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The role of spatial configuration in tests of working memory explored with functional neuroimaging

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While the importance of the prefrontal cortex for "higher-order" cognitive functions is largely undisputed, no consensus has been reached regarding the fractionation of functions within this region. Several recent functional neuroimaging studies have suggested that the mid-ventrolateral frontal cortex may play an important role in various aspects of human memory. Thus, similar patterns of activation have been observed in this region during analogous spatial, verbal and visual span tasks. In the present study, however, activation was observed in a more dorsolateral region of the lateral frontal cortex during a modified version of the spatial span task, which differed *only* in the spatial configuration of the array employed. The results of a supplementary behavioral study, designed to investigate this effect further, suggest that in spatial memory tasks certain stimulus configurations may encourage subjects to adopt mnemonic strategies, which may depend upon dorsolateral, rather than ventrolateral, regions of the frontal cortex.

These findings shed further light on the functional relationship between dorsal and ventral regions of the lateral frontal cortex and, more specifically, how the "executive" processes assumed to be dependent upon these regions might contribute to aspects of human memory.

Key words: Frontal lobe, PET, prefrontal cortex, spatial span

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INTRODUCTION

In recent years, the concept of working memory has been described and discussed in various ways although, most commonly, as a cognitive system for both the temporary storage and manipulation of information (e.g., Baddeley, 1986; 1992). Evidence from the study of patients with excisions of frontal cortex (e.g., Petrides & Milner, 1982; Owen *et al*., 1996a), 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 (for review, see Owen, 2000), suggests that the lateral frontal cortex plays a critical role in certain aspects of working memory, although no consensus has been reached regarding the fractionation of functions within this region. Until recently, one prevalent view has been that working memory processes are organised according to the type (e.g., domain) of information being processed, with dorsolateral frontal regions being concerned principally with memory for spatial material, whilst the anatomically and cytoarchitectonically distinct ventrolateral frontal regions subserve memory for non-spatial material (Goldman-Rakic, 1994; 1995; Levy and Goldman-Rakic, 1999). In general, however, neither functional neuroimaging studies in humans (for reviews, see D' Esposito, *et al*., 1998; Owen, 1997; 2000) nor electrophysiological recording studies in the monkey (Rao *et al*., 1997), have provided convincing support for this "domain-specific" model of lateral frontal-lobe function.

An alternative model for understanding the prefrontal cortex and its role in working memory has been proposed by Petrides (1994; 1998). According to that model, basic memory functions, including storage and immediate processing of incoming and recalled information, are carried out, not within the frontal lobes, but rather within sensory specific and multimodal posterior association areas in the parietal and temporal cortices. The frontal lobes receive and act upon this information via i) bi-directional connections between posterior cortical association areas and ventral frontal regions, which, in turn, are closely connected to the mid-dorsolateral frontal cortex and ii) via direct connections between dorsal regions of the frontal cortex and the medial temporal lobe. Thus, according to this view, the ventrolateral frontal cortex constitutes a critical point of contact between posterior cortical regions and the entire lateral frontal cortex. In this capacity, it is assumed to be essentially involved in various low level "executive" processes, such as comparisons between, or judgements about the occurrence or non-occurrence of remembered stimuli and the initiation of explicit (i.e., intentional), retrieval of information from posterior association cortex. In contrast, the mid-dorsolateral frontal cortex is assumed to be recruited only when active manipulation or "monitoring" of information is required within memory (Petrides, 1994).

The ventrolateral frontal cortex and its role in aspects of working memory has been investigated recently in a series of studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). (Owen *et al*., 1996b; 1999; 2000; Stern *et al*., 2000). For example, Owen *et al*. (1996b; 1999) used a variant of the Corsi Block Tapping ("spatial span") task (see Milner, 1971), which

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required subjects to hold sequences of five previously presented spatial locations in memory, and then to respond directly by touching those same locations following a delay. In the two studies, a significant rCBF increase was observed at almost identical co-ordinates within the right ventrolateral frontal cortex (area 47). In a second task that required the subjects to retrieve and execute a previously learned fixed sequence of responses the same ventrolateral frontal region was significantly activated (Owen *et al.*, 1996b).

A direct analogue of the spatial span task has recently been used to examine whether a similar role could be identified for this region of the right ventrolateral frontal cortex in the verbal domain (Owen *et al.*, 2000). During one experimental task, subjects were required to hold a sequence of auditorily presented numbers in memory (e.g., 7, 3, 8, 2, 9), and then to respond by (verbally) producing those numbers, in order, following a short delay (e.g., 7, 3, 8, 2, 9). Again, a significant increase in rCBF was observed in the right mid-ventrolateral frontal cortex (area 47).

A visual analogue of these span tasks, which uses simple line drawings as stimuli, has recently been developed to investigate whether the ventrolateral frontal cortex plays a similar role in the visual domain (Lee *et al.*, 2000). Subjects were PET scanned while reproducing previously learned (i.e., prior to scanning) "6-stroke" Chinese characters on a touch sensitive computer screen. Again, activation was observed in the mid-ventrolateral frontal cortex (area 47).

While the results described above suggest a common polymodal role for the ventrolateral frontal cortex in working memory, recent findings from the episodic memory literature suggest that this role may generalise to other memory domains. For example, Fletcher *et al.* (1998b) have reported activation in a very similar region of the right mid-ventrolateral frontal cortex during a paired-associates task that required subjects to retrieve previously learned category exemplars, in response to a series of category names. Such similarities strongly suggest that the various processes that are necessary for performing particular working memory tasks or declarative ("long-term") memory tasks may be drawn from a single set of underlying components.

One possible general role for the ventrolateral frontal cortex in memory may be to trigger active low-level encoding strategies such as rehearsal and to initiate explicit (i.e., intentional) retrieval (for discussion, see Owen, 2000). In the case of working memory tasks, this would correspond to the relatively straightforward mapping of stimuli to responses such as that which is assumed to occur in spatial and digit span tasks (e.g., Owen *et al.*, 1996b; 1999), or even simple delayed matching to sample paradigms (e.g., Elliott & Dolan, 1999). In the case of long-term episodic memory (e.g., verbal paired associate learning), these "active" encoding and retrieval processes might correspond to the active mapping and implementation of a somewhat arbitrary learned response (e.g., a category exemplar) to a specific stimulus (e.g., a category name) (e.g., Fletcher *et al.*, 1998a; 1998b).

The dorsolateral frontal cortex, on the other hand, is generally activated in memory tasks when more complex executive processes are required, including the generation and execution of mnemonic strategies which may supplement the more basic memory processes that facilitate encoding and retrieval (e.g., Petrides, 1994; Owen *et al.*, 1996a). For example, in one recent study (Owen *et al.*, 1996b), a self-ordered spatial working memory task was employed which required that subjects generate an encoding strategy for determining the optimal sequence of choices; activation was observed in both dorsal and ventral frontal-lobe areas.

In the present study, a modified version of the spatial span tasks described above was employed to demonstrate that the commonly observed tight coupling between the mid-ventrolateral frontal cortex and tests of working memory is exquisitely sensitive even to relatively subtle changes in task demands. In particular, simply changing the configuration of the stimulus array from a random (e.g., Owen *et al.*, 1996b; 1999) to a spatially ordered arrangement, yielded activation in the mid-dorsolateral frontal cortex. Since the ordered spatial array employed in the current study did not offer any obvious strategic advantage over the random designs used in previous studies, the two types of array were then compared directly in a supplementary behavioral study conducted outside of the scanning environment.

MATERIALS AND METHODS

PET study

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 approximately 4.0 × 5.0 × 4.5 mm. Using the bolus $H_2{}^{15}O$ methodology, rCBF was measured during three separate scans for each of the two conditions. Five additional scans were also conducted using a further task not relevant here. For each scan, subjects received a 20 sec. intravenous bolus of $H_2{}^{15}O$ through a forearm cannula at a concentration of 300 $\mathrm{Mbq\,ml^{-1}}$ and a flow rate of 10 $\mathrm{ml\,min^{-1}}$. The scan length was 90 second from when the tracer first entered the cerebral circulation. For each subject, a 3D MRI volume (whole brain, 256 × 256 × 128 pixels, 3 mm thick at 0.5 T) was also acquired. Using SPM96 (provided by the Wellcome Department of Cognitive Neurology, London, UK), the 11 PET scans for each subject were realigned by bilinear interpolation, using the first scan as a reference, to create a mean image. The 11 PET scans were then realigned a second time by bilinear interpolation, using the mean image as a reference, to create a second mean image. The MRI volume for each subject was re-sliced and co-registered with the second mean image. The co-registered PET data were normalised using bilinear interpolation, based on the T1 image (the MNI standard brain, based on 310 MRI images). The normalised images were then smoothed using an isotropic Gaussian kernel with FWHM set at 16 mm.

For the condition analysis, a subject specific ANCOVA (analysis of covariance) model was fitted to the data at each voxel, using SPM96. All images were scaled to a grand mean value of 50. The grey matter threshold for each voxel over the whole brain was set at 0.8. Given recent evidence suggesting that head movement across scans is a confounding factor in many PET studies (Brett *et al.*, 1999), both time (scan order) and head movement data in the three planes of rotation and three dimensions of translation were set as confounding factors. This procedure is believed significantly to improve sensitivity and reduce noise in the data.

For the whole 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 $p < 0.05$, corrected for multiple comparisons (Worsley *et al.*, 1996; 1992). This equates to a threshold Z score of >4.41.

Subjects. Ten normal right-handed volunteers, all males, participated in the study (age range = 21 to 41, mean age 26.5). Each subject underwent the eleven 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 both conditions were eight red squares (3.5 cm × 3.5 cm) presented on a black background, on a high-resolution, touch sensitive monitor. The stimuli were arranged in two rows of four, one above the other (see Fig. 1), with 3.5 cm between squares horizontally and 7 cm between squares vertically. The monitor was suspended approximately 50 cm in front of the subject's eyes and was comfortably within reach.

Span condition. In this condition (see Fig. 1, top row) one of the eight red squares would turn blue for 750 ms before turning red again. As soon as the first square turned back to red a second square would turn blue for 750 ms and so on, until five of the eight red squares had turned blue. At this point, the subjects were required to respond by touching the five squares on the touch-sensitive monitor in the order that they had just appeared. They were instructed to respond as fast as they could, but not so fast that they started making mistakes. Subjects were given an interval of 3750 ms within which to make their responses, after which another sequence was presented and so on until the end of the scan. This procedure was very similar to that used in previous PET studies of spatial span (e.g., Owen *et al.*, 1996b; 1999), except for the ordered spatial arrangement of the array.

Visuomotor control condition. For this task (see Fig. 1, bottom row), one of the eight red squares would turn blue for 750 ms, and then turn red again. Once the square had returned to red, the subject was required to respond by touching it as fast as they could, but without making any mistakes. They were given 750 ms within which to make their choice, after which another square would turn blue for 750 ms, and so on until the end of the scan.

The choice of which red squares would turn blue and in which order was pseudo-randomly set in both conditions, so that particular span sequences (or particular squares in the case of the visuomotor control condition), did not repeat contiguously. The task period for each PET scan lasted 100 seconds, with an onset of 10 seconds prior to the 90 second scan itself. In addition, a 100 second practice task was given to each subject approximately four minutes before each scanned task. This ensured that the subject understood the task, and was performing proficiently. The scans were separated by eight minutes. The two tasks required an identical number of responses (60 per scanned condition). The scan order was designed in three blocks, with each block comprising the two conditions performed in random order. Scan order was pseudo-randomly varied between subjects.

Supplementary behavioral study. Eighteen subjects performed a dynamic spatial span task, during which the length of the span presented increased by one if the subject correctly reproduced the

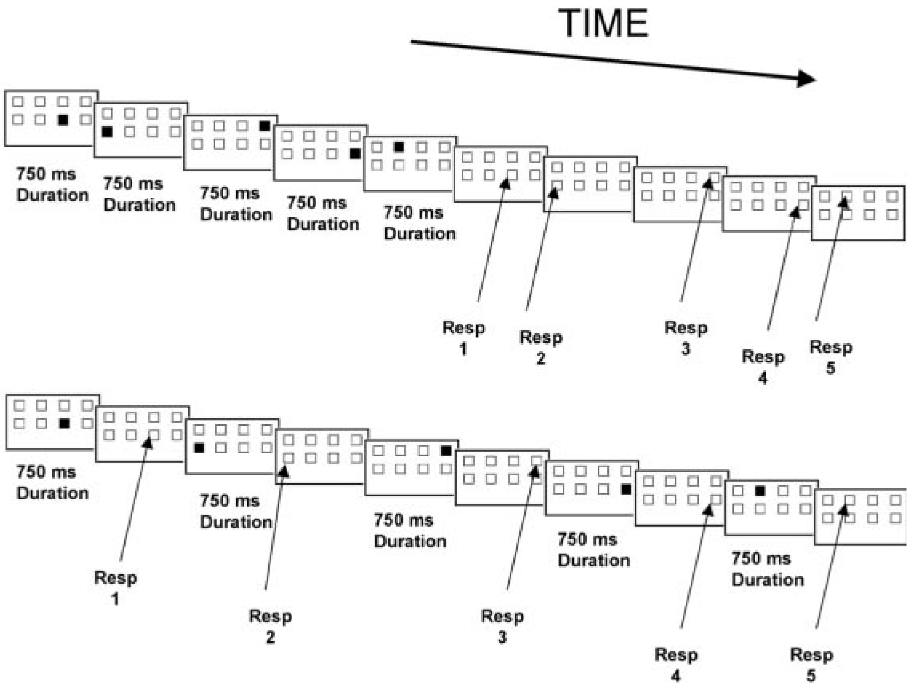

Fig. 1. Examples of trials from the two conditions in the PET experiment. Top Row: For the span task subjects were shown a sequence of five spatial stimuli, which they were then required to copy by touching the locations of the stimuli in the order that they had appeared. Bottom Row: For the visuomotor control task, subjects were required to touch each stimulus as it appeared.

previous span and decreased by one if the subject made any errors (with a minimum span length of 1 and maximum of 8). For each trial, one of eight red squares would turn blue for 750 ms before turning red again. Immediately following this, a second red square would turn blue for 750 ms and so on, until the number of squares that had turned blue equalled the number of the span-length for that trial. Subjects were then required to respond by touching the squares in the order that they had changed colour. If any errors were made in the response, the subsequent trial would begin 4500 milliseconds after that first error. Otherwise, subjects had as much time as they needed to make a fully correct response. Each subject was tested on a randomly distributed spatial array (termed "random array") of eight red squares (as used in two previous PET studies by Owen *et al.*, 1996b; 1999) and on the more spatially ordered array (termed "ordered array") two by four matrix of squares used in the PET study described above (see Fig. 2). Half of the subjects were given the random array first and half of the subjects were given the ordered array first. For each array, 50 trials were given to the subject and mean span length was computed by averaging the span length for all of the 50 trials in that condition. Following the tests, all subjects were questioned about how difficult they found the two types of span and whether or not they had employed any specific strategies to facilitate performance. Specifically, they were asked i) Which of the span tasks did you find the hardest? (random or ordered array) ii) Were you aware of using any strategies for each of the tasks? iii) If so, what were they?

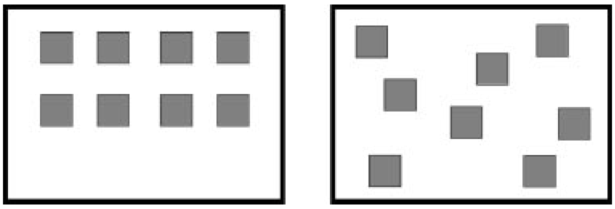

Fig. 2. Comparison of spatially ordered (left) and spatially random (right) array in the supplementary behavioral study designed to investigate further the performance differences between arrays. The ordered array was identical to that used in the PET study, while the random array resembled that used in two previous PET experiments (Owen *et al.*; 1996b; 1999)

RESULTS

PET study

Behavioral results. To score the span task, each trial was given a maximum of five marks (since five responses were required) and a correct mark was given for each square touched in the right spatial location and in the right temporal position. The average number of marks achieved was 4.3 per trial.

Blood flow. When the visuomotor control task was subtracted from the span task (see Table 1 and Fig. 3a), a significant increase in activity was observed in the right dorsolateral frontal cortex, both in mid (BA 9/46) and more

Table 1. *Activation foci in this table represent peaks of statistically significant changes in normalized rCBF. The stereotaxic coordinates (expressed in mm, in "MNI Space"), were generated by SPM96.* x = *medial-to-lateral distance relative to the midline (positive = right hemisphere and negative = left hemisphere);* y = *anterior-to-posterior distance relative to the anterior commisure (positive = anterior and negative = posterior);* z = *superior-to-inferior distance relative to the anterior commisure/posterior commisure line (positive = superior and negative = inferior). For each subtraction, all activation foci above significance (*p < 0.05*, corrected) are shown*

Regions of interest	Brodmann area	Stereotaxic co-ordinates			*Z*-statistic
		x	*y*	*z*	
Span minus Visuomotor Control					
Left					
Cerebellum		−32	−60	−28	4.73
Right					
Anterior DLPFC	46	44	48	12	4.83
mid DLPFC	9/46	38	30	24	5.33
Anterior Cingulate Cortex	24/32	6	8	42	5.16
Mid Parietal Cortex	40/7	36	−50	46	5.97
Medial Superior Parietal Cortex	7	8	−58	44	5.20
Extrastriate Cortex	18	34	−88	6	5.30
Visuomotor Control minus Span					
Left					
Medial Frontal Pole	10	−10	60	20	5.92
Supplementary Motor Area	6	−6	24	64	5.06
Premotor Cortex	6	−22	20	58	4.52
Inferior Mid-temporal Cortex	20	−44	−4	−24	5.50
Inferior Mid-temporal Cortex	20	−54	−18	−22	5.69
Inferior parietal lobule	39	−48	−64	24	4.47
Right					
Anterior Temporal Cortex	21	52	6	−26	4.50

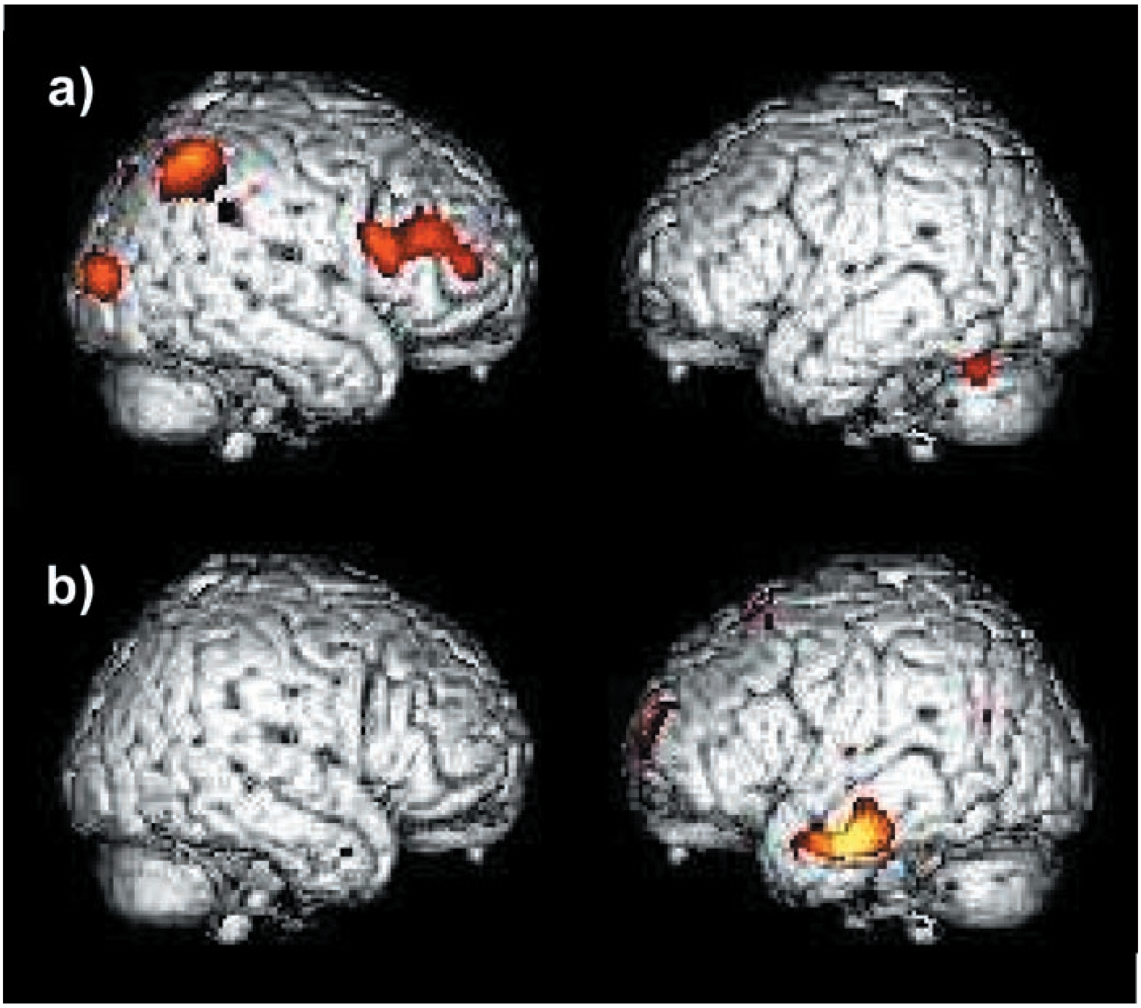

Fig. 3. PET subtraction images rendered onto the surface of a standard (MNI) 3D MRI. a) Span task minus visuomotor control task. b) Visuomotor control task minus Span task. For each image, all activation foci above significance ($p < 0.05$, corrected) are shown.

anterior portions (BA 46). In the left hemisphere, no significant prefrontal cortex increases in activation were observed. Significant increases in activity were also observed in the anterior cingulate cortex (BA 24/32), in the right mid-parietal region (bordering BA 40 and BA 7), in the right medial superior parietal lobule (BA 7), and in the right extrastriate cortex (BA 18). The cerebellum, on the left, was the only non-cortical area to show a significant increase in activation.

In contrast, when the span task was subtracted from the visuomotor control task (see Table 1 and Fig. 3b), significant increases in rCBF were observed in the left medial frontopolar region (BA 10), in left premotor cortex (BA 6) and medially in the left supplementary motor area (BA 6). Outside of the frontal lobe, significant increases in rCBF were observed in the left inferior temporal cortex laterally (BA 20), the right anterior temporal cortex (BA 21), and the left inferior parietal lobule (BA 39).

Supplementary behavioral Study

Overall, there was no significant difference between random and ordered conditions (mean span lengths 5.66 and 5.86, respectively), although there was a tendency for subjects to perform better on the latter. The examination of subjective reports revealed that, for the random array, subjects usually reported using a very simple strategy involving the use of imaginary lines linking the stimuli (“I drew a line between the boxes”). In contrast, for the ordered array more complex strategies were regularly reported, including using imaginary regular shapes (e.g., “I saw squares and triangles”) to connect the stimuli, chunking sets of stimuli together according to their spatio-temporal relations (e.g., “I saw the first three stimuli as one set and the last two as a separate set instead of five single stimuli”), using the grid aspect of the ordered array to encode stimuli (e.g., “I remembered that the first three stimuli were in the top row”), and to rule out sections of the ordered array (e.g., "I remembered that none of the first three stimuli were in the top row"). For subjects who used more strategies in the ordered array condition, 7/9 (77%) reported using strategies more complex than simply drawing imaginary lines between stimuli. In contrast, for subjects who did not use more strategies in the ordered array condition, only 3/9 (33%), reported using strategies more complex than drawing imaginary lines. This difference just failed to reach statistical significance ($\text{Chi}^2 = 3.60$, $df = 1$, $p = 0.058$).

DISCUSSION

The results of this study clearly imply that either the mid-dorsolateral frontal cortex or the mid-ventrolateral frontal cortex may be significantly activated in working memory tasks, depending on the precise cognitive processes that are involved. Compared to the visuomotor control task, the present spatial 5 span task yielded significant increases in regional cerebral blood flow in the right dorsolateral frontal cortex, but not the ventrolateral frontal cortex. This is a truly surprising finding given that the equivalent comparisons of two previous PET studies activated only the ventrolateral frontal cortex (Owen *et al.*, 1996b; 1999). In both of these previous studies a formally identical control to the current study, of the form of a 1-span task, was subtracted from alternative versions of the spatial 5 span task. Parallel investigations have reported similar findings using verbal (Owen *et al.*, 2000) and visual (Lee *et al.*, 2000) analogues of the same general procedure. The combined results from these studies suggest that simply changing the configuration of the stimulus array from a random arrangement (e.g., Owen *et al.*, 1996b; 1999), to an ordered spatial design, may shift the focus of activation from the mid-ventrolateral frontal cortex to the mid-dorsolateral frontal cortex.

Of course, one should be cautious in drawing strong conclusions based on comparisons between different studies in unrelated groups of volunteers. In a recent follow-up study (Bor *et al.*, 2000), however, we have replicated our results in a single group of subjects. In that study the spatially ordered array again yielded activation in the mid-dorsolateral frontal cortex, while the spatially "random" stimulus array produced only mid-ventrolateral frontal activation, in keeping with previous PET studies that used the random array spatial span task (e.g., Owen *et al.*, 1996b; 1999).

It is important to emphasise that the two anatomical regions under consideration here, the mid-ventrolateral and mid-dorsolateral frontal cortices, are quite distinct, both anatomically and cytoarchitectonically, and are easily resolved, even with the relatively limited spatial resolution of PET. In the human brain, the mid-dorsolateral frontal cortex comprises the mid-part of the superior and middle frontal gyri above the inferior prefrontal sulcus, a considerable proportion of this cortex lying within the depths of the middle frontal sulcus (Petrides & Pandya, 1994: Rajkowska & Goldman-Rakic, 1995). The mid-ventrolateral frontal cortex, on the other hand, comprises the tissue which lies on the lateral surface below the inferior frontal sulcus.

The question arises, therefore, why simply altering the spatial configuration of a simple spatial working memory task from a random array to an ordered design de-emphasises the role of the ventrolateral frontal cortex in favour of more dorsolateral frontal regions. The mid-dorsolateral frontal region has been activated in many imaging studies of working memory, particularly during tasks which require active manipulation or "monitoring" of information within memory (e.g., McCarthy *et al.*, 1994; Owen *et al.*, 1996b; for reviews, see Owen, 1997; 2000; Rushworth *et al.*, 1997; D'Esposito *et al.*, 1998), or relatively complex mnemonic strategies (e.g., Owen *et al.*, 1996b). The results of our supplementary behavioral study suggest that changing the random spatial array to an ordered spatial array introduces additional strategic components to the basic span task, according to which subjects use a variety of approaches to augment their memory performance. For example, during the ordered array span condition, subjects often reported "chunking" the stimuli into two or three shapes comprising patterns of temporally adjacent squares, while similar reports were not made for the random array.

The evidence from the current PET and behavioral studies seem contrary to what would be predicted under the commonly held "domain-specific" model of lateral frontal organisation, namely that the dorsolateral prefrontal cortex is preferentially involved in spatial working memory tasks, while the ventrolateral prefrontal cortex is preferentially involved in object-based working memory tasks (Goldman-Rakic, 1994; 1995; Levy and Goldman-Rakic, 1999). Results from the random array condition of the behavioral study reported here indicate that in previous PET studies using random array variants of the spatial span task (Owen *et al.*, 1996b; 1999), only the spatial location of the stimuli could be used for encoding. According to the "domain-specific" model, activation should have been observed in the dorsolateral prefrontal cortex, although it was actually observed in the ventrolateral prefrontal cortex. The apparent common use of object-based mnemonic strategies for the ordered array span of the current PET study (for instance, perceiving parts of sequences as regular shapes) should, under the "domain-specific" model, have yielded activation in the ventrolateral prefrontal cortex. In fact, it was observed in the dorsolateral prefrontal cortex.

However, the current findings are more consistent with reports from frontal lobe patient studies. Since the earliest neuropsychological studies of working memory performance in patients with circumscribed lesions of the frontal lobe (e.g., Petrides & Milner, 1982), organisational strategies have been linked to the dorsolateral region of the lateral frontal cortex, although equivocal evidence has been lacking (see also, Owen *et al.*, 1990; 1996a). Thus, in patient studies it is not possible to establish which areas of the frontal cortex are involved in a given cognitive process with any degree of anatomical precision since the excisions are rarely confined to specific cytoarchitectonic areas. The current imaging findings do provide some support for this notion, however, and suggest that the use of mnemonic strategies in the ordered task underlies the peak of activation observed in the mid-dorsolateral region of the lateral frontal cortex.

While some authors have suggested (Smith *et al.*, 1996) that verbal and spatial working memory tasks will preferentially recruit the left and right frontal cortices, respectively, large scale neuroimaging reviews by Cabeza and Nyberg have indicated that the majority of frontal activation for verbal or spatial working memory is bilateral (Cabeza & Nyberg, 1997; 2000). The results of our two previous investigations (Owen *et al.*, 1996b; 1999), and those of the current study, are broadly consistent with the former view since prefrontal activity was almost exclusively observed in the right hemisphere during the various types of spatial working memory tasks. However, what is clear is that this pattern is by no means absolute. For example, while Cabeza and Nyberg (Cabeza & Nyberg, 2000) suggest that BA 44 (Broca's area) activations are left lateralised for verbal working memory, several previous imaging studies using verbal working memory tasks have reported activation in right, but not left, mid-lateral frontal regions (e.g., Jonides *et al.*, 1997; Owen *et al.*, 2000). One important factor may be the level of working memory load, defined either in terms of the number of stimuli held in working memory, or the level of manipulation that is required. Jonides *et al.* (1997) systematically varied the load of a verbal *n*-back task from zero to three. Relative to a control task, the three back condition yielded significant activation in the dorsolateral frontal cortex, bilaterally. In contrast, the two back condition yielded significant dorsolateral frontal activity in the right hemisphere only, while the one and zero back tasks produced no significant lateral frontal increases relative to a sensorimotor control task.

In summary, recent reviews of the functional neuroimaging literature have clearly demonstrated that in working memory tasks, either, or both, the ventrolateral and dorsolateral frontal cortices may be significantly activated (e.g., D'Esposito *et al.*, 1998; Owen, 1998; 2000). In most previous studies, however, rather large changes in task have been used to shift the balance of activation between the ventrolateral and dorsolateral regions (e.g., Stern *et al.*, 2000; Owen *et al.*, 1996b; 1999). For example, Owen *et al.*, (1996b), compared a random spatial span task, similar to that used in the present study, with a complex spatial search task which required that subjects remember which of a set of previously selected stimuli had been "marked" with a blue circle and which had not. In healthy controls, superior performance on the spatial search task, which was shown to differentially activate the right dorsolateral frontal cortex, relates directly to the use of a systematic searching strategy, which presumably facilitates performance by reducing the overall load on working memory (Owen *et al.*, 1990; 1996a). Moreover, neurosurgical patients with damage to the frontal lobe are selectively impaired in the use of this strategy leading to poorer performance on the task (Owen *et al.*, 1996a). By comparison, the difference between the random span task of previous studies and ordered span task used in the present study is rather subtle; it is sufficient, nevertheless, to change the relative contributions of these two frontal regions.

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