

Active Representation of Shape and Spatial Location in Man

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Neural activity during the delay period of spatial delayed response (DR) and delayed matching (DM) tasks was investigated by positron emission tomography. A distributed cortical system was activated in each condition. The bilateral dorsolateral prefrontal cortex (DLPFC) was activated in the delay period of both tasks; activation was of higher significance on the right in the DR task and the left in the DM task, and extended to the anterolateral prefrontal cortex in the DM condition. Active representation of spatial location in the DR task was associated with co-activation of the medial and lateral parietal cortex and the extrastriate visual cortex. Active representation of shape in the DM task was associated with co-activation of the medial and lateral parietal cortex and the inferior temporal cortex. Response-related activity was observed in both tasks. Activation of anterior cingulate, inferior frontal, lateral premotor and rostral inferior parietal cortex was observed in the DR condition, a task characterized by preparation of a movement to a predetermined location. In contrast, preparation to move to an undetermined location in the DM task was associated with activation predominantly in rostral SMA.

Introduction

The ability to hold 'on-line' a representation of the features of an object or its spatial location following its initial perception is an active process dependent on sustained neural discharge, and is distinct from the passive representation of knowledge in long-term memory (Baddeley, 1986; Goldman-Rakic, 1987). Experimental investigation of active spatial and non-spatial representation in the monkey has utilized a variety of delay tasks and has provided detailed neurophysiological characterization of individual neural responses during the delay period (reviewed in Goldman-Rakic, 1987). In the present study we have used formally analogous spatial delayed response (DR) and delayed matching (DM) tasks to determine the neural system engaged in the process of active representation in man and allow interpretation of activity in this system in the light of studies in the non-human primate.

Lesion studies have demonstrated that the integrity of the frontal lobe cortex is critical to the performance of these tasks. Circumscribed lesions to the dorsolateral prefrontal cortex (DLPFC), specifically the middle third of the principal sulcus, in non-human primates, impair performance on spatial delay tasks while sparing performance on non-spatial delay tasks (Goldman-Rakic, 1987). Conversely, lesions to the ventrolateral prefrontal cortex impair performance on non-spatial delay tasks while sparing performance on spatial delay tasks. Crucially, both lesions spare performance on discrimination tasks that do not involve a delay.

The principal sulcus in the non-human primate is characterized by reciprocal connections with discrete areas of the parietal and temporal cortex (Goldman-Rakic, 1988), which in turn have specific reciprocal connections with the extrastriate visual cortex (Van Essen, 1985; Zeki and Shipp,

1988). Following initial visual processing in the occipital cortex, it has been proposed that the processing of spatial and non-spatial features of objects follow divergent dorsal and ventral pathways to the posterior parietal and the inferior temporal cortex, respectively (Van Essen, 1985; Zeki and Shipp, 1988). Lesions within these pathways impair performance on both discrimination and delay tasks in the respective modality (Glickstein *et al.*, 1963; Fuster *et al.*, 1985; Quintana *et al.*, 1989). Recently, relatively selective activation in the parietal and temporal cortex associated with attention to spatial and non-spatial attributes has been demonstrated in man using positron emission tomography (PET) (Corbetta *et al.*, 1991; Haxby *et al.*, 1991).

The region of the principal sulcus in the non-human primate occupies a pivotal position in relation to motor and sensory systems. In addition to connections with parietal and temporal cortices, it has reciprocal connections with premotor and subcortical motor systems. It has been proposed that the prefrontal cortex may actively maintain a spatial representation in the posterior parietal cortex (Goldman-Rakic, 1987), and an analogous interaction may sustain preparatory activity in motor systems. Within the prefrontal cortex, the discharge of neurons in the principal sulcus during spatial delayed response tasks has been extensively characterized (Niki, 1974; Funahashi *et al.*, 1989, 1990, 1991) with individual neural responses evident in relation to the cue, delay, or response.

Posterior parietal neurons discharge when attention is directed to a target location and during the delay period of a spatial delayed response task (Bushnell *et al.*, 1981; Gnadt and Andersen, 1988). By contrast, neurons in the inferior temporal cortex respond selectively to specific features of a stimulus (Tanaka *et al.*, 1991). The discharge pattern of neurons in this region is also enhanced when attention is directed towards a stimulus and during the delay period of a non-spatial delayed matching task (Fuster, 1990). Neural discharge during the delay period in various tasks can also be recorded from motor systems, including the motor and premotor cortex, the frontal eye fields and the components of a cortico-striatal 'loop' (Wurtz and Goldberg, 1972; Fuster, 1973; Tanji *et al.*, 1980; Hikosaka and Wurtz, 1983; Bruce and Goldberg, 1985; Tanji and Kurata, 1985; Watanabe and Niki, 1985; Hikosaka *et al.*, 1989).

A previous PET study, in normal human subjects, of a delayed spatial recognition task revealed increased regional cerebral blood flow (rCBF) in the right inferior frontal, the premotor, the parietal, and the occipital cortex (Jonides *et al.*, 1993). Surprisingly, this experiment failed to find activation in the DLPFC. Bilateral DLPFC activation, with right hemisphere predominance, has been observed in tasks involving spatial working memory (Petrides *et al.*, 1993; McCarthy *et al.*, 1994). However the 'self-ordering' visuospatial task (Petrides *et al.*, 1993), in common with most tasks designed as tests of 'working

memory', involves performing additional cognitive operations on the material maintained in working memory.

In the present study we investigated neural activity during the delay period of both a spatial delayed response and a delayed matching task with PET, using a bolus infusion of ^{15}O -labelled water. This technique images neural activity in a 30–40 s time window (Silbersweig *et al.*, 1993). Subjects were scanned during the delay period of the DM and DR conditions. Stimuli were presented and responses made outside this window in each condition. The tasks required the active representation of spatial location in the DR task and the local geometry of the shapes in the DM task, and the preparation for a motor response to a predetermined and an unspecified location, respectively.

The experimental paradigm used in this study is formally analogous to previous studies in the non-human primate. The study design allows comparison of each task with the control condition, to reveal *relative* changes in rCBF in neural systems engaged by each task, and comparison of these rCBF changes in the respective tasks, to reveal activation specific to the representation of shape and spatial location.

Materials and Methods

Subjects

Ten male volunteers aged between 18 and 35 years took part in the study, which was approved by the Hammersmith Hospital Ethics Committee and the Advisory Committee on the Administration of Radioactive Substances (ARSAC) UK. All subjects were strongly right-handed. Informed consent was obtained from all subjects.

PET Scanning Techniques

rCBF was measured with a CTI model 953B PET scanner (CTI, Knoxville, TN), with the interplane septa retracted (Spinks *et al.*, 1992). Following a 'slow bolus' infusion of H_2^{15}O , integrated counts per pixel during the 90 s acquisition frame, corrected for background counts, provided an index of rCBF. A total of 11.2 mCi of H_2^{15}O were flushed with normal saline through a cannula in an antecubital vein over 20 s at 10 ml/min by an automatic pump. After a constant delay a rise in radioactive counts at the head was detected, which peaked between 30 and 40 s in individual subjects. Although counts were collected for 90 s, only radioactivity detected during the rising phase of the head count curve contributes significantly to the signal in the final image (Silbersweig *et al.*, 1993). Each subject underwent 12 scans, with a 10 min interval between scans. Correction for attenuation was made by performing a transmission scan with an exposed $^{68}\text{Ge}/^{68}\text{Ga}$ external ring source before each session and a 30 s frame for background activity correction was acquired before each infusion.

Cognitive Activation Paradigms

Two groups of five subjects were studied, one group in the DR condition, the other in the DM condition. In each group, task and control conditions were presented alternately. Subjects were rehearsed before scanning to ensure adequate performance. This was readily achieved after a few trials. Subjects were scanned in the presence of low background noise and dimmed ambient lighting. Stimuli were presented on an Apple Macintosh microcomputer with a touch-sensitive screen. The screen was mounted ~50 cm in front of subjects such that they could easily respond by touching the screen with the index finger of the dominant hand, which rested on the chest between responses.

Spatial Delayed Response

Immediately before the scan, subjects were instructed to fixate on a central cross. The stimulus, an open circle 1 cm in diameter, was displayed for 200 ms, timed according to the constant delay before activity was detected at the head following tracer infusion to occur ~5 s before activity was detected at the head. Subjects continued to fixate on the central cross throughout the delay period. Responses were cued by a question mark replacing the fixation cross 45 s after the initial stimulus

presentation, which occurred between 5 and 15 s after the on-line measurement of head counts had peaked. The remembered location of the stimulus was indicated by touching the appropriate point on the screen. Each stimulus was presented 6.5 cm from the fixation point in a different location selected randomly, avoiding positions subtending an angle of 15° either side of the vertical and horizontal, to prevent a simple categorical encoding of the location.

Delayed Matching

Subjects again fixated a central cross immediately prior to each scan. The stimulus, a filled black rectangle, was displayed centrally for 200 ms, timed according to the constant delay following tracer infusion to occur ~5 s before activity reached the head. Subjects continued to fixate on the central cross during the 45 s delay, after which two filled black rectangles were displayed on either side of the fixation point centred 5 cm from the midline. Subjects were then required to choose the matching rectangle by touching it on the screen. All the stimuli were of the same area, and the non-matching rectangle differed by 15% in the long axis. The rectangular shapes employed in this study are not readily represented in a categorical or verbal code, precluding a long-term encoding strategy in a delayed matching task. In pilot studies subjects found this task demanding but were nevertheless able to perform accurately at this delay.

Control Conditions

In both control tasks, subjects were required to touch a visual stimulus on the monitor after head counts had peaked as determined by the on-line display of radioactivity detected at the head. In the DR control, a 1 cm circular target appeared at a pseudorandom location; in the DM control, subjects touched a rectangle which appeared on the left or right in the lower half of the screen. The stimuli in both control conditions were presented at the end of the delay until the subject touched them.

During each task and control condition subjects maintained visual fixation during the scanning period. Subjects' compliance with task instructions was confirmed by visual inspection. In the task conditions the initial stimuli were presented before activity reached the head, and responses were made after the head count had peaked. rCBF images therefore reflect neural activity during the delay period in each task but not the stimulus presentation or response phases of the trial.

Data Analysis

Image analysis was performed on a SPARC 10 workstation (Sun Microsystems Inc., Surrey, UK) using interactive image display software (ANALYZE, Biodynamic Research Unit, Mayo Clinic; Robb, 1990) and statistical parametric mapping (SPM software, MRC Cyclotron Unit, London, UK). Calculations and image matrix manipulations were performed in PRO MATLAB (Mathworks Inc., New York).

Image Reconstruction

Images were reconstructed into 31 slices by three-dimensional back projection using a Hanning filter with a cut-off frequency of 0.5 cycles per pixel. The resulting images consisting of 128×128 pixels of 2.006×2.006 mm having a resolution of $8.5 \times 8.5 \times 4.3$ mm full width at half maximum (FWHM).

Image Analysis

The 31 original slices were interpolated to 43 planes in order to render the voxels approximately cubic. Images were automatically realigned to correct for head movement between scans (Woods *et al.*, 1992) and transformed into a standard stereotactic space (Friston *et al.*, 1989). The stereotactically normalized images, consisting of 26 planes, correspond to the horizontal sections of the standard stereotactic atlas (Talairach and Tournoux, 1988); each pixel represents 2×2 mm with an interplanar distance of 4 mm. Images were smoothed with a Gaussian filter 10 pixels wide in order to suppress high-frequency noise in the images and accommodate normal variability in functional and gyral anatomy for group analysis.

Statistical Analysis

Differences in global activity within and between subjects were removed

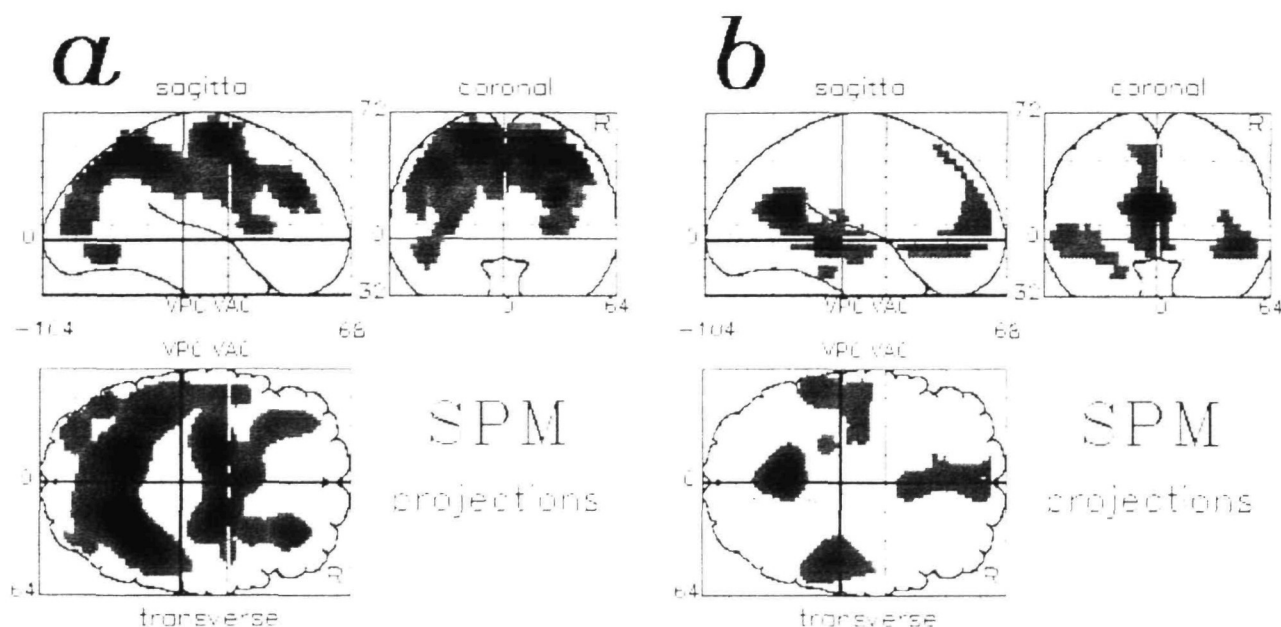


Figure 1. Statistical parametric maps comparing the spatial delayed response (DR) task with the control condition. (a) Increases and (b) decreases in rCBF. Pixels exceeding a threshold level of significance of $P < 0.01$ uncorrected for multiple comparisons are displayed on sagittal, coronal, and transverse projections of the brain; the left side of the brain is on the left side of the images. The coordinates of the foci of maximal increase and decrease of rCBF are given in Tables 1 and 2 respectively.

by analysis of covariance (ANCOVA) on a pixel-by-pixel basis with global counts as covariate and regional activity in each condition across subjects as treatment (Friston *et al.*, 1990). The ANCOVA generated a mean rCBF value, normalized to 50 ml/100 ml/min, and associated error variance for every pixel in each condition. This adjusted rCBF represents a weighted mean over a sphere of ~20 mm. Differences between the adjusted mean pixel values across conditions were assessed using the t -statistic (Friston *et al.*, 1991), the resulting images of pixel t -values constitute a statistical parametric map [SPM(t)]. The omnibus significance of the SPMs was assessed by comparing the expected and observed distribution of the t -statistic under the null hypothesis of no treatment effect. The SPM(t s) were additionally displayed as volume images of the highest t -values in three orthogonal projections and as surface renderings onto a standard cerebral cortex. In the interaction between the tasks and their respective controls, the analysis was constrained by orthogonal masking to pixels of increased rCBF ($P < 0.05$) in the comparison of each task with its control. SPM(t s) were also transformed to unit Gaussian distribution using a probability integral transform so that changes could be reported as z -scores.

Results

Performance of the Spatial DR Task

All subjects performed the task accurately; the mean error (distance from the centre of the stimulus) was 40 mm (SD 22.8 mm) in the spatial DR condition and 17.6 mm (SD 9.4 cm) in the control condition.

Comparison of rCBF in the Spatial DR and Control Conditions

Significant relative increases in rCBF ($P < 0.001$) in the spatial delayed response condition compared to visual fixation were distributed throughout the frontal and posterior cortical regions (Fig. 1). Anteriorly these comprised the DLPFC, two foci in the lateral premotor cortex and the anterior cingulate cortex bilaterally, and the right inferior frontal cortex. Posterior activations comprised the medial and lateral parietal cortex and the

lateral occipital cortex bilaterally, and the left occipito-temporal cortex. In the medial parietal cortex, two foci of increased rCBF could be distinguished bilaterally within the precuneus. The coordinates of maximal significant change are presented in Table 1. Overall the most significant foci of activation were localized to the lateral premotor cortex anteriorly and the medial and lateral parietal cortex posteriorly.

In these right-handed subjects eventually responding with their dominant hands, bilateral activations during the delay period before responding reached higher significance on the right, except for the medial premotor cortex, in which the left premotor activation was of higher significance. At a lower threshold of significance ($P < 0.01$), additional activation was only apparent in the occipital cortex bilaterally.

Decreases in rCBF ($P < 0.001$) were found in a midline swathe of the medial frontal cortex (Fig. 1), extending from the precommissural cingulate cortex (BA 25), through the medial polar cortex (BA 9/10), to the left medial area 8. Posteriorly there were bilateral decreases in the middle temporal gyri, right transverse temporal gyrus, left posterior cingulate cortex, and left posterior insula. No additional foci were apparent at the lower threshold of significance ($P < 0.01$).

Performance of the DM Task

Subjects performed the task with 100% accuracy during the study (one subject initially made a single error which was immediately corrected). Subjects reported that they performed the task with two different strategies—maintaining a mental image of the shape and comparing the lengths of the sides of the imaged rectangles.

Comparison of rCBF in the DM and Control Conditions

Significant increases in rCBF ($P < 0.001$) in the delayed matching condition compared to visual fixation were present in the left DLPFC, left SMA, and bilateral inferior parietal cortex with a right hemisphere predominance. At a lower threshold of

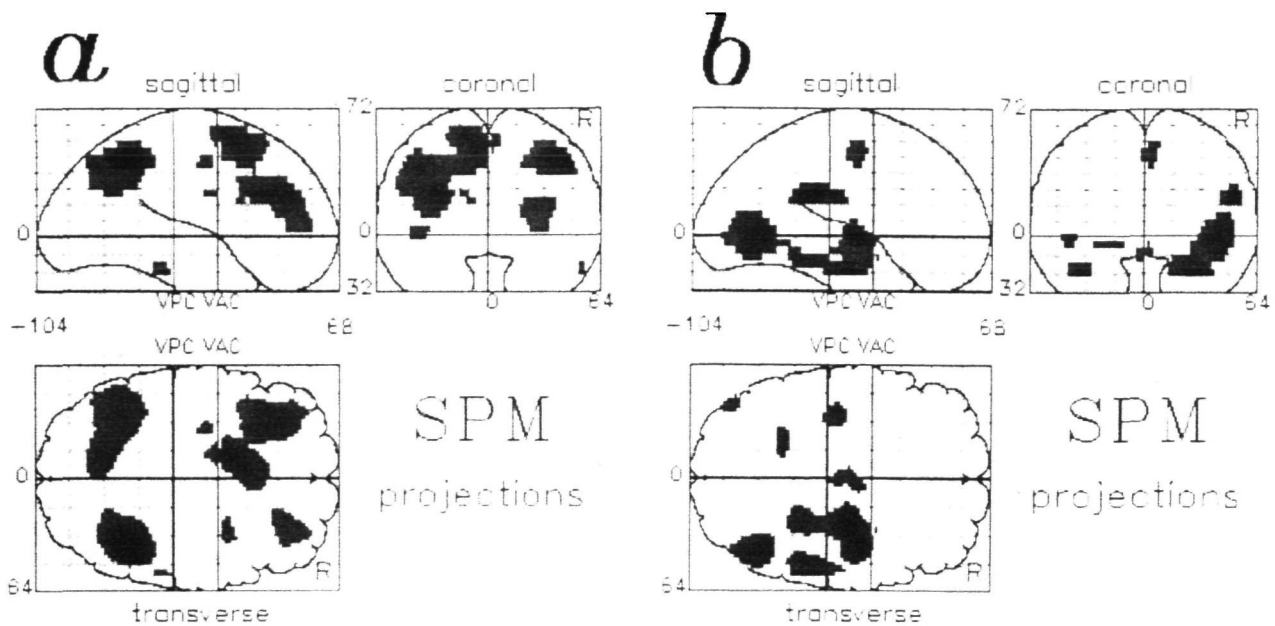


Figure 2. Statistical parametric maps comparing the shape delayed matching (DM) task with the control condition. (a) Increases and (b) decreases in rCBF. The coordinates of the foci of maximal increase and decrease of rCBF are given in Tables 3 and 4 respectively.

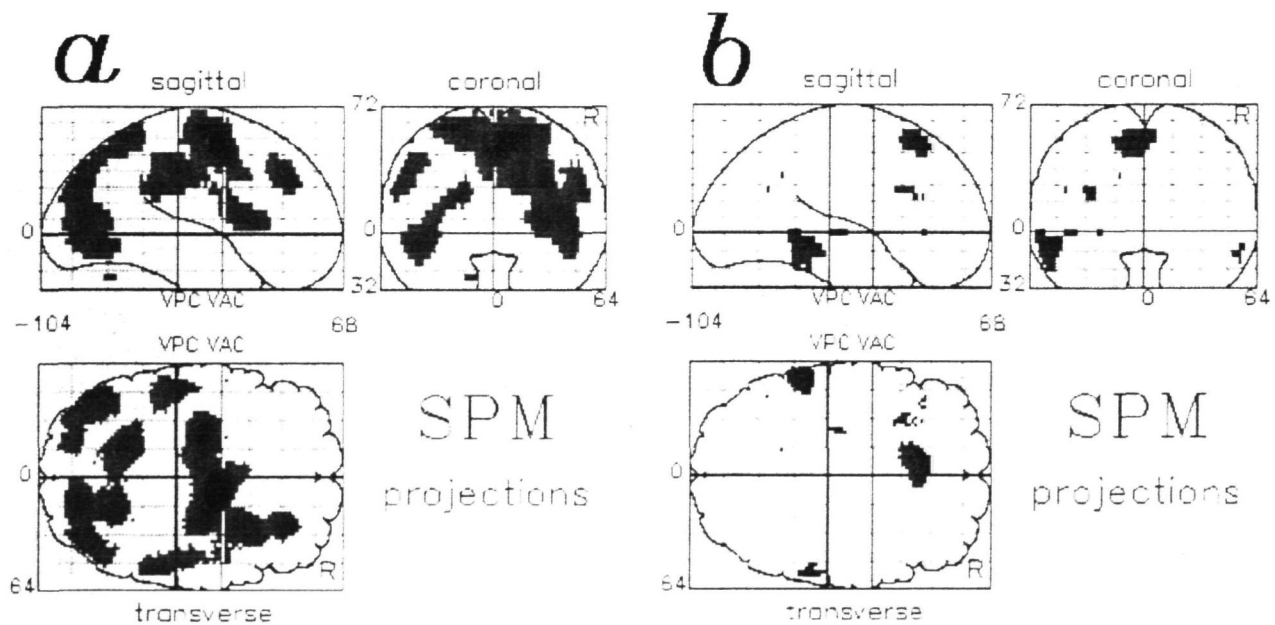


Figure 3. Statistical parametric maps of the changes in rCBF specific to the spatial (DR) and shape (DM) tasks. (a) Increases in rCBF in the DR task compared to the DM task. (b) Increases in rCBF in the DM task compared to the DR task. Pixels exceeding a threshold level of significance of $P < 0.01$ uncorrected for multiple comparisons are displayed as in Figure 1.

significance ($P < 0.01$), activations were apparent bilaterally in the DLPFC, rostral frontal and premotor cortex anteriorly, and in the left precuneus and right inferior temporal cortex posteriorly (Fig. 2).

Decreases in rCBF ($P < 0.001$) were confined to the right hemisphere in the hippocampus, posterior insula, anterior inferior parietal, and lateral occipital cortex. At a lower threshold of significance ($P < 0.01$) additional decreases were revealed in the caudal SMA, anterior cingulate cortex, and left inferior temporal cortex.

Comparison of rCBF Between the Spatial DR and DM Conditions

The differences of interest between the delayed spatial response and delayed matching conditions were treated as an interaction between each pair of task and control conditions. Focal activations of higher significance ($P < 0.001$) in the spatial memory condition (Fig. 3a) were localized to the DLPFC (BA 9), the inferior frontal cortex, and the SMA in the right hemisphere, and bilaterally in the premotor cortex (BA 6), the anterior inferior parietal cortex (BA 40), the medial parietal cortex

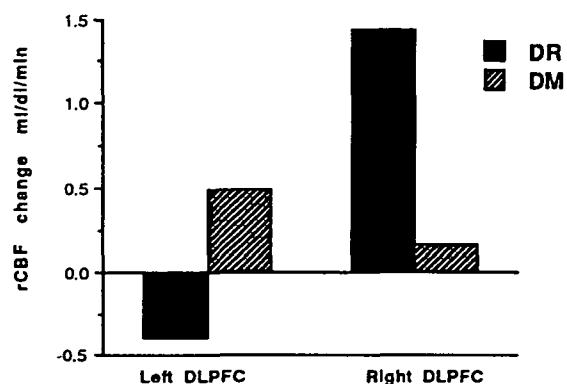


Figure 4. The upper graph illustrates the maximal changes of prefrontal rCBF in the DR and DM conditions. The lower graph illustrates the rCBF changes at the sites of maximal significant difference between the DR and DM conditions.

(precuneus, BA 7), the occipital cortex (BA 18), and the occipito-temporal junction (BA 19/37).

Activations of higher significance ($P < 0.001$) in the shape memory condition (Fig. 3b) were localized to the rostral left SMA and the middle and inferior temporal gyri (BA 21) bilaterally. At a lower threshold of significance ($P < 0.01$) a small activation focus could be observed inferiorly within the left DLPFC. Prefrontal rCBF changes are illustrated in Fig. 4, and confirm that the rCBF increase in this inferior area is specific to the DM condition; there was a corresponding decrease of rCBF in the DR task (Fig. 4b). Although the rCBF increase in the right DLPFC was greater in the DR condition than in the DM condition, a smaller increase was also observed at this location in the DM condition.

Discussion

The principal finding of this study, in which brain activity was imaged during the delay period of spatial and non-spatial delay tasks, is the co-activation of the DLPFC with the medial and inferior parietal cortex in both tasks. Both tasks share a common cognitive component, namely active representation of spatial attributes across a delay. In addition, each task was associated with activation of a discrete set of cortical areas, reflecting cognitive components unique to each task.

The active representation of spatial location in the present study was associated with co-activation of the posterior parietal cortex with the lateral occipital and occipito-temporal cortex. Active representation of shape was associated with co-activation of the posterior parietal cortex with the inferior mid-temporal cortex, an area which projects to both the prefrontal and medial parietal cortex in the monkey (Weller and Kaas, 1987; Goldman-Rakic, 1988; Selemon and Goldman-Rakic, 1988).

Co-activation of the DLPFC and the posterior parietal cortex has recently been demonstrated in a group of monkeys performing a variety of spatial and non-spatial working memory tasks, using the [^{14}C]2-deoxyglucose technique. Within the parietal cortex, enhanced activity was found in each subdivision, 7m, 7ip, 7a, and 7b (Friedman and Goldman-Rakic, 1994), the highest activity being found in the supragranular layers, the origin and target of prefrontal-parietal cortico-cortical interconnections (Schwartz and Goldman-Rakic, 1984).

Cooling of the infero-temporal cortex in monkeys performing a delayed matching task disrupted delay-related discharge in the DLPFC; conversely cooling the DLPFC disrupted delay-related

discharge in infero-temporal cortex, constituting a functional diaschisis (Fuster *et al.*, 1985). These effects were again more common in the supragranular layers that give rise to cortico-cortical connections.

Prefrontal Cortex Activation in DR and DM Tasks

The DLPFC was activated bilaterally in both DR and DM conditions in spite of the fact that response preparation is only possible in the DR task. A component of DLPFC activation must therefore be independent of response selection and preparation. The most significant activations in the DR task were located in the right dorsolateral and inferior prefrontal cortex. Right inferior frontal activation has been associated with imagined movement (Stephan *et al.*, 1995) and has previously been observed in a spatial DR task (Jonides *et al.*, 1993). The absence of dorsolateral prefrontal activation in the Jonides *et al.* study may reflect the choice of control task; although there were no explicit working memory demands in this condition, the working memory system may have been automatically engaged by the task. Activation of the DLPFC has indeed been observed in an analogous dot-location task (McCarthy *et al.*, 1994). The most significant activation in the DM task compared to fixation was located in the left DLPFC. In the explicit comparison of DR and DM conditions, activation specific to the spatial location task was restricted to the right inferior and dorsolateral prefrontal cortex, whereas activation specific to the shape-matching task was located deep within the left DLPFC.

These observations contrast with the experimental evidence derived from both lesion and single-unit recording studies in the non-human primate, which indicate that both left and right prefrontal cortex are involved in the active representation of spatial location, and that the active representation of intrinsic features of objects involves a more ventrolateral region of the frontal cortex (Wilson *et al.*, 1992). The results of the present study are consistent with lateralization of function in this region in man superseding the topographical localization of function in the monkey (Funahashi *et al.*, 1989).

Bilateral focal activations were also present in the antero-lateral prefrontal cortex (BA10) in the DM task. This region has not been well characterized in the primate. However, in PET studies, activation in this region has been observed in various paradigms, including random joystick movement (Deiber *et al.*, 1991), motor sequence learning (Jenkins *et al.*, 1994), and cognitive tasks such as planning (Baker *et al.*, 1996) and encoding and retrieval from episodic memory (Squire *et al.*, 1992; Grasby *et al.*, 1993; Tulving *et al.*, 1994). A common feature is the use of cognitive strategies in these paradigms. In the present study, subjects reported employing a strategy comparing the relative lengths of the sides of the remembered shapes.

Representation of Shape and Spatial Location

Visual Cortex

The representation of spatial location in the DR task was associated with activation of the extrastriate visual cortex and an area at the junction of the lateral occipital and the temporal cortex. Lateral occipital activation has previously been observed in a spatial DR task (Jonides *et al.*, 1993) and a spatial sequence learning task (Decety *et al.*, 1992). In the present study subjects reported visual imagery during the delay period. Although the dominant view is that visual imagery is associated with parietal

activation, activation of early visual areas has also been observed (Kosslyn *et al.*, 1993).

Parietal Cortex

Activation of the medial and lateral parietal cortex was observed in both delay tasks compared to the control condition. Parietal activation was more extensive in the DR task and completely encompassed the areas activated in the DM task. In both conditions the right inferior parietal activation attained the highest significance.

In a comparable spatial DR task (Jonides *et al.*, 1993), activation was not observed in the medial parietal cortex. However, in that study a visual stimulus of matching complexity was presented in the control condition, and this may have elicited equivalent activation in this area. This area was activated by spatial working memory tasks in the monkey (Friedman and Goldman-Rakic, 1994). Activation of the medial parietal cortex (precuneus) in man has been reported in a wide variety of experimental paradigms: with alternating and moving checkerboard stimuli (Fox *et al.*, 1987; Watson *et al.*, 1993), real and imagined joystick movements (Deiber *et al.*, 1992; Stephan *et al.*, 1995), cognitive tasks including retrieval from episodic memory (Petrides *et al.*, 1993; Shallice *et al.*, 1994; Fletcher *et al.*, 1996), and mental imagery (see Roland and Gulyas, 1994, for a review; Fletcher *et al.*, 1995). A common feature of these cognitive tasks is the spatially organized representation of a real or imagined object or movement.

Lateral parietal activation has been associated with tasks involving actual and imaginary movement or covert attentional shifts to a spatial location (Corbetta *et al.*, 1993; Jonides *et al.*, 1993; Stephan *et al.*, 1995). The inferior parietal region may correspond to area 7a in the monkey, which is also activated by DR tasks (Friedman and Goldman-Rakic, 1994). In this study, inferior parietal activation extended further anterolaterally in the DR than the DM task. A significant distinction between the tasks is the specification of the target location and response preparation in the DR task. This rostral parietal area may therefore correspond to area 7b in the monkey, which is activated by DR tasks (Friedman and Goldman-Rakic, 1994) and is responsive to somatosensory stimulation (Hyvarinen, 1981).

The pathway from the visual cortex to the posterior parietal cortex is engaged in spatial analysis (Mishkin *et al.*, 1983) and was activated in man by a dot-location task (Haxby *et al.*, 1991). Parietal activation in the shape-matching task is consistent with a role for this area in the analysis of spatial relations between features intrinsic to an object.

Temporal Cortex

Representation of shape in the DM task was associated with activation in the inferior temporal cortex. In the comparison with the control task, this activation only reached significance on the right; however, bilateral mid-temporal activation was apparent in the comparison with the DR task. This may reflect activation of this area in the control task, which required attention to the fixation cross. Activation in a corresponding region has been found with selective attention to shape (Corbetta *et al.*, 1991), and in a comparison of visual processing of complex objects with sine wave gratings (Sergent *et al.*, 1992). The inferior temporal cortex is engaged in feature analysis of objects (Mishkin *et al.*, 1983). In man, activation in the occipito-temporal cortex, an earlier stage in the pathway, has been observed during active processing of one class of object, namely faces (Haxby *et al.*, 1991).

Attention and Response Preparation

Premotor Cortex

Bilateral activation of the premotor cortex corresponding to the topographic localization of upper limb movement, was observed in both delay tasks compared to the control condition, but attained high significance only in the DR task. Analogous co-activation of the premotor and parietal cortex has previously been observed with shifting spatial attention (Corbetta *et al.*, 1993). The premotor cortex receives afferents from the inferior parietal cortex, area 7b, in the monkey (Cavada and Goldman-Rakic, 1989), and co-activation of these areas is consistent with a common substrate for preparation of movement and direction of attention to a specified target.

Perhaps surprisingly, there was no activation in the premotor frontal eye fields in the present or previous studies (Jonides *et al.*, 1993). The reference state in the present experiments was visual fixation, an active state that will involve activity in the oculomotor system. Activation has, however, been observed in the frontal eye fields in a comparison of 'remembered saccades', an oculomotor task incorporating a brief delay, with a resting state with the eyes closed (O'Sullivan *et al.*, 1994).

SMA

In man the SMA can be functionally subdivided at the level of the anterior commissure. Activation of the SMA rostral to the anterior commissure has been associated with the *preparation* of motor responses and activation of caudal SMA associated with the *execution* of real or imagined responses (Passingham, 1994; Stephan *et al.*, 1996). The predominant activation in the DM task was in the rostral SMA. In this task the response is not fully specified by the initial stimulus and the appropriate response remains to be selected. In the present study, activation in the caudal SMA was apparent in the DR task, in which the response has already been selected prior to the scan, in the comparison with the DM task.

Anterior Cingulate Cortex

Activation in the caudal anterior cingulate cortex has been reported in a variety of motor tasks (Frith *et al.*, 1991; Paus *et al.*, 1993). In the present study, activation in the DR task corresponds to the region activated in both manual and oculomotor tasks (Paus *et al.*, 1993). Corresponding activation was observed with imagined movements (Stephan *et al.*, 1996). Delay-related discharge has been recorded in monkeys, and while some neurons discharge in relation to cue location, the discharge of other neurons reflected a 'preparatory set for responding to a certain position' (Niki and Watanabe, 1976). Although no unitary function can be attributed to this cortical area, activation in this region has been associated with 'attention to action' (Posner *et al.*, 1988) and 'response selection' (Pardo *et al.*, 1990; Bench *et al.*, 1993; Paus *et al.*, 1993).

Decreases in rCBF in the DR and DM Tasks

The striking swathe of medial frontal deactivation in the DR task extends across cytoarchitectonic and functional boundaries, and with deactivation in temporal and posterior cingulate cortex is consistent with direction of attention from processing in these systems. The only common deactivation in both delay tasks was in the posterior insula.

Significant *deactivation* was localized in the right, and at a lower threshold in the left, hippocampus in the DM task. In the monkey hippocampal *activation* has been found in delay tasks at

long delays (Friedman and Goldman-Rakic, 1994). These apparently incompatible findings may reflect the brief attentional span of the monkey. Hippocampal lesions impair DR performance in the monkey only at delays of >15 s (Zola-Morgan and Squire, 1985), and may reflect the use of an alternative strategy involving episodic memory at longer delays. In man, material may be maintained in working memory virtually indefinitely in the absence of distraction. There is extensive neuropsychological evidence associating hippocampal formation with long-term memory, and deactivation in this system in a 'working memory' task is consistent with functional dissociation between short- and long-term memory systems. In support of this contention is the experimental evidence that direction of attention to recently presented items in a memory task facilitates their retention in working memory whilst impairing encoding of earlier items into long-term memory (Shallice, 1975). The present observations are consistent with the direction of attention *towards* maintaining material in working memory systems and *away from* episodic encoding systems.

Conclusions

The observation of a specific deficit in monkeys performing spatial tasks across a delay (Jacobsen, 1936), and the subsequent demonstration of the critical role of the cortex surrounding the principal sulcus, led to the explicit hypothesis that this area 'participates in an essential mechanism for holding spatial information 'on line'' (Goldman-Rakic, 1987).

The present study has taken advantage of the brief temporal window on brain activity conferred by this technique (Silbersweig *et al.*, 1994) to image neural activity restricted to the delay period of the tasks. Delay-related activation of the DLPFC in both tasks provides further direct evidence for the participation of this area in working memory in man.

The model of visuospatial working memory developed by Baddeley (1986) postulates a slave system, the visuospatial 'scratchpad'. The maintenance of material represented in this slave system depends on an interaction with the central executive. The DLPFC comprises a plausible anatomical substrate for this central executive system. Activation in the posterior parietal, the occipital, and the occipito-temporal cortex is consistent with a putative role of these areas as the 'scratchpad of the mind' (Raichle, 1993). Engagement of this system in the shape-matching task indicates that this system is interested not only in 'where' an object is located in global space, but also in its local spatial organization. In contrast, activation of the inferior temporal cortex is associated with representation of the features of an object that determine its identity. What is represented in the scratchpad thus reflects distributed activity in both these systems.

The common feature of both tasks was the co-activation of a network of posterior cortical areas together with the DLPFC. Analogous observations in the monkey (Friedman and Goldman-Rakic, 1994) indicate that working memory is not anatomically modular but represents sustained activity in a distributed neural system.

Notes

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References

- Andersen RA (1989) Visual and eye movement functions of the posterior parietal cortex. *Annu Rev Neurosci* 12:377-403.
- Andersen RA, Asanuma C, Cowan WM (1985) Callosal and prefrontal associational projecting cell populations in area 7a of the macaque monkey: a study using retrogradely transported fluorescent dyes. *J Comp Neurol* 232:443-455.
- Baddeley A (1986) Working memory. Oxford: Oxford University Press.
- Baker SC, Rogers RD, Owen AM, Frith CD, Dolan RJ, Frackowiak RSJ, Robbins TW (1996) Neural systems engaged in planning: a PET study of the Tower of London task. *Neuropsychologia* 34:515-526.
- Bruce CJ, Goldberg ME (1985) Primate frontal eye fields. I. Single neurons discharging before saccades. *J Neurophysiol* 53:603-63
- Bushnell MC, Goldberg ME, Robinson DL (1981) Behavioural enhancement of visual responses in monkey cerebral cortex. I. Modulation in posterior parietal cortex related to selective visual attention. *J Neurophysiol* 46:755-772.
- Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE (1991) Selective and divided attention during visual discriminations of shape, color and speed: functional anatomy by positron emission tomography. *J Neurosci* 11:2383-2402.
- Corbetta M, Miezin FM, Shulman GL, Petersen SE (1993) A PET study of visuospatial attention. *J Neurosci* 13: 1202-1226.
- Deiber M-P, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RSJ (1991) Cortical areas and the selection of movement: a study with positron emission tomography. *Exp Brain Res* 84:393-402.
- Friedman HR, Goldman-Rakic PS (1994) Coactivation of the prefrontal cortex and inferior parietal cortex in working memory tasks revealed by 2DG functional mapping in the rhesus monkey. *J Neurosci* 14:2775-2788.
- Friston KJ, Passingham RE, Nutt JG, Heather JD, Sawle GV, Frackowiak RSJ (1989) Localisation in PET images: direct fitting of the intercommissural (AC-PC) line. *J Cereb Blood Flow Metab* 9:660-695.
- Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammerstma AA, Frackowiak RSJ (1990) The relationship between local and global changes in PET scans. *J Cereb Blood Flow Metab* 10:458-466.
- Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ (1991) Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab* 11:690-699.
- Funahashi S, Bruce JB, Goldman-Rakic PS (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol* 61:331-349.
- Funahashi S, Bruce CB, Goldman-Rakic PS (1990) Visuospatial coding in primate prefrontal neurons revealed by oculomotor paradigms. *J Neurophysiol* 63:814-831.
- Funahashi S, Bruce CB, Goldman-Rakic PS (1991) Neuronal activity related to saccadic eye movements in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol* 65:1464-1483.
- Funahashi S, Chafee MV, Goldman-Rakic PS (1993) Prefrontal neuronal activity in rhesus monkeys performing a delayed antisaccade task. *Nature* 365:753-756.
- Fuster JM (1973) Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *J Neurophysiol* 36:61-78.
- Fuster JM (1989) The prefrontal cortex. New York: Raven Press.
- Fuster JM (1990) Inferotemporal units in selective visual attention and short term memory. *J Neurophysiol* 64:681-697.
- Fuster JM, Bauer RH, Jervey JP (1985) Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. *Brain Res* 330:299-307.
- Glickstein M, Arora HA, Sperry RW (1963) Delayed-response performance following optic tract section, unilateral frontal lesion and commissurotomy. *J Comp Physiol Psychol* 56:11-18.
- Gnadt JW, Andersen RA (1988) Memory related motor planning activity in posterior parietal cortex of macaque. *Exp Brain Res* 70:216-220.
- Goldman-Rakic PS (1987) Circuitry of the primate prefrontal cortex and regulation of behaviour by representational memory. In: Handbook of physiology, the nervous system (Plum F, ed), Vol. 9, pp. 373-417. Bethesda, MD: American Physiological Society.
- Goldman-Rakic PS (1988) Topography of cognition: parallel distributed networks in in primate association cortex. *Annu Rev Neurosci* 11:137-156.
- Grady CL, Maisog JM, Horwitz B, Ungerleider LG, Mentis MJ, Salerno JA,

- Pietrini P, Wagner E, Haxby JV (1994) Age-related changes in cortical blood flow activation during visual processing of faces and location. *J Neurosci* 14:1450-1462.
- Grasby PM, Frith CD, Friston KJ, Bench C, Frackowiak RSJ, Dolan RJ (1993) Functional mapping of brain areas implicated in auditory-verbal memory function. *Brain* 116:1-20.
- Haxby JV, Grady CL, Horvitz B, Ungerleider LG, Mishkin M, Carson RE, Herscovitch P, Schapiro MB, Rapoport SI (1991) Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proc Natl Acad Sci USA* 88:1621-1625.
- Hikosaka O, Wurtz RH (1983) Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. *J Neurophysiol* 49:1268-1284.
- Hikosaka O, Sakamoto M, Usui S (1989) Functional properties of monkey caudate neurons. III. Activities related to expectation of target and reward. *J Neurophysiol* 61:814-831.
- Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RSJ, Passingham RE (1994) Motor sequence learning: a study with positron emission tomography. *J Neurosci* 14:3775-3790.
- Jonides J, Smith EE, Koeppel RA, Awh E, Minoshima S, Mintun MA (1993) Spatial working memory in humans as revealed by PET. *Nature* 363:623-635.
- McCarthy G, Blamire AM, Puce A, Nobre AC, Bloch G, Hyder F, Goldman-Rakic P, Shulman RG (1994) Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proc Natl Acad Sci USA* 91:8690-8694.
- Mishkin M, Ungerleider LG, Macko KA (1983) Object vision and spatial vision: two cortical pathways. *Trends Neurosci* 6:414-417.
- Niki H (1974) Differential activity of prefrontal units during left and right delayed response trials. *Brain Res* 70:346-349.
- Niki H, Watanabe M (1976) Cingulate unit activity and delayed response. *Brain Res* 110:381-386.
- O'Sullivan EP, Jenkins IH, Brooks DJ, Henderson L, Kennard C (1994) A PET study of remembered saccades in normal subjects. *J Neurosci* 244 (Suppl 1):S98.
- Petrides M, Alivisatos B, Evans AC, Meyer E (1999) Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proc Natl Acad Sci USA* 90:873-877.
- Quintana J, Fuster JM, Yajeya J (1989) Effects of cooling parietal cortex on prefrontal units in delay tasks. *Brain Res* 503:100-110.
- Robb RA (1990) A software system for interactive and quantitative analysis of biomedical images. In: 3D imaging in medicine (Hohne KH, Fuchs H, Pizer SM, eds). NATO ASI Series Vol. F60.
- Schwartz ML, Goldman-Rakic PS (1984) Callosal and intrahemispheric connectivity of the prefrontal association cortex in rhesus monkey: relation between intraparietal and principal sulcal cortex. *J Comp Neurol* 226:403-420.
- Selemon LD, Goldman-Rakic PS (1988) Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behaviour. *J Neurosci* 8:4049-4068.
- Shallice T (1975) On the contents of primary memory. In: *Attentional performance*, Vol. 5, pp. 269-280. London: Academic Press.
- Silbersweig DA, Stern E, Frith CD, Cahill C, Schnorr L, Grootoank S, Spinks T, Clark J, Frackowiak R, Jones T (1993) Detection of thirty-second cognitive activations in single subjects with positron emission tomography: a new low-dose H₂¹⁵O regional cerebral blood flow three-dimensional imaging technique. *J Cereb Blood Flow Metab* 13:617-629.
- Spinks TJ, Jones T, Bailey DL, Townsend DW, Grootoank S, Bloomfield PM, Gilardi M-C, Casey ME, Sipe B, Reed J (1992) Physical performance of a positron tomograph for brain imaging with retractable septa. *Phys Med Biol* 37:1637-1655.
- Stephan KM, Fink GR, Passingham RE, Silbersweig D, Ceballos-Bauman AO, Frith CD, Frackowiak RSJ (1995) Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *J Neurophysiol* 73 (in press).
- Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme.
- Tanaka K, Saito H, Fukada Y, Moriya M (1991) Coding of visual images objects in the inferotemporal cortex of the macaque monkey. *J Neurophysiol* 66:170-189.
- Tanji J, Kurata K (1985) Contrasting neuronal activity in supplementary and precentral motor cortex of monkeys. I. Responses to instruction determining motor responses to forthcoming signals of different modalities. *J Neurophysiol* 53:129-141.
- Tanji J, Taniguchi K, Saga T (1980) Supplementary motor area: neuronal response to motor instructions. *J Neurophysiol* 43:60-68.
- Van Essen DC (1985) Functional organization of primate visual cortex. In: *Cerebral cortex* (Peters A, Jones EG, eds), pp 259-329. London: Plenum Press.
- Watanabe T, Niki H (1985) Hippocampal unit activity and delayed response in the monkey. *Brain Res* 325:241-254.
- Weller RE, Kaas JH (1987) Subdivisions and connections of inferotemporal cortex in owl monkeys. *J Comp Neurol* 256:137-172.
- Woods RP, Cherry SR, Mazziotta JC (1992) A rapid automated algorithm for accurately aligning and reslicing positron emission tomography images. *J Comput Asst Tomogr* 16:620-633.
- Wurtz RH, Goldberg ME (1972) Activity of superior colliculus in behaving monkey. III. Cells discharging before eye movements. *J Neurophysiol* 35:575-586.
- Zeki S, Shipp S (1988) The functional logic of cortical connections. *Nature* 335:311-317.