Redefining the functional organization of working memory processes within human lateral prefrontal cortex

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Abstract

It is widely held that the frontal cortex plays a critical part in certain aspects of spatial and non-spatial working memory. One unresolved issue is whether there are functionally distinct subdivisions of the lateral frontal cortex that subserve different aspects of working memory. The present study used positron emission tomography (PET) to demonstrate that working memory processes within the human mid-dorsolateral and mid-ventrolateral frontal regions are organized according to the type of processing required rather than according to the nature (i.e. spatial or non-spatial), of the information being processed, as has been widely assumed. Two spatial working memory tasks were used which varied in the extent to which they required different executive processes. During a 'spatial span' task that required the subject to hold a sequence of five previously remembered locations in working memory a significant change in blood-flow was observed in the right mid-ventrolateral frontal cortex, but not in the anatomically and cytoarchitectonically distinct mid-dorsolateral frontal-lobe region. By contrast, during a '2-back' task that required the subject to continually update and manipulate an ongoing sequence of locations within working memory, significant blood flow increases were observed in both mid-ventrolateral and mid-dorsolateral frontal regions. When the two working memory tasks were compared directly, the one that emphasized manipulation of information within working memory yielded significantly greater activity in the right mid-dorsolateral frontal cortex only. This dissociation provides unambiguous evidence that the mid-dorsolateral and mid-ventrolateral frontal cortical areas make distinct functional contributions to spatial working memory and corresponds with a fractionation of working memory processes in psychological terms.

Introduction

The concept of 'working memory' has replaced that of a passive short-term memory store, incorporating within a single model, a system for temporary storage and a mechanism for the 'on-line' manipulation of stored information that occurs during a wide variety of cognitive activities (Baddeley, 1986). In recent years, evidence has accumulated from the study of patients with excisions of frontal cortex, from lesion and electrophysiological recording work in non-human primates (for reviews see Goldman-Rakic, 1994; Petrides, 1994), and from functional neuroimaging studies in humans, to suggest that the lateral frontal cortex plays a critical part in certain aspects of working memory for both spatial and non-spatial material (e.g. Petrides & Milner, 1982; Funahashi *et al.*, 1989, 1990; Owen *et al.*, 1990, 1995, 1996a,b,c; Jonides *et al.*, 1993; Petrides *et al.*, 1993a,b; Wilson *et al.*, 1993; Cohen *et al.*, 1994, 1997; McCarthy *et al.*, 1994; Smith *et al.*, 1995, 1996; Courtney *et al.*, 1996, 1997; Gold *et al.*, 1996; Goldberg *et al.*, 1996; Sweeney *et al.*, 1996; Rao *et al.*, 1997; for reviews see Owen, 1997a; Rushworth *et al.*, 1997; Rushworth & Owen, 1998). One issue, which has recently provoked considerable discussion in the neuropsychological literature, is whether there are functionally distinct subdivisions of the lateral frontal cortex that subserve different aspects of working memory. Two divergent positions have emerged which, while focusing on a broadly similar anatomical distinction between the dorsolateral and the ventrolateral prefrontal cortical regions, differ fundamentally in terms of the precise functions ascribed to those regions. One prevalent view is that working memory processes are organized according to the type (e.g. domain) of information being processed, with dorsolateral frontal regions being concerned principally with memory for spatial material, while ventrolateral frontal regions subserve memory for non-spatial material (Goldman-Rakic, 1987, 1994, 1995; see also Courtney *et al.*, 1996, 1997, 1998; see Fig. 1). An alternative 'process specific' view is that a functional distinction can be drawn between the mid-dorsolateral and mid-ventrolateral prefrontal cortical regions, based on the type or nature of the processes that are carried out by those regions (Petrides, 1994, 1995a; see also Owen, 1997a,b). According to this general theoretical framework the mid-ventrolateral prefrontal cortex is concerned principally with the active organization of sequences of responses based on conscious, explicit retrieval of information from posterior association systems, while the mid-dorsolateral frontal cortex is recruited when active manipulation or 'monitoring' of such information is required within working memory.
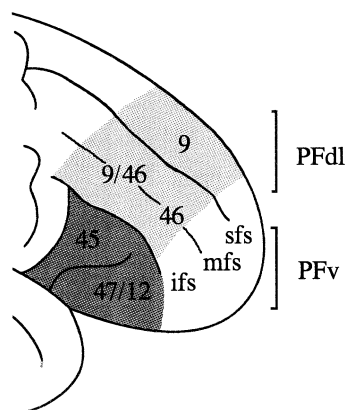
FIG. 1. Schematic drawing of the lateral surface of the human frontal lobe indicating the location of the mid-dorsolateral prefrontal cortex (areas 9 and 9/46), and the mid-ventrolateral prefrontal cortex (areas 45, 47/12). Adapted from Petrides & Pandya (1994). Ifs, inferior frontal sulcus; mfs, middle frontal sulcus; sfs, superior frontal sulcus; PFdl, dorsolateral cortex (light grey); PFv, ventrolateral prefrontal cortex (dark grey).

One central requirement of the 'process specific' model of lateral prefrontal organization (Petrides, 1994, 1995a), is that, within a given domain (i.e. spatial or non-spatial), the mid-dorsolateral and mid-ventrolateral prefrontal cortical regions can be shown to play distinct functional roles in working memory. In one recent study using PET, Owen *et al.* (1996c) demonstrated that either, or both, of these two lateral prefrontal regions can be activated in the right hemisphere during different spatial working memory tasks. Thus, during one task, modelled on the spatial block tapping test (or 'spatial span') of Corsi (see Milner, 1971), a significant increase in regional cerebral blood flow (rCBF) was observed in mid-ventrolateral area 47 of the right hemisphere. Similarly, in a second task that required the subjects to execute a fixed sequence of responses to eight previously learned locations, mid-ventrolateral area 47 was significantly activated bilaterally. During both tasks, however, rCBF changes within the dorsolateral frontal region did not approach significance. Ventrolateral frontal activation foci, at very similar stereotaxic coordinates, have been reported previously during other tasks assumed to require spatial working memory (e.g. Jonides *et al.*, 1993; Smith *et al.*, 1995, 1996). As in those studies, the emphasis of the two tasks described above (Owen *et al.*, 1996c) was on the active retrieval of information from spatial working memory; no manipulation of this information was necessary. In two further tasks used in that same study, the subjects were required to remember which of a set of previously selected locations had been 'marked' with a blue circle and to avoid re-selecting those particular locations. Thus, success depended on the ability to maintain and continually update an on-line record of which particular locations had been 'marked' and which had not. During both tasks, highly significant activation foci were observed in the mid-dorsolateral prefrontal cortex (area 9/46) of the right hemisphere, as well as bilaterally in mid-ventrolateral area 47.

The results of this earlier study clearly indicate that, in human subjects, both mid-dorsolateral and mid-ventrolateral prefrontal regions can be activated during spatial working memory tasks. Two recent independent meta-analyses of the functional neuroimaging literature support this view and have demonstrated that the dorsal and/or ventral prefrontal regions may be independently, or jointly, activated by a wide variety of different tasks assumed to require spatial working memory (Owen, 1997a,b; Rushworth *et al.*, 1997). Moreover, it seems likely that whether one or both of these regions is recruited depends upon the precise cognitive processes that are called upon by the particular task being performed. Unfortunately, however, procedural and methodological variations, both within and between different studies, preclude any formal interpretation of the results in these terms (for discussion, see Owen, 1997a).

In this study, we attempted to extend these preliminary observations by defining, more precisely, the particular executive processes required to activate either the mid-dorsolateral frontal cortex or the mid-ventrolateral frontal cortex. Accordingly, the requirements of a single spatial working memory task were varied in order to emphasize those executive processes which are assumed to depend upon each of these two lateral frontal regions (Petrides, 1994, 1995a; Owen *et al.*, 1996c) within one group of subjects. The first experimental task, which was similar in design to one of those used by Owen *et al.* (1996c), required the subject to hold a sequence of five previously presented spatial locations in memory, and then to respond directly by touching those same locations following a short delay. As the emphasis of this spatial working memory task was on the active (i.e. conscious) retrieval of remembered information and not on the manipulation of that information, we predicted that, as in the previous study, the mid-ventrolateral, but not the mid-dorsolateral prefrontal cortex would be activated. The second experimental task was entirely novel and required that subjects continuously monitor a sequence of 'highlighted' locations on the screen, responding after each stimulus by touching the location that was highlighted two steps earlier in the sequence. As, like the spatial span task, this task involved the continuous retrieval of spatial information from working memory, we predicted the mid-ventrolateral prefrontal cortex would be similarly activated during the two conditions. In addition, however, the spatial manipulation task places significant demands on the 'on-line' manipulation of that information with every new stimulus presented, and therefore, we expected to observe additional activation in the mid-dorsolateral prefrontal region.

Materials and methods

Image acquisition and data analysis

PET scans were obtained with the General Electrics Advance system, which produces 35 image slices at an intrinsic resolution of $\approx 4.0 \times 5.0 \times 4.5$ mm. Using the bolus $H_2^{15}O$ methodology, rCBF was measured during four separate scans for each of the three experimental and control conditions (total = 12 scans). For each scan, subjects received a 20 s intravenous bolus of $H_2^{15}O$ through a forearm cannula at a concentration of 300 Mbq/mL and a flow rate of 10 mL/min. 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 12 PET scans were realigned using the first scan as a reference, normalized for global CBF value and averaged across the five subjects for each activation state. The images were then smoothed using an isotropic Gaussian kernel at 16 mm. Finally, a simple ANCOVA (analysis of covariance) model was fitted to the data at each voxel, as implemented by the method of Statistical Parametric Mapping (SPM 96, provided by the Wellcome Department of Cognitive Neurology, London, UK), with a condition effect for each of the conditions, using global CBF as a confounding covariate. For each subject, a 3D MRI volume ($256 \times 256 \times 128$ pixels, 3 mm thick) was acquired and re-sliced so as to be co-registered with the PET data. Composite stereotaxic MRI and PET volumes were merged to allow direct anatomical localization of regions with statistically significant rCBF change between conditions.

The significance of a given rCBF difference was assessed by application of an intensity threshold to the SPM images (Worsley
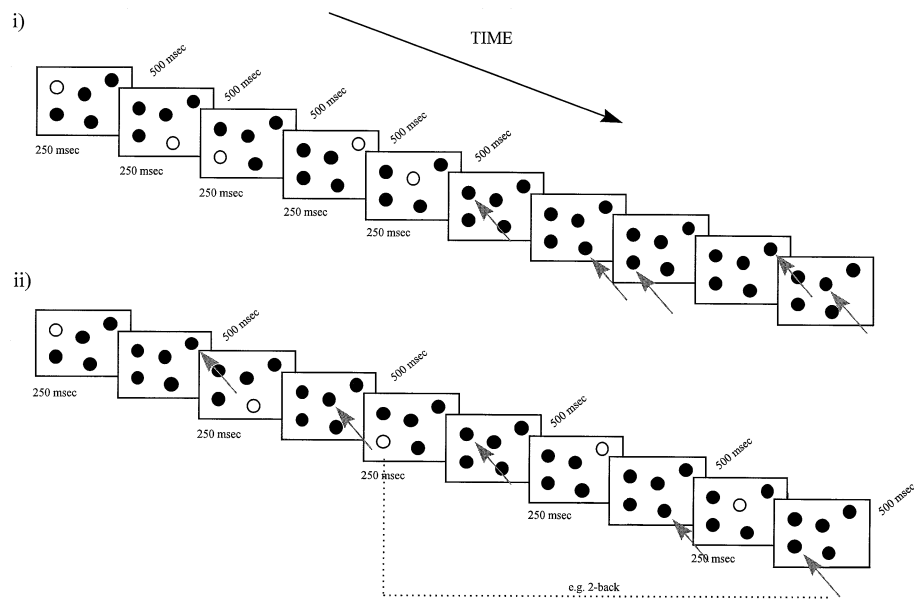
i)

TIME

ii)

FIG. 2. Schematic representation of the two working memory tasks. In the spatial span task (i) subjects remembered and then reproduced sequences of five colour-changing circles. In the spatial manipulation task (ii) subjects responded after each colour-changing circle by touching the circle that changed two steps earlier in the sequence. Grey arrows indicate correct responses by the subjects.

et al., 1992, 1996). This threshold, based on 3-D Gaussian random field theory, predicts the likelihood of obtaining a false positive in an extended 3-D field.

This study was designed to test two anatomically specific hypotheses based directly on previous literature (Rushworth *et al.*, 1997; Owen *et al.*, 1996b, c; Owen, 1997a,b); that is, that during the spatial span task, significant activation would be observed in the right mid-ventrolateral, but not in the mid-dorsolateral prefrontal cortex, while, in the spatial manipulation task, both regions would be significantly activated. Accordingly, two directed searches were conducted for activation foci located within these frontal regions. Two conservative search volumes were defined a priori based on the spread of activation foci that have been reported within the right ventrolateral prefrontal region (stereotaxic coordinates $x = +26$ to $x = +50$, $y = +16$ to $y = +24$ and $z = -9$ to $z = 8$), and within the right dorsolateral prefrontal region (coordinates $x = +28$ to $x = +39$, $y = +26$ to $y = +44$ and $z = +12$ to $z = +36$), in previous functional neuroimaging studies of working memory (for details, see Owen, 1997a). Within these defined regions, the corrected *P*-values for all activation foci observed were calculated according to the formula provided by Worsley and colleagues (Worsley *et al.*, 1992, 1996):

$$\frac{R}{4\pi^2} \times (4 \log_e 2)^{1.5} \times (t^2 - 1) \times e^{-t^2/2}$$

The coordinates chosen for the analysis described above were intentionally broad in order to take full account of the wealth of spatial working memory data that have been produced by different research groups working with functional neuroimaging techniques.

For the rest of the brain, an exploratory search involving all peaks within the grey matter (volume 600 cm^3) was conducted and the threshold for reporting a peak as significant was set at $P < 0.001$, corrected for multiple comparisons.

Subjects

Five normal right-handed volunteers, all males, participated in the study (age range = 44–55). Each subject underwent 12 PET scans and one MRI scan within a single session. All subjects gave informed, written consent for participation in the study after its nature and

possible consequences had been explained to them. The study was approved by the Local Research and Ethics Committee.

Stimuli and testing conditions

The stimuli used in all three conditions of this study were coloured circles (1 cm in radius) presented, on a black background, on a high-resolution, touch sensitive screen. The screen was suspended ≈ 50 cm above the subject and was therefore within comfortable reach. Each of the three conditions was performed four times, making 12 scans in all. During each scan, the spatial positions of all of the stimuli presented were fully randomized within 80 possible screen locations. In addition, the order in which the three conditions were administered was randomly arranged across subjects with the restriction that no two subjects performed all the tasks in the same order. Each PET scan lasted 90 s and testing on the task was initiated 15 s before scanning began. Performance data were collected during this entire period. The scans were separated by 8 min, during which time the requirements of the next task to be performed were explained to the subject. Prior to the first scan, all subjects were fully trained on all three of the tasks to at least 80% proficiency. During this period they were also instructed to maintain a constant response rate of approximately one touch per second during each of the tasks and practice trials were given to ensure that this was the case. This provision ensured that all subjects completed the same number of trials, viewed the same number of stimuli, and made the same number of responses during each of the 12 scans.

There were two experimental conditions and one control condition in this study. The three tasks involved identical visual stimuli and required an identical number of similar responses (see Fig. 2). In the first experimental task ('spatial span'), five red circles were presented in random locations on the touch-sensitive screen. One of these red circles then turned blue, for 250 ms, before returning to red. Following a 500 ms delay, another circle turned blue and so on until all five of the stimuli had changed colour in this way. Immediately following the presentation of the fifth stimulus, the subjects were required to touch each of these five 'target' locations in the correct order before the next trial began (see Fig. 2). The other experimental working memory task ('spatial manipulation') required that subjects continuously monitor a sequence of colour changing circles on the screen,

TABLE 1. Regions exhibiting significant task-related activity. Activation foci in this table represent peaks of statistically significant changes in normalized rCBF. The stereotaxic coordinates (expressed in mm), were generated by SPM96. 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). The corrected P-value was obtained using the formula provided by Worsley *et al.* (1992, 1996)

Region	Stereotaxic coordinates				
	x	y	z	Z-statistic	P-value (corrected)
Spatial span minus visuomotor control					
Right hemisphere					
Mid-ventrolateral frontal cortex (area 47)	28	18	–4	3.03	0.0319
Premotor cortex (area 6/8)	34	–2	48	4.78	0.0046
Posterior parietal cortex (area 7)	22	–62	52	7.15	7.9×10^{-9}
Spatial manipulation minus visuomotor control					
Right hemisphere					
Mid-dorsolateral frontal cortex (area 9/46)	34	34	24	3.48	0.0102
Mid-ventrolateral frontal cortex (area 47)	38	14	0	4.54	1.62×10^{-4}
Premotor cortex (area 6/8)	32	0	48	5.08	0.0012
Posterior parietal cortex (area 7)	22	–64	52	6.88	4.44×10^{-8}
Spatial manipulation minus spatial span					
Right hemisphere					
Mid-dorsolateral frontal cortex (area 46)	38	42	20	3.03	0.0379
Mid-dorsolateral frontal cortex (area 46)	32	36	24	2.90	0.05

NB, No left hemisphere peaks reached corrected significance.

responding immediately after each stimulus by selecting the circle that changed colour two steps earlier in the sequence. Thus, on each 'trial' of the ongoing sequence, one of the five red circles was randomly selected by the computer and momentarily (250 ms) changed colour to blue and then back again to red, indicating that it was the next in the series to be remembered (see Fig. 2). The subject responded immediately not by touching the circle just indicated, but by touching the one two steps earlier in the sequence (i.e. *n*-2 or 'two-back'). Following a 500 ms delay, the next circle in the sequence changed colour and so on for the entire period of the scan. In the matched visuomotor control condition five red circles were again presented in random locations on the screen. On each trial, one of the red circles changed colour to blue and the subject responded immediately by touching that circle. Following a 500 ms delay, another circle turned blue and so on for the duration of the scan. The visuomotor control task provided a baseline against which to examine the extent of activation within the lateral frontal cortex in the two experimental conditions.

Pilot testing revealed that, in order to equate the two working memory tasks for level of difficulty, the parameters should be set to a sequence of five stimuli for the spatial span task and '*n*-2' for the spatial manipulation task This provision also ensured that the time between the presentation of a stimulus and the subjects' response *to that stimulus* (e.g. the actual memory time) was identical for the two tasks (see Fig. 2). Moreover, this experimental design ensured that the amount of information that had to be remembered and retrieved during the scan was equivalent for the two working memory tasks. For example, during one 'trial' of the span task, the subject was required to retrieve five items from memory. During the same time frame five 'trials' would have been completed in the spatial manipulation task, requiring the retrieval of five items from memory. Thus, these settings also ensured that the subjects were exposed to the same number of stimuli and made the same number of responses during the scan.

Results

The spatial span and spatial manipulation conditions were well matched for task difficulty with subjects scoring 88% and 92%

correct, respectively. When the spatial span task was compared with the visual motor control condition, a significant increase in cerebral blood flow was observed in area 47 of the right mid-ventrolateral prefrontal cortex (Table 1 and Fig. 3). These data are shown graphically in Fig. 4. The stereotaxic coordinates of this rCBF change ($x = 28$, $y = 18$, $z = -4$), are remarkably consistent with those reported previously ($x = 36$, $y = 20$, -5), during an almost identical version of the same task (Owen *et al.*, 1996c). In both the earlier and the current investigations, no significant blood flow changes were observed in the mid-dorsolateral prefrontal region during the spatial span task (see Figs 3 and 4). In fact, in the present study, the highest peak rCBF change within this region, identified relative to the inferior and superior frontal sulci, was $z = 1.2$ ($x = 40$, $y = 28$, $z = 28$, $P = 0.88$). Other significant rCBF changes during this task were observed in the right premotor region (area 6; see Table 1), and in the right posterior parietal cortex (area 7), findings which are entirely consistent with the results of previous functional neuroimaging studies of spatial working memory (e.g. Owen *et al.*, 1996c).

When the spatial manipulation task was compared with the control condition, significant rCBF increases were observed in area 47 of the right mid-ventrolateral prefrontal cortex and, in addition, in the mid-dorsolateral prefrontal region (area 9/46) of the same hemisphere (Table 1 and Fig. 3). These data are shown graphically in Fig. 4. An additional change in rCBF was observed slightly more dorsally within area 9 of the right mid-dorsolateral frontal cortex at coordinates $x = 36$, $y = 20$, $z = 40$ (Fig. 3). However, as this region falls just outside our search volume (defined a priori on the basis of previous imaging studies of spatial working memory), it failed to reach statistical significance (z-score = 3.24, $P \approx 1$). Elsewhere in the cortex, the peaks of activation observed were very similar to those seen in the previous subtraction (see Fig. 3), namely in the right premotor region (area 6), and in the right posterior parietal cortex (area 7). Again, these latter findings concur fully with those of previous studies (for reviews, see Owen, 1997a; Rushworth *et al.*, 1997).

In summary, as can be seen from Fig. 4, relative to the control task, significant rCBF changes in the right mid-dorsolateral frontal cortex were only observed during the spatial manipulation task, while significant changes were observed in the right mid-ventrolateral
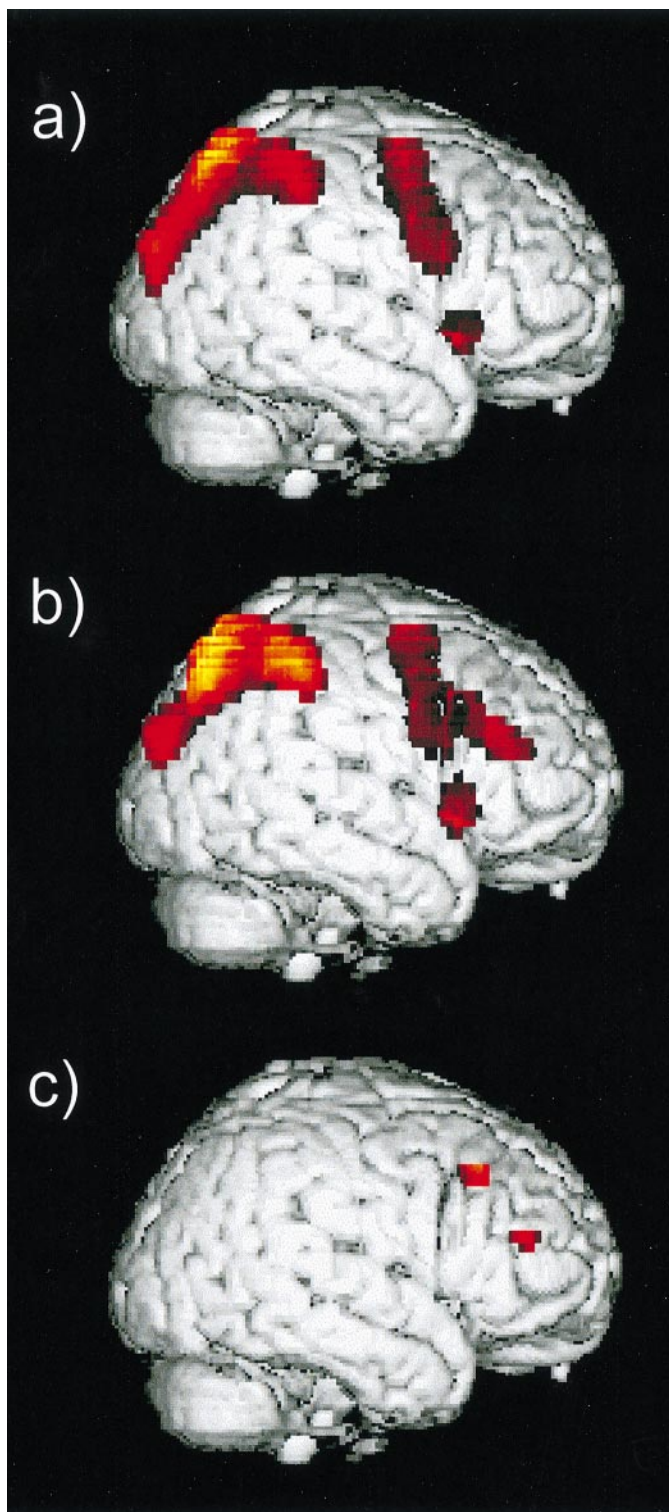
FIG. 3. Schematic illustration of the averaged PET subtraction images rendered on to the surface of a standard 3-D MRI. (a) Spatial span minus visuomotor control. Within the prefrontal cortex a significant rCBF change is evident within mid-ventrolateral area 47. (b) Spatial manipulation minus visuomotor control. Within the prefrontal cortex significant rCBF changes are evident within mid-ventrolateral area 47 and, in addition, within mid-dorsolateral areas 9 and 9/46). (c) Spatial manipulation minus spatial span. The two working memory conditions differ only with respect to rCBF changes in the mid-dorsolateral frontal cortex (areas 9 and 9/46).

prefrontal cortex during both of the spatial working memory conditions, thereby confirming both a priori hypotheses.

A final comparison was made between the two working memory conditions to confirm, more directly, that the additional requirements of the spatial manipulation task were responsible for the significantly increased activity in the mid-dorsolateral prefrontal cortex, rather than a more general aspect of spatial working memory processing which would be expected to produce similar activity patterns in both tasks (and would therefore be subtracted out when the two conditions were compared directly). This subtraction is also important theoretically because the two experimental tasks were more closely matched with respect to a number of task parameters than either task with the visuomotor control. For example, while the visuomotor control task involved an externally prompted response (a circle changed colour), both memory tasks required that the subject made internally generated responses on the basis of remembered information. Similarly, the two experimental tasks were identical with respect to 'memory time'; that is the time between the presentation of a stimulus to be remembered and the response to that stimulus (see Fig. 2). When rCBF in the spatial span task was subtracted from that in the spatial manipulation task only three peaks emerged in the entire cortical volume. (Table 1 and Fig. 3). Two of these peaks were located within the right mid-dorsolateral prefrontal cortex (area 46) at coordinates very similar to those of the peak observed within area 9/46 in the comparison between the spatial manipulation task and the visuomotor control task (Table 1). An additional change in rCBF was observed slightly more dorsally within area 9 of the right mid-dorsolateral frontal cortex at coordinates $x = 34$, $y = 24$, $z = 40$. However, like the similar peak observed in the comparison between the spatial manipulation task and the visuomotor control task, this region falls just outside our conservative search volume and consequently, failed to reach statistical significance (z-score $= 3.39$, $P \approx 0.7$). When rCBF in the spatial manipulation task was subtracted from that in the spatial span task no significant rCBF changes were observed within the entire grey matter volume.

Discussion

The results presented here provide the first unambiguous evidence for a two-stage model of spatial working memory processing within the human lateral prefrontal cortex (Petrides, 1994, 1995a). Thus, during one variant of a general spatial working memory paradigm, which simply required active (i.e. conscious) retrieval and reproduction of stored information, a significant rCBF increase was observed in the mid-ventrolateral prefrontal cortex. In contrast, both the mid-ventrolateral and the mid-dorsolateral prefrontal regions were significantly activated during a variant of the task which required 'on-line' manipulation of information within working memory. It should be emphasized that the two putative levels of mnemonic processing described here are certainly intimately related and likely to be involved simultaneously, but to varying degrees, in many working memory tasks.

Previous functional imaging studies of spatial working memory have yielded inconsistent activation foci within the prefrontal cortex. For example, several studies have reported activation in ventrolateral area 47 (Jonides *et al*., 1993; Owen *et al*., 1996c; Smith *et al*., 1995, 1996), while in others activation in mid-dorsolateral areas 9 and 46 has been observed (e.g. McCarthy *et al*., 1994, 1996; Baker *et al*., 1996; Goldberg *et al*., 1996; Owen *et al*., 1996c; Smith *et al*., 1996; for reviews, see Owen, 1997a; Rushworth *et al*., 1997). In the light of the findings of the present study, these apparently conflicting results can be reconciled. Thus, in general, the tasks that have

i) Mid-ventrolateral prefrontal cortex (area 47)
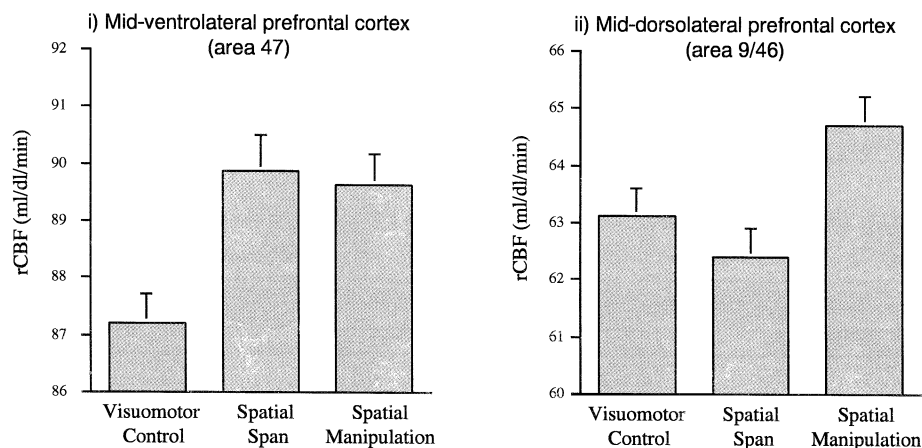
ii) Mid-dorsolateral prefrontal cortex (area 9/46)

FIG. 4. A graphic representation of cerebral blood flow equivalents across the three tasks with (i) the mid-ventrolateral cortex ($x, y, z = 28, 18, -4$) and (ii) the mid-dorsolateral frontal cortex ($x, y, z = 32, 36, 24$).

produced activation foci in mid-ventrolateral area 47 tend to emphasize the active retrieval of one, or a few, pieces of information and the sequencing of responses based directly on that stored information. For example, in the tasks used in the working memory studies by Jonides and colleagues (Jonides *et al.*, 1993; Smith *et al.*, 1995, 1996), the subjects were required to remember the location of three simultaneously presented stimuli and then to decide whether or not a probe circle occupied one of those same three locations following a 3 s delay. These requirements are very similar to those of the spatial span tasks used in the current study and in the previous investigation by Owen *et al.* (1996c) and, accordingly, remarkably similar activation foci were observed within the mid-ventrolateral prefrontal cortex in all three studies [stereotaxic coordinates (x, y, z) = 35, 19, –2 (Jonides *et al.*, 1993); 36, 20, –5; (Owen *et al.*, 1996c); 28, 18, –4 (current study)].

In contrast, the tasks producing increases in rCBF more dorsally, in areas 9 and 46, generally require the subject to 'monitor' or 'manipulate' an on-going series of spatial locations within working memory, and to make comparisons between each new stimulus and stimuli presented earlier in the sequence (e.g. McCarthy *et al.*, 1994, 1996; Owen *et al.*, 1996c; Smith *et al.*, 1996; for further description, see Owen, 1997a). For example, McCarthy *et al.* (1994, 1996), used functional MRI to measure changes in rCBF while subjects judged whether each of a series of 14 or 15 stimuli was located in a position that had already been occupied earlier in the sequence. The key feature of such tasks appears to be that the response required following each stimulus is invariably not specified directly by that stimulus, but rather, has to be computed by comparing that stimulus with information assimilated earlier in the trial (e.g. from previous stimuli). One notable exception to this general pattern is a study by Baker *et al.* (1996), in which dorsolateral activation foci were reported during a task that required the subject to remember a single spatial location during the scan. One possible explanation for this apparent anomaly is that these foci reflect the use of more complex mnemonic strategies by the subjects in order to maintain the representation during the unusually long time delay used (e.g. + 45 s).

The current study focused, specifically, on *spatial* working memory processes. The occurrence of activation foci within the right prefrontal cortex in both experimental conditions is consistent with the known dominant role of the right hemisphere in the processing of spatial information (De Renzi, 1982). However, the results of emerging studies suggest that a similar functional dissociation between the dorsolateral and the ventrolateral frontal cortical regions may be observed when non-spatial (verbal and visual) material is used (Owen *et al.*, 1998; Stern *et al.*, 1998), findings which concur fully with recent meta-analyses of the non-spatial working memory literature (Owen, 1997a; Rushworth *et al.*, 1997).

In a recent study using fMRI, Courtney *et al.* (1998) have shown that sustained activity during a task that required memory for three locations was observed in the caudal most part of the superior frontal sulcus, immediately anterior to the area defined as the frontal eye field on the basis of activity observed during an occulomotor task. According to a recent cytoarchitectonic analysis of this region (Petrides & Pandya, 1994), this peak is located within area 8. [Note that in both the monkey and in the human brain, the physiologically defined frontal eye field does not correspond to area 8 proper, but rather to the border between area 8 and rostral area 6 (Stanton *et al.*, 1989; Paus, 1996).] A peak in the same location has been reported in previous studies of spatial working memory (e.g. Jonides *et al.*, 1993; Owen *et al.*, 1996c), as well as in studies of spatial attention (e.g. Corbetta *et al.*, 1993; Nobre *et al.*, 1997). A similar peak was also observed in the present study when the visuomotor control task was subtracted from either the spatial span task or the spatial manipulation task. However, when the spatial span task was subtracted from the spatial manipulation task, there was no difference in this region, the only surviving rCBF difference being in the more anteriorly located mid-dorsolateral prefrontal cortex. Given these results, it is now clear that activation in the mid-dorsolateral prefrontal cortex is related to the monitoring and manipulation of information within working memory, whereas the peak observed in the posterior dorsolateral cortex (area 8) in this study and in previous studies (e.g. Jonides *et al.*, 1993; Owen *et al.*, 1996c; Courtney *et al.* 1998) is more likely related to the maintenance of visuospatial attention to the cued locations during the delay period of working memory tasks. Such an interpretation would be entirely consistent with the fact that area 8 is anatomically linked to prestriate visual areas (Barbas & Mesulam, 1981). Thus, the mid-ventrolateral, mid-dorsolateral and the posterior dorsolateral prefrontal regions may all be involved in spatial working memory tasks, but for entirely different reasons.

The results of the current study, and those of our earlier investigation (Owen *et al.*, 1996c), are also supported by the findings of a recent paired-associates study of word retrieval (Fletcher *et al.*, 1998). In that study, activation of the mid-ventrolateral frontal cortex was observed in a condition that required subjects to retrieve previously learned category exemplars, in response to a series of category names. As in the spatial span task used in the current study, this paired associates task emphasizes the active (conscious) retrieval of remembered information; no manipulation of that information is required as, in both cases, a direct 'mapping' exists between the response made and the stimulus that signalled that response. In contrast, during

a second condition that required subjects to free recall items from a previously learned list, activation in the mid-dorsolateral frontal cortex was observed (Fletcher *et al.*, 1998). One key component of this task, like other tasks that have activated the mid-dorsolateral frontal region (e.g. McCarthy *et al.*, 1994, 1996; Owen *et al.*, 1996c; Smith *et al.*, 1996; for further description, see Owen, 1997a), is that each response cannot be made in isolation, but rather, can only be made with reference to responses made and information assimilated earlier in the trial. Similar 'monitoring' requirements have been shown to be critical in accounting for the impairment in spatial and non-spatial working memory tasks observed after mid-dorsolateral prefrontal lesions in the monkey (Petrides, 1995b).

By providing direct evidence that the mid-ventrolateral and mid-dorsolateral prefrontal cortical regions play distinct functional roles in working memory, the present results suggest that the nature of stimulus material being processed may not be the decisive factor determining activity differences between these two regions, as previously thought (Courtney *et al.*, 1998; Wilson *et al.*, 1993; Goldman-Rakic, 1995; also see Courtney *et al.*, 1996, 1997). The present study does not rule out the possibility that some functional differentiation based on stimulus material might still exist *within* these particular frontal cortical regions. Nevertheless, it is important to emphasize that even if one were to detect such subtle differences in activation, that would still not be evidence for functional separation between the anatomically and cytoarchitectonically distinct regions under consideration here. Moreover, such a subtle distinction was recently tested in humans using high-resolution functional magnetic resonance imaging and was not confirmed (Owen *et al.*, 1998). This conclusion concurs fully with the results of a recent electrophysiological recording study in the monkey designed to investigate where and how information about object-identity is integrated with information about object-location in working memory (Rao *et al.*, 1997). In that study, approximately half of the neurons with delay-related activity were tuned both to visual pattern ('what') and location ('where'). Furthermore, neurons that were tuned only to location or only to visual pattern were equally distributed between the dorsolateral and the ventrolateral prefrontal cortex, neurons tuned to location not being predominant in the dorsolateral prefrontal cortex (Rao *et al.*, 1997; for further discussion, see Rushworth & Owen, 1998). The present study provides support for the notion that there are two distinct levels of information processing within these two regions of human prefrontal cortex.

Acknowledgements

Abbreviations

MRI, magnetic resonance imaging; PET, positron emission tomography; rCBF, regional cerebral blood flow

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