A Specific Role for the Right Parahippocampal Gyrus in the Retrieval of Object-Location: A Positron Emission Tomography Study

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Abstract

■ A plethora of studies, across many species, have now demonstrated that the hippocampal region plays a critical role in memory for spatial location. In spite of this compelling evidence, a number of important neuropsychological and neuroanatomical issues remain unresolved. In the present study, the functional anatomy of object-location memory was investigated using positron emission tomography (PET) with magnetic resonance imaging (MRI). Regional cerebral blood flow (rCBF) was measured while normal volunteers encoded, and then retrieved, the locations of eight familiar objects presented on a computer screen. In two analogous conditions, designed to fractionate object-location memory into its component processes, the subjects were simply required to encode, and then to retrieve, eight distinct locations represented by identical white boxes on the screen. An increase in rCBF was observed in the region of the right parahippocampal gyrus corresponding to entorhinal cortex when the Retrieving Location condition was subtracted from the Retrieving Object-Location condition. In contrast, when the Encoding Location condition was subtracted from the Encoding Object-Location condition, no significant rCBF changes were observed in the hippocampal region although significant activation was observed, bilaterally, in the anterior fusiform gyrus. In addition, the two encoding conditions activated left-hemisphere regions preferentially, whereas the two retrieval conditions activated right-hemisphere regions.

Together, these findings suggest that the human right hippocampal region is critically involved in retrieving information that links object to place. The secondary finding that encoding and retrieval appear to be lateralized to the left and right hemispheres respectively, is discussed with reference to current models of episodic memory, and alternative hypotheses are considered. ■

INTRODUCTION

There is now considerable evidence to suggest that the hippocampal region plays a critical role in object-location memory. This evidence comes from the study of patients with excisions from the mesial temporal-lobe structures (Corsi, 1972; Crane et al., 1995; Milner, 1978; Smith & Milner, 1981, 1984, 1989; Owen et al., 1995, 1996a), and from lesion work in both rats (Morris et al., 1982; O'Keefe & Nadel, 1978; Olton et al., 1979) and monkeys (Parkinson et al., 1988). In human subjects, deficits in the recall of the location of familiar objects have been demonstrated after right anterior temporal lobectomy, this impairment being contingent upon extensive removal of the hippocampus and/or the parahippocampal gyrus (Smith & Milner, 1981, 1984, 1989). Patients with such lesions performed normally when tested at zero delay, but showed abnormally rapid forgetting after both short (4 minutes) and long (24 hours) time intervals. In contrast, no deficits in recalling object location were observed after left anterior temporal lobectomy (even when the procedure included a radical excision of the hippocampus), or after frontal-lobe removals from either hemisphere. Related studies in the monkey have demonstrated that both bilateral hippocampectomy (Parkinson et al., 1988) and transection of the fornix (Gaffan & Saunders, 1985; Gaffan & Harrison, 1989)—a major subcortical pathway of the hippocampal system—impair the acquisition and retention of object-place associations. These findings concur fully with models of spatial memory developed, from work in the rat, which also emphasize the role of the hippocampus (O'Keefe & Nadel, 1978; Morris et al., 1982).

Nevertheless, a number of important neuropsychological and neuroanatomical issues remain unresolved. First, in the patient studies described above, the subjects were always required to remember the locations of real objects (Smith & Milner, 1981, 1984, 1989). It is unclear,

therefore, whether the critical contribution of the hippocampal system lies in spatial memory per se, or in mediating the necessary associations between objects and their spatial locations. Second, the impairment observed in patients after right hippocampal lesions appears to depend on the interpolation of a short delay between stimulus presentation and recall (Smith & Milner, 1989). This finding suggests a more critical role for the hippocampal region in the maintenance and retrieval of object-location than in the initial encoding of this information. Third, on the basis of the patient data alone it is difficult to assign any role specifically to the hippocampus because, in such cases, the anterior temporal resection typically included the amygdala, together with varying amounts of the parahippocampal gyrus and the anterior temporal neocortex. Finally, while these lesion studies favor a central role for the human right hippocampus in object-location memory, the precise nature of this involvement and its dependence on reciprocal connections with other cortical and subcortical areas remains unclear. For example, regions of the parietal lobe, which has been implicated in a variety of spatial processes, project to both the parahippocampal gyrus and the presubiculum (Jones & Powell, 1970; Seltzer & Pandya, 1976; Seltzer & Van Hoesen, 1979). The parahippocampal gyrus projects via the entorhinal cortex to the hippocampus (Van Hoesen, 1982; Van Hoesen & Pandya, 1975a), while the presubiculum projects directly to the hippocampus (Shipley, 1975). Similarly, Goldman-Rakic et al. (1984) have described several multisynaptic connections between the frontal cortex and the hippocampal formation, which may imply a reciprocal functional relationship between these areas in certain aspects of mnemonic processing. Although Smith and Milner (1984) found no impairment on the object-location task in patients with frontal-lobe damage, specific frontal areas have been implicated in both the encoding and the retrieval of information held in long-term memory (Incisa & Milner, 1993; Petrides et al., 1995; Shallice et al., 1994; Tulving et al., 1994).

The present PET study was designed to investigate these issues further, using four tasks that emphasized different aspects of object-location memory. Normal subjects were scanned while performing a computerized version of the object-location memory task, which required them to monitor and encode the positions of eight representational drawings presented on the computer screen. In a separate scanning condition, presented eight minutes later, they were required to select, from two alternatives, which was the appropriate location for each of these objects.

In two analogous conditions, designed to fractionate object-location memory into its component processes, the subjects were simply required to encode, and then to retrieve, eight distinct locations represented by identical white boxes on the computer screen. On the basis of studies in other primates (Gaffan & Saunders, 1985; Gaffan & Harrison, 1989; Parkinson et al., 1988), it was predicted that the hippocampal region, would be particularly involved when subjects were required to combine information about objects with information about their spatial locations. In addition, given previous findings in patients (Smith & Milner, 1981, 1984, 1989), we hypothesized that this involvement would be more salient in the right than in the left hippocampal region, and that it would be more clearly evident during the retrieval than during the encoding of object-location. Finally, the experimental design allowed us to test the generality of recent proposals, derived from verbal paradigms, that encoding is associated with increased activity in the left frontal lobe, while retrieval preferentially activates right frontal regions (Shallice et al., 1994; Tulving et al., 1994).

RESULTS

Performance

Both the Retrieving Object-Location and the Retrieving Location tasks were performed well, although subjects tended to be slightly more accurate at retrieving object-location (98% mean correct) than at retrieving location alone (90% mean correct; paired t-test: $t(11) = 2.16, p = 0.053$).

Blood-Flow Changes

This study was designed to permit specific comparisons, accomplished via subtractions, between any two of the four experimental conditions. The results of these subtractions, in terms of statistically significant changes in rCBF, are given in Tables 1 through 4, together with the corresponding stereotaxic coordinates. These coordinates are based on the system used in the brain atlas of Talairach and Tournoux (1988).

Object-Location versus Location

Encoding. When blood flow in the *Encoding Location* condition was subtracted from that in the *Encoding Object-Location* condition (Table 1), a significant change was observed in the right anterior fusiform gyrus and, slightly more laterally, in the left anterior fusiform gyrus (Fig. 3). Other significant rCBF changes were all located in the visual cortex bilaterally. No significant changes in blood flow were observed in the hippocampus or in the parahippocampal gyrus, the highest t-values in these regions being $t = 1.45$ (left hemisphere) and $t = 2.6$ (right hemisphere). When the *Encoding Object-Location* condition was subtracted from the *Encoding Location* condition significant changes in rCBF were only observed in

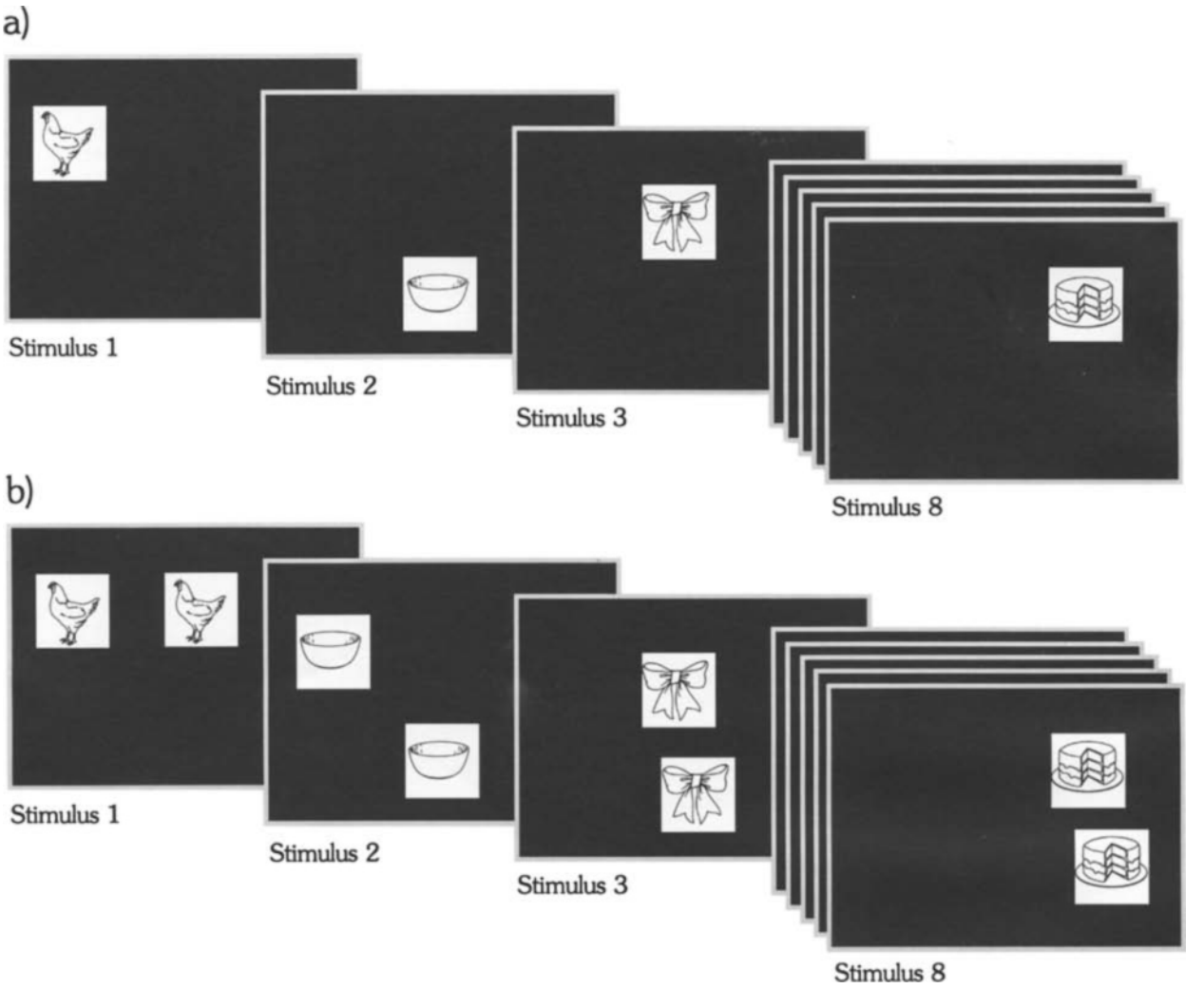

Figure 1. Encoding and recalling object-location. (**a**) *Encoding Object-Location:* The subjects were instructed to attend to each object, to remember its location, and then to touch it in order to move on to the next object in the sequence. (**b**) *Retrieving Object-Location:* The subjects were instructed to decide which of the two possible locations was correct for each object, and to respond by touching that position in order to move on to the next pair in the sequence. In both the encoding and recall conditions the entire sequence of eight squares was shown four times in random order during the scanning period.

the orbitofrontal and medial frontal cortices of the right hemisphere (Table 1).

Retrieval. When blood flow in the *Retrieving Location* condition was subtracted from that in the *Retrieving Object-Location* condition (Table 2), a significant change was observed in the area of the right anterior parahippocampal gyrus that corresponds to entorhinal cortex (Fig. 3). No significant rCBF change was observed in the corresponding region in the left hemisphere (maximum *t*-value = 0.98). Other significant rCBF changes were located in visual areas 17 and 18 bilaterally. In contrast, when the *Retrieving Object-Location* condition was subtracted from the *Retrieving Location* condition, significant changes in rCBF were observed in posterior parietal cortex, ventrolateral and mid-dorsolateral frontal cortex in the right hemisphere, and the caudate nucleus in the left hemisphere (Table 2).

Encoding versus Retrieval

Object-Location. When blood flow in the *Retrieving Object-Location* condition was subtracted from that in the *Encoding Object-Location* condition (Table 3) significant changes in rCBF were observed in the left hemisphere only, in ventral and dorsolateral frontal areas, in both posterior and anterior regions of the inferior temporal gyrus, and in parietal area 40 (Fig. 4). In contrast, when the *Encoding Object-Location* condition was subtracted from the *Retrieving Object-Location* condition

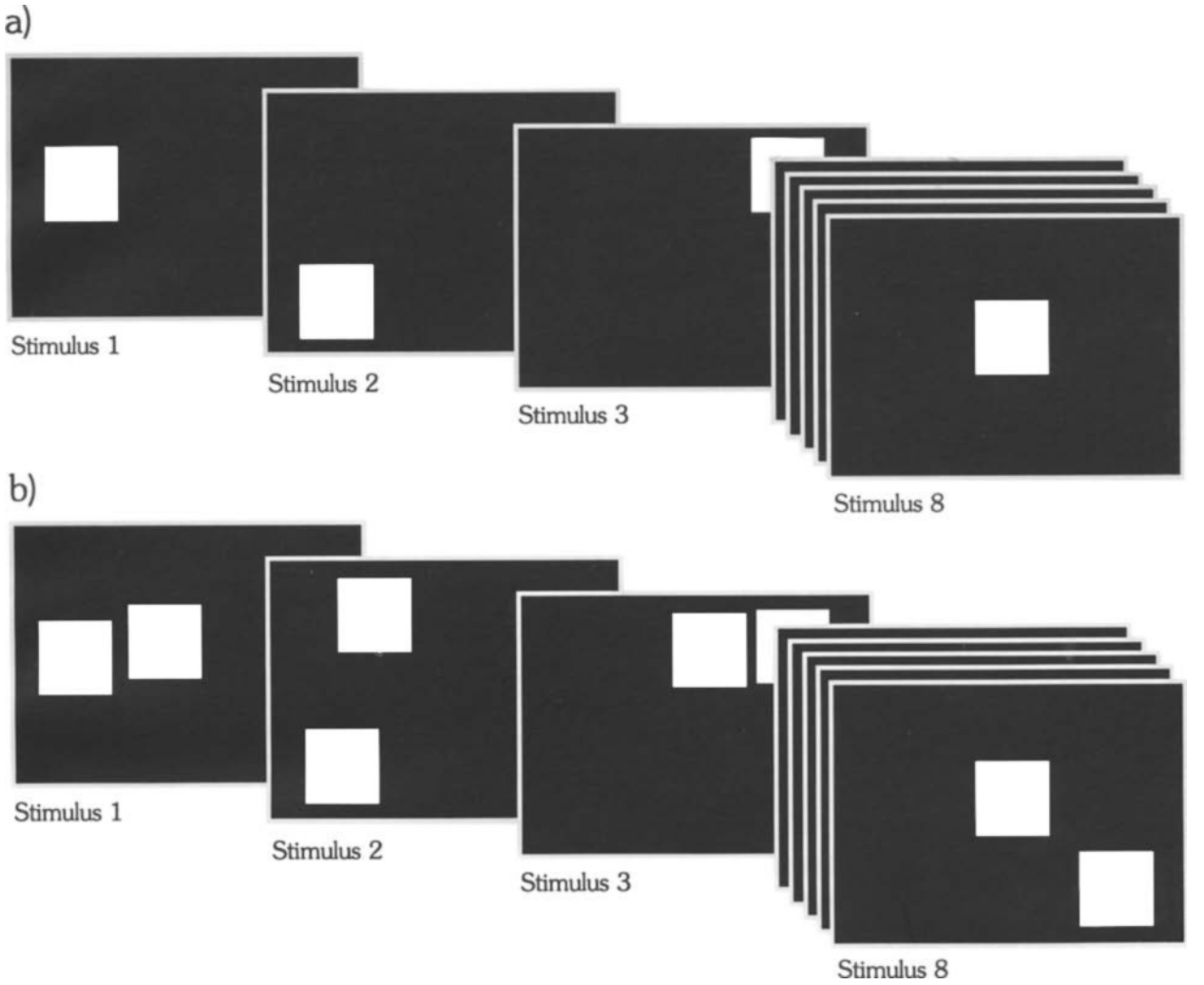

Figure 2. Encoding and recalling location. (**a**) *Encoding Location:* The subjects were instructed to attend to each square as it was presented, to remember its location, and then to touch it in order to move on to the next square in the sequence. (**b**) *Retrieving Location:* The subjects were instructed to decide which of the two locations in each pair had been seen previously, and to respond by touching that square in order to move on to the next pair in the sequence. In both the encoding and recall conditions the entire sequence of eight squares was shown four times in random order during the 60 sec scanning period.

significant rCBF changes were observed in the right hemisphere only, in medial and ventral frontal areas, posterior cingulate cortex, and in visual areas 17 and 18. There were no significant rCBF differences between the two conditions in the hippocampus or in the parahippocampal gyrus of either hemisphere (maximum *t*-value = 1.0, *Retrieving Object-Location* minus *Encoding Object-Location*).

Location. A broadly similar pattern was observed when the *Encoding Location* condition was compared with the *Retrieving Location* condition (Table 4), although the hemispheric specialization observed previously was far less striking. Thus, when blood flow in the *Retrieving Location* condition was subtracted from that in the *Encoding Location* condition, significantly greater rCBF was observed in the left hemisphere, in mid-dorsolateral frontal cortex, inferior and middle temporal gyri, parietal cortex, and posterior cingulate cortex. In the right hemisphere, significantly greater rCBF was observed in the superior and middle temporal gyri and in the cerebellum (Fig. 5). In contrast, when the *Encoding Location* condition was subtracted from the *Retrieving Location* condition, left hemisphere rCBF increases were restricted to visual areas 17 and 19. In the right hemisphere however, increases were observed in both dorsal and ventral lateral frontal cortex, posterior parietal cortex, and visual areas 17, 18, and 19. There were no significant rCBF differences between the two conditions in the hippocampus or in the parahippocampal gyrus of either hemisphere (maximum *t*-value = 1.52, *Encoding Location* minus *Retrieving Object-Location*).

Table 1. Stereotaxic Coordinates of Activation when *Encoding Object-Location* Was Compared with *Encoding Location.*

Encoding Object-Location minus Encoding Location				
	Stereotaxic Coordinates			
Region	*X*	*Y*	*Z*	*t-statistic*
Left Hemisphere				
Anterior fusiform gyrus	−40	−35	−24	5.28
Prestriate cortex (area 18)	−36	−76	−14	6.15
Prestriate cortex (area 18)	−38	−87	−6	5.66
Prestriate cortex (area 18)	−27	−97	3	6.29
Right Hemisphere				
Anterior fusiform gyrus	31	−30	−24	4.93
Prestriate cortex (area 18)	34	−85	−12	8.52
Encoding Location minus Encoding Object-Location				
Left Hemisphere				
No significant peaks				
Right Hemisphere				
Medial frontal cortex (area 9)	9	48	27	3.56
Orbitofrontal cortex (area 11)	39	37	−18	3.92

Activation foci in this and the other tables represent peaks of statistically significant (see text) changes in normalized rCBF. The stereotaxic coordinates are expressed in mm. x = medial-to-lateral distance relative to the midline (positive = right hemisphere); y = anterior-to-posterior distance relative to the anterior commissure (positive = anterior); z = superior-to-inferior distance relative to the anterior commissure-posterior commissure line (positive = superior). Significance levels are given in *t*-test units (see Methods section for details).

DISCUSSION

A Specific Role for the Human Right Parahippocampal Gyrus in Object-location Memory

A major question addressed by the present investigation was whether there would be a significant functional activation of the right hippocampal region when subjects were required to retrieve information about the relationship between objects and their spatial locations. Deficits in the recall of the location of real objects have been demonstrated after right anterior temporal lobectomy (Smith & Milner, 1981, 1989), this impairment being contingent upon extensive removal of the hippocampus and/or the parahippocampal gyrus. Similarly, bilateral hippocampectomy in monkeys produces profound impairments in an object-location memory task, comparable to the one used here (Parkinson et al., 1988). In the current study, when activation in the *Retrieving Location* condition was subtracted from that in the *Retrieving Object-Location* condition, a significant positive rCBF change was observed in a region of the parahippocampal gyrus equivalent to the entorhinal cortex. In the primate brain, widespread cortical and subcortical projections converge upon the hippocampus and terminate within the entorhinal area (Room & Groenewegen, 1986; Van Hoesen & Pandya, 1975a, 1975b; Van Hoesen et al., 1975), which therefore occupies a pivotal position within the hippocampal system (Amaral et al., 1993). Little is known about the functional significance of this region, although, by virtue of its dense cortical connectivity, it may subserve some functions independent of hippocampal processing. There is no evidence available from patient studies to support such a dissociation, since the standard temporal lobectomy includes anterior regions of both the hippocampus and the parahippocampal gyrus. In monkeys, however, selective lesions of entorhinal and the adjacent perirhinal cortex impair learning and memory for both objects and for locations (Murray & Gaffan, 1993; E.A. Murray, personal communication). Furthermore, single-cell recording studies in the monkey have identified entorhinal neurons that respond selectively to objects (Suzuki et al., 1995; W.A. Suzuki, personal communication), to spatial locations (Suzuki et al., 1995; Quirk et al., 1992), and to a combination of both (Rolls et al., 1989). A model, based on lesion studies in the rat, has recently been proposed to describe the functions of the parahippocampal gyrus in relation to the hippocampus itself (Eichenbaum & Bunsey, 1995). According to this model, the parahippocampal region

Table 2. Stereotaxic Coordinates of Activation when *Retrieving Object-Location* Was Compared with *Retrieving Location.*

Retrieving Object-Location minus Retrieving Location				
	Stereotaxic coordinates			
Region	*X*	*Y*	*Z*	*t-statistic*
Left Hemisphere				
Prestriate cortex (area 18)	−34	−88	−14	4.26
Prestriate cortex (area 18)	−36	−92	−9	4.19
Prestriate cortex (area 18)	−23	−97	5	4.50
Striate cortex (area 17)	−8	−99	−9	4.20
Striate cortex (area 17)	−16	−99	−3	4.36
Right Hemisphere				
Anterior parahippocampal gyrus/entorhinal cortex	28	−13	−29	4.89
Prestriate cortex (area 18)	32	−92	1	3.99
Striate cortex (area 17)	21	−97	−6	5.01
Retrieving Location minus Retrieving Object-Location				
Left Hemisphere				
Caudate nucleus	−12	12	14	3.85
Right Hemisphere				
Mid-dorsolateral frontal cortex (area 9)	47	18	35	3.47
Mid-dorsolateral frontal cortex (area 9)	48	22	32	3.45
Ventrolateral frontal cortex (area 45)	36	25	2	3.70
Posterior parietal cortex (area 40)	44	−44	45	4.07

(including the entorhinal cortex) would have the capacity to hold stimulus representations for extended periods and, in doing so, could combine simultaneously occurring stimuli into associated representations in memory (Gluck & Myers, 1995). The current findings suggest that this model may be extended to include different aspects of compound stimuli, such as location or figural detail, which may also be combined in the parahippocampal gyrus to form "fused" or configural representations in memory.

Previous studies in patients have demonstrated that right temporal-lobe excisions that include the hippocampus do not impair recall of object-location, when subjects are tested immediately after exposure to the array (Smith & Milner, 1989). This finding suggests that the hippocampal region may be less important for encoding information about the relationship between objects and their location than in maintaining and retrieving this information (Smith & Milner, 1989).

We have addressed this question directly by subtracting activation in the *Encoding Location* condition from activation in the *Encoding Object-Location* condition. No significant rCBF changes were observed in either the hippocampus, or in anterior portions of the parahippocampal gyrus (maximum $t = 2.6$), a finding that is consistent with the preserved pattern of performance observed in patients with hippocampal removals (Smith & Milner, 1989). Bilateral activation was observed more caudally, however, in the anterior fusiform gyrus, just lateral to the collateral sulcus. This region of the occipitotemporal cortex constitutes part of the ventral visual pathway or "ventral stream" that is assumed to subserve the perception of object identity (Ungerleider & Mishkin, 1982; Desimone & Ungerleider, 1989). Significant increases in blood flow have been observed in this area previously during a face-matching task, but not during an analogous location-matching task (Haxby et al., 1994; see also Moscovitch et al., 1995). Thus, it seems likely that in the present study the bilateral increases in blood flow observed in this region reflect the processes of object perception that are implicit in any encoding task of this sort.

In summary, these findings suggest that the human right parahippocampal gyrus is critical for maintaining and retrieving associations between objects and their locations, but less important for the initial encoding of

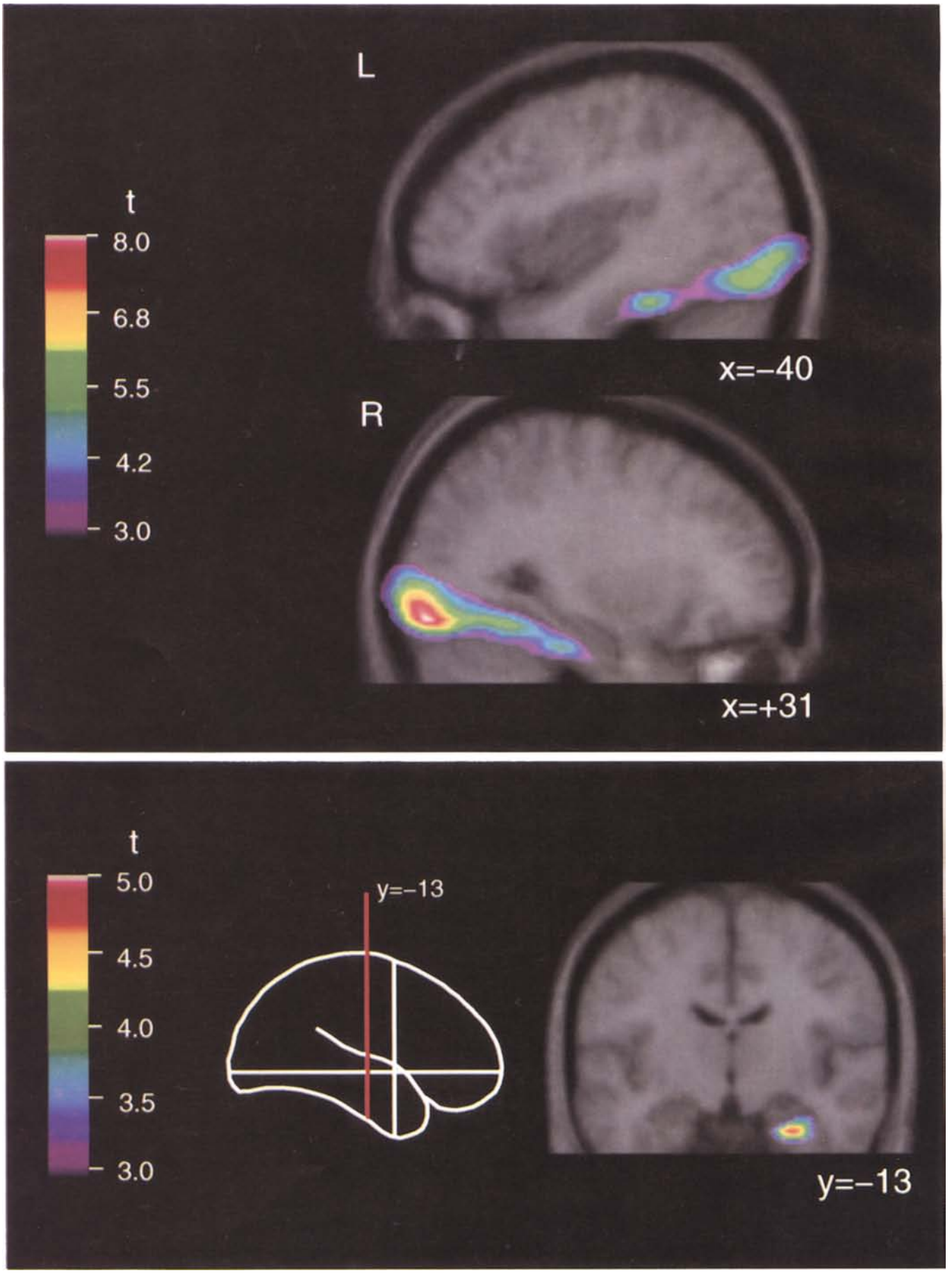
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Table 3. Stereotaxic Coordinates of Activation when *Encoding Object-Location* Was Compared with *Retrieving Object-Location.*

Encoding Object-Location minus Retrieving Object-Location				
	Stereotaxic coordinates			
Region	*X*	*Y*	*Z*	*t-statistic*
Left Hemisphere				
Mid-dorsolateral frontal cortex (area 46)	−38	48	29	3.60
Orbito-frontal cortex (area 11)	−36	44	−15	3.79
Ventrolateral frontal cortex (area 45/47)	−47	24	0	3.84
Inferior temporal gyrus ant. (area 20)	−48	−30	−24	4.60
Inferior temporal gyrus post. (area 37)	−51	−52	−11	4.41
Posterior parietal cortex (area 40)	−59	−37	38	3.50
Right Hemisphere				
No significant peaks				
Retrieving Object-Location minus Encoding Object-Location				
Left Hemisphere				
No significant peaks				
Right Hemisphere				
Medial frontal cortex (area 9)	5	48	27	3.08
Orbito-frontal cortex (area 11)	36	29	−20	4.31
Ventromedial frontal cortex (area 47/11)	24	24	−5	3.06
Posterior cingulate cortex (area 31)	11	−59	26	3.84
Striate cortex (area 17)	1	−70	3	5.86
Prestriate cortex (area 18)	1	−85	−6	3.87

this information. It is important to acknowledge that, given the subtraction method employed, these results do not conflict with the notion that the hippocampal region is also critically involved in spatial memory per se. Patients with right temporal-lobe lesions that include radical removal of the hippocampus are impaired on tests that require the recall of simple spatial position (Corsi, 1972; Rains & Milner, 1994), on spatial tests that assess learning over multiple trials (Corkin, 1965; Milner, 1965), and on the incidental learning of supraspan spatial sequences (Corsi, 1972; Milner, 1978). Similarly, rats with damage to the hippocampus and related structures are impaired on a variety of tasks involving spatial memory (Aggleton et al., 1986; Olton & Papas, 1979; Olton et al., 1978; Rawlins & Olton, 1982; Rawlins & Tsaltas, 1983; Sziklas & Petrides, 1993). In the present study, all four scanning conditions involved memory for spatial information, the neural correlates of which may have been "subtracted out," leaving only those changes in blood flow specifically related to memory for the location of objects. The results of the present study also do not conflict, of course, with the suggestion that the hippocampal region is critically involved in other aspects of memory not directly investigated here (Cave & Squire, 1991; Schacter et al., 1996).

Figure 3. The averaged PET subtraction images are shown superimposed upon the corresponding averaged MRI scan. Subtraction of one condition from another yielded the focal changes in blood flow shown as a *t*-statistic image, whose range is coded by the color scale placed to the left of each figure. In this and subsequent figures, the left hemisphere is on the left of the image, and the right hemisphere is on the right of the image. (**a**) *Encoding Object-Location* minus *Encoding Location:* The sagittal sections at coordinates x = −40 and x = 31 illustrate the significant rCBF increases observed in the left and right anterior fusiform gyri respectively (see Table 1). Significant bilateral changes are also visible on this image, more posteriorly, in prestriate cortex. (**b**) *Retrieving Object-Location* minus *Retrieving Location:* The coronal section, at coordinate y = −13 illustrates the significant rCBF increase observed in the right anterior parahippocampal gyrus in the region corresponding to the entorhinal cortex (see Table 2).

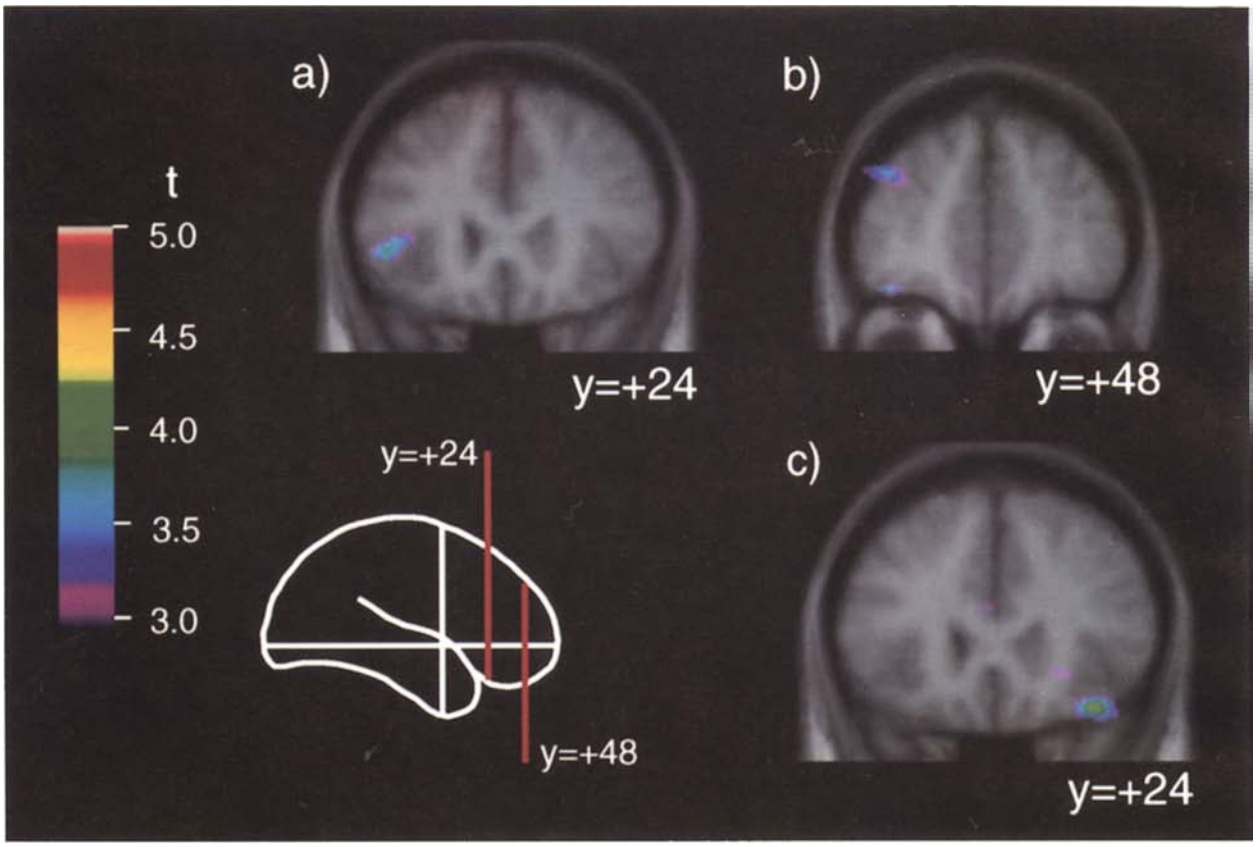

Figure 4. *Encoding Object-Location* minus *Retrieving Object-Location* (see Table 3): The coronal sections at coordinates y = +24 and y = +48 illustrate the significant rCBF increases observed in (**a**) left ventrolateral frontal cortex and (**b**) left mid-dorsolateral and orbitofrontal cortex. *Retrieving Object-Location* minus *Encoding Object-Location:* The coronal section at coordinate y = +24 illustrates the significant rCBF increase observed in (**c**) right orbitofrontal cortex.

The frontal cortex has also been implicated in spatial memory, although usually in tasks that involved shorter delays than those used in this study (Funahashi et al., 1989, 1990; Goldman-Rakic, 1990; Jonides et al., 1993; Owen et al., 1990; Owen, Morris et al., 1996; Owen, Evans et al., 1996). For example, patients with frontal-lobe excisions are impaired on a spatial-location memory task, similar to the one used here, when recall is tested 25 sec after encoding (Owen et al., 1995). Therefore, it is interesting that, in the present study, subtraction of the Object-Location memory conditions from the corresponding Location memory conditions yielded significant activation foci in both dorso and ventral regions of the right frontal cortex, during both encoding and retrieval. Similar changes in blood flow have been reported recently during spatial search tasks that required subjects to monitor and manipulate stimuli within working memory (Owen et al., 1996). The present findings argue that memory for spatial location, in the absence of relevant cues about object identity or figural detail, requires encoding and retrieval strategies that preferentially involve the frontal cortex, even after delays of several minutes.

Functional Lateralization of Encoding and Recall

In addition to the main questions addressed above, the design of the current study allowed direct comparisons to be made between the encoding and retrieval conditions. It has recently been proposed that, for verbal material at least, left frontal regions are preferentially involved in encoding information, while right frontal regions are involved in retrieval of that information (Tulving et al., 1994; Shallice et al., 1994). When activation in the *Retrieving Object-Location* condition was subtracted from activation in the *Encoding Object-Location* condition, significant changes in rCBF were only observed in the left hemisphere. In contrast, the reverse subtraction (retrieval minus encoding) yielded significant foci in the right hemisphere only. Although it is possible to interpret these findings in terms of the proposed hemispheric asymmetry in encoding and retrieval, there may be a more parsimonious explanation based on differences in the two conditions used. For example, to encode object-location, subjects almost certainly use internal (i.e., nonvocal) verbal descriptions of each object and its spatial location, as well as information about the

Table 4. Stereotaxic Coordinates of Activation when *Encoding Spatial Location* Was Compared with *Retrieving Spatial Location.*

Encoding Location minus Retrieving Location				
	Stereotaxic coordinates			
Region	*X*	*Y*	*Z*	*t-statistic*
Left Hemisphere				
Mid-dorsolateral frontal cortex (area 46)	−32	46	23	4.16
Inferior temporal gyrus (area 37)	−66	−44	−3	4.46
Middle temporal gyrus (area 37/21)	−55	−56	6	4.85
Parietal cortex (area 40)	−59	−49	29	3.70
Supramarginal gyrus (area 40)	−60	−57	33	3.90
Posterior cingulate cortex (area 31)	−5	−31	42	5.15
Right Hemisphere				
Mid-dorsolateral frontal cortex (area 9)	38	29	45	3.05
Orbito-frontal cortex (area 11)	20	39	−12	3.20
Superior temporal gyrus (area 22)	51	−2	−8	3.90
Middle temporal gyrus (area 21)	54	−16	−5	3.55
Cerebellum	27	−66	−23	3.66
Retrieving Location minus Encoding Location				
Left Hemisphere				
Striate cortex (area 17)	−13	−68	2	4.06
Prestriate cortex (area 19)	−35	−68	−12	3.82
Right Hemisphere				
Mid-dorsolateral frontal (area 9)	44	25	29	3.20
Ventrolateral frontal (area 45/47)	34	25	0	3.05
Ventrolateral frontal (area 44)	48	17	24	3.38
Medial parietal cortex (area 7)	5	−71	47	4.05
Posterior parietal cortex (area 7)	29	−76	33	4.47
Striate cortex (area 17)	9	−62	20	6.13
Prestriate cortex (area 18)	35	−84	−12	4.26
Medial prestriate cortex (area 18)	5	−85	14	3.87

relationship between the two. These verbally mediated rehearsal strategies are likely to involve left-hemisphere mechanisms (Milner, 1971, 1974). During retrieval, verbal descriptions of object or location are of limited value, because the subjects are required to choose between two drawings of the same familiar object presented in positions that have both been encoded previously. For accurate performance, subjects may rely more heavily on nonverbal representations of the association between object and place that are less likely to involve left-hemisphere regions (Milner, 1971, 1974). On the basis of this reasoning, the apparent lateralization of encoding and retrieval to left and right hemisphere regions would be expected to be less pronounced for location memory than for object-location memory because, in the former condition, each item to be remembered did not differ with respect to its visual features. Accordingly, when activation in the *Encoding Location* condition was com-

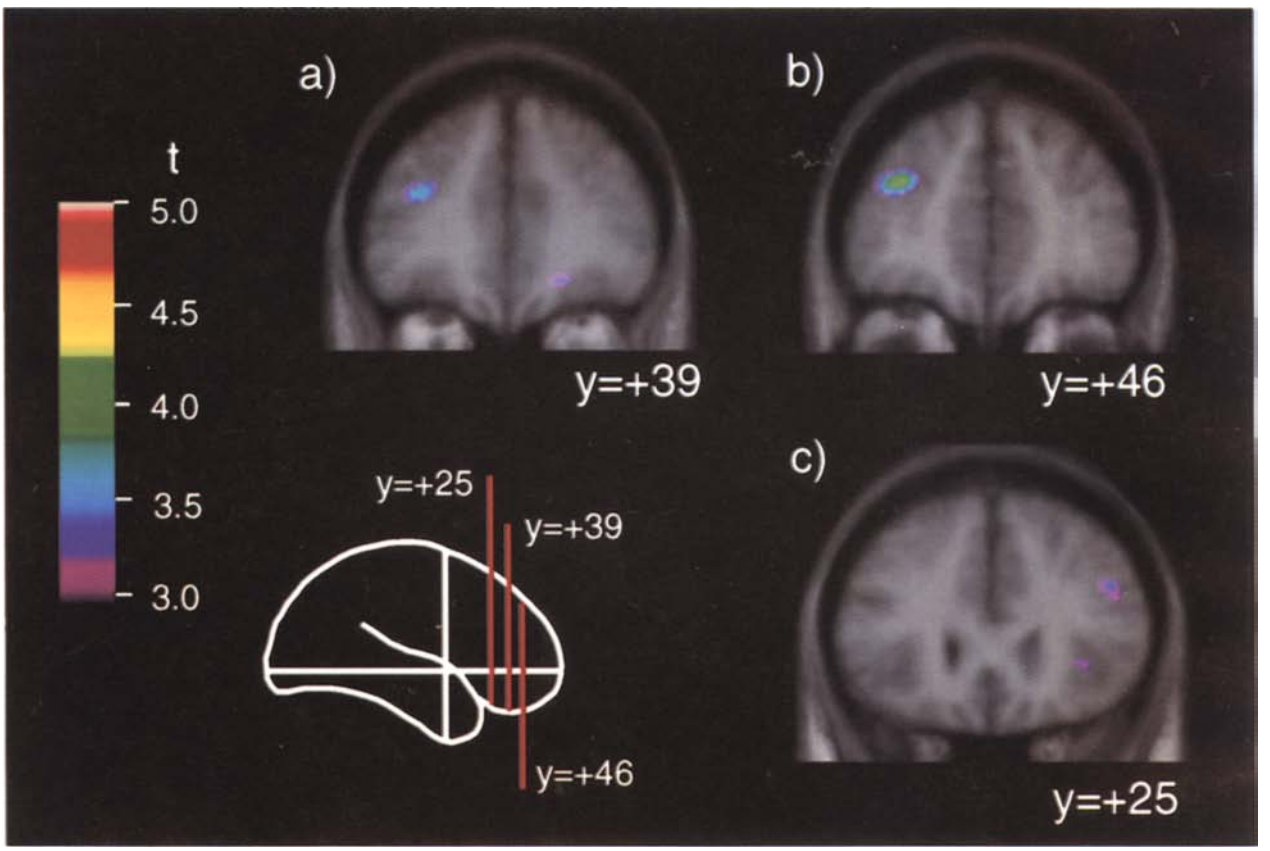

Figure 5. *Encoding Location* minus *Retrieving Location* (see Table 4): The coronal sections at coordinates y = +39 and y = +46 illustrate the significant rCBF increases observed in (**a**) left mid-dorsolateral frontal cortex and right orbitofrontal cortex, (**b**) left mid-dorsolateral frontal cortex. *Retrieving Location* minus *Encoding Location:* The coronal section at coordinate y = +25 illustrates the significant rCBF increase observed in (**c**) right mid-dorsolateral and ventrolateral frontal cortex.

pared to that in the *Retrieving Location* condition the observed asymmetry was far less striking.

MATERIALS AND METHODS

Subjects

Six male and six female right-handed undergraduate volunteers with no history of neurological or psychiatric illness participated in the study. Each subject underwent seven, 60-sec PET scans within a single session and an MRI scan on a different day. Four of the seven scanning conditions administered pertain to the current study and will be described here. The ages of the subjects ranged from 18 to 35 years (mean age 26.8 years). All subjects gave informed, written consent for participation in the study after its nature and possible consequences were explained to them. The study was approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital.

Scanning Methods and Data Analysis

PET scans were obtained with the Scanditronix PC-2048 system, which produces 15 image slices at an intrinsic resolution of 5.0 mm × 5.0 mm × 6.0 mm (Evans et al., 1991a). The relative distribution of regional cerebral blood flow (rCBF) was measured with the bolus $H_2{}^{15}O$ methodology (Raichle et al., 1983), without arterial sampling (Fox & Raichle, 1984). For each subject, a high-resolution magnetic resonance imaging (MRI) study (160 sagittal slices, 1 mm thick) was also obtained from a Philips Gyroscan 1.5T and resliced so as to be coregistered with the PET data (Evans et al., 1991b). An orthogonal coordinate frame was then established, based on the AC-PC line as defined in the MRI volume (Evans et al., 1992). These coordinates were used to resample each pair of MRI and PET data-sets into a standardized stereotaxic coordinate system (Talairach & Tournoux, 1988). To overcome residual anatomical variability persisting after stereotaxic standardization, the PET images were reconstructed with a 20 mm filter and then normalized for

global rCBF value, averaged across subjects for each activation condition. The mean CBF-change image was obtained (Fox et al., 1985) and converted to a *t*-statistic volume by dividing each voxel by the mean standard deviation in normalized rCBF for all intracerebral voxels (Worsley et al., 1992).

Individual MRI images were subjected to the same averaging procedure, such that composite stereotaxic image volumes sampled at approximately 1.5 mm in each dimension were obtained for both *t*-statistic and MRI volumes. Anatomical and functional images were merged to allow direct localization on the MRI images of *t*-statistic peaks identified by an automatic peak-detection algorithm. The significance of a given change in rCBF was assessed by application of an intensity threshold to the *t*-statistic images (Worsley et al., 1992). This threshold, based on 3-D Gaussian random-field theory, predicts the likelihood of obtaining a false positive in an extended 3-D field. For an exploratory search involving all peaks within the grey matter volume of 600 cm^3, the threshold for reporting a peak as significant was set at $t = 3.5$, corresponding to an uncorrected probability of $p < 0.0002$ (one tailed). Correcting for multiple comparisons, a t value of 3.5 yields a false positive rate of only 0.58 in 200 resolution elements (each of which has dimensions 20 × 20 × 7.6 mm, and includes approximately 880 voxels), which approximates the volume of cortex scanned. Thus, when searching over the entire grey matter volume, one would expect one resolution element to be activated by chance, every two searches. We also carried out a directed search for predicted activation foci within the frontal cortex and the hippocampus. For these analyses, the threshold for significance was set at $t = 3.00$, corresponding to an uncorrected probability of $p < 0.0013$.

Experimental Procedure

The stimuli used in all four experimental conditions were white squares (5 cm × 5 cm) presented on a black background, on a high resolution, touch-sensitive screen (39 cm × 29 cm). The screen was suspended approximately 50 cm above the subject, and was therefore within comfortable reach. In two of the conditions, which we refer to as *Encoding Object-Location* and *Retrieving Object-Location,* the white squares contained digitized representational drawings of common objects (brush, cake, glasses, bowl, candle, butterfly, hen, bow). In the other two conditions, which we refer to as *Encoding Location* and *Retrieving Location,* the white squares remained unfilled. For all subjects, the same locations and/or objects were used in each condition, although the order in which the stimuli were presented was randomly varied. The order in which the Location and the Object-Location conditions were administered across scans was also randomized for the different subjects, with the necessary restriction that each of the retrieval tasks was presented during the scan following the corresponding encoding condition. To discourage verbal labeling of spatial location, the four corners of the monitor and any of the positions immediately adjacent to the edge of the screen were not used in any of the conditions. Each PET scan lasted 60 sec and testing on each condition was initiated approximately 10 sec before scanning began. All subjects completed the same fixed number of trials in each condition, the performance lasting for approximately 90 sec in total. Performance data were collected during this 90 sec period.

Successive scans were separated by approximately 10 min during which time the requirements of the task to be administered in the next scanning condition were explained to the subject and practice problems were administered to ensure that the task had been fully understood. In all cases, these practice problems involved objects and/or locations different from those used during the scanning conditions. In addition, the subjects were instructed not to spend too long encoding or recalling any particular stimulus during the scan, because each stimulus would be presented more than once, and to maintain a constant response rate of approximately one touch per second.

Encoding Object-Location

During scanning, eight white squares were presented on the computer screen, one at a time and in different locations (Fig. 1). Each of the squares contained a digitized monochrome image of a different everyday object (representational drawing). Thus, eight different objects were presented in eight different locations on the screen. The subjects were instructed to attend to each object, to remember its location, and then to touch it in order that the next object should be presented. When an object was touched, it disappeared, and, after 1 sec, the next object appeared. The entire set of eight objects was shown four times, the order of presentation being randomized within each block of eight.

Retrieving Object-Location

Eight pairs of white squares were presented on the computer screen, one pair at a time (Fig. 1). Both squares contained an identical image of one of the eight objects presented in the previous *Encoding Object-Location* condition. Of each pair, one of the locations had been occupied by that particular object in the *Encoding Object-Location* condition, and the other location had been occupied by one of the eight objects, but not by the one currently being presented. Thus, the choice could not be made on the basis of location alone, because both of the locations presented had been encoded previously. However, only one of the two locations was correct for that

particular object. The subjects were instructed to decide which of the two locations was correct, and to respond by touching it in order to move on to the next pair. Immediately following a touch, both squares disappeared and, 1 sec later, the next pair was presented. This procedure was followed regardless of whether the location selected was correct or incorrect, and the subjects were given no feedback about their performance during the task. The accuracy of each response was recorded by the computer, and subjects were informed of the results when the entire scanning session was complete. The series of eight pairs was presented four times during the scanning period, the order of presentation being randomized within each block of eight.

Encoding Location

The procedure for this condition was identical to that for the Encoding Object-Location task described above, except that the stimuli used were eight identical white squares that contained no objects. The subjects were required to encode the location of each of these squares, which were presented, one at a time, on the screen (Fig. 2).

Retrieving Location

The procedure for this condition was similar to that of the Retrieving Object-Location condition described above, except that the stimuli to be recalled were the eight locations presented in the Encoding-Location condition. Thus, eight pairs of white squares were presented on the screen, one pair at a time (Fig. 2). Of each pair, one of the locations presented corresponded exactly to one of the eight locations used in the previous Encoding-Location condition and the other location was one that had not been used previously in any practice or experimental condition. The subjects were required to choose which of the two locations had been seen previously, and to respond by touching that square in order to move on to the next pair.

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