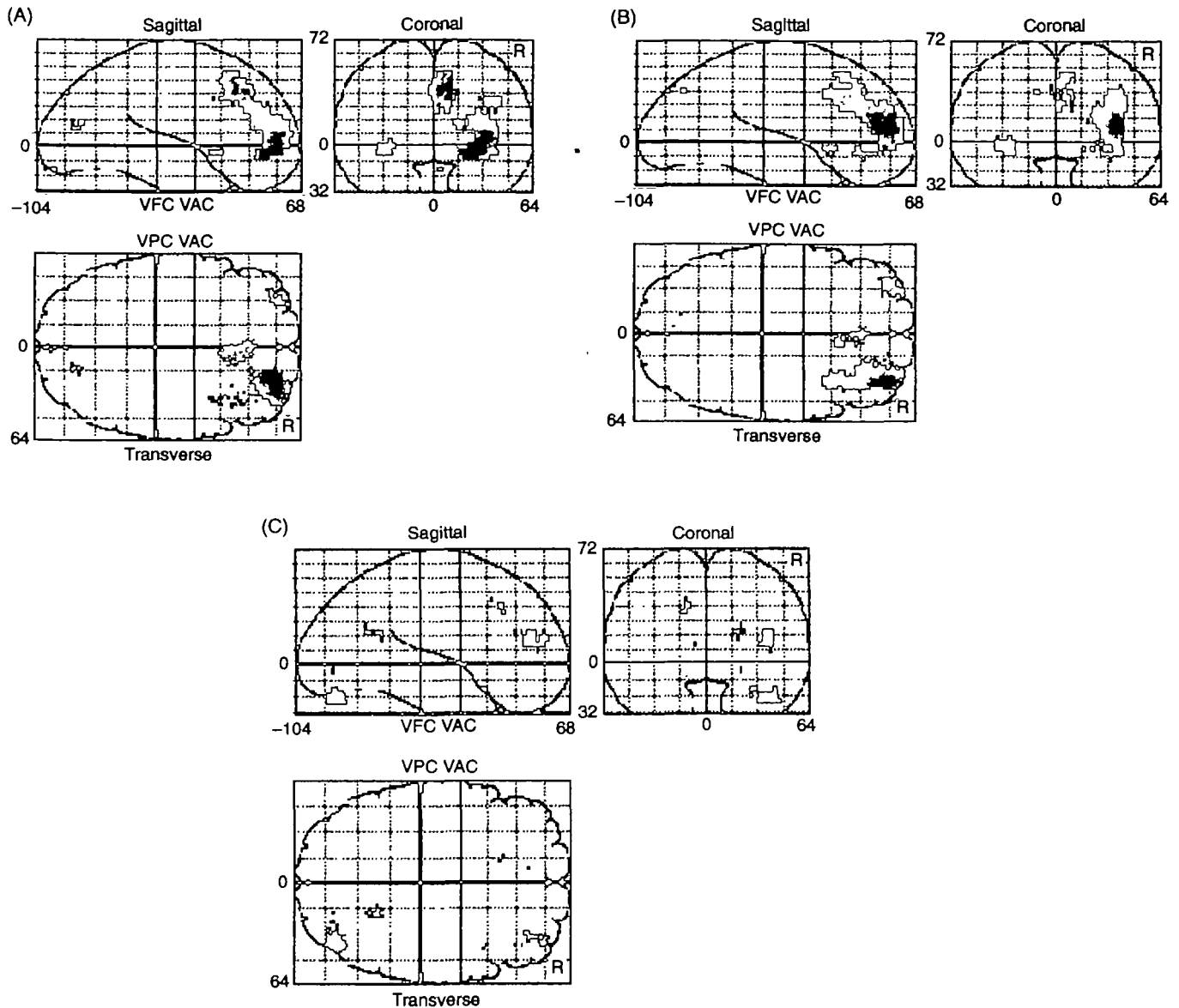
Fig. 4 Cerebral regions showing blood flow increases in the memory task for low target density relative to zero target density (A), for high target density relative to zero target density (B) and/or high target density relative to low target density (C). For each contrast the corresponding control conditions were used as a covariate, and the between-task contrast illustrated in Fig. 2 was employed as a mask. All contrasts are shown thresholded at $P < 0.001$.

present or absent. For example, in the face of repeated retrieval failure, subjects may have given up attempting to retrieve information in the zero density condition. This possibility seems unlikely, however, as the experimental design prevented subjects from identifying the different conditions at least until well into the critical part of each test sequence. Furthermore, such a strategy might be expected to carry over into the final part of the test sequence, when the old/new ratio reverted to 50:50, and to reveal itself by a lower hit rate in the zero density condition. There was no evidence of such an effect: the hit rates for the final five target items of the three types of memory test sequence averaged 88%, 100% and 83%, for the zero, low and high

density conditions, respectively, and these values did not differ significantly from one another.

An alternative explanation for the non-linear relationship between increases in prefrontal rCBF and target density, compatible with the proposal that these increases are indeed a direct consequence of retrieval success, is that the rCBF increases elicited by each memory target persisted for several seconds. As rCBF was estimated by the accumulation of counts over a 30 s period, the longer the duration of each target-related activation, the smaller would be the difference in accumulated counts between the low and high density conditions. The findings from the ERP studies described previously show that differences in stimulus-locked neural
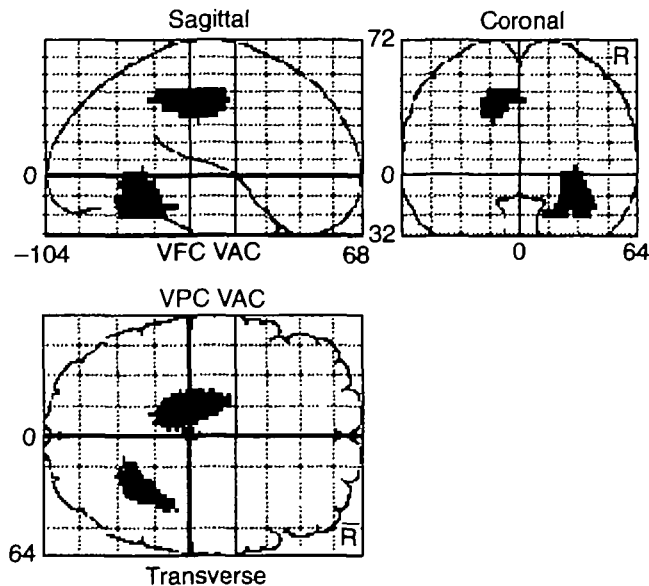
Fig. 5 Cerebral regions in which blood flow decreased as a function of increasing target density in the memory task. The analysis was performed unmasked on the data from the three memory conditions alone, employing weights of 1, −0.25 and −0.75 for the zero, low and high density conditions, respectively. The contrast is thresholded at $P < 0.001$ uncorrected for multiple comparisons.

activity elicited by target and non-target items in recognition memory tasks can persist for at least 1.5 s. Because of the smearing effect of the haemodynamic time-constant, the duration of the corresponding differences in rCBF would be some three to four times longer (Friston *et al.*, 1994). Thus the ERP data give support to the proposal that the small differences that were found between the low and high density conditions reflect the persistence of each target-evoked rCBF response, rather than the insensitivity of the prefrontal cortex to target density.

The comparison of high and low target conditions here corresponds to the one on which Kapur *et al.* (1995) based their conclusion that the prefrontal cortex is insensitive to retrieval success. Thus there is less conflict between that study and the present one than might appear at first glance, as the failure to find a difference between the low and high density conditions of that study is presumably attributable to the factors discussed in preceding paragraph. There is, however, a clear conflict between the present results and those of Nyberg *et al.* (1995). Of the numerous procedural differences between the two studies, we suspect that the superior memory performance of the subjects in the present study is the most important reason why the two sets of results are so divergent (*see* Introduction).

The prefrontal cortex and post-retrieval processing

As was noted in the Introduction, lesions of prefrontal cortex give rise to relatively mild impairments on standard tests of

memory, such as recognition and cued recall, but they are associated with more marked impairment on tasks where information about a specific event must not only be retrieved from memory, but must also be placed in its correct spatiotemporal context. This pattern of findings has led to the proposal that the prefrontal cortex supports processes that act to integrate retrieved information about an item with information about its encoding context (Squire *et al.*, 1993; Knowlton and Squire, 1995; *see* also Moscovitch, 1992). From this perspective, the insensitivity to prefrontal damage of many standard memory tests reflects the fact that performance on such tests, unlike that on, for example, tests of source memory or temporal order, does not depend on access to fully-formed representations of past events. For example, recognition judgements can be made accurately in the absence of detailed information about an item's study context (Johnson *et al.*, 1993). By contrast, source memory judgements cannot be made on the basis of item information alone; accurate source judgements also require the retrieval of the item's study context and the integration of the contextual information with that about the item.

Another view of the role of the prefrontal cortex in memory retrieval stresses the importance of prefrontal regions in monitoring the products of retrieval, and verifying that the retrieved information is relevant to current goals (Shallice, 1988). By this view, as with the preceding one, memory deficits following prefrontal lesions can occur not only because of an impairment in retrieval *per se*, but also from the failure to process information generated by a succesful retrieval operation adequately. To be consistent with the neuropsychological evidence, it would be necessary to suppose (not implausibly) that some kinds of memory task, notably recency, temporal ordering and source memory, place heavier demands upon monitoring and verification operations than do others, such as recognition and cued recall.

The foregoing views of the role of the prefrontal cortex in memory (which are not mutually exclusive) share the idea that one of the functions of this region is to support processes that operate on the products of retrieval (henceforth 'post-retrieval processing'). This idea provides an attractive framework in which to interpret the findings of the present study because it predicts that prefrontal activity will differ according to whether retrieval is successful; post-retrieval processing can proceed only if there is information to process. The present and previous findings converge to suggest that three prefrontal regions in particular are implicated in post-retrieval processing: the right dorsolateral, right medial and bilateral frontopolar regions. Since the prefrontal cortex is highly differentiated anatomically, with each region having distinct patterns of interconnectivity, both with other prefrontal regions and with structures outside the frontal lobes (Petrides, 1994; Petrides and Pandya, 1994), it is very unlikely that these three regions are functionally homogeneous. It will therefore be of interest to determine whether activation of these regions during memory retrieval can be experimentally dissociated.

Working memory and episodic retrieval

The present results can also be interpreted in the light of the findings from functional neuroimaging studies of working memory (for a review, *see* McCarthy, 1995). These studies have consistently reported that working memory tasks (tasks in which a relatively small number of items must be actively maintained in memory for a limited time) are associated with activation of the dorsolateral prefrontal cortex (area 46) and, more variably, with activation of medial prefrontal and frontopolar regions. For example, Petrides *et al.* (1993*b*) reported activation of dorsolateral prefrontal cortex bilaterally, and frontopolar cortex on the right, in a task that required subjects to monitor a series of spoken digits in order to identify the one that was missing from the series. In the same study, the authors found that a 'self-ordered' task (generating the digits between 1 and 10 in a random order without repetition) also activated bilateral dorsolateral prefrontal cortex, as well as medial cortex (in the vicinity of the anterior cingulate) on the left side. These and similar findings (Cohen *et al.*, 1994; McCarthy *et al.*, 1994; Schumacher at al., 1996) suggest that working memory tasks engage some of the same prefrontal functions that are also engaged during episodic retrieval. This congruence between the rCBF correlates of working memory and episodic retrieval led Petrides *et al.* (1995) to propose that the activation of dorsolateral prefrontal cortex during episodic retrieval reflects its role 'in the on-line monitoring, within working memory, of the output from long-term memory . . .' (Petrides *et al.*, 1995, p. 5806).

This proposal is consistent with both views of the role of the prefrontal cortex in post-retrieval processing outlined above. It is most obviously compatible with, and perhaps indistinguishable from, Shallice's (1988) proposal that the prefrontal cortex supports verification and monitoring operations on retrieved information. However, it is not difficult to conceive why the integration of item and contextual information into a coherent representation might also depend heavily upon working memory. For instance, if retrieval proceeds iteratively, such that information about an episode is retrieved piecemeal, a system permitting the products of retrieval to be temporarily stored and manipulated would seem to be essential.

While an account that proposes a link between post-retrieval processing and working memory may go a considerable way towards explaining the present findings, it leaves one issue in particular outstanding: Why was activation of the dorsolateral prefrontal cortex confined to the right hemisphere? Right-sided activation of this region has been reported in some studies of working memory, but only for tasks employing non-verbal stimuli (e.g. Petrides *et al.*, 1993*a*; McCarthy *et al.*, 1994). With verbal working memory tasks, activation of dorsolateral prefrontal cortex has been reported to be bilateral (e.g. Petrides *et al.*, 1993*b*; Cohen *et al.*, 1994) or lateralized to the left hemisphere (e.g. Petrides *et al.*, 1993*a*; Schumacher *et al.*, 1996). To the extent that

verbal episodic retrieval engages verbal working memory, one would therefore expect a similar pattern of dorsolateral prefrontal activation in episodic memory tasks employing verbal stimuli, rather than the marked right-sided lateralization evident in both the present and previous studies.

Reductions in rCBF related to increasing target density

Two cortical regions, the left posterior cingulate and right ventral occipito-temporal cortex, showed reliable rCBF decreases as target density in the memory task increased. The decrease in posterior cingulate cortex was unexpected, and any suggestion about its functional significance can only be speculative. It is noteworthy, however, that in two previous studies, activation of the posterior cingulate was found during tasks that engaged memory encoding (Grasby *et al.*, 1993*a*; Fletcher *et al.*, 1995). Although the loci of the activations found in these studies were inferior and posterior to the deactivation found here, their findings suggest a possible explanation of the present data. The higher rCBF in the posterior cingulate for the zero density condition may have been a reflection of the fact that new items were more likely to be subjected to memory encoding operations than were items that had recently been experienced (*see* Tulving *et al.*, 1996).

The deactivation of occipito-temporal cortex in the target-present conditions can be related to the findings of two studies of word-stem priming (Buckner *et al.*, 1995; Schacter *et al.*, 1996; *see* also Squire *et al.*, 1992). These studies reported right-lateralized deactivations in the vicinity of the fusiform gyrus when completions were made to word stems derived from previously studied items, relative to a control task in which stems could be completed only with unstudied words. These findings suggest that this cortical region is sensitive to whether a word has been primed by a recent presentation, and that one effect of priming is to reduce the perceptual processing required subsequently to identify the word (Squire *et al.*, 1992). The present results, which indicate that activation of this region declines as the proportion of recently studied (and hence primed) words increases, fit comfortably with this proposal. Together with recent neuropsychological evidence (Gabrieli *et al.*, 1995; Swick and Knight, 1995), they converge with the previous neuroimaging studies to suggest that the right occipito-temporal cortex plays an important role in visual word priming.

Absence of hippocampal activation

Despite extensive evidence that the hippocampus and adjacent medial temporal cortex play a critical role in episodic memory (Squire, 1992), neither the global comparison between the memory and control tasks, nor unmasked across-condition comparisons within the memory task (data not shown), revealed any sign of differential engagement of the hippocampal formation. These negative results are in keeping

with the findings from several previous studies of recognition memory for words and sentences (Tulving *et al.*, 1994; Andreasen *et al.*, 1995; Kapur *et al.*, 1995; Nyberg *et al.*, 1995), as well as from studies of the encoding and retrieval of paired associates (Fletcher *et al.*, 1995) and of cued recall when modality or typecase changed between study and test (Buckner *et al.*, 1995). A number of other studies have, however, reported increases in hippocampal blood flow in memory tasks, relative to a variety of control conditions. The increases have tended to be lateralized to the right hippocampal formation, and the critical task has either required or encouraged memory for the visual attributes of test items (Squire *et al.*, 1992; Grady *et al.*, 1995; Schacter *et al.*, 1995; Schacter *et al.*, 1996). The right hippocampal activation observed in these studies may therefore reflect the role played by this structure in memory for visually coded information, a proposal consistent with neuropsychological evidence showing that long-term visual memory relies mainly upon the medial temporal lobe memory system of the right hemisphere (Smith, 1989). As the same body of evidence demonstrates equally clearly that the left medial temporal lobe is pre-eminent for verbal memory, it is puzzling that PET studies have thus far had such little success in detecting activation of the left hippocampal formation during encoding or retrieval of words, relative to a range of baseline tasks. The reports of right-sided activation mean that it is very unlikely that this failure reflects a general insensitivity of blood-flow measures to task-related changes in hippocampal activity, as has sometimes been suggested (Fletcher *et al.*, 1995). Rather, it may be that the left hippocampal formation is more continuously active than that on the right, and therefore more difficult to activate differentially. If so, a rather different experimental strategy from the one employed here and in most previous studies may be required. One alternative approach that shows promise is to design studies so that performance indices can be correlated with measures of hippocampal rCBF (Grasby *et al.*, 1993b; Nyberg *et al.*, 1996).

Conclusions

The most important finding from this study is that, during recognition memory, several regions of the prefrontal cortex are sensitive to whether a test item elicits successful memory retrieval. This finding is consistent with the idea that the prefrontal cortex supports processes that operate selectively on the products of successful retrieval. It remains to be determined whether the different prefrontal regions identified in this study as sensitive to retrieval success belong to a functionally homogeneous circuit, or whether instead they make separate contributions to memory function.

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References

Allan K, Rugg MD. An event-related potential study of explicit memory on tests of cued recall and recognition. Neuropsychologia 1996. In press.

Andreasen NC, O'Leary DS, Arndt S, Cizadlo T, Hurtig R, Rezai K, et al. Short-term and long-term verbal memory. a positron emission tomography study Proc Natl Acad Sci USA 1995; 92: 5111–5.

Buckner AL, Tulving E. Neuroimaging studies of memory: theory and recent PET results. In: Boller F, Grafman J, editors. Handbook of neuropsychology, Vol. 10. Amsterdam: Elsevier, 1995: 439–66.

Buckner RL, Petersen SE, Ojemann JG, Miezin FM, Squire, LR, Raichle ME. Functional anatomical studies of explicit and implicit memory retrieval tasks. J Neurosci 1995; 15: 12–29.

Cohen JD, Forman SD, Braver TS, Casey BJ, Servan-Schreiber D, Noll DC. Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. Hum Brain Map 1994; 1: 293–304.

Coles MGH, Rugg MD. Event-related brain potentials· an introduction. In: Rugg MD, Coles MGH, editors. Electrophysiology of mind: event-related brain potentials and cognition. Oxford: Oxford University Press, 1995: 1–26.

Fletcher PC, Frith CD, Grasby PM, Shallice T, Frackowiak RSJ, Dolan RJ. Brain systems for encoding and retrieval of auditory-verbal memory. An in vivo study in humans. Brain 1995; 118: 401–16.

Friston KJ, Passingham RE, Nutt JG, Heather JD, Sawle GV, Frackowiak RSJ. Localisation in PET images: direct fitting of the intercommissural (AC-PC) line. J Cereb Blood Flow Metab 1989; 9: 690–5.

Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Comparing functional (PET) images: the assessment of significant change J Cereb Blood Flow Metab 1991; 11: 690–9.

Friston KJ, Jezzard P, Turner R. Analysis of functional MRI time-series. Hum Brain Map 1994; 1: 153–71.

Gabrieli JDE, Fleishman DA, Keane MM, Reminger SL, Morrell F. Double dissociation between memory systems underlying explicit and implicit memory in the human brain. Psychol Sci 1995; 6: 76–82.

Grady CL, McIntosh AR, Horwitz B, Maisog JM, Ungerleider LG, Mentis MJ, et al. Age-related reductions in human recognition memory due to impaired encoding. Science 1995; 269: 218–21.

Grasby PM, Frith CD, Friston KJ, Bench C-J, Frackowiak RSJ, Dolan RJ. Functional mapping of brain areas implicated in auditory-verbal memory function. Brain 1993a; 116: 1–20.

Grasby PM, Frith CD, Friston, KJ, Frackowiak RSJ, Dolan RJ. Activation of the human hippocampal formation during auditory-verbal long-term memory function. Neurosci Lett 1993b; 163: 185–8.

Janowsky JS, Shimamura AP, Squire LR. Source memory impairment in patients with frontal lobe lesions. Neuropsychologia 1989; 27: 1043–56.

Johnson MK, Hashtroudi S, Lindsay DS. Source monitoring. [Review]. Psychol Bull 1993; 114: 3–28.

Kapur S, Craik FIM, Jones C, Brown GM, Houle S, Tulving E. Functional role of the prefrontal cortex in retrieval of memories: a PET study. Neuroreport 1995; 6: 1880–4.

Kesner RP, Hopkins RO, Fineman B. Item and order dissociation in humans with prefrontal cortex damage. Neuropsychologia 1994; 32. 881–91.

Knowlton BJ, Squire LR. Remembering and knowing: two different expressions of declarative memory. J Exp Psychol Learn Mem Cogn 1995; 21: 699–710.

Kucera H, Francis WN. Computational analysis of present-day American English. Providence (RI): Brown University Press, 1967.

McAndrews MP. Milner B. The frontal cortex and memory for temporal order. Neuropsychologia 1991; 29: 849–59.

McCarthy G. Functional neuroimaging of memory. Neuroscientist 1995; 1: 155–63.

McCarthy G, Blamire AM, Puce A, Nobre AC, Bloch G. Hyder F, et al. Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. Proc Natl Acad Sci USA 1994; 91: 8690–4.

Mayes AR. Human organic memory disorders. Cambridge: Cambridge University Press, 1988.

Milner B. Corsi P, Leonard G. Frontal-lobe contribution to recency judgements. Neuropsychologia 1991; 29: 601–18.

Moscovitch M. Memory and working-with-memory: a component process model based on modules and central systems. J Cognit Neurosci 1992; 4: 257–67.

Nyberg L. Tulving E, Habib R, Nilsson L-G, Kapur S, Houle S, et al. Functional brain maps of retrieval mode and recovery of episodic information. Neuroreport 1995; 7: 249–52.

Nyberg L, McIntosh AR, Houle S, Nilsson L-G, Tulving E Activation of medial temporal structures during episodic memory retrieval. Nature 1996; 380: 715–7.

Petrides M. Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In: Boller F, Grafman J, editors. Handbook of neuropsychology. Vol. 9. Amsterdam: Elsevier, 1994: 59–82.

Petrides M, Pandya DN. Comparative architectonic analysis of the human and the macaque frontal cortex. In: Boller F, Grafman J, editors. Handbook of neuropsychology. Vol. 9. Amsterdam: Elsevier, 1994: 17–58.

Petrides M. Alivisatos B, Evans AC, Meyer E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci USA 1993a; 90: 873–7.

Petrides M. Alivisatos B, Meyer E, Evans AC. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proc Natl Acad Sci USA 1993b; 90: 878–82.

Petrides M, Alivisatos B, Evans AC. Functional activation of the human ventrolateral frontal cortex during mnemonic retrieval of verbal information. Proc Natl Acad Sci USA 1995; 92: 5803–7.

Schacter DL, Reiman E, Uecker A. Polster MR, Yun LS. Cooper LA. Brain regions associated with retrieval of structurally coherent visual information. Nature 1995; 376: 587–90.

Schacter DL. Alpert NM, Savage CR. Rauch SL, Albert MS. Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. Proc Natl Acad Sci USA 1996; 93: 321–5.

Schumacher EH, Lauber E, Awh E, Jonides J, Smith EE, Koeppe RA. PET evidence for an amodal verbal working memory system. Neuroimage 1996: 3: 79–88.

Shallice T. From neuropsychology to mental structure. Cambridge: Cambridge University Press, 1988.

Shimamura AP, Squire LR. A neuropsychological study of fact memory and source amnesia. J Exp Psychol Learn Mem Cogn 1987; 13: 464–73.

Silbersweig DA, Stern E, Frith CD. Cahill C, Schnorr L, Grootoonk S, et al. Detection of thirty-second cognitive activations in single subjects with positron emission tomography: a new low-dose $H_2^{15}O$ regional cerebral blood flow three-dimensional imaging technique. J Cereb Blood Flow Metab 1993; 13: 617–29.

Smith ML. Memory disorders associated with temporal lobe lesions. In: Boller F. Grafman J, editors. Handbook of neuropsychology, Vol. 3. Amsterdam: Elsevier. 1989: 91–106.

Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans [published erratum appears in Psychol Rev 1992; 99: 582]. Psychol Rev 1992: 99: 195–231.

Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME. Activation of the hippocampus in normal humans: a functional anatomical study of memory. Proc Natl Acad Sci USA 1992; 89: 1837–41.

Squire LR, Knowlton B, Musen G. The structure and organization of memory. [Review]. Annu Rev Psychol 1993; 44: 453–95.

Stuss DT, Eskes GA, Foster JK. Experimental neuropsychological studies of frontal lobe functions. In: Boller F, Grafman J, editors. Handbook of neuropsychology, Vol. 9. Amsterdam: Elsevier, 1994: 149–85.

Swick D, Knight RT. Contributions of right inferior temporal-occipital cortex to visual word and nonword priming. Neuroreport 1995; 7: 11–16.

Swick D, Knight RT. Is prefrontal cortex involved in cued recall? A neuropsychological test of PET findings. Neuropsychologia 1996; 34: 1019–28.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme, 1988.

Tulving E, Kapur S, Markowitsch HJ, Craik FIM, Habib R, Houle S. Neuroanatomical correlates of retrieval in episodic memory: auditory sentence recognition [see comments]. Proc Natl Acad Sci USA 1994; 91: 2012–5. Comment in: Proc Natl Acad Sci USA 1994; 91: 1989–91.

Tulving E, Markowitsch HJ, Craik FIM, Habib R, Houle S. Novelty and familiarity activations in PET studies of memory encoding and retrieval. Cereb Cortex 1996; 6: 71–9.

Wilding EL, Rugg MD. An event-related potential study of recognition memory with and without retrieval of source. Brain 1996; 119: 889–905.

Woods RP, Cherry SR, Mazziotta JC. Rapid automated algorithm for aligning and reslicing PET images. J Comput Assist Tomogr 1992; 16: 620–33.