Neuropsychologia, Vol. 31, No. 9, pp. 907–922, 1993.
Printed in Great Britain.

0028–3932/93 $6.00 + 0.00
Pergamon Press Ltd

INVESTIGATIONS OF THE FUNCTIONAL ANATOMY OF ATTENTION USING THE STROOP TEST

C. J. BENCH,*†‡ C. D. FRITH,‡§ P. M. GRASBY,†‡ K. J. FRISTON,‡ E. PAULESU,‡ R. S. J. FRACKOWIAK‡ and R. J. DOLAN†‡

†Royal Free Hospital and School of Medicine, Rowland Hill St., London NW3; ‡MRC Cyclotron Unit, Hammersmith Hospital, Du Cane Road, London W12 0HS; and §Psychology Department, University College, Gower St., London WC1, U.K.

(*Received* 6 *October* 1992; *accepted* 17 *March* 1993)

Abstract—In two separate experiments positron emission tomography (PET) was used to measure changes in regional cerebral blood flow while normal subjects performed the Stroop colour word interference test, a test of selective attention. In the first experiment performance of the Stroop task was associated with activation of right orbito-frontal and bilateral parietal structures, an unexpected result in view of previously reported findings. In addition, there were highly significant time related focal changes in rCBF. A second experiment was therefore carried out which altered the experimental parameters to replicate an earlier study. In this second experiment focal activation of the right anterior cingulate and right frontal polar cortex occurred during the Stroop task. As in the first experiment significant time effects were again apparent. To determine the functionally related brain systems during the performance of the Stroop task a correlation analysis was carried out in relation to blood flow changes induced by experimental manipulation in the right anterior cingulate. This analysis indicated the engagement of a widespread network of anterior brain regions and reciprocal inhibition of posterior brain regions during the performance of the task. The results provide evidence for the involvement of anterior right hemisphere and medial frontal structures in attentional tasks but also indicate that time effects can confound task specific activations. Furthermore subtle experimental treatment parameters, such as stimulus presentation rate, influence the degree and distribution of observed activations.

INTRODUCTION

ONE OF THE MOST critical abilities of higher organisms is to deal coherently with the constant stream of sensory information and, in parallel, to decide the appropriateness and timing of responses. This ability is generally called attention and was described by James as "the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought" [20]. Attention in this framework is a key component of normal consciousness.

In a simplified psychological model attentional mechanisms can act at either the input or output levels of information processing. At the input or sensory level they enable discriminations between relevant and irrelevant material and set priorities for the processing of input information, processes corresponding to selection or directed attention. At the output level they efficiently orchestrate the responses appropriate to the task, processes corresponding to motor intention. The range of deficits in attentional behaviour evident after

*Address for correspondence: Dr C. J. Bench, MRC Cyclotron Unit, Hammersmith Hospital, London W12 0HS, U.K.

focal damage to different brain loci [19] are in keeping with an hypothesis that attentional mechanisms influence distinct stages of information processing.

From a study of unilateral neglect syndromes, Mesulam has proposed that three cortical regions provide an integrated network for the modulation of directed attention [25]. These comprise a sensory representation in posterior parietal cortex, a schema for exploratory movements in frontal cortex, and a motivational map in cingulate cortex. Further support for Mesulam's network hypothesis comes from functional imaging studies in neglect patients with subcortical vascular lesions. In these patients there was reduced function (indexed by reduced blood flow or metabolism) in ipselateral parietal and frontal cortex [2, 4, 30]. Similarly, Posner has proposed a system for directed spatial attention mediated by the posterior parietal lobe, superior colliculus and thalamus, and a second attentional system in the anterior cingulate required to limit the effect of conflicting responses to stimuli [33]. This putative system has the ability to interface with modality specific attentional systems such as those involved in vision and language. Posner has also proposed that a third sub-system responsible for alerting/vigilance is located in the right anterior hemisphere [33], in accord with the predominance of neglect syndromes following right sided brain lesions.

Positron emission tomography (PET) allows measurement of regional cerebral blood flow (rCBF) which is closely coupled to neuronal activity [35]. The use of short lived isotopes such as ^{15}O allows several estimations of rCBF in a single subject at one sitting. Appropriate paradigm design allows for the mapping of rCBF changes during individual tasks. Differences in neural activity between two tasks provides a map of activity specific to a particular process that distinguishes the two tasks. In this way PET has established the brain areas involved in processing specific visual stimuli [6, 45], motor tasks [8], single word processing [32, 43] and internally generated actions [17]. PET studies of attentional processes suggest that, regardless of the modality or laterality of sensory input, sustained attention to localized sensory stimuli is associated with activation of the right parietal and prefrontal cortices [28]. Other evidence suggests that response/target selection, i.e. selective attention or "attention for action", may be mediated by the anterior cingulate cortex [16, 32].

Selective attention is required in tasks that involve the inhibition of competing responses. STROOP [40] devised such a task in which subjects name the colour of the ink in which a colour name is presented [5, 23, 40]. In the experimental condition the ink colour is in conflict with the printed colour name (e.g. the word "GREEN" printed in red letters). There is a strong interference effect in this task, which is manifest as an increase in the reaction time in naming the ink colours of conflicting stimuli compared with naming colours of patches or crosses. Interference occurs because subjects are unable to stop reading the words. In clinical settings the Stroop test is considered a test of prefrontal function based on its poor performance by patients with frontal lobe lesions [31]. Pardo *et al.* measured regional cerebral blood flow (rCBF) during the performance of a paired Stroop paradigm which involved naming the colour of colour congruent words in the first scan and the colour of colour incongruent words in the second scan [29]. The difference in regional brain activity between these conditions, measured in eight normal subjects, showed that maximal activation occured in the right anterior cingulate cortex during performance of the incongruent task. The authors proposed that this result was consistent with the selection of response components of the task and that the extensive network of brain areas activated, in addition to the cingulate, suggested that the interference effect could not simply be explained in terms of stimulus encoding nor response interference.

Functional imaging techniques offer new possibilities for exploring the relationship

between brain activity and particular psychological functions (in normal volunteers) or symptoms (in psychiatric patients). Resting state studies in patients with depression, in whom attentional deficits are common, have identified cingulate abnormalities [3, 24]. A neuropsychological paradigm which is sensitive to selective attention and which, in normal controls, produces a focal activation in the cingulate cortex, might be considered to be an ideal task with which to further investigate the functional anatomy of depressive illness. We therefore performed a study using the Stroop paradigm with PET and Statistical Parametric Mapping [11] in an attempt to replicate the result of Pardo *et al.* in normal volunteers prior to applying the task to depressed patients.

METHODS

Subjects

Twelve normal male volunteers were studied, six in each experiment (age range 24–33, Experiment 1; 21–34, Experiment 2). All were right-handed as assessed according to OLDFIELD [27] and had no significant medical or psychiatric history. All subjects gave informed written consent. Studies were approved by the local ethics committee and approval to administer radioisotopes was granted by the Administration of Radioactive Substances Advisory Committee (ARSAC) U.K.

Paradigm design (Experiment 1)

Each scanning session consisted of six 2.5 min PET scans. Each scan was separated by approx. 10 min to allow decay of radioactivity to $<5\%$ of the peak value in the preceding scan. Three tasks were each performed twice during the session. The order of the tasks was designed to control for systematic changes over time due to factors such as arousal and habituation (ABCCBA). The software to generate and present the stimuli was written by one of the authors (Dr Frith) in BASIC on a BBC Microcomputer (Acorn Computers Ltd, Cambridge, England). Coloured stimuli (Blue, Green, Red or Yellow) were presented on a 12 in. RGB monitor (KAGA Electronics Co. Ltd, Tokyo, Japan) placed approx. 40 cm from each subject. A white cross 5 mm by 3 mm presented 5 mm below the coloured stimuli served as a fixation point. The stimuli measured 15–32 mm by 12 mm and were displayed for 1 sec with an interstimulus interval of 1 sec. Subjects were instructed to name the colour of the presented stimulus as quickly as possible. The order of the colours presented was varied randomly within and between each task. Prior to the PET scanning sessions the subjects' reaction times were measured for the three tasks using a voice activated microphone (Voice Key Model 340, Campden Instruments Ltd, U.K.). The three conditions were as follows:

(A) Naming the colour of coloured crosses. A single row of between 3 and 6 Blue, Green, Red or Yellow crosses was presented at the predetermined rate. The number of crosses in each row was varied randomly between presentations.
(B) Naming the colour of neutral words. The words "front", "back", "top" and "down" were presented in random order.
(C) Naming the incongruent colour of a colour word—the Stroop task—(e.g. the word "red" written in green ink).

These tasks were designed to differ so that comparisons with each other might demonstrate the processes of interest. Components involved in each task are illustrated below.

	(A) Crosses	(B) Neutral words	(C) Stroop task
INTERFERENCE	O	+	++
READING	O	√	√
NAMING COLOURS	√	√	√
COLOUR VISION	√	√	√

From this design it can be seen that we would not expect to identify those brain areas involved in colour vision or colour naming. Comparison of tasks B or C with task A will highlight areas involved in the reading of words and inhibition of the automatic tendency to name those words. The latter response is probably the crucial process of interest in this experiment. A greater interference effect is evident when the words presented are incongruent colour names rather than neutral words. Task C and task B are therefore similar except for the *degree* to which they cause interference with colour naming.

Paradigm design (Experiment 2)

In view of unexpected results in the first experiment a second experiment was carried out in which the stimulus presentation rate and reaction time measurement were changed so as to replicate, as closely as possible, the study design of PARDO *et al.* [29]. Firstly, the stimuli were displayed for 1.3 sec with an interstimulus interval of 0.35 sec. Secondly, the subjects' reaction times for the three tasks were measured after the PET scans in order to eliminate potential practice effects. Thirdly, task B was changed so that colour names were presented in congruent colours. The scanning procedure was identical to the first experiment with three tasks each performed twice during the session in an ABCCBA design. The three conditions were therefore as follows:

(A) Naming the colour of coloured crosses.
(B) Naming the colour of congruent colour words.
(C) Naming the incongruent colour of a colour word (Stroop task).

The components involved in these tasks are illustrated below.

	(A) Crosses	(B) Congruent words	(C) Stroop task
INTERFERENCE	O	− −	+ +
READING	O	√	√
NAMING COLOURS	√	√	√
COLOUR VISION	√	√	√

This experiment allowed an examination of the facilitatory effect of naming congruently coloured words by the comparison of task B with the other two tasks. Tasks B and C are identical except for interference/facilitation. The comparison of tasks B and A is not matched for reading (present in B but not A).

Data acquisition

PET scans were performed using an ECAT 931-08/12 tomograph (CTI, Knoxville, TN) which produced 15 transaxial slices with an axial field of view of 10.5 cm [39]. Scans were reconstructed with a Hanning filter (cut-off frequency 0.5 Hz) giving a transaxial resolution of 8.5 mm and an axial resolution of 7 mm full width at half maximum (FWHM). The room was dimly illuminated and background noise was limited to that of the tomograph's cooling equipment. Subjects inhaled $C^{15}O_2$ mixed with air at a concentration of 6 MBq/ml and a flow rate of 500 ml/min through a standard oxygen face mask for a period of 2 min. Dynamic PET scans were collected for 2.5 min starting 0.5 min prior to $C^{15}O_2$ delivery (background scan duration 0.5 min, second scan duration 2 min) according to a well established protocal [21]. In this study the integrated counts per pixel for the 2 min build-up phase of radioactivity in the brain during $C^{15}O_2$ inhalation were used as an index of rCBF [9]. Reaction times (RTs) were measured outside the scanner using a voice activated microphone interfaced with the stimulus presentation software. For each stimulus presentation the time taken for the subject to respond verbally was stored automatically and the accuracy of the response was noted by an observer using a computer keyboard. Stimuli were presented for 150 sec and reaction times over this period were averaged. The background noise in the PET camera and the necessity for observer interaction precluded the measurement of RTs during the PET scans.

Image analysis

PET images were analysed using statistical parametric mapping (SPM software, MRC Cyclotron Unit, U.K.) and interactive image display software (Analyze, Biodynamics Research Unit, Mayo Clinic) on a SPARC 2 workstation (SUN Microsystems Europe Inc., Surrey, U.K.). Calculations and matrix manipulations were performed in PRO MATLAB (Mathworks Inc., New York, U.S.A.).

Image preprocessing and stereotaxy

The 15 original planes of data for each scan were bilinearly interpolated to 43 planes to render the voxels approximately cubic. For each individual subject, the set of six PET scans were preprocessed using automatic image alignment software to minimize the effects of any head movement between scans. This process is described in detail elsewhere [44] but in brief uses anatomical information from the brain images themselves to calculate the linear and angular displacements necessary to align the images to a reference image, in this case the first in the set of six. The alignment algorithm calculates the ratio of one image to another at each voxel in the brain and then aligns the two images such that the variance of this ratio across all voxels is minimized.

In order to allow within and between subject averaging of data collected during performance of the same task the realigned scans were then stereotactically normalized. This procedure involves a series of least squares minimization algorithms that resize the brain relative to a normal population of PET images and then reorientate and reslice to produce a stereotactically normalized image of 26 planes parallel to the anterior–posterior commissural line. Each

transverse plane is resampled in a non-linear fashion to reduce variation in brain shape [13]. Finally, in order to remove high spatial frequency noise and to accommodate the normal variability of functional and gyral anatomy the scans are smoothed with a Gaussian filter (FWHM = 10 pixels).

Statistical analysis

Methods of analysis were identical for Experiments 1 and 2. Within each experiment the six PET scans were considered as different "conditions". A pixel by pixel analysis of covariance was performed over the six conditions for all subjects with global counts as covariate and activation condition as treatment [12]. This resulted in a condition-specific adjusted (to a global CBF of 50 ml/100 ml/min) rCBF value, and an associated error variance. In order to identify differences between tasks a one-way analysis of variance with planned comparison of condition means was performed using the t statistic and linear contrasts of the six group means and associated error variance [15]. The resulting set of t values were transformed to the normal distribution to generate Gaussian statistical parametric maps (SPMs) of change significance [15]. SPMs were thresholded to allow for the multiple comparisons made, so that for the chosen significance of $P<0.05$ a false positive would be expected every 20 planes. The SPMs were displayed in three orthogonal projections showing only those pixels that exceeded the threshold of $P<0.05$. Although this method generates the foci of pixels with significant t values to the millimetre, this is not the true resolution of the statistical map. Because of smoothing in the original scans each pixel in the blood flow images represents the weighted average of pixels in a sphere that is 20 mm in diameter centred on that pixel. Thus the areas highlighted in the (t) SPM are the peaks of an activated area that is much larger. Only increases in rCBF specific to each task performance are reported here.

Correlation analysis

To determine the related brain areas engaged during the performance of the Stroop task, correlation SPMs were generated. These maps reveal in which pixels throughout the brain volume rCBF correlated systematically with rCBF in a reference location (pixel). This analysis assumes that in certain brain regions rCBF (reflecting neural activity) will be affected by performance of the Stroop task whereas in unaffected regions rCBF will be entirely independent of the task. For a particular neuropsychological function regions collectively involved should constitute a correlated network. Therefore by choosing a reference pixel in one region within this system the remaining, or most strongly engaged, components of the system should be identified in the corresponding correlation SPM. For this analysis the right anterior cingulate was selected as a reference region because (a) it showed the most focal and robust activation and (b) there was *a priori* evidence for this area being part of an anterior attentional system. The location chosen was the pixel with the maximum Z score in the comparison of the Stroop task and naming coloured crosses in Experiment 2.

RESULTS

Experiment 1

Reaction times. There was a significant difference in mean reaction times (RTs) across the three tasks (one-way ANOVA, $F=8.38$, d.f. 2, 10, $P<0.007$) (Table 1). Comparisons between individual tasks confirmed significant increases in RTs in the Stroop task vs naming colours of crosses (Scheffé test, $F=7.83$, d.f. 5, $P<0.05$) and vs naming colours of neutral words (Scheffé test, $F=4.15$, d.f. 5, $P<0.05$). Naming colours of neutral words was not significantly slower than naming colours of crosses (Scheffé test, $F=0.58$, d.f. 5, n.s.).

Global activity. There was no significant difference in mean global activity across the six scans (one-way ANOVA, $F=1.51$, d.f. 5, 30, n.s.).

Comparison of task means. The increases in rCBF (adjusted to a global mean of 50 ml/100 ml/min) seen in the Stroop task in comparison with the two other tasks separately produced common areas of increases but there were also important differences (Table 2). The areas activated in common were the parietal cortices bilaterally. Selective activations were seen comparing the Stroop task with naming colour crosses in the right orbitofrontal cortex (Brodmann's area 47) and the cingulate cortex at the junction of Brodmann's areas 23 and 24. The comparison of naming colour crosses with naming colour of neutral words produced small foci of rCBF increases in the cingulate cortex (BA 23, 24) and in the left middle frontal gyrus (BA 9/10).

Table 1. Reaction times for the tasks performed in the two experiments. Times given are the means for six subjects and are given in msec ± S.D.

Experiment 1		
CROSSES	NEUTRAL	STROOP
547 (±52)	541 (±78)	713 (±121)
Experiment 2		
CROSSES	CONGRUENT	STROOP
538 (±59.2)	420.7 (±67)	671 (±73)

Table 2. Coordinates of the pixels where the most significant increases in blood flow were identified in each comparison for both experiments. Coordinates refer to the stereotaxic atlas of Talairach and Tournoux. The rCBF values are in units of ml/dl tissue/min, and have been adjusted for a global mean blood flow of 50 ml/dl/min. The Z score is a measure of the degree of significance of the difference and is the number of standard deviations from the mean t value in the (t) statistical map of the t value for the most significant pixel in the plane

Comparison	Region	Coordinates x	y	z	rCBF		Z score
Experiment 1					C	A	
Task C vs Task A	(R) Orbitofrontal	32	32	−8	57.3	55.8	3.73
STROOP vs CROSSES		32	28	−4	59.9	58.7	4.29
		32	26	0	61.1	60.0	3.89
	(R) Cingulate	4	−4	20	41.7	40.4	3.83
	(L) Inf. Parietal	−20	−66	44	56.5	55.2	3.85
	(R) Inf. Parietal	20	−68	48	38.9	37.0	3.66
					C	B	
Task C vs Task B	(L) Inf. Parietal	−32	−64	44	51.4	49.9	4.29
STROOP vs NEUTRAL	(R) Sup. Parietal	38	−44	48	59.8	58.2	3.74
					B	A	
Task B vs Task A	(R) Cingulate	10	−4	24	39.2	38.1	3.87
NEUTRAL vs CROSSES	(L) Prefrontal	−32	44	28	38.6	37.5	3.70
Experiment 2					C	A	
Task C vs Task A	(R) Ant. cingulate	18	40	4	50.8	49.3	4.16
STROOP vs CROSSES		20	42	8	52.5	50.8	4.38
		22	42	12	53.8	51.9	4.29
	(R) Frontal polar	26	40	16	54.7	52.8	4.24
		30	44	20	49.4	47.7	3.96
Task C vs Task B	—						
STROOP vs CONGRUENT							
					B	A	
Task B vs Task A	(R) Post. cingulate	10	−44	24	51.4	49.8	3.67
CONGRUENT vs CROSSES							

Time effects. For this analysis the linear contrasts of the six group means were set to detect any systematic changes in rCBF over the course of the experiment. Highly significant ($P<0.05$ Bonferroni corrected) time related **increases** in rCBF were found bilaterally in the anterior and posterior cingulate cortex, inferior parietal lobule, primary sensorimotor cortex

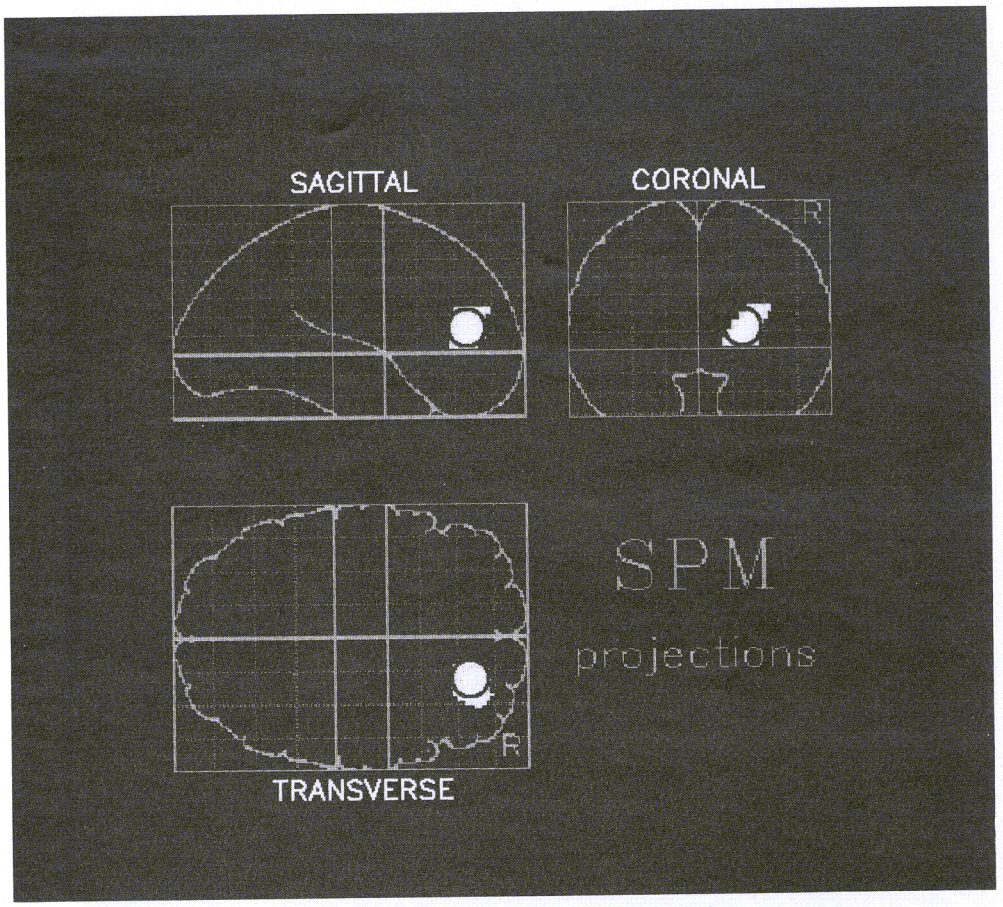

Fig. 1. Statistical parametric maps showing pixels at which there were significant increases in blood flow comparing the Stroop task with naming the colour of crosses in Experiment 2. The pixels are distributed within the stereotactic space of Talairach and Tournoux and are displayed in three orthogonal projections. The focus of most significant activation (the right anterior cingulate cortex) lies within the black circle.

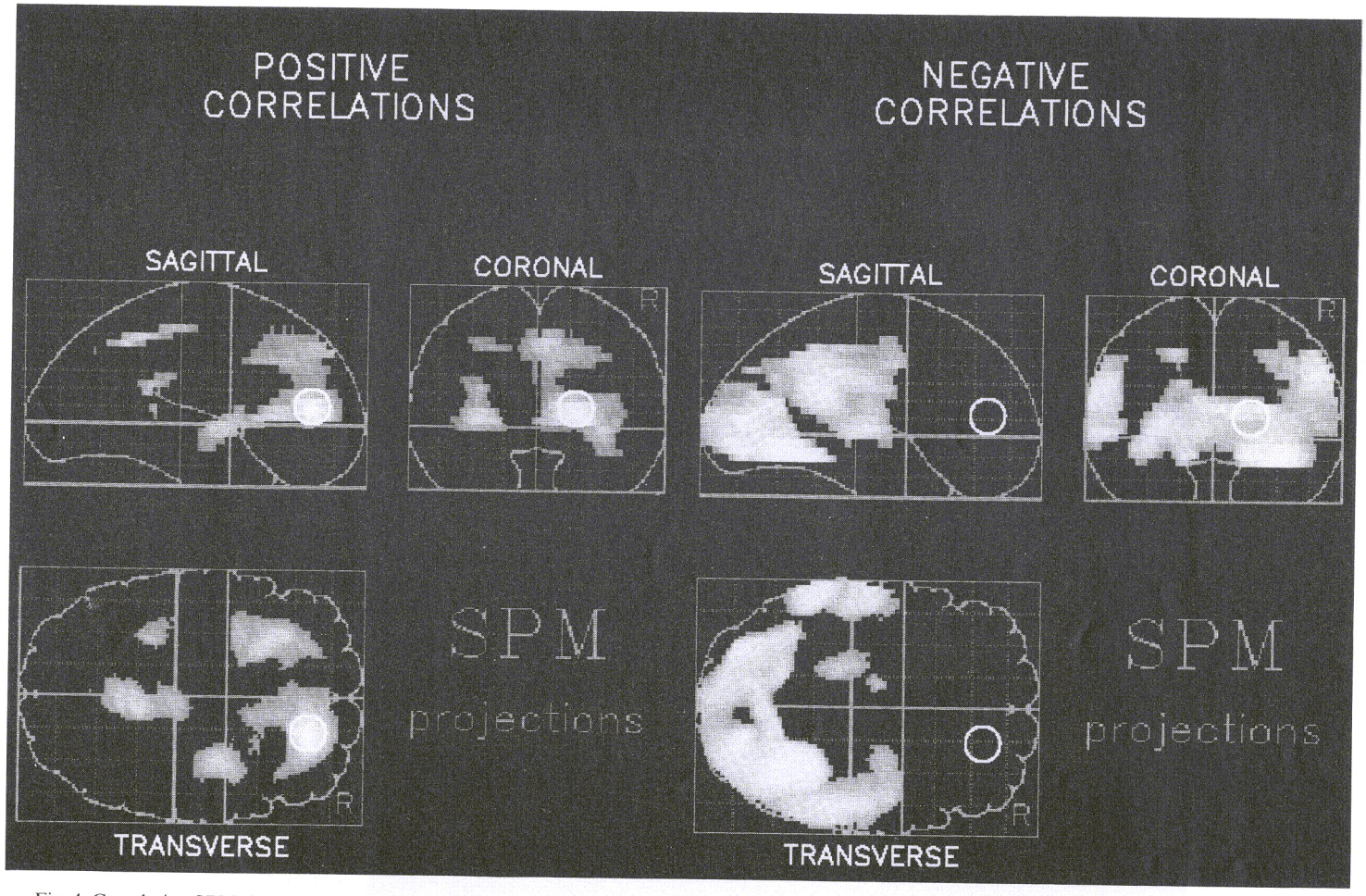

Fig. 4. Correlation SPM showing those pixels at which there are significant positive (left) and negative (right) correlations with rCBF at the reference pixel (located at the centre of the white circle) in the right anterior cingulate in the second experiment. The pixels are distributed within the stereotactic space of Talairach and Tournoux and are displayed in three orthogonal projections.

and supplementary motor area. Significant time related **decreases** in rCBF were found bilaterally in extrastriate cortex (fusiform and lingual gyri), middle and superior temporal gyri and in the left parahippocampal region. To illustrate the time effects, Fig. 2 shows a scatter plot of each subject's rCBF values in the right sensorimotor cortex, the site of the most significant increases in rCBF with time.

Experiment 2

Reaction times. There was a highly significant difference in mean reaction times (RTs) across the three tasks (one-way ANOVA, $F=109.3$, d.f. 2, 10, $P<0.0001$) (Table 1). Comparisons between individual tasks confirmed significant increases in RTs in the Stroop task vs naming colours of crosses (Scheffé test, $F=30.8$, d.f. 5, $P<0.01$) and vs naming colours of congruent words (Scheffé test, $F=109.2$, d.f. 5, $P<0.001$). Naming colours of congruent colour words was significantly faster than naming colours of crosses (Scheffé test, $F=24$, d.f. 5, $P<0.01$).

Global activity. There was no significant difference in mean global activity across the six scans (one-way ANOVA, $F=0.41$, d.f. 5, 30).

Comparison of task means. Significant right anterior cingulate (BA 24, 32) and right frontal polar (BA 10) activation was seen in the comparison of the Stroop task vs naming coloured crosses (Table 2, Fig. 1). These areas were not activated in the comparison of the Stroop task vs the congruent task, the comparison reported by PARDO *et al.* [29]. Comparison of the congruent task with naming coloured crosses revealed relative right anterior cingulate activation, but at a lower level of significance ($P<0.001$, non-corrected) and a significant activation in the right posterior cingulate (BA 29).

Time effects. Highly significant ($P<0.05$ Bonferroni corrected) time related **increases** in rCBF were found bilaterally in the anterior and posterior cingulate cortex and primary sensorimotor cortex. Significant time related **decreases** in rCBF were found bilaterally in extrastriate cortex (fusiform and lingual gyri), superior temporal gyri and in the left insula and right inferior parietal lobule.

rCBF changes in the anterior cingulate. The rCBF equivalents for the six conditions are shown in Fig. 3. The location chosen was the pixel with the maximum Z score in the anterior cingulate for the comparison of task C with task A. This illustrates the increase in activity from task A to task B to task C. No significant correlation was found between reaction times and rCBF in the right anterior cingulate during the Stroop (interference) task ($r^2=0.1$, $P<0.54$, d.f. 1, 4).

Correlation analysis (*Experiment* 2). In the second experiment, with a reference pixel in the right anterior cingulate, positive correlations were demonstrated bilaterally, more prominently on the right, with the insula/claustrum, orbitofrontal cortex and frontal eye fields (BA 8). In addition there were correlations within the anterior cingulate itself and an extensive area of the superior right frontal region involving the medial and dorsolateral prefrontal cortices. A smaller area of positive correlations was seen in the midline precuneus (BA 7). Negative correlations were seen bilaterally, again more prominently on the right, with the primary visual and extrastriate cortex. In addition there were significant bilateral negative correlations with the middle and superior temporal gyri extending upwards into inferior parietal lobule, left sided correlations in retrosplenial cortex and thalamus, and right sided correlations in sensorimotor cortex. The significance of these correlations was assessed for the whole brain volume using the χ^2 statistic. The number of pixels with a positive correlation coefficient at $P<0.001$ greatly exceeded the number expected by chance

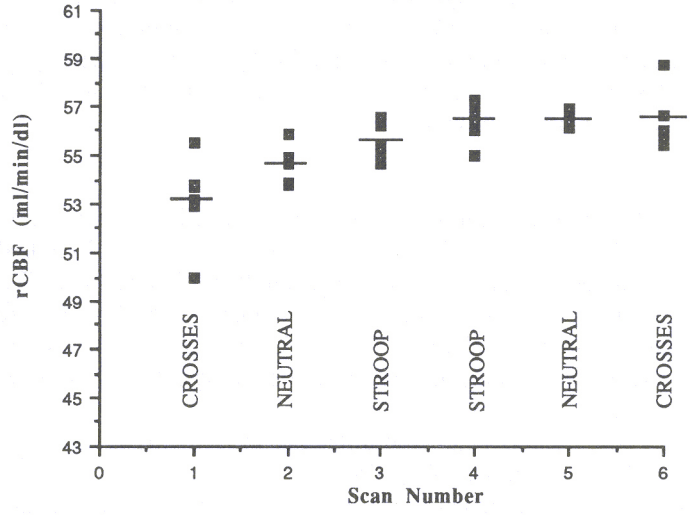

Fig. 2. Scatter plot of each subject's rCBF values in the right primary sensorimotor cortex for each condition in the first experiment, to illustrate systematic time effects. The rCBF values are adjusted to a global mean of 50 ml/dl/min. The horizontal lines indicate the mean values for each condition.

($\chi^2 = 2474$, d.f. $= 1$, $P < 0.00001$). Negative correlations were also highly significant ($\chi^2 = 7341$, d.f. $= 1$, $P < 0.00001$). Figure 4 shows the spatial distribution of pixels with significant positive (left) and negative (right) correlation coefficients at $P < 0.001$.

DISCUSSION

The results in the second experiment are in accordance with the previous finding of activation of anterior and medial prefrontal structures in the right cerebral hemisphere during performance of the Stroop colour word interference test [29]. The failure to detect such changes in the first experiment may indicate that patterns of activation depend crucially upon experimental parameters, in particular the rate of presentation of the stimuli and/or practice and learning effects. Response latencies (reaction times) did not correlate with rCBF for any of the tasks. Of particular importance, both experiments indicate significant regional time effects which have considerable implications for experimental design and interpretation.

In the second experiment there was significant right anterior cingulate activation when the Stroop task was compared with naming coloured crosses and not when compared with the congruent task. In addition the performance of the congruent task was associated with a (less significant) increase in right anterior cingulate activity. Thus the observed facilitatory process in colour naming appeared to involve a small **increase** in cingulate activity. A larger increase in activity in the same area was then seen during the more difficult conflict task. Furthermore, for the congruent task vs naming coloured crosses, in addition to modest activation in the right anterior cingulate, there was also increased rCBF in the posterior cingulate, and a strong trend to activation in parietal association cortices bilaterally ($P < 0.001$). The latter have a crucial role in several models of attention. The lack of correlation between reaction times and rCBF in the anterior cingulate may be due to the

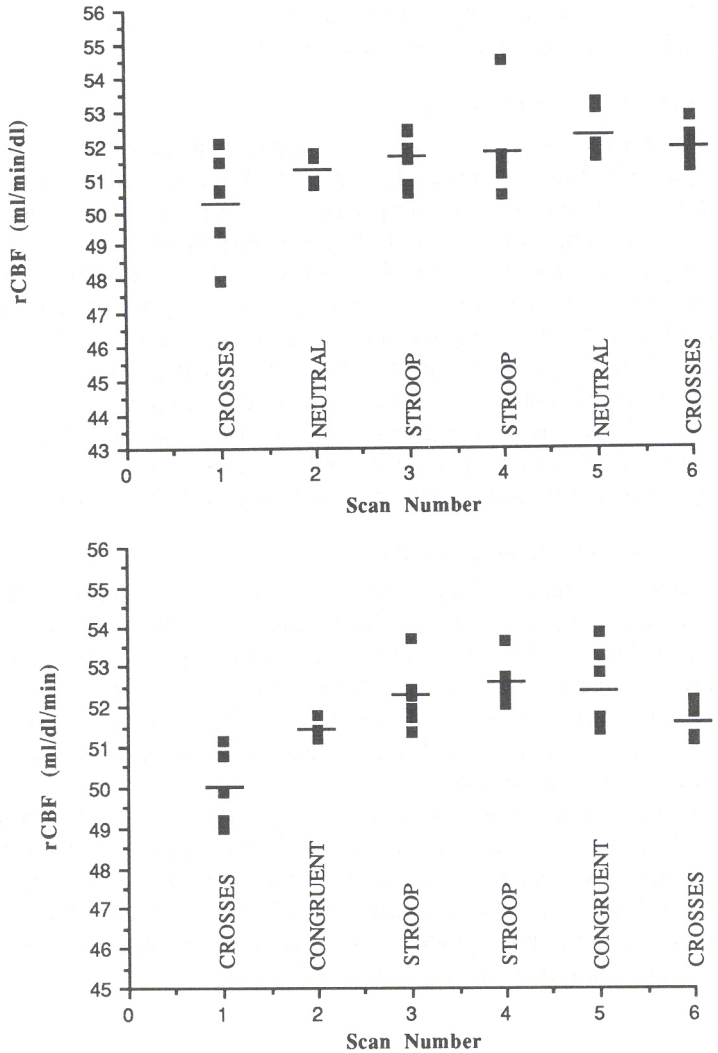

Fig. 3. Scatter plot of each subject's rCBF values in the right anterior cingulate cortex for each condition in the first (a) and second (b) experiments. The rCBF values are adjusted to a global mean of 50 ml/dl/min. The horizontal lines indicate the mean values for each condition.

variety of strategies used by individual subjects and suggests that facilitation and interference cannot be explained in terms of decreased or increased activity in this brain area.

The difference in the patterns of activation between the first and second experiment in our study was surprising and is of relevance for the design and interpretation of future PET activation experiments. The first and second experiments had two conditions in common—naming colours of crosses and incongruent words, but the identical comparisons of these conditions gave disparate results. The main difference between the two experiments involved the stage at which practice (and measurement of reaction times) was performed and the rate of stimulus presentation. In addition, the appropriate weighting of task means allowed an

examination of time effects in each experiment. The possible role of these variables in affecting the results of the experiments is discussed below.

Potential effects of practice and learning

There is evidence from PET studies that the practice and learning of motor tasks has cerebral neurophysiological correlates [14, 18, 37]. Reduced activity over time in the prefrontal cortex in the first study was interpreted as representing an attenuation of activity in an attentional system required in the early stages of the performance of a novel task, such as the supervisory attentional system (SAS) proposed by SHALLICE [38]. It is not known whether the practice and learning of tasks invoking higher cognitive functions has similar effects. However, the persistence of significantly increased reaction times for the Stroop task after completion of the PET scanning protocol in Experiment 2 (during which the Stroop task was performed twice) suggests that the effect of performing the task once before the scanning protocol in Experiment 1 is unlikely to account for the major differences seen in the profile of activations between these two experiments. Reaction times for the Stroop task were not significantly different between experiments (unpaired $t=0.71$, d.f. 10, $P<0.49$).

Potential effects of stimulus presentation rate

It is established that in primary visual cortex rCBF increases as a simple linear function of stimulus temporal frequency up to 7.8 Hz, above which rCBF plateaus and eventually falls [10]. More recently, Price *et al.* have demonstrated a similar linear relationship between the rate of presentation of heard words and blood flow response in primary auditory cortex [34]. From experiment one to experiment two the stimulus presentation rate increased from 0.5 to 0.61 Hz. This increase in the frequency of stimulus presentation is almost certainly too small to explain the difference in activation.

An additional difference between the experiments is the decrease, by 65%, in stimulus "off time" from Experiments 1 to 2. The absence of right medial and prefrontal cortex activation in the first experiment may reflect that under these conditions the performance of the task becomes routine. A longer interstimulus interval facilitates such a process. In the second experiment the shorter "off time" might demand continuous input from an attentional system involved in the performance of novel tasks [38].

Time/habituation effects

In both experiments there were highly significant regional increases and decreases in blood flow systematically with time. These effects were most marked in the first experiment (Fig. 2) and provide an alternative explanation for the lack of activation seen in the anterior cingulate when the task means were compared (Fig. 3a). In our study six PET scans were performed in a single session with the tasks ordered to balance for time effects. However, many functional imaging protocols involve paired scans and, if performed in a fixed order, time or order effects may confound the interpretation of observed activations. Examination of the individual rCBF values in the cingulate (Fig. 3b) suggests that a relative increase in flow in the second congruent task (scan 5) accounts for the lack of significance in our comparison of Stroop and congruent condition means. Thus, a paired study, in which there were single scans during performance of the congruent and Stroop tasks would have detected significant right anterior cingulate activation. RISBERG *et al.* [36] first reported decreases in frontal rCBF as a habituation effect during performance of a cognitive task and WARACH *et al.* [42] have recently described regionally specific decreases in rCBF as habituation effects that were

most pronounced in frontal and parietal regions. The time related increases in cingulate and parietal cortices that we have described support an hypothesis that habituation is mediated by a neural system that overlaps topographically that subserving attention.

The inclusion of a colour-congruent task allowed a replication of the Stroop experiment reported by PARDO *et al.* [29] in which there was activation of the superior right anterior cingulate cortex. In the appropriate comparison (incongruent task vs congruent task) we did not detect significant activations at the chosen threshold. Although the presentation of stimuli was identical in both experiments there were a number of experimental and methodological differences. The major differences between the two studies relate to the scanning protocols and statistical analysis. In the present study we included three tasks, each repeated twice, giving six scans of 120 sec duration that were ordered to control for time effects. This compares with paired scans of 40 sec duration in the Pardo study which were performed in a fixed order (congruent task before incongruent task) with no measures of performance recorded. It is conceivable that data acquisition over 120 sec as opposed to 40 sec could allow time for **within** scan habituation, particularly for an attentional process. However, this does not explain the robust activation seen in our comparison of incongruent task and colour naming. A further possibility is that time dependent changes in blood flow **between** scans account for the disparate results, as discussed above. The differences between the statistical methods used in the two studies have been discussed elsewhere [12] and are unlikely to account for the qualitatively different results.

Correlation studies

In the SPM analysis "adjusted" rCBF values (to a global mean CBF of 50 ml/100 ml/min) are used. Thus any focal increases in adjusted rCBF must be accompanied by decreases elsewhere to maintain the mean value. However, these decreases will occur randomly as "noise" unless the data set is constrained by an imposed pattern of brain activation as occurs during the performance of a cognitive task. In this case the topography of the decreases will have meaning in terms of decreased brain activity specific to the task performed. In the present study a large number of brain areas showed significant correlation of activity with the area of maximal activation in the anterior cingulate which indicates that a widespread network of cortical regions are engaged during the execution of the Stroop task. The most striking finding from this analysis is the strong negative correlation with the posterior cingulate and a large number of other posterior brain regions (Fig. 4). This observation of reciprocal changes in rCBF between anterior and posterior brain regions has been observed in other studies in our unit. Visual activation studies, based on either colour or motion detection, show that striate and extrastriate cortical activations are associated with striking reciprocal negative correlations with anterior hemisphere structures (J. D. G. Watson personal communication). The principal areas of negative correlation in the present study are the primary visual cortex, the superior temporal cortices and parietal association cortex. This suggests that the cingulate and dorsolateral prefrontal cortices may act in tandem to modulate the activity of other cortical regions. The efficient performance of the Stroop task requires inhibition of components of visual processing including the cortical regions concerned with word representation and regions involved in spatial attention.

The involvement of medial and right-sided anterior prefrontal cortex in the Stroop task is consistent with current theories of attentional processes. MESULAM [25] proposed three interacting representations of extrapersonal space, all of which have been identified in this study, with the parietal component negatively correlating with the cingulate and frontal

components. The areas we have highlighted overlap, to varying degrees, with the tripartate attentional systems of POSNER [33]. Luria postulated that patients with lesions of the medial frontal cortex had an impairment in the voluntary control of attention [22]. MILNER [26] proposed that right frontal areas are important in modulating/monitoring external events. The Stroop task is highly effortful and requires heightened external monitoring. The anterior areas descirbed in this study could also subtend the supervisory attentional system (SAS) of SHALLICE [38] which is involved in selection of operations for non-routine tasks (such as the Stroop) or equally the "central executive" of BADDELEY [1] which engages the component of working memory which maintains the context in which a task is performed.

There is now a considerable body of evidence from functional imaging studies that at least two distinct neural systems mediate attention. A system involving right prefontal and parietal cortex is activated during sustained attention across sensory modality [28]. A midline (cingulate) system appears to be involved in response selection [16, 32]. Both of these systems were activated in the second study. These findings indicate that a complex ensemble of neuronal inhibitions and activations is associated with the execution of an attentional task.

The functions of the cingulate cortex appear to differ along its extent. This heterogeneity of function is suggested by electrical stimulation studies, which, according to the site of stimulation within the cingulate, demonstrate arousal and heightened attention, simple movements or affective changes [7]. Increased anterior cingulate activity has been found in a number of PET activation studies involving attention and response selection, language and painful stimuli [6, 17, 29, 32, 41]. The coordinates of these activations vary across 30–40 mm generally caudal and dorsal to the location we have described (Table 3). The activation of various parts of the cingulate shown by different comparisons in the present study is not surprising in view of the different components of the tasks.

Table 3. Coordinates of anterior cingulate activations in various PET studies

Authors	Activation paradigm	Coordinates		
		x	*y*	*z*
PARDO *et al.* [29]	Stroop test	10	19	30
		7	17	30
		17	25	28
TALBOT *et al.* [41]	Painful heat	−15	1	33
FRITH *et al.* [16]	Verbal fluency	4	23	36
	Motor generation	−3	16	34
PETERSEN *et al.* [32]	Auditory sensory task	−12	34	18
	Visual association task	2	24	28
CORBETTA *et al.* [6]	Divided attention	−7	13	34
		−11	35	24

The present study also indicates that the pattern of cerebral activation induced by a cognitive task is highly dependent upon the experimental design. We believe that attentional tasks may be particularly susceptible to confounding systematic time effects. Classical neuropsychological tests do not necessarily transpose immediately into good functional imaging paradigms and the optimization of experimental parameters is essential before such tasks can be applied to patient populations.

Acknowledgements—C.J.B. and K.J.F. were funded by the Wellcome Trust. We wish to thank our colleagues at the MRC Cyclotron Unit, in particular Graham Lewington, Claire Taylor and Andreanna Williams, for making these studies possible.

REFERENCES

1. Baddeley, A. D. The central executive and its malfunction. In *Working Memory*. Oxford University Press, Oxford, 1986.
2. Baron, J. C., D'Antona, R., Pantano, P., Serdaru, M., Samson, Y. and Bousser, M. G. Effects of thalamic stroke on energy metabolism of the cerebral cortex. *Brain* **109,** 1243–1259, 1986.
3. Bench, C. J., Dolan, R. J., Friston, K. J., Brown, R. G., Scott, L. and Frackowiak, R. S. J. The anatomy of melancholia. Abnormalities of regional cerebral blood flow in major depression. *Psychol. Med.* **22,** 607–615, 1992.
4. Bogousslavsky, J., Miklossy, J., Regli, F., Deruaz, J.-P., Assal, G. and Delaloye, B. Subcortical neglect: Neurophysiological, SPECT, and neuropathological correlations with anterior choroidal artery territory infarction. *Ann. Neurol.* **23,** 448–452, 1988.
5. Cohen, J. D., Dunbar, K. and McClelland, J. L. On the control of automatic processes: A parallel distributed processing account of the Stroop effect. *Psychol. Rev.* **97,** 332–361, 1990.
6. Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L. and Petersen, S. E. Selective and divided attention during visual discriminations of shape, colour, and speed: Functional anatomy by positron emission tomography. *J. Neurosci.* **11,** 2383–2402, 1991.
7. Damasio, A. R. and Van Hoesen, G. W. Emotional distubance associated with focal lesions of the limbic frontal lobe. In *Neuropsychology of Human Emotion*, K. Heilman and P. Satz (Editors), pp. 85–110. Guilford, New York, 1983.
8. Deiber, M.-P., Passingham, R. E., Colebatch, J. G., Friston, K. J., Nixon, P. D. and Frackowiak, R. S. J. Cortical areas and the selection of movement: A study with positron emission tomography. *Exp. Brain Res.* **84,** 393–402, 1991.
9. Fox, P. T. and Mintun, M. A. Noninvasive functional brain mapping by change-distribution analysis of averaged PET images of $H_2{}^{15}O$ tissue activity. *J. Nucl. Med.* **30,** 141–149, 1989.
10. Fox, P. T. and Raichle, M. E. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by Positron Emission Tomography. *J. Neurophysiol.* **51,** 1109–1120, 1984.
11. Friston, K. J. and Frackowiak, R. S. J. Imaging functional anatomy. In *Brainwork* 2: *Alfred Benzon Symposium*, pp. 1–11. Munksgaard, Copenhagen, 1991.
12. Friston, K. J., Frith, C. D., Liddle, P. F., Dolan, R. J., Lammertsma, A. A. and Frackowiak, R. S. J. The relationship between global and local changes in PET scans. *J. cerebr. Blood Flow Metab.* **10,** 458–466, 1990.
13. Friston, K. J., Frith, C. D., Liddle, P. F. and Frackowiak, R. S. J. Plastic transformation of PET images. *J. comp. assist. Tomogr.* **15,** 634–639, 1991.
14. Friston, K. J., Frith, C. D., Liddle, P. F. and Frackowiak, R. S. J. The cerebellum in skill learning. *J. cerebr. Blood Flow Metab.* **11,** S440, 1991 (Abstract).
15. Friston, K. J., Frith, C. D., Liddle, P. F. and Frackowiak, R. S. J. Comparing functional (PET) images: The assessment of significant change. *J. cerebr. Blood Flow Metab.* **11,** 690–699, 1991.
16. Frith, C. D., Friston, K. J., Liddle, P. F. and Frackowiak, R. S. J. A PET study of word finding. *Neuropsychologia* **29,** 1137–1148, 1991.
17. Frith, C. D., Friston, K. J., Liddle, P. F. and Frackowiak, R. S. J. Willed action and the prefrontal cortex in man: A study with PET. *Proc. R. Soc. Lond. B* **244,** 241–246, 1991.
18. Grafton, S. T., Mazziotta, J. C., Presty, S., Friston, K. J., Frackowiak, R. S. J. and Phelps, M. E. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. *J. Neurosci.* **12,** 2542–2548, 1992.
19. Heilman, K. M., Watson, R. T., Valenstein, E. and Goldberg, M. E. Attention: Behaviour and neural mechanisms. In *Handbook of Physiology*, Section 1: The Nervous System, Vol. 5: Higher Functions of the Brain, Part 1, F. Plum (Editor), pp. 461–481. American Physiological Society, Bethesda, 1987.
20. James, W. *The Principles of Psychology*. Holt, New York, 1890.
21. Lammertsma, A. A., Cunningham, V. J., Deiber, M.-P., Heather, J. D., Bloomfield, P. M., Nutt, J. G., Frackowiak, R. S. J. and Jones, T. Combination of dynamic and integral methods for generating reproducible functional CBF images. *J. cerebr. Blood Flow Metab.* **10,** 675–686, 1990.
22. Luria, A. R. *Traumatic Aphasia*. Mouton, The Hague, 1970.
23. MacLeod, C. M. Half a century of research on the Stroop effect: An integrative review. *Psychol. Bull.* **109,** 163–203, 1991.
24. Mayberg, H. S., Jeffery, P. J., Wagner, H. N. and Simpson, S. G. Regional cerebral blood flow in patients with refractory unipolar depression measured with TC-99m HMPAO SPECT. *J. Nucl. Med.* **32,** 951, 1991 (Abstract).

25. MESULAM, M.-M. A cortical network for directed attention and unilateral neglect. *Ann. Neurol.* **10,** 309–325, 1981.
26. MILNER, B. and PETRIDES, M. Behavioural effects of frontal lobe lesions in man. *Trends Neurosci.* **7,** 403–407, 1984.
27. OLDFIELD, R. C. The assessment and analysis of handedness; the Edinburgh inventory. *Neuropsychologia* **9,** 97–113, 1971.
28. PARDO, J. V., FOX, P. T. and RAICHLE, M. E. Localization of a human system for sustained attention by positron emission tomography. *Nature* **349,** 61–64, 1991.
29. PARDO, J. V., PARDO, P. J., JANER, K. W. and RAICHLE, M. E. The anterior cingulate cortex mediates processing selection in the Stroop attenentional conflict paradigm. *Proc. Natn. Acad. Sci.* **87,** 256–259, 1990.
30. PERANI, D., VALLAR, G., CAPPA, S. F., MESSA, C. and FAZIO, F. Aphasia and neglect after subcortical stroke. A clinical/cerebral perfusion correlation study. *Brain* **110,** 1211–1229, 1987.
31. PERRET, E. The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia* **12,** 323–330, 1974.
32. PETERSEN, S. E., FOX, P. T., POSNER, M. I., MINTUN, M. and RAICHLE, M. E. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* **331,** 585–589, 1988.
33. POSNER, M. I. and PETERSEN, S. E. The attention system of the human brain. *Ann. Rev. Neurosci.* **13,** 25–42, 1990.
34. PRICE, C., WISE, R., RAMSAY, S., FRISTON, K. J., HOWARD, D., PATTERSON, K. and FRACKOWIAK, R. Regional response differences within the human auditory cortex when listening to words. *Neurosci. Lett.* **146,** 179–182, 1992.
35. RAICHLE, M. E. Circulatory and metabolic correlates of brain function in normal humans. In *Handbook of Physiology*. The Nervous System. Higher Functions of the Brain, F. PLUM (Editor), pp. 643–674. Am. Physiol. Soc., Bethesda, MD, 1987.
36. RISBERG, J., MAXIMILLIAN, A. V. and PROHOVNIK, I. Changes of cortical activity patterns during habituation to a reasoning test: A study with the ^{133}Xenon inhalation technique for measurement of regional cerebral blood flow. *Neuropsychologia* **15,** 793–798, 1977.
37. SEITZ, R. J. and ROLAND, P. E. Learning of sequential finger movements in man: A combined kinematic and Positron Emission Tomography (PET) study. *Eur. J. Neurosci.* **4,** 154–165, 1992.
38. SHALLICE, T. The allocation of processing resources. In *From Neuropsychology to Mental Structure*. Cambridge University Press, Cambridge, 1988.
39. SPINKS, T. J., JONES, T., GILARDI, M. C. and HEATHER, J. D. Physical performance of the latest generation of commercial positron scanner. *IEEE Trans. Nucl. Sci.* **35,** 721–725, 1988.
40. STROOP, J. R. Studies of interference in serial verbal reactions. *J. exp. Psychol.* **18,** 643–662, 1935.
41. TALBOT, J. D., MARRETT, S., EVANS, A. C., MEYER, E., BUSHNELL, M. C. and DUNCAN, G. H. Multiple representations of pain in human cerebral cortex. *Science* **251,** 1355–1358, 1991.
42. WARACH, S., GUR, R. C., GUR, R. E., SKOLNICK, B. E., OBRIST, W. D. and REIVICH, M. Decreases in frontal and parietal lobe regional cerebral blood flow related to habituation. *J. cerebr. Blood Flow Metab.* **12,** 546–553, 1992.
43. WISE, R., CHOLLET, F., HADAR, U., FRISTON, K. J., HOFFNER, E. and FRACKOWIAK, R. S. J. Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain* **114,** 1803–1817, 1991.
44. WOODS, R. P., CHERRY, S. R. and MAZZIOTTA, J. C. A rapid automated algorithm for accurately aligning and reslicing Positron Emission Tomography images. *J. comp. assist. Tomogr.* **16,** 620–633, 1992.
45. ZEKI, S., WATSON, J. D. G., LUECK, C. J., FRISTON, K. J., KENNARD, C. and FRACKOWIAK, R. S. J. A direct demonstration of functional specialisation in the human visual cortex. *J. Neurosci* **11,** 641–649, 1991.