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Mapping the network for planning: a correlational PET activation study with the Tower of London task

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Summary

We used the Tower of London task (TOL) and $H_2{}^{15}O$-PET to map the network of brain structures involved in planning. Six healthy right-handed subjects had 12 measurements of relative regional cerebral blood flow (rrCBF) during six conditions, each performed twice. There was one rest condition, and five sets of TOL problems at different complexity levels, performed on a touch-sensitive computer monitor with the right arm. Complexity was defined as the number of moves required to solve each problem. Activation was analysed in two ways: a category analysis comparing levels of rrCBF during rest and task was done to identify all structures involved in performance of the TOL; and a correlation analysis was carried out to delineate a subset of structures where the levels of rrCBF correlated with task complexity. Activated brain areas in which rrCBF increases did not correlate with complexity could be grouped into: (i) regions belonging to the dorsal stream of visual input processing, namely visual cortical areas 17, 18 and 19, and posterior parietal cortical areas 7 and 40; and (ii) regions involved in the execution and sequencing of arm movements (right cerebellum, left primary motor cortex and supplementary motor area). Brain regions where levels of rrCBF correlated with task complexity included lateral premotor cortex (area 6), rostral anterior cingulate cortex (areas 32 and 24), dorsolateral prefrontal cortex (areas 9 and 46) bilaterally, and right dorsal caudate nucleus. We propose that dorsolateral prefrontal, lateral premotor, anterior cingulate and caudate areas form a network for the planning of movement that interacts with brain areas primarily involved in visual processing and movement execution.

Keywords: prefrontal cortex; anterior cingulate cortex; PET; Tower of London task; basal ganglia; caudate nucleus

Abbreviations: BA = Brodmann area; rrCBF = relative regional cerebral blood flow; SMA = supplementary motor area; TOL = Tower of London task; VCA line = vertical line traversing the posterior margin of the anterior commissure

Introduction

Planning refers to the volitional organization of behaviour for the attainment of a specific goal. The Tower of London task (TOL) (Shallice, 1982; Morris *et al*., 1988; Owen *et al*., 1990) is a test of motor planning in which subjects must move coloured balls on a computer screen to match a specified arrangement in the minimum number of moves possible. In this task, the complexity depends on the minimum number of moves needed to arrive at the correct solution. The TOL is thought to be a test of planning because it is possible to solve the problems by mentally testing sequences of moves before carrying out the appropriate solution on the computer screen.

Deficiencies on the TOL have been demonstrated in patients with frontal lobe lesions (Owen *et al*., 1990), as well as in patients with Parkinson's disease (Morris *et al*., 1988; Owen *et al*., 1992). Although there is evidence that the planning impairment in Parkinson's disease is due to dopamine deficiency (Lange *et al*., 1992; Owen *et al*., 1995), it is not clear whether the site of dopamine loss critical to this planning dysfunction is the mesial frontal and prefrontal cortex, or the striatum. Previous $H_2{}^{15}O$-PET-activation studies have shown that the TOL activates frontal association cortex (dorsolateral prefrontal, premotor, anterior cingulate and frontopolar cortex) and basal ganglia, as well as posterior parietal areas (Baker *et al*., 1996; Owen *et al*., 1996*a*). A follow-up study comparing Parkinson's disease patients with

age-matched healthy subjects suggested that the deficiency in planning in the Parkinson's disease group reflected primary striatal rather than prefrontal dysfunction (Owen *et al*., 1998).

Solving TOL problems requires numerous mental activities: selection by trial and error of different strategies, visual imagery, working memory, appropriate arm movement selection and sequencing, and movement execution, all of which may activate brain areas during the 60–90 s of PET scanning. Planning can be taken to include all of the above except for movement execution. The authors of previous activation studies attempted to remove the confounding effects of movement during scanning, by subtracting levels of relative regional cerebral blood flow (rrCBF) during appropriately chosen baseline conditions from those during performance of the TOL (Baker *et al*., 1996; Owen *et al*., 1996*a*). However, in both these studies, while the yoked control conditions required the same arm movements as the activation conditions, they differed in that the movements were visually triggered. Since both animal and human studies have suggested that self-generated movements activate different brain areas to externally triggered ones (Deiber *et al*., 1991, 1996; Jahanshahi *et al*., 1995), particularly if they are visually guided, it is conceivable that these cued control states were not appropriate.

In humans, PET studies using a joystick task have shown that freely selecting the direction of joystick movements activates dorsolateral prefrontal cortex and parietal association cortex bilaterally when compared with moving the joystick in one predetermined direction (Deiber *et al*., 1991; Playford *et al*., 1992). Jahanshahi and colleagues showed that in normal subjects, self-paced index finger extensions caused greater activation of right dorsolateral prefrontal cortex than externally triggered finger movements (Jahanshahi *et al*., 1995). Finally, another PET study comparing visually cued with internally generated finger movements showed that internally generated movements caused greater activation of the presupplementary motor area (pre-SMA), anterior cingulate cortex, dorsolateral prefrontal cortex, lateral premotor cortex and left parietal cortex (Deiber *et al*., 1996). These studies therefore suggest that volitional movements activate dorsal prefrontal and mesial frontal areas over and above externally generated movements, so that the use of a yoked visually cued control condition will not guarantee that only areas involved in planning will be identified in TOL studies.

We therefore designed this study to differentiate the brain areas involved in motor planning from those involved in visual processing or execution of the solution using a correlational approach, where rrCBF was measured while subjects performed the TOL at different levels of complexity. Similar correlational designs have been used to identify brain areas activated in response to force (Dettmers *et al*., 1996), frequency (Jenkins *et al*., 1997) or complexity of learned sequential finger movements (Boecker *et al*., 1998). Our hypothesis was that, while primary motor and visual areas would be activated by the TOL, only structures involved in planning itself, such as prefrontal cortex and basal ganglia, would have levels of rrCBF that correlate with task difficulty.

Methods

Subjects

Six healthy right-handed subjects participated (four females, two males; age range 49–70 years; mean ± SD, 58.6 ± 9.7). None had a history of neurological, psychiatric or cardiovascular disease, or drug or alcohol abuse. All had normal neurological examinations. The age range was chosen so that these subjects could act as a control group for patients with Parkinson's disease, to be scanned at a later date. All subjects gave informed consent prior to taking part in the study, which was approved by the Research Ethics Committee at the Royal Postgraduate Medical School, Hammersmith Hospital. Permission to administer radioactive $H_2{}^{15}O$ was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC) of the Department of Health, UK.

PET scanning

PET scanning was performed using a CTI/Siemens 953B PET camera (CTI, Knoxville, Tenn., USA) with lead septa retracted (Spinks *et al*., 1992). This camera has a field of view of 10.65 cm. All scans were performed to include the vertex of the brain in the field of view. The subjects were placed in a vacuum-operated head holder with line markings drawn on their orbitomeatal lines and forehead. These lines were aligned with two perpendicular lasers located on the gantry so that subject position could be verified before each scan. At the start of each scanning session, a transmission scan was performed using a 68a/68e rotating rod source for the purpose of attenuation correction. Each emission scan was performed after intravenous injection of 11 mCi of $H_2{}^{15}O$ into the left antecubital vein over 20 s. Data were acquired over 90 s and patients started solving problems 10 s before the start of data acquisition (except for the two rest conditions). Emission scans were performed 10 min apart to allow radioactive decay of the injected tracer. The PET data were reconstructed using a Hanning filter with a cut-off frequency of 0.5 cycles per voxel to produce 31 image planes with a resolution of 8.5 × 8.5 × 6.0 mm full-width at half-maximal, and 128 × 128 pixels of dimensions 2.05 × 2.05 mm.

Experimental design

Each TOL problem starts with the presentation of two sets of three coloured balls on a touch-sensitive computer monitor (Owen *et al*., 1996*a*). The three balls are different colours (red, green or blue) and are distributed amongst three 'pockets' that can hold one, two or three balls (Fig. 1). Subjects are instructed to rearrange the balls in the bottom half of the screen to match the distribution in the top half of the screen.

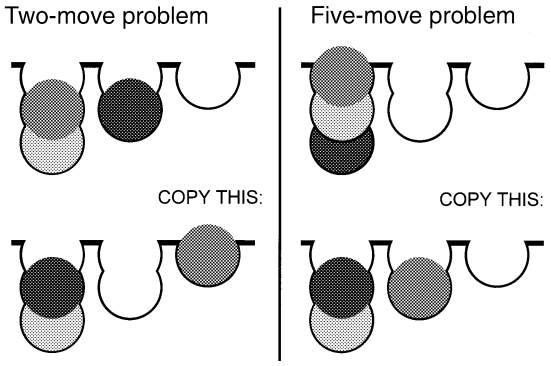

Fig. 1 The Tower of London task. The object is to rearrange the balls in the bottom half of the screen to match the top half. Subjects move the balls with their index finger via a touch-sensitive computer monitor. In the actual task, the balls are red, green or blue.

They move a ball by touching it with the right index finger, and then touching the empty position where they want to move it. After a ball is touched, it becomes circled by a yellow ring to indicate that it can be moved. Two moves are prohibited: (i) attempting to place a ball where it is not supported either by another ball or by the bottom of the pocket; and (ii) trying to remove a ball when there is another sitting above it in the same pocket. When such a move is attempted, there is no response from the computer. Task complexity was defined as the number of moves required to solve each problem (from one to five).

All subjects underwent 12 $H_2{}^{15}O$-PET scans after a 30 min training session during which the task was taught to them. Scans were performed in a darkened room, with a touch-sensitive computer monitor suspended ~18–24 inches above the subject's face so that it could be touched comfortably with the right index finger. During 10 of these scans, they performed the TOL at one of five different complexity levels. Problems were presented in succession during each 90 s scan without pause. All problems during a scan were of the same complexity (i.e. required the same number of moves for a solution). Two scans were performed with the subjects at rest staring at a blank computer screen. The order of the scans was the same for all subjects: rest, 1-move, 2, 3, 4, 5, 5, 4, 3, 2, 1, rest. For each trial, the number of moves and number of mistakes were recorded, and a performance index consisting of the percentage of perfect solutions for each trial was calculated. In addition, the time taken to solve the problems was recorded: the initial thinking time is defined as the time between the presentation of each problem and the first touch of a ball, and the subsequent thinking time is the time between the first touch of a ball and the final solution of the problem. These estimates of performance are similar to those used previously, except for the fact that in this study we have not attempted to differentiate movement execution times from thinking times (Owen *et al*., 1990, 1992). Performance and thinking times for the different levels of difficulty were assessed using one-way analysis of variance.

Data analysis

Data were analysed using SPM96 software (Wellcome Department of Cognitive Neurology, London, UK; Friston *et al*., 1995*b*) and MATLAB (The Mathworks Inc., Natick, Mass., USA) running on Silicon Graphics workstations (SGI, Mountain View, Calif., USA). Each individual's scan was realigned to his/her first scan using a six-parameter rigid-body transformation with least-squares optimization (Friston *et al*., 1995*a*). A mean image of the 12 realigned scans was created for calculation of parameters to transform each subject's images into stereotaxic space. This was done by applying a 12-parameter linear transformation, a six-parameter quadratic deformation, and a nonlinear 3D deformation to the mean image in order to match it to a template in standard stereotaxic space (Collins *et al*., 1994). Finally, each scan was smoothed using an isotropic Gaussian kernel of 12 mm full-width at half-maximum to increase signal to noise ratio and allow for inter-individual differences in gyral anatomy. SPM was used for statistical analysis (Friston *et al*., 1995*b*). The effect of variance due to global blood flow was removed by using a voxel-by-voxel ANCOVA (analysis of covariance) with global blood flow as the confounding variable (Friston *et al*., 1990), and all scans were normalized to a mean of 50.

Two types of statistical parametric maps were generated using SPM. First, a category analysis was performed in which the resting scans were subtracted from the activation scans (i.e. scans done during performance of the TOL). A threshold of $P < 0.001$ was taken as significant when identifying brain structures involved in the performance of the task. Then a correlation analysis was carried out by applying a linearly weighted contrast to the 10 planning scans. The contrast was set equal to the difficulty level of the problems for each scan (defined as the number of moves required to solve each problem). This correlation analysis, by looking for brain regions where rrCBF varied with task complexity, was designed to identify structures involved in planning. For this analysis, all activations above the threshold of $P < 0.005$ are listed. This slightly lower level of significance is thought to be acceptable for structures about which there is an a priori hypothesis based on previous PET experiments with the TOL (Owen *et al*., 1996*a*, 1998), such as the dorsolateral prefrontal cortex and basal ganglia. A second correlation analysis was carried out using the number of hand movements executed per scan as a covariate of interest. This was done to identify brain areas primarily involved in movement execution as opposed to those involved in planning.

Results

Task performance

The percentage of correct solutions is shown in Fig. 2A. These performance results, ranging from 93% correct for three-move problems to 47% for five-move problems, are in keeping with previous results in healthy elderly populations

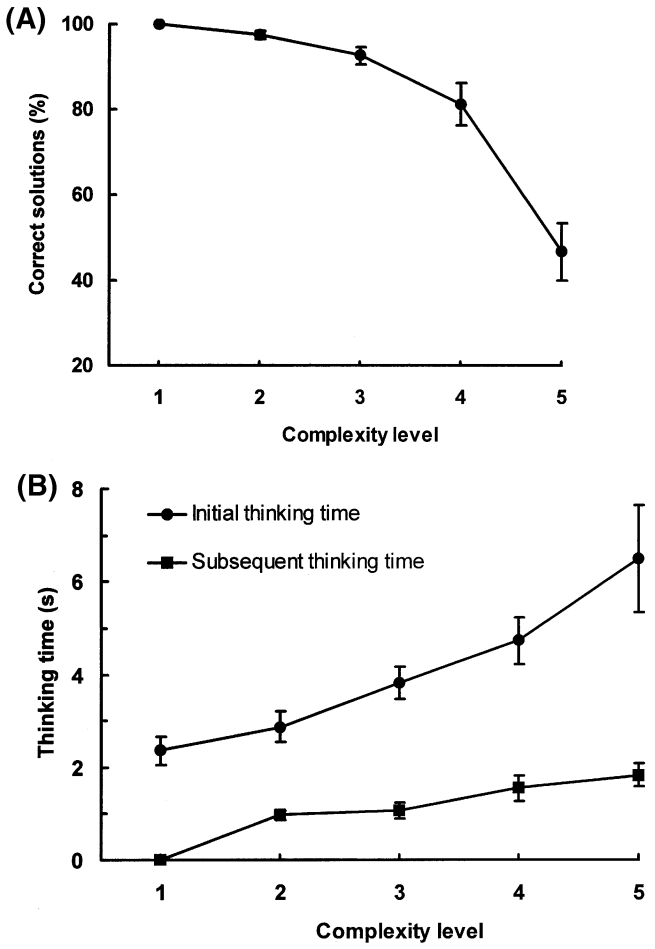

Fig. 2 Performance on the TOL task during scanning. (**A**) Percentage of correct solutions at each complexity level. A correct solution is one in which the subject arrives at the solution in the minimum number of moves. (**B**) Mean thinking time at each level. The initial thinking time is defined as the time elapsed between presentation of the problem and subject's first touch on the computer screen. The subsequent thinking time is defined as the remaining time until achievement of the correct solution of the problem. All data points represent averages for all subjects. Error bars represent the standard error of the mean.

(Owen *et al*., 1990, 1992, 1996*a*). Analysis of variance on the data from two- to five-move problems showed a deterioration in task performance related to complexity level [$F(3,44) = 27.8$; $P < 0.0001$]. There was also an increase in initial thinking time [$F(3,44) = 10.44$; $P < 0.0001$] and subsequent thinking time [$F(3,44) = 7.11$; $P = 0.0005$] as the problems became more complex (Fig. 2B). The number of hand movements during the scans is shown in Fig. 3. There was a significant difference between the number of movements done during one-move problems and all other problems ($P < 0.0001$); however, there were no significant differences in movements at all the other levels of complexity [$F(3,44) = 0.24$; $P = 0.87$].

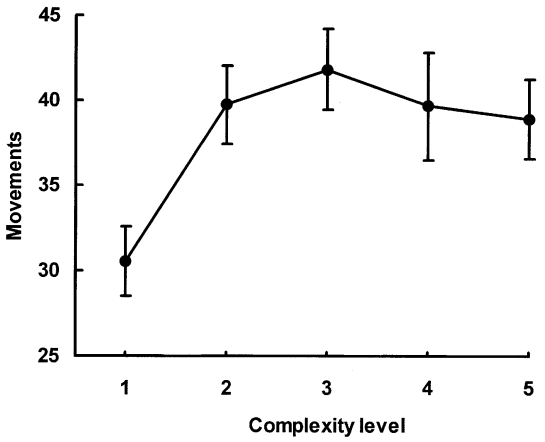

Fig. 3 Arm movements. Mean number of touches made on the computer screen during each scanning period. Error bars represent the standard error of the mean.

Cerebral blood flow (category analysis)

The category analysis involved comparing all activation scans to the resting or baseline scans. Brain areas significantly activated by the task (Table 1; Figs 4A, 5 and 6) were, on the left: primary motor cortex arm area, corresponding to Brodmann area (BA) 4, lateral premotor cortex (BA 6), anterior insula, superior and inferior parietal lobules (BA 7 and 40), occipital cortex and cerebellum. On the right the same structures, except for primary motor cortex, were activated. In addition, there was activation in several premotor and prefrontal areas: pre-SMA (defined as the part of the SMA rostral to the VCA line), dorsolateral prefrontal cortex (two sites: BA 9 and 9/46), anterior cingulate cortex (rostral anterior zone, BA 32), ventrolateral prefrontal cortex (BA 47), frontal operculum (BA 44), frontopolar cortex (BA 10) and superior frontal cortex (BA 8). There was also activation of the right inferior temporal cortex.

In addition, areas of significant reduction in rrCBF during task performance were observed (Table 2) in medial prefrontal cortex (BA 8, 9 and 10) and temporal cortex (superior, middle and inferior temporal gyri bilaterally, as well as parahippocampal gyrus on the right). There were also rrCBF reductions in the face area of primary motor cortex bilaterally, and in the arm area of primary motor cortex on the right (i.e. ipsilaterally).

Cerebral blood flow (correlation analysis)

The significance threshold for the correlation analysis was set lower ($P < 0.005$). There were bilateral increases in rrCBF with task complexity (Table 3; Figs 4B and 7) in the rostral anterior cingulate cortex (several peaks in BA 24 and 32), lateral premotor cortex (BA 6), medial frontal gyrus (BA 8) and dorsolateral prefrontal cortex (BA 9 and 9/46). On the left, there were also correlated increases in the anterior putamen and in two parietal association areas: the precuneus (BA 7) and inferior parietal cortex (BA 40); while, on the

Table 1 *Planning minus rest: categorical analysis (brain regions showing increased rrCBF during performance of the planning task at all complexity levels compared with the resting state)*

Structure	BA	Coordinates (mm)			*Z* value
		x	*y*	*z*	
Left hemisphere					
Striate cortex†	17	–16	–86	–10	7.67
Fusiform gyrus†	19	–38	–68	–12	7.17
Superior parietal lobule	7	–22	–62	52	6.70
Superior parietal lobule	7	–28	–54	56	6.59
Inferior parietal lobule	40	–52	–34	52	6.48
Cerebellum (midline)		–2	–74	–26	6.32
Inferior parietal lobule†	7	–40	–44	52	6.08
Primary motor cortex (arm)‡	4	–32	–26	64	5.88
Primary motor cortex (arm)	4	–30	–12	62	4.95
Lateral premotor cortex	6	–30	–4	60	5.35
Anterior insula		–32	20	4	4.13
Right hemisphere					
Cerebellum‡		20	–74	–24	6.99
Superior parietal lobule	7	26	–68	44	6.66
Superior parietal lobule	7	18	–60	56	6.57
Striate cortex	17	16	–86	6	6.43
Superior occipital gyrus	19	28	–72	34	6.24
Inferior parietal lobule	40	38	–52	46	5.95
Medial occipital gyrus	18	28	–80	4	5.77
Pre-SMA‡	6	10	12	48	5.64
Lateral premotor cortex	6/8	34	2	54	5.63
Lateral premotor cortex	6/8	50	10	52	5.14
Frontal operculum	44	50	12	26	5.05
Inferior temporal gyrus	37	44	–60	0	4.74
Lateral premotor cortex	8	44	20	52	4.71
Anterior cingulate	32	10	24	30	4.39
Frontopolar cortex	10	32	56	–4	4.37
Dorsolateral PFC	9/46	60	20	28	4.19
Dorsolateral PFC	46	46	46	6	3.81
Ventrolateral PFC	47	58	20	–4	3.57

All regions with a *Z* value >3.50 are listed. The coordinates of peak activations follow the conventions of Talairach and Tournoux (Talairach and Tournoux, 1988). Superscripts refer to the plots in Fig. 5 (†) and Fig. 6 (‡). PFC = prefrontal cortex.

right, increases were observed in the caudate nucleus and three additional prefrontal structures: the frontopolar cortex (BA 10), the medial frontal gyrus (BA 47), and the inferior frontal gyrus (BA 44). There were correlated reductions in rrCBF with task complexity in the left SMA and the right temporal cortex, hippocampus and cerebellum (Table 4).

We also performed a correlation of rrCBF levels with the number of moves executed during each scan (Table 5). This was done in order to differentiate areas involved in the planning of movements from those involved in movement execution. With the threshold set at $P < 0.005$, there were, in the left hemisphere, correlated increases in rrCBF in the primary motor hand area and anterior putamen, lateral premotor cortex, postcentral gyrus, inferior frontal gyrus (BA 44), and in the visual cortex (BA 17 and 18) and superior and inferior parietal lobules (BA 40). On the right, there were increases in the SMA, primary motor hand area, lateral premotor cortex and inferior parietal lobule. There were also correlated rrCBF increases in the right anterior cingulate cortex, both in the caudal cingulate zone and the posterior part of the rostral cingulate zone. The right SMA peak was large and extended rostrally into the pre-SMA and inferiorly into the anterior cingulate cortex (Fig. 9).

Discussion

This study was designed to identify brain areas activated during motor planning by correlating changes in levels of rrCBF with task complexity. Two analyses were carried out: a categorical analysis comparing rrCBF during all tasks with rest, which identified all structures activated during the performance of the TOL; and a correlation analysis, which identified those areas specifically involved in planning (Fig. 8). In order to separate activation due to motor execution from that due to planning the correct solution, we also carried out a correlational analysis of levels of rrCBF with the number of movements made during each scan.

Saccadic eye movements were not measured in this study, and it is conceivable that they increased as the problems became more complex. The absence of activation in the frontal eye fields (Paus, 1996) argues against this; however, a contribution from eye movements to the activations detected

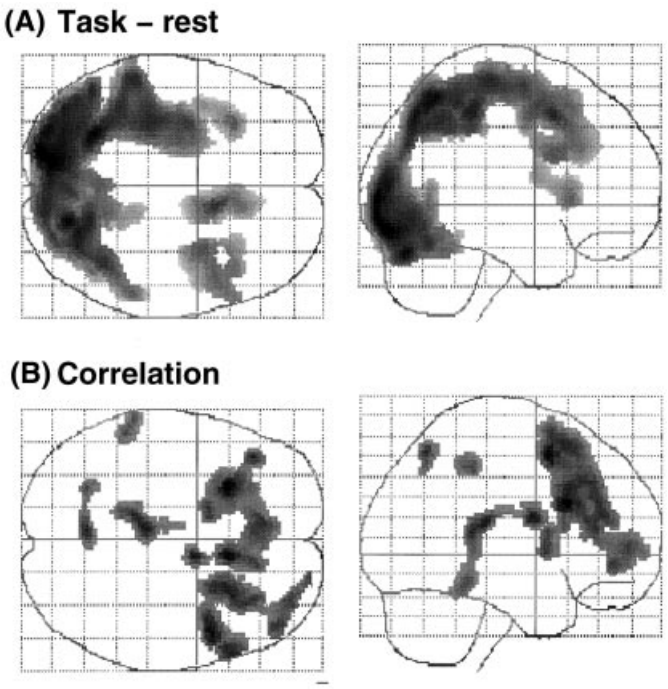

Fig. 4 Parametric maps. Glass brain views of activated areas. (**A**) Category analysis comparing task with rest. (**B**) Correlation analysis: brain areas where activation was correlated with task complexity.

within the anterior cingulate cortex cannot be excluded (Paus *et al*., 1993; Picard and Strick, 1996).

Dorsolateral prefrontal and parietal association cortex

In this study, rrCBF in the dorsolateral prefrontal cortex and lateral premotor cortex correlated with task complexity, suggesting a role for these structures in the cognitive aspects of planning. This result concurs with previous imaging studies using the TOL (Baker *et al*., 1996; Owen *et al*., 1996*a*) and with studies of TOL performance in neurosurgical patients with excisions of the frontal cortex (Shallice, 1982; Owen *et al*., 1990).

There was also extensive activation in visual and posterior parietal areas bilaterally when comparing performance of the TOL with rest, but levels of rrCBF did not correlate with problem complexity (Figs 5 and 8). These structures are components of the occipitoparietal or dorsal stream of visual information processing. This network responds to the spatial characteristics of a visual stimulus (Ungerleider and Mishkin, 1982) and is thought to process visual information in order to guide skilled action (Goodale, 1997). PET studies have demonstrated activation of areas within the dorsal stream during a variety of visuomotor tasks: tracking a moving target (Grafton *et al*., 1992); pointing (Grafton *et al*., 1996); preparation for reaching (Kawashima *et al*., 1995); mental rotation of the hand (Bonda *et al*., 1995) or objects (Parsons *et al*., 1995; Alivisatos and Petrides, 1997); and imagination of movement (Decety *et al*., 1994; Stephan *et al*., 1995). The posterior parietal cortex is extensively connected with the lateral prefrontal cortex, as reviewed by Petrides (Petrides, 1994), who suggested, based on animal and PET-activation experiments, that the dorsolateral prefrontal cortex monitors and manipulates information stored in the posterior parietal areas.

In the present study, the activation observed in the dorsolateral prefrontal cortex was complexity dependent, while that in posterior parietal and occipital cortex was complexity independent. In the TOL used here, the actual stimulus features are unrelated to the complexity of the problem, each problem comprising the same number of balls (three) and empty spaces into which they may be placed (nine) (Fig. 1). As complexity increases, the manipulations on the stimulus increase. Thus, if the role of posterior parietal cortex is to store basic stimulus features while dorsolateral prefrontal cortex performs computations on this stored information (Petrides, 1994), one would expect to see both areas activated compared with baseline, but to see a correlation between levels of rrCBF and problem complexity only in dorsolateral prefrontal cortex.

It could be argued that in our study, prefrontal cortex activation correlating with complexity is merely a feature of the greater amount of visuospatial processing required to solve more difficult problems; however, the results of several PET studies argue against this. In a matching study for the location of stimuli, activation was found within the occipitoparietal areas, but not in the frontal lobe, when subtracting a yoked motor control condition from the matching task (Haxby *et al*., 1994). Two studies using a similar matching task modified by the addition of a simple working memory component found activation in the posterior regions of the lateral frontal cortex (BA 6/8) but not in prefrontal cortex (Courtney *et al*., 1996; Owen *et al*., 1996*c*). In another study, mental construction of 3D images activated regions in the dorsal stream as well as the lateral premotor cortex, but again, not prefrontal cortex (Mellet *et al*., 1996). These paradigms, which all required processing and working memory of visuospatial stimuli, activated occipitoparietal regions and lateral premotor cortex but not prefrontal cortex. It is also unlikely that greater complexity of sequential movements during execution of the solutions to the harder TOL problems accounted for the prefrontal cortex activation seen in our study. Two PET studies involving performance of learned sequences of finger movements found levels of rrCBF that correlated with sequence complexity in lateral premotor (Sadato *et al*., 1996) or supplementary motor cortex (Boecker *et al*., 1998), but not prefrontal cortex. Taken together, these reports suggest that our finding of levels of rrCBF in dorsolateral prefrontal cortex that correlated with problem complexity is not simply due to an increase in visual or sequential movement complexity, but due to the planning component *per se*.

Owen and colleagues studied subjects while they performed a spatial monitoring task that required pointing to boxes on

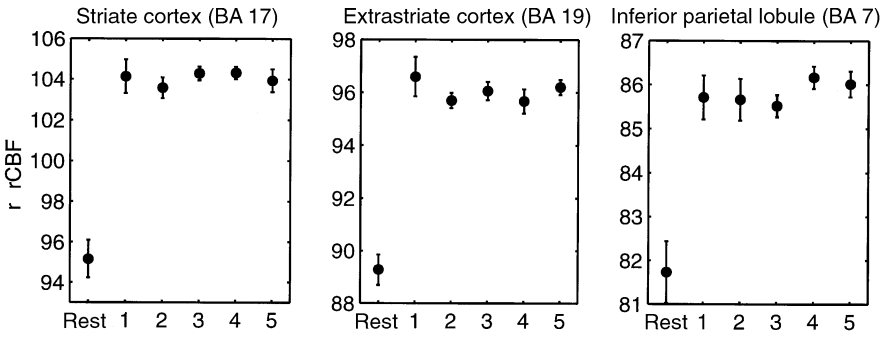

Fig. 5 Occipitoparietal structures involved in the TOL. Relative rCBF (normalized to a whole-brain mean of 50) plotted as a function of task complexity level in selected areas (BA in parentheses) of the dorsal stream of visual processing (structures labelled with † in Table 1). Relative rCBF did not correlate with complexity, suggesting that these areas are not involved in planning. The rrCBF patterns were similar in all other areas listed in Table 1. Error bars represent the standard error of the mean.

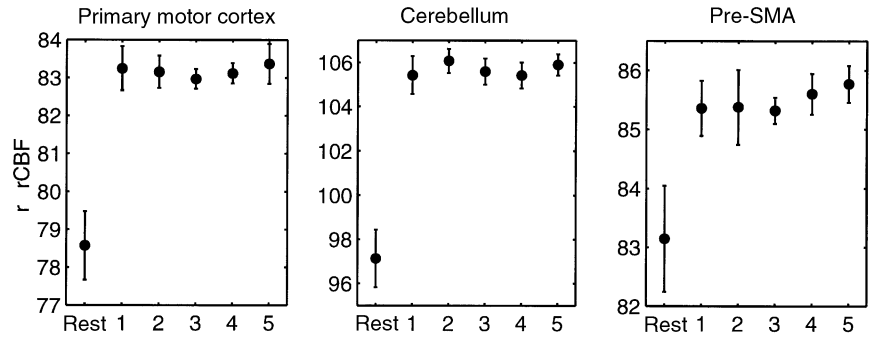

Fig. 6 Primary motor areas involved in the TOL. Relative rCBF (normalized to a whole brain mean of 50) plotted as a function of task complexity level in selected motor areas (structures labelled with ‡ in Table 1). As in Fig. 5, the rrCBF level did not correlate with complexity.

a computer screen to find a hidden token (Owen *et al*., 1996*b*). Subjects had to remember the locations containing tokens within each trial. The task therefore required spatial working memory, as well as planning and execution of a search strategy, and was associated with activation of the occipital and posterior parietal cortex, dorsolateral prefrontal cortex (BA 9 and 46), ventrolateral prefrontal cortex (BA 47), lateral premotor and anterior cingulate cortex. In a simpler monitoring task, there was also activation of dorsal stream structures and ventrolateral prefrontal cortex, but not of dorsolateral prefrontal cortex. The authors concluded that the role of the dorsolateral prefrontal cortex within this network was the complex processing of information stored in posterior parietal areas, an interpretation that is especially relevant to our current study since the task of Owen and colleagues bears a resemblance to the TOL (Owen *et al*., 1996*b*), requiring both spatial working memory and the generation of a plan of action to arrive at a solution.

Studies of motor sequence learning have also demonstrated activation of the prefrontal cortex (Jenkins *et al*., 1994; Doyon *et al*., 1996; Jueptner *et al*., 1997*b*). A recurrent finding in these studies is greater rrCBF in the dorsolateral or ventrolateral prefrontal cortex during learning of novel sequences by trial and error compared with automatic performance of a task. Berns and colleagues performed serial PET scans during a reaction time task resulting in implicit learning of a complex sequence (Berns *et al*., 1997). As implicit learning occurred and reaction times decreased, there was an increase in rrCBF in the right dorsolateral prefrontal cortex and inferior parietal lobule. These PET studies all suggest a role for prefrontal cortex in the monitoring and retention of task-related information required for learning by trial and error, whether it occurs implicitly (Berns *et al*., 1997) or explicitly (Jenkins *et al*., 1994; Jueptner *et al*., 1997*b*). In addition, in all of these studies of trial-and-error sequence learning, there was task-related activation in the basal ganglia. This supports the view that prefrontal cortex and basal ganglia form part of a functional network involved in the planning of behaviour (Wise *et al*., 1996), as does our finding of complexity-related activation in these two structures during the TOL. A monitoring role may also explain the increases in rrCBF in dorsolateral prefrontal cortex reported during the generation of random as opposed to stereotyped movements (Deiber *et al*., 1991), during the performance of internally generated as opposed to externally cued movements (Jahanshahi *et al*., 1995), and during the sustained generation of static force (Dettmers *et al*., 1995).

Table 2 *Rest minus planning: categorical analysis (brain regions showing increased rrCBF during rest compared with performance of the planning task at all complexity levels)*

Structure	BA	Coordinates (mm)			*Z* value
		x	*y*	*z*	
Left hemisphere					
Medial frontal gyrus	9	–14	50	24	7.18
Superior frontal gyrus	10	–12	60	16	6.70
Medial frontal gyrus	8	–24	36	42	5.82
Precuneus	31	0	–58	26	7.12
Medial temporal gyrus	21	–58	–14	–8	6.24
Anterior cingulate cortex	24	–10	34	16	5.58
Anterior cingulate cortex	32	–22	42	12	4.27
Superior temporal gyrus	22	–52	–62	18	4.94
Inferior temporal gyrus	20/21	–60	–40	–8	4.60
Primary motor cortex (face)	4	–56	–6	28	3.37
Right hemisphere					
Superior temporal gyrus	42	54	–14	8	6.24
Superior temporal gyrus	22	38	–36	18	4.95
Primary motor cortex (arm)	2/4	34	–32	60	3.98
Insula		44	–16	6	5.63
Transverse temporal gyrus	41	46	–30	14	5.45
Primary motor cortex (face)	4	50	–4	10	5.10
Medial temporal gyrus	21	58	–12	–4	4.79
Inferior parietal cortex	40	46	–24	24	3.72
Parahippocampal gyrus		38	–16	–10	3.64
Medial frontal gyrus	9	16	50	22	4.69
Anterior cingulate cortex	32	8	52	10	4.61
Medial frontal gyrus	8	22	42	36	4.22

Table 3 *Correlational analysis: rrCBF increases [brain regions where rrCBF correlated positively with the complexity level of the planning task (see text)]*

Structure	BA	Coordinates (mm)			*Z* value	*P* (uncorrected)
		x	*y*	*z*		
Left hemisphere						
Lateral premotor cortex	6	–26	16	28	3.76	<0.001
	6	–28	16	46	2.69	0.004
	6	–26	12	56	2.68	0.004
Anterior cingulate cortex	32	–8	38	22	3.10	0.001
	32	–8	36	32	2.93	0.002
Precuneus	7	–4	–62	54	3.18	0.001
Dorsolateral PFC	9	–42	32	30	2.95	0.002
	9/46	–24	28	34	2.49	0.006
Putamen		–16	6	2	2.90	0.002
Inferior parietal gyrus	40	–62	–36	46	2.71	0.003
Medial frontal gyrus	8	–28	26	46	2.67	0.004
Right hemisphere						
Anterior cingulate cortex†	24	8	18	26	3.65	<0.001
Anterior cingulate cortex	24	12	30	18	2.83	0.002
Anterior cingulate cortex	24/32	26	18	30	3.28	0.001
Lateral premotor cortex	6	48	8	54	3.63	<0.001
Lateral premotor cortex		24	16	58	3.24	0.001
	6/8	28	22	54	3.09	0.001
Caudate nucleus†		10	–2	20	3.41	<0.001
Dorsolateral PFC†	9	58	20	32	3.22	0.001
		32	32	38	3.07	0.001
Frontopolar cortex	10	32	52	4	2.90	0.002
Ventrolateral PFC	47	44	44	–4	2.76	0.003

All regions above a threshold of $P = 0.005$ uncorrected for multiple comparisons are shown. Superscripts (†) refer to the plots in Fig. 7. PFC = prefrontal cortex.

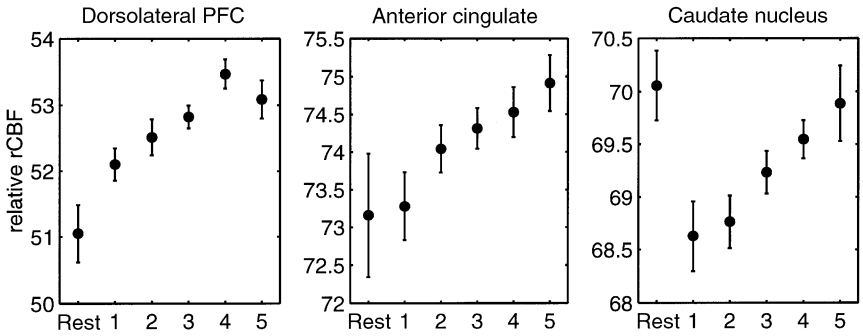

Fig. 7 Areas involved in the cognitive component of the TOL. Unlike the structures shown in Figs 5 and 6, the rrCBF in these areas correlated with task complexity (structures labelled with † in Table 3), suggesting that they are involved in motor planning. A similar pattern was found in lateral premotor cortex. Relative rCBF was normalized to a whole brain mean of 50.

Table 4 *Correlational analysis: rrCBF decreases [brain regions where rrCBF correlated negatively with the complexity level of the planning task (see text)]*

Structure	BA	Coordinates (mm)			*Z* value	P (uncorrected)
		x	*y*	*z*		
Left hemisphere						
SMA	6	–12	–10	58	3.03	0.001
Right hemisphere						
Superior temporal gyrus	22	48	–16	2	3.60	<0.001
Inferior temporal gyrus	21	52	–24	–4	2.89	0.002
Hippocampus		28	–18	–14	3.44	<0.001
Hippocampus		26	–28	–20	2.92	0.002
Cerebellum		8	–76	–20	3.35	<0.001

All regions above a threshold of $P = 0.005$ uncorrected for multiple comparisons are shown.

Supplementary and cingulate motor areas

Several motor areas on the medial wall of the frontal lobe were activated during performance of the TOL (Fig. 9). In the SMA (caudal to the VCA line) and pre-SMA (rostral to the VCA line), levels of rrCBF correlated with the number of moves made during the scan but not with task complexity. In addition, the pre-SMA was activated in the categorical analysis comparing task performance with rest. Previous PET (Boecker *et al*., 1998) and single-cell recording experiments (Shima *et al*., 1996) have led to the theory that the pre-SMA plays a role in the execution of movement sequences. In the current study, there were no complexity-correlated activations in either subdivision of the SMA, suggesting that it may not be specifically involved in the planning of movements. This appears to contradict a previous PET-activation study with the TOL, where pre-SMA activation was found when comparing planning with a yoked visually cued control task (Owen *et al*., 1996*a*). However, in that study, the control task consisted of repeating the movements made during planning by following visual prompts from the computer, and it has been demonstrated that internally generated movements cause greater activation of the pre-SMA than externally cued ones (Deiber *et al*., 1991, 1996). Indeed, when two different levels of planning (easy versus difficult problems) were compared directly, no SMA or pre-SMA activation was seen (Owen *et al*., 1996*a*). Furthermore, in two other PET-activation studies using a one-touch version of the TOL (Owen *et al*., 1995), which does not require motor output in an ordered sequence, there was no activation in the pre-SMA when problem solving was compared with performing a pre-instructed movement (Baker *et al*., 1996; Elliott *et al*., 1997). We therefore conclude that neither the SMA nor the pre-SMA is activated by motor planning.

In contrast to the SMA, the rostral anterior cingulate cortex exhibited a correlation between rrCBF and TOL complexity with peaks located in BA 24 and 32. Paus and colleagues studied rrCBF changes in the anterior cingulate cortex during motor, oculomotor and speech tasks, and concluded that activation of the rostral portion of this structure depended on the need for selection among several possible movements (Paus *et al*., 1993). Picard and Strick reviewed all PET studies with activation foci on the medial wall of the frontal cortex and found that one could divide the anterior cingulate cortex on the basis of task complexity (Picard and Strick, 1996). Simple motor tasks, involving repetitive or over-learned movements, activated areas caudal to the VCA line, while more complex tasks, involving selection or planning of movement, tended to activate areas rostral to this line. A more recent review of the PET literature confirmed that difficulty of a motor task was the major determinant of the

Table 5 *Correlational analysis: effect of movement (brain regions where rrCBF correlated positively with the number of arm movements made during the scan)*

Structure	BA	Coordinates (mm)			Z value
		x	*y*	*z*	
Left hemisphere					
Primary motor cortex (arm)	4	–28	–18	58	4.46
Anterior putamen		–18	4	8	3.82
Occipital cortex	18	–12	–66	4	3.71
Inferior parietal lobule	40	–46	–62	0	3.54
Striate cortex	17	–20	–88	–6	3.38
Superior temporal gyrus	22	–66	–18	12	3.45
Postcentral gyrus	2	–64	–20	30	3.44
Precuneus	18	–60	8	28	3.42
Lateral premotor	6	–24	10	56	3.33
	8	–52	12	36	3.16
Inferior frontal gyrus	44	–54	8	18	2.67
Right hemisphere					
SMA	6	2	0	50	4.43
	6	2	–18	58	4.07
Anterior cingulate cortex	32	2	10	44	3.84
Primary motor cortex (arm)	4	22	–16	66	3.87
Primary motor cortex (arm)	4	38	–12	52	3.47
Anterior cingulate cortex	32	28	18	34	3.83
Inferior parietal lobule	40	42	–52	38	3.64
	40	58	–32	32	3.48
	40	32	–44	54	3.30
Lateral premotor cortex	6	36	–4	52	3.53

There were no negative correlations (at a threshold of $Z = 3.50$).

presence of rostral anterior cingulate cortex activation (Paus *et al*., 1998). The results of our current study are consistent with this notion in that rrCBF correlated with task complexity in rostral anterior cingulate cortex (Table 3; Fig. 9), but with the number of arm movements in caudal anterior cingulate cortex (Table 5; Fig. 9).

While paradigms requiring response selection activate the rostral anterior cingulate cortex, its role in these tasks remains unclear. The anterior cingulate cortex has been implicated in an anterior system of selective attention, activated when conflicting responses to different stimuli are possible (Posner and Petersen, 1990). This theory has been supported by functional neuroimaging studies of the Stroop task (Pardo *et al*., 1990); a divided attention task (Corbetta *et al*., 1991); the simultaneous performance of two different cognitive tasks (D'Esposito *et al*., 1995); and in a continuous performance task where response competition could be varied from trial to trial (Carter *et al*., 1998). In all cases, response competition led to increased rostral anterior cingulate cortex (BA 24 and 32) activation. In the present study, the number of potential responses increases as the TOL problems become more complex, therefore our finding of rostral anterior cingulate cortex activation could be a reflection of response competition. However, attention to movement in the absence of potentially conflicting responses can also activate the anterior cingulate cortex. Jueptner and colleagues asked subjects to attend specifically to an over-learned sequential finger movement task and found greater rrCBF in rostral anterior cingulate cortex (Talairach coordinates: 18, 10, 28) during performance of the movements with attention than without (Jueptner *et al*., 1997*b*). Finally, it is also possible that anterior cingulate cortex activation is a reflection of increasing arousal as the problems become more complex. Anterior cingulate cortex rrCBF has been shown to increase with vigilance (Paus *et al*., 1997) and arousal (Hofle *et al*., 1997), even in the absence of increasing cognitive demands.

Basal ganglia

The TOL planning task activated both the left anterior putamen and the right caudate nucleus. In the left putamen, rrCBF correlated with the number of movements made during the scan, whereas in the right caudate nucleus, it correlated with task complexity but not with the number of movements. The activation of the caudate, therefore, followed a pattern similar to that seen in the dorsolateral prefrontal cortex, lateral premotor and rostral anterior cingulate cortex (Fig. 7). Interestingly, the rrCBF in the right caudate was lower during task performance than at rest, even though it then gradually increased with complexity. A similar reduction in right caudate rrCBF during performance of the TOL was seen in our previous study when comparing task performance with a visuomotor control task (Owen *et al*., 1998). Since it reflects a change in neuronal firing, a reduction in rrCBF can be interpreted as indicating involvement of the structure in the task. Caudate activity as measured by PET is probably a

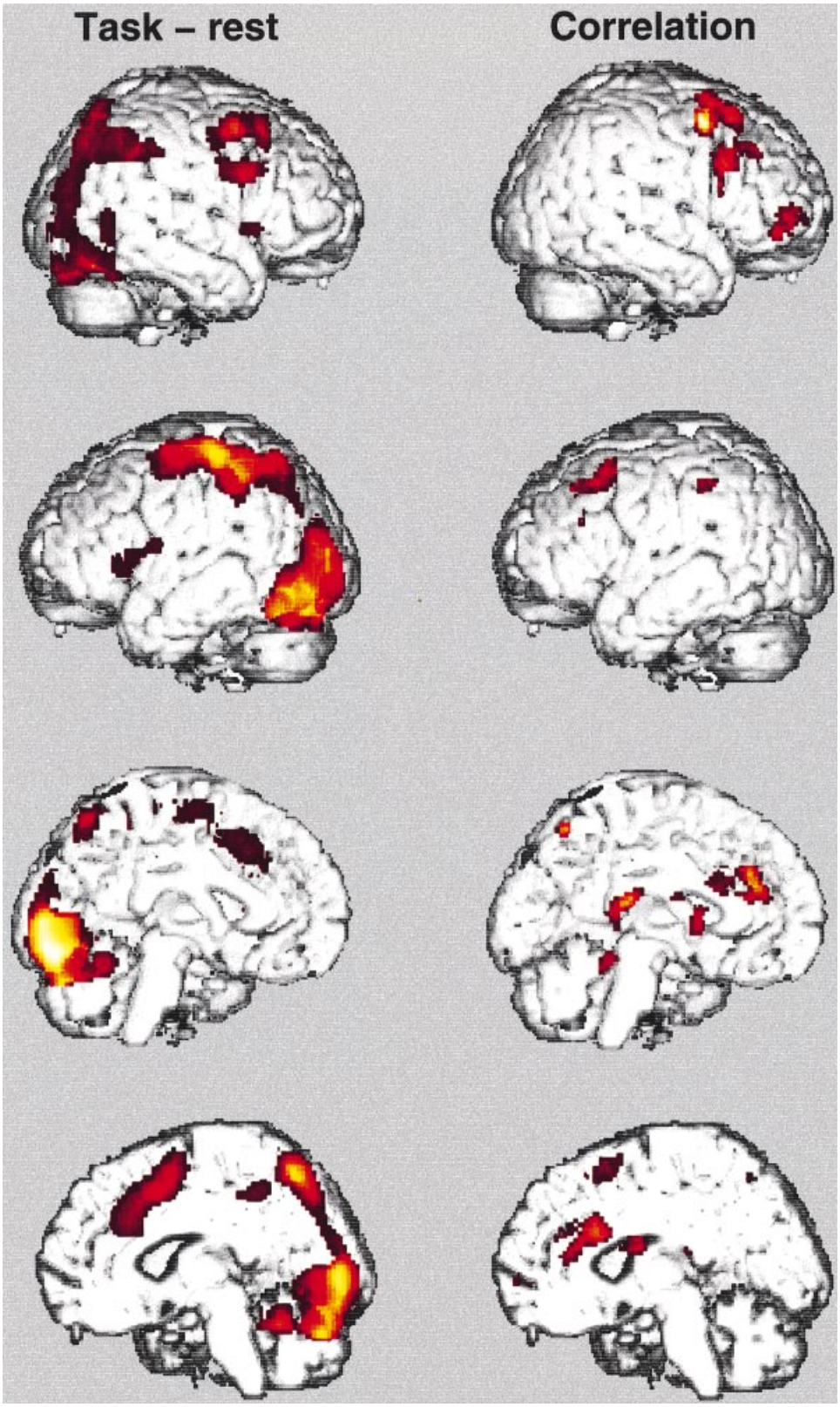

Fig. 8 Cortical activations. Statistical parametric maps rendered upon a canonical MRI in stereotaxic space. In the task minus rest category analysis there is activation of visual cortex, posterior parietal cortex, and motor and premotor areas. Only in more anterior areas does rrCBF correlate with task complexity (correlation).

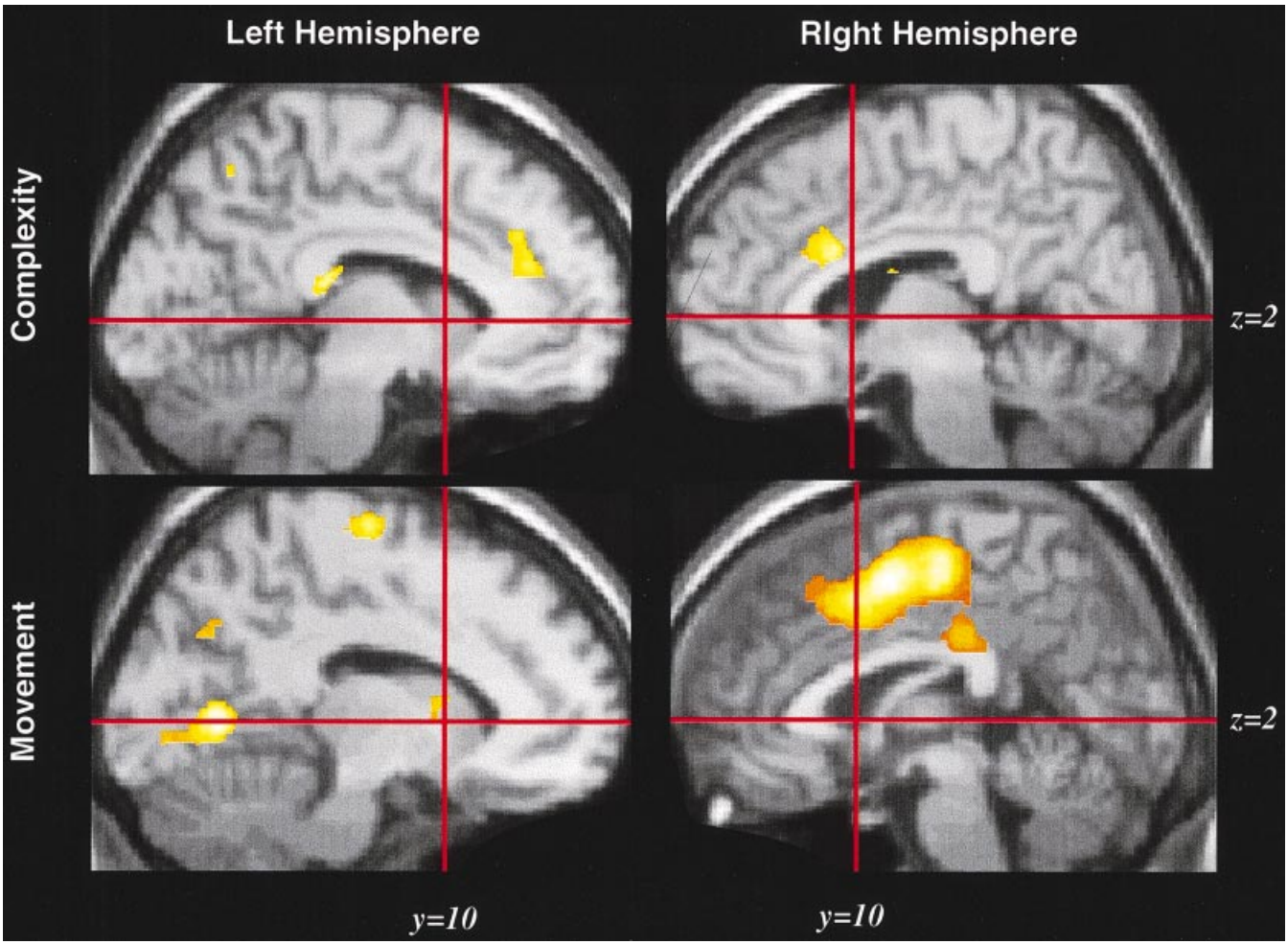

Fig. 9 Activations on the medial frontal lobe. Areas of activation on the medial wall of the frontal lobe overlaid on a canonical MRI in stereotaxic space. The top panels correspond to the correlation with complexity (Table 3), and the bottom panels to the correlation with number of hand movements (Table 5). The vertical red line ($y = 10$ mm) is 10 mm anterior to the VCA line, and represents the demarcation between caudal and rostral cingulate motor areas as proposed by Paus and colleagues (Paus *et al.*, 1998). The horizontal red line corresponds to $Z = 2$ mm and separates subcallosal from supracallosal anterior cingulate cortex. Relative rCBF correlates with task complexity in the rostral anterior cingulate, but with movement number in the caudal anterior cingulate and SMA.

result of the combined effects of corticostriatal glutamatergic inputs modulated by nigrostriatal dopamine projections. Schultz and colleagues, among others, have proposed a model of basal ganglia function that predicts a reduction in striatal medium spiny neuron firing during performance of certain tasks, and an increase in the activity of the same neuronal population during Hebbian learning tasks (which resemble planning, as discussed above) (Schultz *et al.*, 1995). This is based on the fact that dopamine release immediately leads to a reduction in spiny neuron excitability, allowing only the strongest corticostriatal inputs to get through (focusing), but that, during a complex learning task, phasic dopamine release could also cause an overall increase in spiny neuron excitability. While such a model could account for our findings, it is difficult to link events at the cellular level with PET activation results. Nonetheless, it is reasonable to assume that the pattern of rrCBF found in the caudate nucleus (Fig. 7) reflects involvement of that structure in the planning task.

Jueptner and colleagues recently reported a PET study of learning by trial and error a sequence of finger movements (Jueptner *et al.*, 1997*a*). They measured rrCBF during active sequence learning and during performance of a pre-learned sequence and found that rrCBF was relatively greater during learning in the dorsolateral prefrontal cortex, premotor cortex, anterior cingulate cortex and caudate nucleus. In contrast, while the anterior putamen was activated when comparing all finger movement sequences with rest, there was no relative difference in levels of rrCBF between the learning and automatic phases. This suggests that the head of caudate and anterior putamen perform different roles in motor control; the caudate nucleus appears to be involved in motor learning and the putamen in the execution of learned sequential movements. This hypothesis is supported by the different patterns of caudate and putamen activation found in the present study.

We previously had demonstrated activation of the caudate

nucleus during planning compared with visually cued movements in healthy subjects (Owen *et al*., 1996*a*). When Parkinson's disease patients were compared with age-matched controls (Owen *et al*., 1998), they performed less well on the task, and the main difference in the rrCBF activation pattern was in the internal segment of the right globus pallidus. Since this nucleus is the main output structure of the basal ganglia (Alexander and Crutcher, 1990), and since no difference in activation was seen in the prefrontal cortex between the two groups, we concluded that corticostriatal circuitry was involved in motor planning, and that the cause of the cognitive deficit in Parkinson's disease was abnormal processing within the basal ganglia. Another study with the TOL looked at the effect of feedback on the pattern of activation (Elliott *et al*., 1997). In the feedback conditions, subjects were given either positive ('you are right') or negative ('you are wrong') feedback after each trial; however, the occurrence of the two feedback cues was predetermined and bore no relationship to the actual performance. There was increased rrCBF in the caudate nucleus bilaterally when comparing feedback with no feedback. These results, along with the previously mentioned data on trial-and-error learning, suggest that processing within frontostriatal circuits involves the monitoring of outcomes and selection of appropriate responses (Wise *et al*., 1996).

Conclusion

PET studies of cognitive function usually involve the subtraction of a visually cued control task from the cognitive task in an attempt to map the areas of the brain involved in the cognitive process itself. However, similar movements made under cued and volitional contexts are known to be associated with different activation patterns within motor areas. In this study, we sought to overcome this limitation of the traditional PET subtraction technique by using a correlational design. We postulated that planning would involve premotor and prefrontal cortex and basal ganglia based on three lines of evidence: (i) planning deficiencies are seen in patients with frontal lobe lesions and Parkinson's disease (Morris *et al*., 1988; Owen *et al*., 1990); (ii) animal studies have shown that learning involves basal ganglia and frontal cortex (White, 1997) and (iii) human PET activation studies of planning and related tasks have implicated these structures (Baker *et al*., 1996; Owen *et al*., 1996*a*, 1998).

In our study, motor areas believed to control movement execution (primary motor cortex, SMA, caudal anterior cingulate cortex, putamen) were activated in the categorical comparison, and the rrCBF correlated with the number of arm movements made during the scan, but not with the complexity of the task. Areas within the dorsal visual processing stream were also activated, but not in a manner that correlated with task complexity. We conclude that these two groups of neuronal structures are involved in the production of motor output, and the processing of visual input, respectively, but not in motor planning itself. Both of these neuronal networks interact with the key areas involved in planning, which our study identified as the dorsolateral prefrontal cortex, lateral premotor cortex, rostral anterior cingulate cortex, and caudate nucleus. One aspect of this interaction would involve the storage and simple processing of the visual stimulus in posterior parietal areas upon which dorsolateral prefrontal cortex and basal ganglia could perform computations aimed at planning an appropriate behavioural response (Petrides, 1994).

The above may explain why patients with mild to moderate Parkinson's disease are impaired on a variety of so-called frontal tasks (e.g. planning, attentional set shifting, spatial working memory), even in the early stages of the illness before there is significant reduction in dopamine levels in the frontal cortex (Agid *et al*., 1987). Our previous work had suggested that the site of the functional abnormality in Parkinson's disease during planning was the basal ganglia (Owen *et al*., 1998). Others have suggested that prefrontal cortex interacts with anterior cingulate cortex (Paus *et al*., 1993) or basal ganglia (Wise *et al*., 1996) in the selection and planning of motor behaviour. It is likely that the basal ganglia, anterior cingulate cortex, and prefrontal and premotor cortex work together in tasks involving complex motor response selection, although the exact mechanism of the interaction is unclear. A dissection of each structure's role, and of the interactions between them, may be possible using imaging methods with greater temporal resolution such as functional magnetic resonance imaging.

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References

Agid Y, Ruberg M, Dubois B, Pillon B. Anatomoclinical and biochemical concepts of subcortical dementia. In: Stahl SM, Iversen SD, Goodman EC, editors. Cognitive neurochemistry. Oxford: Oxford University Press; 1987. p. 248–71.

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing [see comments]. Trends Neurosci 1990; 13: 266–71. Comment in: Trends Neurosci 1991; 14: 55–9.

Alivisatos B, Petrides M. Functional activation of the human brain during mental rotation. Neuropsychologia 1997; 35: 111–8.

Baker SC, Rogers RD, Owen AM, Frith CD, Dolan RJ, Frackowiak RS, et al. Neural systems engaged by planning: a PET study of the Tower of London task. Neuropsychologia 1996; 34: 515–26.

Berns GS, Cohen JD, Mintun MA. Brain regions responsive to novelty in the absence of awareness. Science 1997; 276: 1272–5.

Boecker H, Dagher A, Ceballos-Baumann AO, Passingham RE, Samuel M, Friston KJ, et al. Role of the human rostral supplementary

motor area and the basal ganglia in motor sequence control: investigations with H2 15O PET [published erratum appears in J Neurophysiol 1998; 79: 3301]. J Neurophysiol 1998; 79: 1070–80.

Bonda E, Petrides M, Frey S, Evans A. Neural correlates of mental transformations of the body-in-space. Proc Natl Acad Sci USA 1995; 92: 11180–4.

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. Science 1998; 280: 747–9.

Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr 1994; 18: 192–205.

Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE. Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. J Neurosci 1991; 11: 2383–402.

Courtney SM, Ungerleider LG, Keil K, Haxby JV. Object and spatial visual working memory activate separate neural systems in human cortex. Cereb Cortex 1996; 6: 39–49.

Decety J, Perani D, Jeannerod M, Bettinardi V, Tadary B, Woods R, et al. Mapping motor representations with positron emission tomography. Nature 1994; 371: 600–2.

Deiber MP, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RS. Cortical areas and the selection of movement: a study with positron emission tomography. Exp Brain Res 1991; 84: 393–402.

Deiber MP, Ibanez V, Sadato N, Hallett M. Cerebral structures participating in motor preparation in humans: a positron emission tomography study. J Neurophysiol 1996; 75: 233–47.

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. Nature 1995; 378: 279–81.

Dettmers C, Fink GR, Lemon RN, Stephan KM, Passingham RE, Silbersweig D, et al. Relation between cerebral activity and force in the motor areas of the human brain. J Neurophysiol, 1995; 74: 802–15.

Dettmers C, Lemon RN, Stephan KM, Fink GR, Frackowiak RS. Cerebral activation during the exertion of sustained static force in man. Neuroreport 1996; 7: 2103–10.

Doyon J, Owen AM, Petrides M, Sziklas V, Evans AC. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur J Neurosci 1996; 8: 637–48.

Elliott R, Frith CD, Dolan RJ. Differential neural response to positive and negative feedback in planning and guessing tasks. Neuropsychologia 1997; 35: 1395–404.

Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RS. The relationship between global and local changes in PET scans [see comments]. J Cereb Blood Flow Metab 1990; 10: 458–66. Comment in: J Cereb Blood Flow Metab 1993; 13: 1038–40.

Friston KJ, Ashburner J, Poline JB, Frith CD, Heather JD, Frackowiak RSJ. Spatial registration and normalisation of images. Hum Brain Mapp 1995a; 2: 165–89.

Friston KJ, Holmes AP, Worsley KJ, Frith CD, Poline JB, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995b; 3: 189–210.

Goodale MA. Visual routes to perception and action in the cerebral cortex. In: Boller F, Grafman J, editors. Handbook of neuropsychology, Vol. 11. Amsterdam: Elsevier; 1997. p. 91–109.

Grafton ST, Mazziotta JC, Presty S, Friston KJ, Frackowiak RS, Phelps ME. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. J Neurosci 1992; 12: 2542–8.

Grafton ST, Fagg AH, Woods RP, Arbib MA. Functional anatomy of pointing and grasping in humans. Cereb Cortex 1996; 6: 226–37.

Haxby JV, Horwitz B, Ungerleider LG, Maisog JM, Pietrini P, Grady CL. The functional organization of human extrastriate cortex: a PET-rCBF study of selective attention to faces and locations. J Neurosci 1994; 14: 6336–53.

Hofle N, Paus T, Reutens D, Fiset P, Gotman J, Evans AC, et al. Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. J Neurosci 1997; 17: 4800–8.

Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects [see comments]. Brain 1995; 118: 913–33. Comment in: Brain 1996; 119: 1045–8.

Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RS, Passingham RE. Motor sequence learning: a study with positron emission tomography. J Neurosci 1994; 14: 3775–90.

Jenkins IH, Passingham RE, Brooks DJ. The effect of movement frequency on cerebral activation: a positron emission tomography study. J Neurol Sci 1997; 151: 195–205.

Jueptner M, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning. II. Subcortical structures and learning by trial and error. J Neurophysiol 1997a; 77: 1325–37.

Jueptner M, Stephan KM, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning. I. Frontal cortex and attention to action. J Neurophysiol 1997b; 77: 1313–24.

Kawashima R, Roland PE, O'Sullivan BT. Functional anatomy of reaching and visuomotor learning: a positron emission tomography study. Cereb Cortex 1995; 5: 111–22.

Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology (Berl) 1992; 107: 394–404.

Mellet E, Tzourio N, Crivello F, Joliot M, Denis M, Mazoyer B. Functional anatomy of spatial mental imagery generated from verbal instructions. J Neurosci 1996; 16: 6504–12.

Morris RG, Downes JJ, Sahakian BJ, Evenden JL, Heald A, Robbins TW. Planning and spatial working memory in Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 757–66.

Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW.

Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 1990; 28: 1021–34.
Owen AM, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 1992; 115: 1727–51.

Owen AM, Sahakian BJ, Hodges JR, Summers BA, Polkey CE, Robbins TW. Dopamine-dependent frontostriatal planning deficits in early Parkinson's disease. Neuropsychology 1995; 9: 126–40.

Owen AM, Doyon J, Petrides M, Evans AC. Planning and spatial working memory: a positron emission tomography study in humans. Eur J Neurosci 1996a; 8: 353–64.

Owen AM, Evans AC, Petrides M. Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. Cereb Cortex 1996b; 6: 31–8.

Owen AM, Milner B, Petrides M, Evans AC. Memory for object features versus memory for object location: a positron-emission tomography study of encoding and retrieval processes. Proc Natl Acad Sci USA 1996c; 93: 9212–7.

Owen AM, Doyon J, Dagher A, Sadikot A, Evans AC. Abnormal basal ganglia outflow in Parkinson's disease identified with PET: implications for higher cortical functions. Brain 1998; 121: 949–65.

Pardo JV, Pardo PJ, Janer KW, Raichle ME. The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proc Natl Acad Sci USA 1990; 87: 256–9.

Parsons LM, Fox PT, Downs JH, Glass T, Hirsch TB, Martin CC, et al. Use of implicit motor imagery for visual shape discrimination as revealed by PET. Nature 1995; 375: 54–8.

Paus T. Location and function of the human frontal eye-field: a selective review. [Review]. Neuropsychologia 1996; 34: 475–83.

Paus T, Petrides M, Evans AC, Meyer E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. J Neurophysiol 1993; 70: 453–69.

Paus T, Zatorre RJ, Hofle N, Caramanos Z, Gotman J, Petrides M, et al. Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. J Cogn Neurosci 1997; 9: 392–408.

Paus T, Koski L, Caramanos Z, Westbury C. Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: a review of 107 PET activation studies. [Review]. Neuroreport 1998; 9: R37–47.

Petrides M. Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In: Boller F, Grafman J, editors. Handbook of neuropsychology, Vol. 9. Amsterdam: Elsevier; 1994. p. 59–82.

Picard N, Strick PL. Motor areas of the medial wall: a review of their location and functional activation. [Review]. Cereb Cortex 1996; 6: 342–53.

Playford ED, Jenkins IH, Passingham RE, Nutt J, Frackowiak RS, Brooks DJ. Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. Ann Neurol 1992; 32: 151–61.

Posner MI, Petersen SE. The attention system of the human brain. [Review]. Annu Rev Neurosci 1990; 13: 25–42.

Sadato N, Campbell G, Ibanez V, Deiber M, Hallett M. Complexity affects regional cerebral blood flow change during sequential finger movements. J Neurosci 1996; 16: 2691–700.

Schultz W, Romo R, Ljungberg T, Mirenowicz J, Hollerman JR, Dickinson A. Reward-related signals carried by dopamine neurons. In: Houk JC, Davis JL, Beiser DG, editors. Models of information processing in the basal ganglia. Cambridge (MA): MIT Press; 1995. p. 233–48.

Shallice T. Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci 1982; 298: 199–209.

Shima K, Mushiake H, Saito N, Tanji J. Role for cells in the presupplementary motor area in updating motor plans. Proc Natl Acad Sci USA 1996; 93: 8694–8.

Spinks TJ, Jones T, Bailey DL, Townsend DW, Grootoonk S, Bloomfield PM, et al. Physical performance of a positron tomograph for brain imaging with retractable septa. Phys Med Biol 1992; 37: 1637–55.

Stephan KM, Fink GR, Passingham RE, Silbersweig D, Ceballos-Baumann AO, Frith CD, et al. Functional anatomy of the mental representation of upper extremity movements in healthy subjects. J Neurophysiol 1995; 73: 373–86.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Ungerleider LG, Mishkin M. Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW, editors. Analysis of visual behavior. Cambridge (MA): MIT Press; 1982. p. 549–86.

White NM. Mnemonic functions of the basal ganglia. [Review]. Curr Opin Neurobiol 1997; 7: 164–9.

Wise SP, Murray EA, Gerfen CR. The frontal cortex-basal ganglia system in primates. [Review]. Crit Rev Neurobiol 1996; 10: 317–56.

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