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 loca-
tion 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}Ge/^{68}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 × 8.5 × 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.

Stastistical Analysis
Differences in global activity within and between subjects were removed
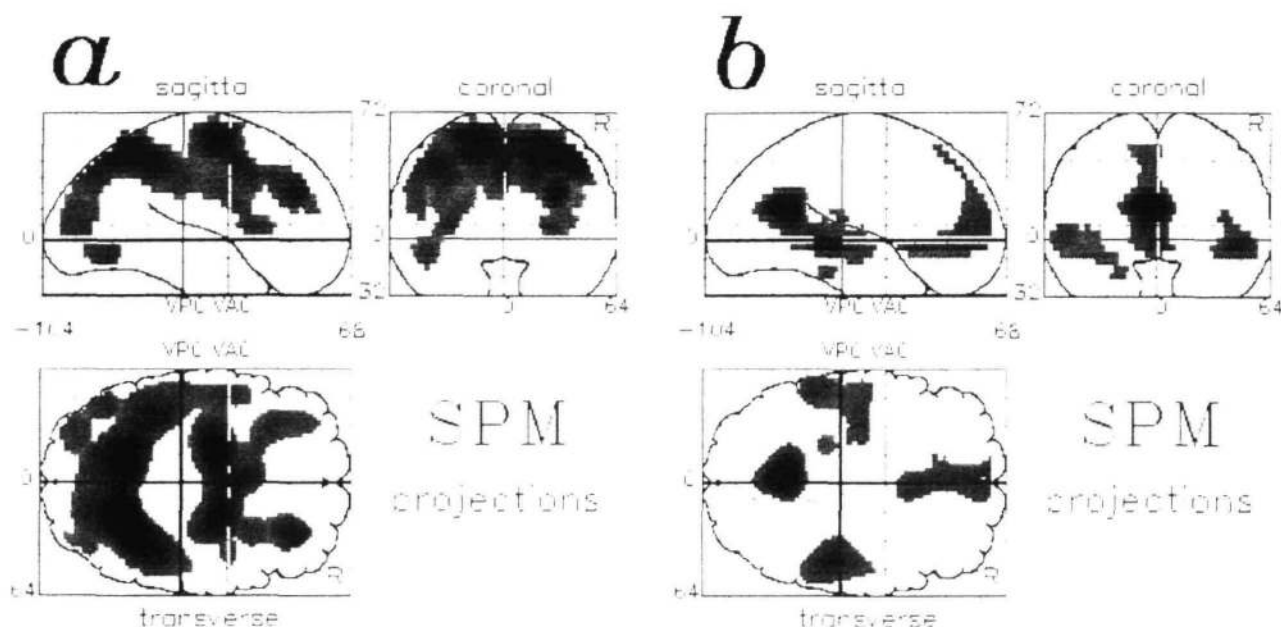
Figure 1. Statistical parametric maps comparing the spatial delayed response (DR) task with the control condition. (a) Increases and (b) decreases in rCBF. Pixels exceeding a threshold level of significance of P < 0.01 uncorrected for multiple comparisons are displayed on sagittal, coronal, and transverse 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
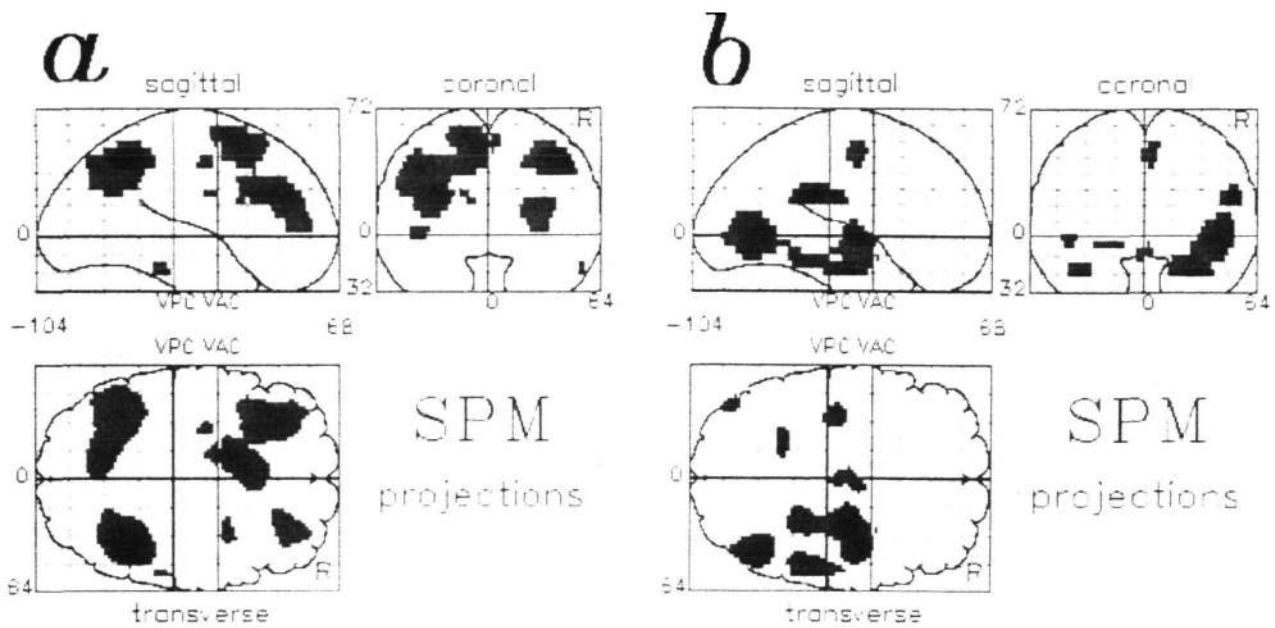
Figure 2. Statistical parametric maps comparing the shape delayed matching (DM) task with the control condition. (a) Increases and (b) decreases in rCBF. The coordinates of the foci of maximal increase and decrease of rCBF are given in Tables 3 and 4 respectively.
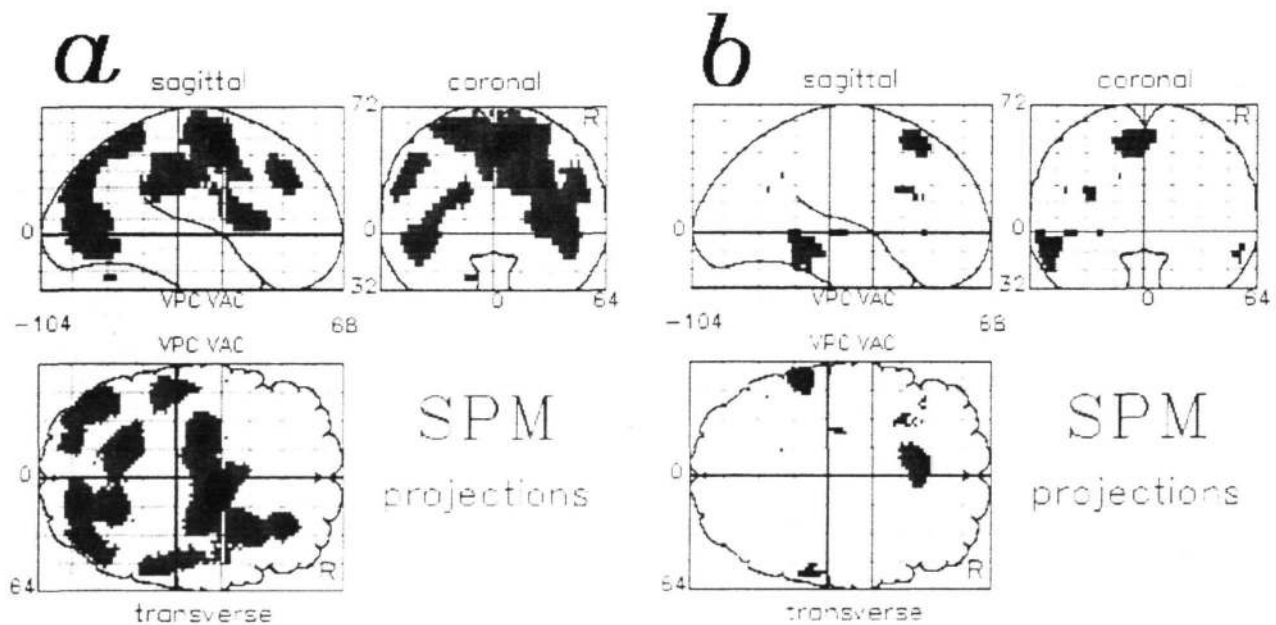

Figure 3. Statistical parametric maps of the changes in rCBF specific to the spatial (DR) and shape (DM) tasks. (a) Increases in rCBF in the DR task compared to the DM task. (b) Increases in rCBF in the DM task compared to the DR task. Pixels exceeding a threshold level of significance of $P < 0.01$ 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
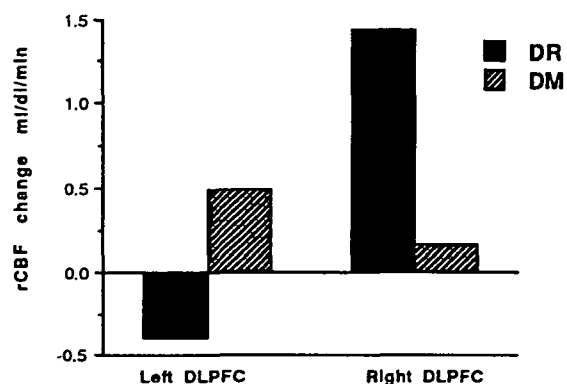
Figure 4. The upper graph illustrates the maximal changes of prefrontal rCBF in the DR and DM conditions. The lower graph illustrates the rCBF changes at the sites of maximal significant difference between the DR and DM conditions.

(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 (Freidman 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 commisure. Activation of the SMA rostral to the anterior commisure 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 incompatable 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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