Contrasting Cortical and Subcortical Activations Produced by Attentional-Set Shifting and Reversal Learning in Humans

R. D. Rogers, T. C. Andrews, P. M. Grasby, D. J. Brooks, and T. W. Robbins

University of Cambridge and Medical Research Council, United Kingdom

Abstract

■ Much evidence suggests that lesions of the prefrontal cortex (PFC) produce marked impairments in the ability of subjects to shift cognitive set, as exemplified by performance of the Wisconsin Card Sorting Test (WCST). However, studies with humans and experimental primates have suggested that damage to different regions of PFC induce dissociable impairments in two forms of shift learning implicit in the WCST (that is, extradimensional (ED) shift learning and reversal shift learning), with similar deficits also being apparent after damage to basal ganglia structures, especially the caudate nucleus. In this study, we used the same visual discrimination learning paradigm over multidimensional stimuli, and the $H_2{}^{15}O$ positron emission tomography (PET) technique, to examine regional cerebral blood flow (rCBF) changes associated with these subcomponent processes of the WCST. In three conditions, subjects were scanned while acquiring visual discriminations involving either (i) the same stimulus dimension as preceding discriminations (*intradimensional (ID) shifts*); (ii) different stimulus dimensions from previous discriminations (*ED shifts*) or (iii) reversed stimulus-reward contingencies (*reversal shifts*). Additionally, subjects were scanned while responding to already learnt discriminations ('performance baseline'). ED shift learning, relative to ID shift learning, produced activations in prefrontal regions, including left anterior PFC and right dorsolateral PFC (BA 10 and 9/46). By contrast, reversal learning, relative to ID shift learning, produced activations of the left caudate nucleus. Additionally, compared to reversal and ID shift learning, ED shift learning was associated with relative deactivations in occipito-temporal pathways (for example, BA 17 and 37). These results confirm that, in the context of visual discrimination learning over multidimensional stimuli, the control of an acquired attentional bias or 'set', and the control of previously acquired stimulus-reinforcement associations, activate distinct cortical and subcortical neural stations. Moreover, we propose that the PFC may contribute to the control of attentional-set by modulating attentional processes mediated by occipito-temporal pathways. ■

INTRODUCTION

Shifting cognitive set, as measured by performance of the Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948), is widely considered a cardinal function of the human prefrontal cortex (PFC). However, it has been widely documented (for example, Anderson, Damasio, Dallas, Jones, & Tranel, 1991) that interpretation of the impairments shown on this task by patients who have sustained damage to the PFC (Drewe, 1974; Milner, 1963, 1964; Robinson, Heaton, Lehman, & Stilson, 1980) is complicated by a number of neuropsychological and cognitive factors. Thus, at the level of clinical practice, both the *sensitivity* and *specificity* of the WCST to human PFC involvement has been questioned on the basis of studies that have either failed to demonstrate significant deficits in patient samples with known PFC lesions (Anderson et al., 1991; Eslinger & Damasio, 1985; Grafman, Jonas, & Salazar, 1990; Heck & Bryer, 1986), or shown marked impairments in patients with specifically *nonfrontal* brain damage (for example, Anderson et al., 1991; Hermann, Wyler, & Richey, 1988; Teuber, Battersby, & Bender, 1951). Notwithstanding these acknowledged difficulties, the balance of evidence indicates that PFC damage is associated with impaired performance of the WCST and, thus, the task continues to be used to probe prefrontal dysfunction in an expanding range of neurological and neuropsychiatric conditions (for example, Parkinson's and Huntington's disease: Bowen, Kamienny, Burns, & Yahr, 1975; Josiassen, Curry, & Mancall, 1983; schizophrenia: Berman et al., 1986; Weinberger, Berman, & Zee, 1986; depression: Martin, Wiggs, Ungerleider, & Haxby, 1996).

At a cognitive level of analysis, there has been surprisingly little experimental research on the precise psychological basis of the impairments shown by frontal lobe patients in performance of the WCST. The finding that such patients tend to continue to sort the stimulus cards by the previously correct, but currently *incorrect* rule,

has generally been taken at face value, as supportive evidence for damage to some sort of executive system responsible for reorganising the patients' cognitive resources in order to replace one previously appropriate behavior with another more in line with altered behavioral goals (as defined by the experimenter's change-of-sorting rule). In this way, the frontal deficit is often presented as the persistence of a 'central set' (in the sense of Mishkin, 1964). However, inflexible or perseverative responding can originate from an inability to modulate processing at any one of several levels within the cognitive system (for example, Sandson & Albert, 1984, 1987). Thus, a difficulty in shifting from one sorting rule to another in the WCST might involve a failure to reorganise attentional, decisional or response-related cognitive operations. Despite the widely accepted view of failure on the WCST as the hallmark of PFC dysfunction, very little is understood about which particular aspects of cognitive processing fail to be appropriately modified when patients with PFC damage are required to shift from sorting the cards according to one rule to sorting the cards according to another.

Such difficulties are particularly relevant to recent suggestions that impairments on the WCST arise from damage to 'working memory' systems subserved by the PFC and interconnected posterior cortical systems (Berman, Zee, & Weinberger, 1995; Goldman-Rakic, 1987, 1991 for review). On this view, the failure of frontal lobe patients to shift from one sorting rule to another reflects their relative inability to maintain an integrated representation of the information necessary for identifying and then shifting to the newly relevant sorting rule. Undoubtedly, access to information held in short-term memory is important in the performance of the WCST, as it has to be in any task in which a subject's responses are contingent upon previously presented, but now absent, stimuli or cues (Goldman-Rakic, 1987). However, an important but neglected feature of the WCST is the involvement of associative as well as working memory processes. Essentially, the WCST is a series of visual discriminations over multidimensional stimuli, in which different aspects of the stimuli are relevant to reinforcement at different times (Teuber et al., 1951). Thus, a series of successful responses (*sorts*) across a number of trials results in positive feedback that will strengthen associative links between various aspects of the stimulus cards (for example, individual exemplars of stimulus dimensions) and reinforcement. It is likely that PFC mechanisms play an important role in modulating the powerful effects that such associative links can exert on subsequent behavior (Jones & Mishkin, 1972; Mishkin, 1964). However, it seems that the complexity of the WCST—even in its revised forms (Nelson, 1976; van den Broek, Bradshaw, & Szabadi, 1993)—presents formidable obstacles to distinguishing the relative importance of disrupted associative vs. working memory in the deficits shown by frontal lobe patients.

Intra- and Extradimensional (ID/ED) Shift Learning

In recent years, visual discrimination learning has been used more precisely to develop a simplified experimental setting in which to investigate the set-shifting deficits seen in both human and animal subjects bearing various forms of brain lesion (Dias, Robbins, & Roberts, 1996a, 1996b, 1997; Downes et al., 1989; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991, 1993; Roberts, Robbins, & Everitt, 1988). Like the WCST, the ID/ED shift learning task consists of a series of simultaneous visual discriminations over multidimensional stimuli. In the version used in the present study, the test stimuli vary independently along the dimensions of colour, shape, and value, although each discrimination features only two exemplars from each of these dimensions (for example, white and green, one and six, arrow and square; see Figure 1), and the correct stimulus for a given discrimination is specified by just one exemplar from one dimension (for example, the color green). An important experimental tradition suggests that acquisition of such discriminations is best understood in terms of *two-process* accounts in which subjects identify the stimulus dimension relevant for reinforcement, and then associate individual exemplars of that dimension with their reinforcement value (Mackintosh, 1965; Sutherland & Mackintosh, 1971; Zeaman & House, 1963). By carefully structuring a sequence of transfers between different types of discrimination (see Slamecka, 1968), it is possible to offer *separable* tests of distinct forms of shift learning implicit in the WCST.

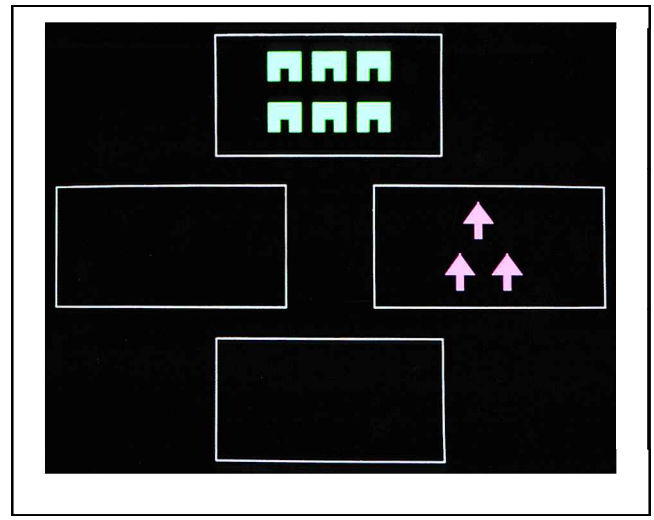

Figure 1. A typical display from the ID/ED task used for PET scanning different kinds of shift learning.

During the ID/ED task, the subject first learns a series of discriminations in which the same stimulus dimension (for example, shape) is relevant, and which is likely to promote the development of an attentional bias towards that dimension (Issacs & Duncan, 1962; Mackintosh, 1965; Shepp & Eimas, 1964; Shepp & Schrier, 1969; Sutherland & Mackintosh, 1971; Zeaman & House, 1963). The development of this bias is tested by the presentation of a critical discrimination in which the same stimulus dimension is relevant but consists of completely novel test stimuli (that is, an 'ID shift'). Since none of the new test stimuli have any reinforcement history that might influence responding through specific stimulus-reinforcement associations, efficient acquisition of this ID shift discrimination strongly suggests that the subject has indeed 'tuned' an attentional bias towards the currently relevant stimulus dimension, possibly at the expense of other currently irrelevant dimensions (Slamecka, 1968). However, the task culminates with the presentation of a second critical discrimination, again with novel test stimuli, in which a *different* stimulus dimension is now relevant (for example, colour), and which requires the subject to override their acquired bias in order to attend to this newly relevant dimension and learn the new discrimination (that is, accomplish an 'ED shift'). Consistent with a well-established body of experimental research (Issacs & Duncan, 1962; Kruschke, 1996; Nolan, Stoneking, & Hatch, 1978; Shepp & Eimas, 1964; Shepp & Schrier, 1969), acquisition of the culminating ED shift has been found to be harder (that is, to take more trials) than acquisition of the earlier ID shift discrimination (for example, Roberts et al., 1988).

Thus, the ID/ED task captures one central feature of the WCST by which a succession of correct sorts through a sequence of trials (that is, a series of ID shifts) has the effect of promoting an attentional bias towards the stimulus dimension on which the current sorting rule is based. This bias is then challenged on trials that require the subject's attention to be directed away from that dimension towards another on which the new sorting rule is based (that is, an ED shift). In both tasks, a change of sorting rule (WCST), or the acquisition of this new visual discrimination (ID/ED), must occur in the face of an *attentional-set* established over the course of recent reinforcement history.

Accumulating evidence indicates that focal damage to PFC in both human neurological patients and experimental primates impairs such ED shift learning (Dias et al., 1996a, 1996b, 1997; Owen et al., 1991, 1993), suggesting that at least part of the deficit seen in frontal lobe patients on the WCST arises through a failure to redirect attention away from those perceptual aspects of the stimulus cards on which the previous sorting rule was based. Moreover, the finding of complementary patterns of deficits in patients with early in the course Huntington's disease (Lawrence et al., 1996), and both early and late in the course Parkinson's disease (Downes et al., 1989; Owen et al., 1993) suggests that ED shift learning is also supported by the processing of basal ganglia structures, such as the striatum, and is influenced by the ascending mesostriatal and cortical dopaminergic projection systems (see also Roberts et al., 1994). In summary, the available evidence is consistent with recent suggestions that tasks involving 'executive functions', including ED shift learning, are mediated by the combined operation of frontocortical and subcortical mechanisms, possibly involving discrete 'fronto-striatal loops' routed from various areas of the PFC through the striatum, pallidal and thalamic nuclei back to the originating prefrontal region (Alexander, DeLong, & Strick, 1986).

Attentional-Set Shifting vs. Stimulus-Reward Learning

Complementing the issue of how attention is focused upon the currently relevant stimulus dimension is the issue of individual stimulus-reinforcement associations. One important feature of the WCST is that, over the course of successful sorts with the same sorting rule, the individual exemplars of the currently relevant stimulus dimension become associated with reinforced behavior (that is, matching responses with their appropriate reference cards). However, since these exemplars continue to be present when the sorting rule is changed, subjects not only have to modulate their acquired attentional bias towards the previously relevant stimulus dimension as a whole (for example, towards the dimension of 'shape' in general), but also override recently acquired stimulus-reinforcement associations attached to the individual exemplars of that dimension (for example, the 'circle', 'star', 'triangle', and 'cross'). Behavioral evidence from both animal and human learning experiments suggests that learning about stimulus-reward associations (that is, their so-called 'affective' valence), and learning about which stimulus dimensions are generally relevant to reinforced behavior are mediated by distinct learning mechanisms (Kruschke, 1996; Mackintosh, 1965; Sutherland & Mackintosh, 1971 for review), yet both are clearly implicit in the WCST.

In order to explore the control of previously acquired stimulus-reward associations, the ID/ED task also includes additional discriminations in which the stimulus-reinforcement pairings (for example, green $\surd$/red $\times$) of an immediately preceding discrimination are swapped without warning (that is, green $\times$/red $\surd$). Since both the test stimuli and the relevant stimulus dimension are *unchanged*, reversal learning simply requires the subject to learn the opposite pairing of stimuli and reinforcement value (that is, a 'reversal shift'). While initial acquisition of such stimulus-reward associations is prob-

ably mediated by lateral occipital, and inferior temporal cortices (Cowey & Gross, 1970; Gross, 1973 for review; Iwai & Mishkin, 1969), the reversal of such associations appears to depend on the processing of specifically orbito-frontal cortical areas, and the amgydaloid complex (Dias et al., 1996a; Iversen & Mishkin, 1970; Jones & Mishkin, 1972). Although there have been few studies of reversal learning with human neurological patients, some evidence of impairments has been seen in patients with Korsakoff's syndrome (Oscar-Berman & Zola-Morgan, 1980), and patients sustaining unilateral frontal lobe lesions (Daum, Schugens, Channon, Polkey, & Gray, 1991; Rolls, Hornak, Wade, & McGrath, 1994), further suggesting that disruption of the circuitry incorporating temporal cortices and PFC impairs the acquisition of changed associations between stimuli and reinforcement.

In the specific case of the ID/ED task, it appears that reversal shift and ED shift learning are highly dissociable in both experimental primates and human subjects. For example, lesions of the orbitolateral PFC in nonhuman primates have been found to impair reversal learning, but not ED shift learning, with lesions of the dorsolateral PFC producing the opposite pattern of deficits (Dias et al., 1996a, 1996b, 1997). Similarly, depletions of the ascending cholinergic projections from the basal forebrain appear to produce highly specific deficits in reversal learning (Roberts, Robbins, Everitt, & Muir, 1992), while depletion of prefrontal dopamine has its greatest effect on ED shifting (Roberts et al., 1994). Finally, reversal learning has been shown to be impaired in late but not early Huntington's disease (Lange, Sahakian, Quinn, Marsden, & Robbins, 1995; Lawrence et al., 1996; Oscar-Berman & Zola-Morgan, 1980), suggesting that the course of the disease, with its claimed dorsolateral/ventromedial progress through the caudate nucleus (Hedreen & Folstein, 1995) eventually disrupts the orbito-frontal striatal circuitry required for acquisition of a swapped set of previously acquired stimulus-reinforcement associations.

To summarise, visual discrimination learning provides a highly controlled setting in which to study the different kinds of learning processes implicit in performance of the WCST (for example, shifts between stimulus dimensions, as opposed to individual stimulus-reward associations). Experiments in both human and primate subjects suggest that these different kinds of shifts involve dissociable psychological and neural mechanisms, possibly involving discrete cortico-striatal circuitry.

The Present Study

In the present experiment, 12 right-handed, healthy adult volunteers were positron emission tomography (PET) scanned, using the slow bolus infusion method of water activation ($H_2{}^{15}O$), while acquiring reversal shift discriminations (in *reversal* scans), ID shift discriminations (in *ID shift* scans) and ED shift discriminations (in *ED shift* scans). The subjects were also scanned while responding to already-learnt discriminations (in *performance* scans). The experiment had two purposes: (i) to investigate the wider neural network underlying simultaneous visual-discrimination learning over multidimensional stimuli, as revealed by comparisons of the regional cerebral blood flow (rCBF) associated with the reversal, ID and ED shift scans, and the rCBF associated with the performance scans; and (ii) to isolate modulatory changes in this network associated with different forms of shift discrimination learning (as revealed by planned comparisons between the rCBF in each of the reversal, ID and ED shift scans (see below)).

Our predictions were that, relative to both the ID shift scans and each other, rCBF in the ED shift and reversal scans would show dissociable changes, perhaps involving different portions of the proposed functional circuitry incorporating different areas of the PFC and striatum (Alexander et al., 1986). Specifically, we hypothesised that rCBF in the ED shift scans would show particular increases within the dorsolateral regions of the PFC, while rCBF in the reversal scans would show increases in more inferior, orbital areas. In addition, given the evidence of deficits in reversal learning following striatal lesions or dysfunction (Divac, Rosvold, & Szwarcbart, 1967; Lange et al., 1995; Oscar-Berman & Zola-Morgan, 1980), we also expected rCBF changes within the caudate nucleus associated with the reversal scans.

The design consisted of three runs of four scans, each presented in the following order: performance, reversal, ID and ED shifts. Thus, each run contained one scan taken while the subject performed each type of discrimination. These discriminations were embedded in longer sequences designed to mimic as closely as possible the clinical form of the ID/ED shift task used previously in studies with neurological patient groups (see Methods section below). However, at the start of the scan itself (that is, when the *head count* began to rise; see below), the appropriate learning discrimination was presented to the subject. In this way, we were able to ensure that the acquisition of the count data corresponded precisely to the different types of shift learning manipulated in the scans. Finally, response rate (that is, the number of trials per scan window) was controlled across the scans (by means of a 'pacing' auditory cue) in order to make it unlikely that the rCBF differences described below were due merely to differences in motor activity. Scan order was entered as a covariate in all analyses in order to remove confounding time effects associated with earlier vs. later scans.

RESULTS

Task Performance

Reversal, ID, ED, Shift Learning

The behavioral data associated with each scan were recorded in a fixed 45-sec interval between the point at which the 'head count' began to rise and shortly after the point at which it peaked. The principal measure was simply the number of errors made by each subject in learning the reversal, ID and ED shift discriminations. No errors were recorded for any subject during the performance scans (and these scans were excluded from the analysis). Following previous studies with the ID/ED task (for example, Owen et al., 1991), the data were subjected to square-root transformation to make them suitable for repeated-measures analysis of variance (ANOVA). The within-subject factors were those of run (first, second or third) and discrimination-type (reversal, ID or ED shift). Due to technical problems, the data of one subject were lost so that the behavioral results represent the performance of 11 of the 12 subjects.

Mean error rate for each type of scan is shown in Figure 2. Overall, there was a highly significant effect of discrimination-type, $F(2, 20)=26.08$, $p<.0001$, by which errors in the reversal and ED shift scans were generally increased, compared to those in the ID shift scans. The relative differences between the three types of discrimination were slightly altered across the three runs of the study, reflected in a near-significant two-way interaction between discrimination-type and run, $F(4, 40)=2.48$, $p=.06$. Thus, the number of errors in the reversal scan was increased by 1.8 relative to those of the ID shift scan in the first run, by only 0.2 errors in the second, and then by 1.9 errors in the third. Similarly, mean errors in the ED shift scans showed a more marked increase relative to the ID shift scans in the first run compared to the second and third (3.7 vs. 1.9 and 2.3, respectively) with a trend towards a significant reduction over the course of the three runs, $F(2, 20)=2.71$, $p=.09$. Overall, these data show slightly higher rates of reversal and ED shift errors in the first run of the study.

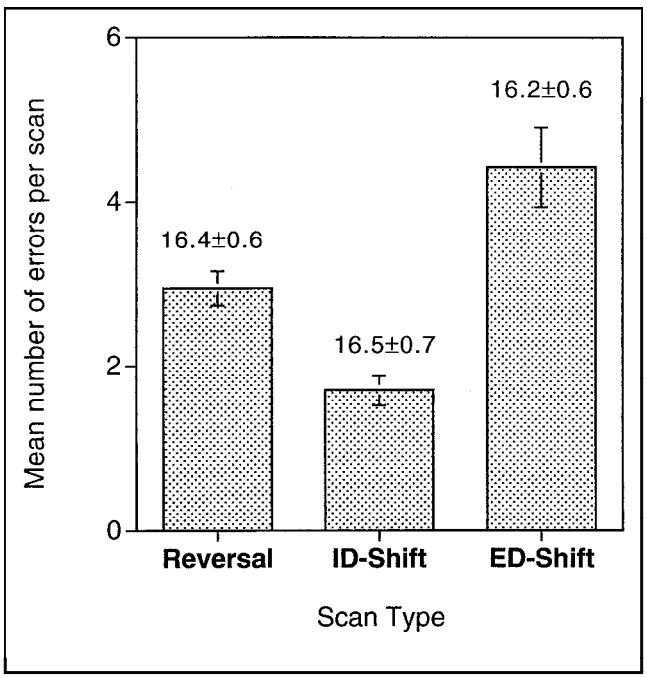

Figure 2. Performance (number of errors required by subjects to reach criterion) during the reversal, ID and ED shift discriminations that were scanned. Mean rate of responding over the 45-sec data acquisition per scan are also shown (± *SE*).

Figure 2 also shows the mean number of responses (or equivalently, the mean number of trials) associated with the scan windows of each discrimination-type. Note that response rate is very closely matched. Subjecting these data to ANOVA with the within-subject factors of run (first, second or third) and discrimination-type (reversal, ID or ED shift), revealed that neither the main effect of run, discrimination-type, or the interaction between them approached significance, $F<2.5$ in all cases. However, a second analysis incorporating the mean number of responses associated with the three performance scans did reveal a significant main effect of run, $F(2, 20)=4.2$, $p<.05$, and a significant interaction between run and discrimination-type, $F(2, 20)=3.47$, $p<.01$. This was due to a very slight, but reliable, decrease in response rate in the first performance scan (14.82 ± 0.60) relative to the second (16.64 ± 0.90) and third scans (16.82 ± 0.64). However, in general, there were no consistent differences across the three runs in the overall rate of responding associated with either the performance or the learning scans.

Cognitive Activations

The data were subjected to two sets of analyses. First, in order to assess the wider neural network supporting simultaneous visual discrimination learning over multidimensional stimuli, the combined rCBF associated with the reversal scans, ID and ED shift scans were compared to the rCBF associated with the performance scans. Since the intention of this comparison was simply to highlight which cortical areas, other than the PFC, are implicated in visual discrimination learning, we set our threshold for significance at $p<.05$ corrected for multiple comparisons in terms of height.

Second, in order to isolate differences in the rCBF associated with reversal and ED shift learning, further comparisons were made between the different kinds of learning scans. In the first instance, the rCBF from the ID shift scans was compared with that from the reversal scans, and with that from the ED shift scans. The use of the ID shift scans as a common baseline for these subtractions is especially appropriate for isolating acti-

Table 1. Significant Activations in the Learning Scans (that is, Combination of Reversal, ID and ED Shift Scans) Compared with Performance Scans

			z-value	*x*	*y*	*z*
(a) Discrimination–Performance						
Frontal cortex	10/46 (GFm)	L	*5.43*	– 42	50	10
	10 (GFm)	R	*4.92*	38	54	4
	10/11 (GFm)	L	*4.48*	– 24	52	– 10
	9 (GFi)	L	*4.49*	– 48	14	38
	45 (GFi)	R	*5.00*	52	20	22
	6 (GFs)	L	*5.18*	– 10	14	56
	6 (GFd)	R	*5.31*	4	20	46
	6 (GFm)	R	*4.76*	42	10	44
Occipital cortex	18 (GF)	L	*4.43*	– 30	– 92	– 10
Parietal cortex	7 (LPs)	L	*5.14*	– 32	– 64	44
	7 (LPs)	R	*5.45*	34	– 66	44
Cerebellum		L	*4.74*	– 18	– 76	– 20
		R	4.74	44	– 60	– 26
(b) Performance–Discrimination						
Frontal cortex	6 (GFd)	R	*4.84*	4	– 18	56
Temporal cortex	22 (GTs)	L	*5.43*	– 46	– 6	6
	41 (GTs)	R	*5.71*	40	– 30	14
	41 (GTs)	R	*4.94*	50	– 14	10

GFm=middle frontal gyrus; GFi=inferior frontal gyrus; GFs=superior frontal gyrus; GF=fusiform gyrus; LPs=superior parietal lobule; GFd=medial frontal gyrus; GTs=superior temporal gyrus. A threshold of $p<.05$ corrected for multiple comparisons (z-value=4.42) was set for all rCBF changes.

vations (and deactivations) associated with the psychological processes specific to reversal learning and ED shift learning. Specifically, subtraction of the rCBF in the ID shift scans from that in the Reversal scans controls for both the gross visual and motor characteristics of visual discrimination learning over multidimensional stimuli, as well as new learning within a previously relevant stimulus dimension, but isolates the rCBF associated with learning a switched pair of stimulus-reward associations. Similarly, subtraction of the rCBF in the ID shift scans from that in the ED shift scans also controls for the visuomotor characteristics of the paradigm, and new learning with novel stimulus exemplars, but isolates the rCBF specifically associated with shifting an acquired attentional bias towards a newly relevant stimulus dimension.

Finally, in order to isolate the wider differences in the neural systems mediating reversal and ED shift learning, direct subtractions were made between the two (that is, reversal scans–ED shift scans, ED shift scans–reversal scans). For the intralearning comparisons, we set a threshold of $p<.001$ uncorrected for hypothesis-led, anatomically constrained activations. Additional activations (and deactivations) not predicted a priori are reported descriptively with those surviving the additional threshold of $p<.05$ corrected noted in the text. As noted above, task-unrelated changes in rCBF associated with linear time effects were removed by covarying for scan order.

Visual Discrimination Learning Network

Discrimination–Performance

Subtraction of rCBF collected in the baseline performance scans from that collected in the discrimination learning scans revealed a set of distributed activations, incorporating both anterior and posterior cortices (see Table 1(a); Figure 3). Significant, but distinct, bilateral increases were particularly evident in frontal cortex, along anterior parts of the middle frontal gyri (BA 10) and the posterior parts of the inferior frontal gyrus (BA 9 and 45). Extensive activations were also clear along the superior frontal gyrus (BA 6 and 8). More posteriorly, significant peaks were found bilaterally in the superior parietal lobule (BA 7), as well in left occipital cortex along the fusiform gyrus (BA 18). Finally, rCBF was also significantly increased in bilateral regions of the cerebellum.

Performance–Discrimination

Subtraction of the rCBF from the discrimination learning scans from that in the baseline performance scans—isolating relative deactivations associated with

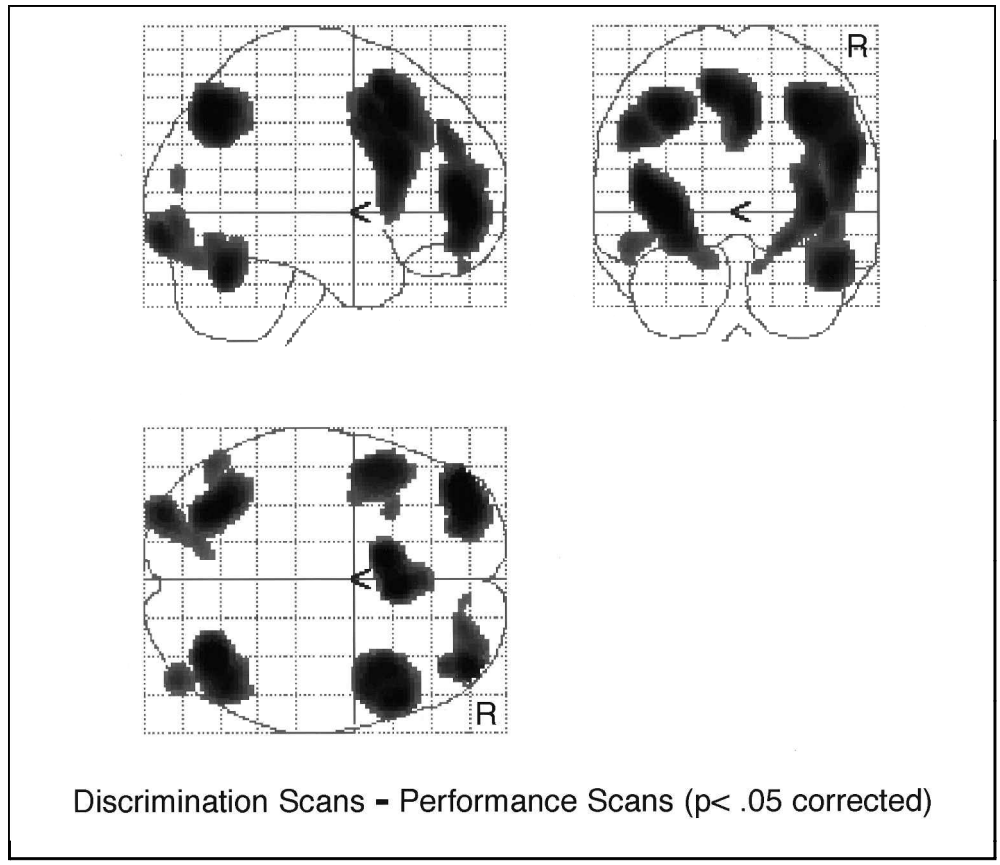

Figure 3. Significant rCBF change in visual discrimination learning (averaging over all learning scans) compared to performance of already learnt discriminations: discrimination scans- performance scans. Significance levels set at a threshold of $p < .05$ corrected for multiple comparisons.

learning compared to already-learnt performance—yielded significant rCBF reductions in right medial premotor cortex along the medial frontal gyrus (BA 6), as well as in the anterior superior temporal gyrus on the left (BA 22) and the posterior superior temporal gyrus on the right (BA 41; see Table 1(b)).

In summary, simultaneous visual discrimination learning over multidimensional stimuli activated a distributed network of cortical sites, incorporating bilateral regions of polar, dorsolateral, superior medial and lateral frontal cortex, bilateral posterior visuospatial areas, left visual association cortex, and the cerebellum. Complementary deactivations were evident in auditory association cortex bilaterally.

Reversal vs. ED Shift Learning (Activations Against Common Baseline)

In order to examine more subtle differences between the pattern of brain activation associated with reversal shift learning and ED shift learning, we subtracted the rCBF averaged over the ID shift scans from that averaged over the reversal scans, and from that averaged over the ED shift scans.

Reversal–ID Shift

As predicted, subtraction of the rCBF in the ID shift scans from the rCBF in the reversal scans revealed significant increases within the left caudate, one peak located anteriorly within the medial part of the nucleus and another located posteriorly within the tail (see Table 2(a)). Additional rCBF increases were evident along the ventral part of the left cingulate gyrus (BA 24/32), along the right medial frontal gyrus (BA 9/10), and more posteriorly along the left angular gyrus (BA 39). None of these activations survived correction for multiple comparisons. There was no indication of rCBF changes in orbito-frontal cortex associated with reversal learning.

ED–ID Shift

Predicted activations were present in dorsolateral PFC along the right middle frontal gyrus (BA 9/46; see Table 2(b), Figure 4(a)), as well as anteriorly along the left medial frontal gyrus (within BA 10), and posteriorly along the left middle frontal gyrus (BA 8). An additional unpredicted peak along the left middle temporal gyrus (BA 39) was not significant after correction for multiple comparisons.

In summary, compared to ID shift learning (that is, learning discriminations with new stimuli from the previously relevant stimulus dimension), reversal learning (that is, learning merely switched stimulus-reward associations) activated caudate nucleus and left temporal/parietal cortex, while ED shift learning (that is, learning discriminations with new stimuli from a previously *irre-*

Table 2. Increased rCBF in Reversal Shift Learning and ED Shift Learning (Expressed Relative to the Common Baseline of ID Shift Learning)

			z-value	*x*	*y*	*z*
(a) Reversal–ID Shift						
Hypothesis-led, anatomically constrained activation						
Basal ganglia	caudate nucleus	L	*3.51*	– 6	16	8
	caudate nucleus	L	*3.16*	– 16	8	20
Areas not predicted a priori						
Frontal cortex	9 (GFd)	R	*3.27*	8	56	20
Cingulate cortex	24/32 (CG)	L	*3.20*	– 6	34	0
Parietal cortex	39 (Ga)	L	*3.10*	– 54	– 70	34
(b) ED–ID Shift						
Hypothesis-led, anatomically constrained activation						
Frontal cortex	10 (GFd)	L	*3.73*	– 8	60	8
	8 (GFm)	L	*3.16*	– 54	8	44
	9/46 (GFm)	R	*4.22*	16	46	26
Areas not predicted a priori						
	39 (GTm)	R	*3.37*	38	– 58	24

(a) rCBF in reversal scans–rCBF in ID shift scans; (b) rCBF in ED shift scans–rCBF in ID shift scans. GFd=medial frontal gyrus; GC=cingulate gyrus; Ga=angular gyrus; GFi=inferior frontal gyrus; GTm=middle temporal gyrus. A threshold was set at $p<.001$ uncorrected (z-value=3.09) for activations predicted a priori, *unprecedented activations significant at $p<.05$ corrected (z-value=4.42).

levant dimension) activated left lateral and polar PFC, and right dorsolateral PFC.

ED vs. Reversal Shift Learning (Deactivations Against Common Baseline)

Further information about the neural activity associated with ED shift learning and reversal shift learning can be gleaned from examining the distribution of relatively reduced rCBF seen in each case, when compared to the rCBF associated with ID shift learning.

ID Shift–Reversal

Subtracting the rCBF of the reversal scans from that in the ID shift scans revealed relative deactivations associated with reversal learning along the precentral gyrus on the right (BA 6). Additional reductions in rCBF were present in the region of the right middle occipital gyrus (BA 19) and along the right inferior temporal gyrus (BA 37). However, none of these deactivations remained significant after correction for multiple comparisons (see Table 3(a)).

ID–ED Shift

Comparison of the rCBF in the ED shift scans with that in the ID shift scans revealed evidence of relative deactivation associated with ED shift learning in extensive areas of occipito-temporal pathways (see Table 3 and Figure 4(b)), including the left lingual and occipital gyri (BA 17 and 18) and right middle occipital gyrus (BA 18/19). There was also a significant deactivation along the right inferior temporal gyrus (BA 37). Of these, only the deactivation along the left lingual gyrus (BA 17) remained significant after correction for multiple comparisons (all $z>4.42$).

In summary, compared to ID shift learning, reversal-shift learning was associated with relative deactivation in right-occipital and infero-temporal cortices. By contrast, ED shift learning produced more extensive reductions in rCBF within both left and right occipito-temporal pathways, and especially within the left primary-visual cortex.

Reversal vs. ED Shift Learning (Direct Comparison)

In order to isolate the wider differences in the neural networks mediating changed stimulus-reinforcement linkages and mediating the control of attentional bias, direct subtractions were made between the rCBF associated with the reversal scans, and that associated with the ED shift scans.

Reversal–ED Shift

Compared to rCBF in the ED shift scans, rCBF in the reversal scans showed activations along the fusiform

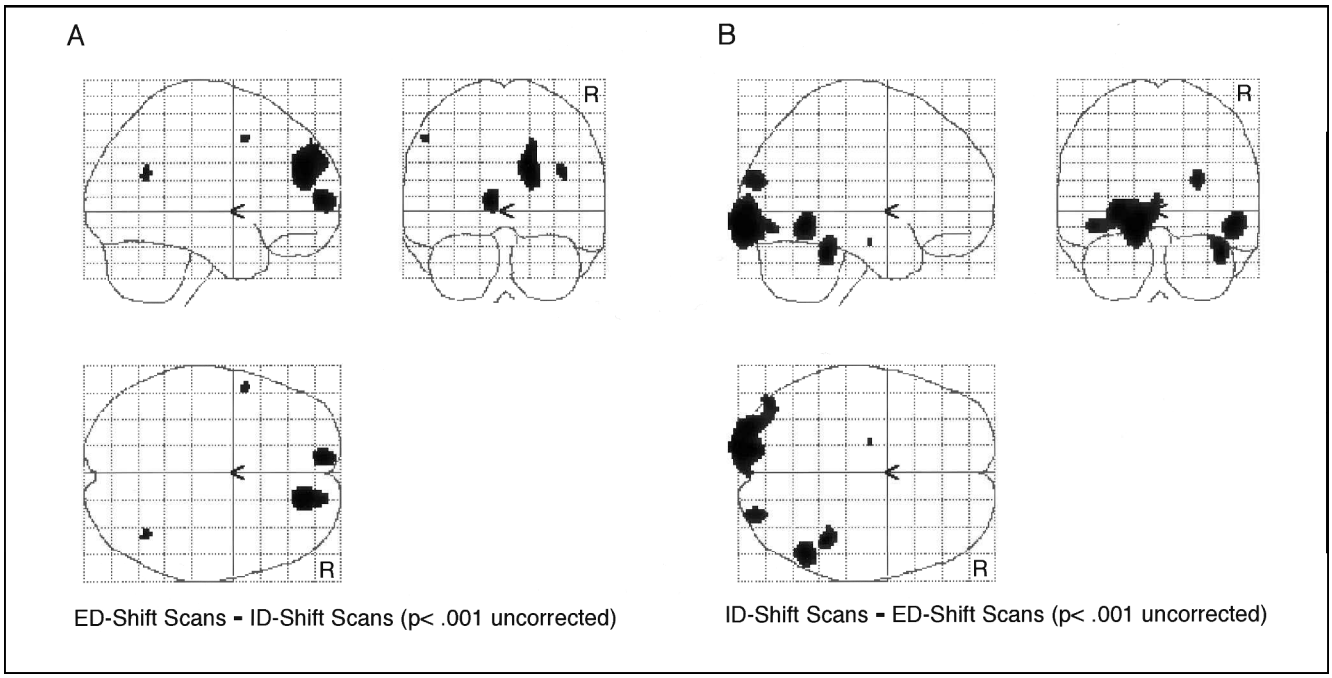

Figure 4. (a) Significant peaks of rCBF change for ID vs. ED shift learning. (A) ED shift scans- ID shift scans; (B) ID shift scans- ED shift scans. Significance levels set at a threshold of $p < .001$ uncorrected.

gyrus on the left (BA 17) and along inferior temporal gyrus on the right (BA 20; Table 4(a)). An additional increase in rCBF was seen in the anterior part of the superior temporal gyrus on the right (BA 22). None of these activations remained significant after correction for multiple comparisons. There was no indication of increased rCBF within inferior, orbital areas of the PFC associated with reversal learning.

ED Shift–Reversal

As predicted, there were significant bilateral increases in rCBF in the PFC (see Table 4(b)), notably along the right middle and inferior frontal gyri (BA 9/46 and 47). A further peak was present in the posterior part of the left medial frontal gyrus (BA 6).

In summary, reversal learning produced increases in rCBF in occipito-temporal cortices compared to ED shift learning. By contrast, ED shift learning activated right dorsolateral, ventrolateral PFC and medial premotor cortex.

Summary

- Relative to an appropriate visuomotor performance baseline, simultaneous visual discrimination learning of multidimensional stimuli activated a distributed network of anterior and posterior cortical areas, involving bilateral polar, dorsolateral PFC and premotor cortex, as well as bilateral superior parietal cortex, ventral areas of left visual association cortex and cerebellum. Discrimination learning deactivated bilateral auditory association cortex (see Table 1, Figure 3).
- Compared to ID shift learning, reversal shift learning activated the left caudate nucleus (see Table 2(a)), while ED shift learning activated left polar and right dorsolateral regions of PFC (see Table 2(b) and Figure 4(a)).
- Relative to ID shift learning, reversal learning was associated with reduced rCBF in right lateral premotor and posterior inferotemporal cortices, while ED shift learning was associated with bilateral deactivations in extensive areas of exclusively occipito-temporal cortices, especially within left primary visual cortex (see Table 3(a) and (b)).
- Reversal learning produced larger increases in rCBF in left visual association cortex and right occipito-temporal cortex than ED shift learning (see Table 4(a)), while ED shift learning activated right dorsolateral PFC, right ventrolateral PFC, as well as parts of right medial premotor cortex (see Table 4(b)).

DISCUSSION

These data provide important new information about the neural bases of different kinds of shift-learning implicit in 'concept-formation' tasks, such as the WCST (for example, Milner, 1963, 1964). First, we have demonstrated, for the first time, the assembly of neural structures activated when healthy adult volunteers learn new simultaneous visual discriminations over multidimensional stimuli. Second, we have succeeded in isolating relatively specific modulatory changes within this net-

Table 3. Reduced rCBF in Reversal Shift Learning and ED Shift Learning (Expressed Relative to the Common Baseline of ID Shift Learning)

			z-value	*x*	*y*	*z*
(a) ID Shift–Reversal						
Areas not predicted a priori						
Frontal cortex	6 (GPrC)	R	*3.20*	50	0	24
Occipital cortex	19 (GOm)	R	3.71	32	– 82	24
Temporal cortex	37 (GTi)	R	3.99	56	– 50	– 14
(b) ID–ED Shift						
Areas not predicted a priori						
Occipital cortex	17 (GL)*	L	*4.44*	– 16	– 100	– 8
	18 (GO)	L	*4.07*	– 26	– 96	0
	19 (GOi)	L	*3.52*	– 44	– 80	– 10
	18/19 (GOm)	R	*3.62*	26	– 90	20
Temporal cortex	37 (GTi)	R	*3.97*	50	– 56	– 8
Cerebellum		R	*3.96*	42	– 40	– 26

(a) rCBF in ID-shift scans–rCBF in reversal scans; (b) rCBF in ID-shift scans–rCBF in ED-shift scans. GPrC=precentral gyrus; GOm=middle occipital gyrus; GTi=inferior temporal gyrus; GL=lingual gyrus; GO=occipital gyrus; GOi=inferior occipital gyrus. A threshold was set at $p<.001$ uncorrected (z-value=3.09). *Unpredicted activations significant at $p<.05$ corrected (z-value=4.42)

work associated with different kinds of shift between discriminations. In the following discussion, we first examine interpretative issues concerning the design of the present study. Then, we consider the significance of these findings for understanding the role of the PFC, and other neural substrates, in forms of shift learning implicit in the WCST and ID/ED task (Milner, 1963, 1964; Owen et al., 1991).

The performance of our normal adult volunteers—that is, consistent increases in the errors associated with reversal and ED shift learning compared with those associated with ID shift learning—replicate the results of several dozen studies that have examined these different forms of shift learning in different species (for example, Issacs & Duncan, 1962; Roberts et al., 1988; Shepp & Eimas, 1964; Shepp & Schrier, 1969; Sutherland & Mackintosh, 1971 for review). Thus, our subjects found learning new discriminations with either newly relevant stimulus dimensions (that is, ED shifts) or switched stimulus-reinforcement associations (that is, reversal shifts) harder than simply learning new discriminations with previously relevant stimulus dimensions (that is, ID shifts) for which an attentional bias or 'attentional-set' was already tuned (see Sutherland & Mackintosh, 1971).

In this context, it is important to note that the present rCBF data are not attributable to simple differences in task difficulty. For example, the evidence available from animal and human learning experiments strongly suggests that the increased difficulty of ED and reversal shift learning compared to ID shift learning relates to the operation of distinct learning mechanisms: controlling attentional bias in the former and acquiring revised stimulus-reinforcement associations in the latter (see Sutherland & Mackintosh, 1971 for review of 'two-process' theories of visual discrimination learning; also Kruschke, 1996). Moreover, extensive research specifically employing the ID/ED task has begun to isolate the neural bases of these mechanisms by demonstrating doubly dissociable patterns of impairment in both human and primate subjects bearing different forms of brain lesion (Dias et al., 1996a,b; Lawrence et al., 1996; Owen et al., 1991, 1993; Roberts et al., 1992). Indeed, the present rCBF data confirm this dissociability by demonstrating increased activation of dorsolateral PFC activity when acquiring ED shifts (with little evidence of change in the caudate nucleus), together with increased activation of the caudate nucleus when learning reversals (with little change in dorsolateral PFC).

Second, our experimental procedure was carefully designed so that the presentation of each of these different kinds of shift discrimination coincided with the rise in 'head counts' associated with each scan. In this way, there is good reason to believe that the rCBF data we have presented reflects the separate patterns of brain activity associated with reversal, ID and ED shift learning. Third, the subtractive data reported in our study has been corrected for task-unrelated changes in rCBF associated with time effects across scans. Fourth, response rate was carefully controlled across scans (see Figure 2), minimising the risk that our results reflect differences in gross motor activity

Table 4. Direct Comparison Between the rCBF Associated with the Reversal and ED Shift Learning

			z-value	*x*	*y*	*z*
(a) Reversal–ED Shift						
Activations not predicted a priori						
Occipital cortex	17 (GF)	L	*3.75*	– 20	– 102	– 10
Temporal cortex	20 (GTi)	R	*4.36*	36	– 24	– 4
	22 (GTs)	R	*3.45*	44	6	– 12
(b) ED Shift–Reversal						
Hypothesis-led, anatomically constrained activation						
Frontal cortex	9/46 (GFm)	R	*3.48*	18	44	24
	6 (GFd)	R	*3.18*	28	8	62
	47 (GFi)	R	*3.24*	36	40	– 8

(a) rCBF in reversal scans–rCBF in ED shift scans; (b) rCBF in ED shift scans–rCBF in reversal scans; GF=fusiform gyrus; GTi=inferior temporal gyrus; GTs=superior temporal gyrus; GFm=middle frontal gyrus; GFi=inferior frontal gyrus. A threshold was set at $p<.001$ uncorrected (z-value=3.09) for activations predicted a priori, *unprecedented activations significant at $p<.05$ corrected (z-value=4.42).

(for example, few responses while learning harder discriminations; many responses while learning easier discriminations).

Finally, the use of the ID/ED task, with its careful separation of different forms of shift learning was well-suited to the subtractive method offered by PET technology. Thus, our design afforded several precisely controlled subtractions with which to answer different kinds of questions about the cognitive and neural bases of different forms of shift learning. For instance, at a cognitive level of analysis, subtractions of the rCBF in the ID shift scans from that in the ED shift scans accurately controlled for the gross visual and motor processing characteristics of the discrimination learning task and the involvement of those cognitive processes mediating the acquisition of new discriminations within a previously relevant stimulus dimension, while isolating the rCBF associated with specifically shifting an acquired attentional bias towards a newly relevant stimulus dimension. By contrast, at a systems level of analysis, direct comparison of the rCBF in the Reversal scans and the ED Shift scans allowed examination of the gross differences in the neural networks associated with stimulus-reward learning and shifting an attentional bias towards newly relevant stimulus dimensions. In summary, the ID/ED task was well-suited to the subtractive methodology, and yields multiple sources of information relevant to our understanding of the neural basis of normal and impaired performance of the WCST.

Neural Mechanisms of Visual Discrimination Learning

One important contribution of the present study is the discovery of a relatively widespread and distributed network of cortical areas activated by learning new visual discriminations when compared to baseline performance of previously learnt discriminations (see Table 1(a)). Careful examination of this network reveals a conjunction of multiple, and widespread, activations in frontal cortices (for example, anterior and dorsolateral PFC, along the middle and inferior frontal gyri; BA 10, 9 and 45), together with activations in other cortical fields associated with orienting, attentional and response-related operations. Specifically, accumulating evidence from neuropsychological, electrophysiological and brain-imaging sources stress the importance of the parietal cortex (around the superior parietal lobules, BA 7 and 40), as well as the cerebellum in various aspects of visuospatial function. These include the control of covert attention (Corbetta, Meizin, Shulman, & Petersen, 1993, 1995; Nobre et al., 1997; Petersen, Corbetta, Miezin, & Shulman, 1994), control of saccades (Anderson et al., 1994; Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975), and conjunction search and related mechanisms of selective attention (Bushnell, Goldberg, & Robinson, 1981; Corbetta, Meizin, Dobmeyer, Shulman, & Petersen, 1991, Corbetta, Shulman, Meizin, & Petersen, 1995; Rafal & Robertson, 1985). Furthermore, both lateral and medial areas of premotor cortex (BA 6 and 8), and the cerebellum, are also associated with visuospatial function, and with the control of voluntary action (see Colebatch, Deiber, Passingham, Friston, & Frackowiak, 1991; Deiber, Colebatch, & Friston, 1991; Fox, Raichle, & Thach, 1985; Passingham, 1993 for review).

In the present study, the discovery that PFC activations are accompanied by additional activity in systems pivotal to visuospatial function (for example, Desimone & Duncan, 1995; Rafal & Robertson, 1985 for review) suggests that the contribution of the PFC is coordinated

with the activity of multiple premotor and posterior cortical fields mediating the attentional selection and processing of task-relevant stimulus information. This impression is reinforced by the presence of an additional rCBF increase in secondary, but *not* primary, visual cortex (around the lingual gyrus), raising the possibility of top-down enhanced processing of task-relevant stimulus dimensions such as colour and shape (Corbetta et al., 1991; Maunsell, 1995 for review; Watson et al., 1995; Zeki et al., 1991). By contrast, the differential activations seen in auditory-association cortex, when performing already-learnt discriminations compared to learning new discriminations (see Table 1(b)) suggest relatively attenuated activity in these areas under conditions of new learning or, alternatively, activation somehow associated with retrieval.

Mechanisms of ED and Reversal Learning: Implications for the WCST

A principal aim of this study was to investigate the neural correlates of various forms of shift learning implicit in the WCST. Of particular interest was the relative contributions of two distinct kinds of shift associated with the functioning of the PFC: (i) shifting attention away from previously relevant stimulus dimensions, and towards newly relevant dimensions (that is, as measured by the efficiency of acquiring ED shifts); and (ii) acquiring altered stimulus-reward associations (as measured by the efficiency of acquiring reversal shifts).

The results of our study unequivocally demonstrate that shifting attention away from a previously reinforced stimulus dimension towards a previously irrelevant stimulus dimension is particularly associated with predicted rCBF increases within the PFC. Specifically, Table 2(b) shows that subtraction of rCBF collected in the ID shift scans from that collected in the ED shift scans revealed predicted activations within the PFC, specifically in lateral and anterior regions on the left (BA 8 and 10), and dorsolateral regions on the right (BA 9 and 46). Therefore, these data augment evidence, obtained from studies with both neurological human subjects (Owen et al., 1991, 1993) and experimental primates (Dias et al., 1996a,b, 1997), that control of attentional biases is crucially mediated by predominantly prefrontal cortical regions. Since the control of such attentional biases (reinforced through a sequence of successful 'sorts') is a crucial component of successful performance of the WCST (Milner, 1963, 1964), it is likely that disruption of this control is at least partly responsible for the deficits repeatedly seen on the WCST in patients sustaining frontal-lobe damage (Drewe, 1974; Milner, 1963, 1964; Robinson et al., 1980).

In contrast to the frontal involvement in ED shift learning, there was little evidence that learning revised stimulus-reward associations differentially activated prefrontal cortical areas. In particular, subtraction of the rCBF associated with ID shift scans from that associated with the reversal scans did not reveal significant activations in orbito-frontal regions of PFC, as might have been expected on the basis of several studies with experimental primates (for example, Dias et al., 1996a; Iversen & Mishkin, 1970; Jones & Mishkin, 1972). However, the same subtraction did isolate significant and predicted peaks in the region of the caudate nucleus, as well as additional peaks in medial PFC (BA 9), cingulate cortex (BA 24/32) and a region around the angular gyrus (BA 39), indicating that reversal and ED shift discrimination differentially activate distinct neural stations.

For the moment, it is unclear why reversal learning was not associated with significantly increased rCBF in orbito-frontal cortex. However, we suggest two speculative explanations. One possibility is that both the ID and ED conditions were themselves associated with increased rCBF in orbito-frontal cortex. In this case, any similar activation present in the reversal scans was 'subtracted out' in the comparisons with either the ID or ED shift scans. Consistent with this, additional comparisons of the rCBF associated with each of the learning scans with the performance scans revealed some evidence of increased activation in orbito-frontal rCBF in all three cases, and comparison of the combined learning scans against the performance scans confirms this increased activity (see Table 1(a)). Therefore, it seems likely that some of the predicted rCBF in the reversal scans was simply subtracted out in this manner. A second possibility relates to recent suggestions that orbito-frontal neurones implement a mechanism for specifically rapid recoding of existing stimulus-reinforcement associations (see Rolls, 1996 for review). For example, electrophysiological data suggest that neurones firing preferentially to a rewarded visual stimulus, but not to an unrewarded visual stimulus, reverse this pattern of firing within only a few seconds of these stimulus-reward associations being switched (see Thorpe, Rolls, & Maddison, 1983). In this case, it is possible that the additional contribution of neural activity in orbito-frontal cortex to reversal shift learning is too rapid to change the rCBF integrated over the 90-sec period of data acquisition in a PET scan, or that the changed activity of the subpopulations of neurones coding the rewarded and the unrewarded stimulus cancel each other out so that the net activity in this cortical region remains unchanged. Further studies with alternative brain-imaging paradigms with greater temporal resolution (for example, functional magnetic resonance imaging, fMRI) might clarify this issue.

The isolation of significant rCBF increases within the caudate nucleus is consistent with previous reports of deficits in reversal learning following lesions of the striatum in experimental animals (for example, Divac et al., 1967), and in patients with late in the course

Huntington's disease (Lange et al., 1995; Oscar-Berman & Zola-Morgan, 1980). We propose that these activations may reflect the operation of at least two cortico-striatal circuits implicated in the acquisition of stimulus-reinforcement associations. First, so-called 'limbic' circuitry involving the orbito-frontal PFC and amygdala—lesions of which have each been shown to impair reversal learning (Dias et al., 1996a,b; Iversen & Mishkin, 1970; Jones & Mishkin, 1972)—encompass the ventromedial portion of the caudate through projections from the orbital PFC (Haber, Kunishio, Mizobuchi, & Lynd Balta, 1995). In this context, the apparent dependence of Huntington's disease patients' deficits with the ID/ED task on the dorsal-to-ventral direction of the neuronal loss within the caudate nucleus (Hedreen & Folstein, 1995; Lawrence et al., 1996) may prove to be especially significant. Specifically, early in the course, Huntington's patients have been found to be impaired at ED shift learning, presumably reflecting disruption of circuitry incorporating the head of the caudate and lateral PFC (Lawrence et al., 1996), while late in the course patients have been found to be additionally impaired at reversal learning (Lange et al., 1995), presumably reflecting developing disruption of the circuitry incorporating the ventromedial caudate nucleus and those limbic areas thought to be central to reversal learning (Haber et al., 1995).

Alternatively, recent anatomical advances have highlighted the possibility that output pathways from the caudate nucleus to occipito-temporal cortical areas (for example, Middleton & Strick, 1996) form part of *posterior* cortico-striatal loops involving those visual pathways already known to project to the 'visual striatum' (Webster, Bachevalier, & Ungerleider, 1993; Yeterian & Pandya, 1995). Similarly, behavioural evidence that these pathways may mediate aspects of so-called 'habit memory' (Mishkin, Malamut, & Bachevalier, 1984) have recently been supplemented by reports that cortico-striatal projections from the *visual* cortex to the striatum have a specific role in stimulus-reinforcement learning (Gaffan, 1996 for review). Clearly, further research will be needed in order to discover whether the activations seen here in the caudate nucleus during reversal learning reflect its contribution to anterior or posterior cortico-striatal function.

In summary, it appears that ED shift learning differentially activates PFC (reflecting the control of attentional set), while reversal learning is associated with increased rCBF in portions of the striatum (reflecting the acquisition of swapped stimulus-reward associations). Since ED shift learning is central to the WCST, impairments shown by patients with either damage to, or disruption of, the PFC are likely to reflect, at least partially, a failure to control attentional-set (Milner, 1963, 1964; Robinson et al., 1980). Moreover, difficulties with revising stimulus-reward associations, also implicit in performance of the WCST, may exacerbate the impairments shown by patients with various forms of striatal pathology (for example, Bowen et al., 1975; Joiassen et al., 1983).

The Role of the PFC in the ID/ED Task: Evidence for Working Memory Processes?

As discussed in the Introduction section, it has been proposed that the PFC contributes to performance of the WCST by mediating the short-term maintenance of task-relevant information required for computing the newly correct mode of response following a change of sorting rule (Berman et al., 1995; Goldman-Rakic, 1987, 1991). Evidence that the verbal subsection of this working memory system (Baddeley, 1986) might indeed be involved in this way has been supplied by an innovative brain-imaging study, in which performance of the WCST was shown to differentially activate left-sided cortex around Broca's area and the supramarginal gyrus (BA 44 and 40) compared to a simultaneous pattern-matching control task (Berman et al., 1995). Increased rCBF in these areas has, within the context of verbal working memory performance, been assumed to reflect the subvocal rehearsal of recently presented material through a phonological store/loop (see Cohen et al., 1997; Paulesu, Frith, & Frackowiak, 1993; Smith, Jonides, & Koeppe, 1996).

It is notable that, relative to any of the baselines used in the present study, neither ED nor reversal learning were associated with increased rCBF in left BA 44 or 40, suggesting that neither of these forms of shift learning *differentially* taxed verbal working memory processes assumed to be subserved by these regions. Neither was it the case that, relative to performance, these cortical areas were activated by any of the intralearning comparisons. Thus, although we believe that working memory processes must make some contribution to the acquisition of ED shift discriminations (perhaps by coding recent responses and positive (reward) and negative (punishing) feedback), we can find little evidence from the present study that ED shifting was particularly associated with increased activation in the posterior portion of the inferior frontal sulcus (around BA 44) as demonstrated in a recent single-trial fMRI study of the WCST (Konishi et al., 1998), and believed to mediate some aspect of the working memory contribution to subjects' ability to shift cognitive set (Konishi et al., 1998; see also Berman et al., 1995).

On the other hand, relative to ID shift learning, ED shift learning did differentially activate an area of right mid-dorsolateral PFC, along the middle frontal gyrus (BA 9/46), also activated in studies involving a variety of verbal and visual working memory tasks (for example, Cohen et al., 1997; Goldberg, Berman, Randolph, Gold, & Weinberger, 1996; McCarthy et al., 1996; Owen et al., 1996; Smith et al., 1996). Thus, this activation may reflect some kind of 'active representation' in a work-

ing memory system (see Cohen et al., 1997) needed for the acquisition of an ED shift. However, currently available theories of the organisation of working memory within PFC do not provide an adequate account of the nature of the mid-dorsolateral activation seen in the present study. For example, according to a modality-specific theory of working memory, by which different parts of the PFC are hypothesized to mediate memory for different types of information (Goldman-Rakic, 1994, 1995), increased rCBF around the middle frontal gyrus (BA 46) has tended to be associated with memory for explicitly spatial material (for example, Goldberg et al., 1996; McCarthy et al., 1996). However, spatial information is no more necessary for the acquisition of ED shifts than it is for the acquisition of ID shifts, suggesting that the enhanced mid-dorsolateral activation associated with ED shifting in the present study reflects either uncontrolled, and functionally unimportant, visuospatial encoding of the stimuli, or else neural activity associated with some other kind of cognitive activity. Furthermore, there was little indication of increased rCBF in more ventral regions of PFC (for example, BA 47) that, according to the modality-specific hypothesis of working memory, are implicated in the processing of nonspatial or object-based information (Goldman-Rakic, 1994, 1995; McCarthy et al., 1996), and which might have been expected to be activated by the *pattern/object-based* discriminanda of the ID/ED visual discrimination task.

Slightly different difficulties face attempts to fit the present data to an alternative theoretical approach according to which different areas of the PFC are hypothesized to mediate different kinds of cognitive *process* implicated in working memory function (see Petrides, 1994, 1995). Within this framework, activations of more ventrolateral parts of the PFC (for example, BA 47) have been associated with the organisation of responses in preparation for recall, while those in more dorsolateral regions (for example, BA 46) have been associated with more extensive manipulation of the remembered material (Owen et al., 1996). Thus, the increased rCBF seen here around the middle frontal gyrus in ED relative to ID shift learning may reflect some additional *manipulation* or 'monitoring' of information in working memory necessary for the acquisition of discriminations involving previously irrelevant stimulus dimensions. However, as we noted in the introduction, an extensive animal and human learning tradition (Kruschke, 1996; Issacs & Duncan, 1962; Mackintosh, 1965; Shepp & Eimas, 1964; Shepp & Schrier, 1969; Slamecka, 1968; Sutherland & Mackintosh, 1971; Zeaman & House, 1963) suggests that the *principal* difference between these two forms of shift learning is not the greater degree of 'manipulation' within working memory, but rather the requirement to override an acquired attentional bias that, by dragging attention back towards previously relevant but currently irrelevant stimulus dimensions, interferes with new learning. Thus, the ED shift is predominantly a test of attentional control (although the misallocation of attention may consequently place greater strain on ancillary processes, including working memory). In the absence of an adequate characterisation of the contribution of working memory to ED shift discrimination learning, it seems more parsimonious to attribute the present pattern of rCBF changes within the PFC to the control of attentional-set. Moreover, other features of the our results suggest that the PFC may also contribute to ED shift learning by modulating specifically *attentional* aspects of object-based processing mediated in posterior occipito-temporal pathways.

The Role of the PFC in the ID/ED Task: Modulating Attention?

We have argued that the ID/ED task makes explicit an often neglected feature of the WCST; that it consists of a series of shifts between visual discriminations over multidimensional stimuli (Teuber et al., 1951). In this context, one important feature of our results is the discovery that acquisition of ED shift discriminations is associated with relative deactivation of occipito-temporal pathways widely believed to subserve important object encoding and recognition processes (Haxby et al., 1991, 1994; Kohler, Kapur, Moscovitch, Winocur, & Houle, 1995; Martin, Oren, & Boon, 1991; Moscovitch, Kapur, Kohler, & Houle, 1995; see Ungerleider, 1995; Ungerleider & Mishkin, 1982 for review). Thus, subtractions of the rCBF associated with the ED Shift from that associated with the ID Shift scans—revealing relative rCBF reductions in ED compared to ID shift learning—isolated extensive areas of deactivation within left visual cortex (for example, BA 17) and right inferotemporal cortex (BA 37; see Table 3(b) and Figure 4(b)).

How can we account for the relative inactivity in occipito-temporal pathways in ED shift learning? One answer begins with the observation that neither reversal shift learning nor ID shift learning require an alteration of attentional-set. The former requires the acquisition of swapped stimulus-reward associations, while the latter involves only the association of reward values with entirely novel stimuli. However, in each case, the relevant stimulus dimension is unchanged. Under these conditions, it may be that the benefit to new learning conferred by a preexisting attentional-set towards a particular stimulus dimension or attribute is mediated by activity in occipital (Motter, 1994), and inferotemporal cortices (Chelazzi, Miller, Duncan, & Desimone, 1993; Maunsell, 1995 for review; Richmond & Sato, 1987; Spitzer & Richmond, 1991) that has been tuned over the course of training to permit privileged processing of relevant stimulus attributes. By contrast, under the conditions of an ED shift, the process of overriding such an acquired attentional set—perhaps initiated by PFC

projections to both occipito-temporal cortices (see Jones & Powell, 1970)—may involve the temporary modulation of this activity within posterior 'object-processing' pathways implicated in various aspects of object-based learning. This suggestion is consistent with evidence that posterior occipito-temporal cortices, deactivated in the ED shift scans contribute to visual discrimination learning by mediating processes of perceptual analysis (Cowey & Gross, 1970; Gross, 1973; Iwai & Mishkin, 1969 for review).

Notwithstanding the above possibilities, the present study has demonstrated that, in the context of visual discrimination learning, shifting an acquired attentional bias (that is, accomplishing an ED shift) and reversing recently learnt stimulus-reward associations (that is, accomplishing a reversal shift) are associated with increased rCBF in dissociable cortical and subcortical neural structures. Thus, these data complement a rich tradition of research involving animal and human learning theory (for example, Kruschke, 1996; Mackintosh, 1965; Sutherland & Mackintosh, 1971; Zeaman & House, 1963), human subjects bearing different forms of brain damage (Downes et al., 1989; Lawrence et al., 1996; Owen et al., 1991, 1993) and experimental primates (Dias et al., 1996a,b, 1997; Roberts et al., 1994), suggesting that these different forms of shift learning are mediated by distinct psychological, neuronal and neurochemical substrates.

METHOD

Subjects

Twelve right-handed volunteers (11 male, 1 female), with no history of psychiatric or neurological illness, participated in the study. Their mean age was 43.3 years (±1.7) while their mean verbal IQ, estimated with the National Adult Reading Test (Nelson, 1982), was in the above average range at 118.8 (±1.2). The study was approved by the Hammersmith Hospital Ethics Committee and the Advisory Committee on the Administration of Radioactive Substances (ARSAC), UK. All subjects gave informed consent.

Adapted ID/ED Task

Each subject was scanned in the presence of low background noise and dimmed ambient lighting. Stimuli were presented on a Taxan SV-775EV touch-sensitive screen controlled by an IBM PS/2 microcomputer. The screen was mounted at a viewing distance of approximately 50 cm so that the subject could touch all areas of the screen with the index finger of the dominant hand, which was rested on the chest between responses.

The test stimuli of the ID/ED visual discrimination learning task varied independently along the dimensions of colour, value and shape, with each dimension represented by two exemplars only (for example, white and green, one and six, and arrow and square; see Figure 1). The correct stimulus for a discrimination was specified by one exemplar from one dimension (for example, the colour green).

On any one trial, two test stimuli appeared randomly in two of four rectangles positioned towards the sides of the screen, and the subject was required to touch the box containing the correct stimulus with the index finger of the right-hand (see Figure 1). If the subject chose correctly, the word 'Correct', written in green ink, appeared in the centre of the screen accompanied by a brief, high-pitched auditory tone (frequency: 1200 Hz; duration: 164 msec). If the subject chose incorrectly, the word 'Incorrect', written in red ink, appeared accompanied by a longer, lower-pitched tone (frequency: 200 Hz; duration: 550 msec). The subject was considered to have learnt a given discrimination to 'criterion' after choosing the correct stimulus six times in succession. Before PET scanning commenced, but after the subject had been positioned in the scanner, the experimenter explained the nature of the test stimuli and responses. Following this, the subject learnt one discrimination with each of the dimensions of color, value, and shape, in order to emphasize that the discriminations related to the most obvious perceptual features of the stimuli, and that other information was irrelevant. (In particular, presenting the test stimuli randomly within any two of the four boxes as opposed to randomly within just two boxes (for example, left and right) effectively emphasised that spatial location was irrelevant for learning the discriminations.)

Testing consisted of three runs of four scans. Each run contained one scan taken while the subject performed one of four types of discrimination. These discriminations were embedded in longer sequences designed to mimic as closely as possible the clinical form of the ID/ED shift task used previously in studies with neurological patient groups (for example, Downes et al., 1989; Owen et al., 1991). As described in the introduction, the task consists of several ID and reversal shifts, in which just one stimulus dimension is relevant, and that induce, on the part of the subject, a bias or 'attentional-set' towards that dimension. The task culminates in an ED shift to a dimension which was previously irrelevant, and, therefore, requires the subject to modulate that acquired bias in order to attend to this newly relevant dimension and learn the discrimination.

For each scan, the subject began acquiring discriminations approximately 2.5 min before rCBF measurement was taken. However, at the start of the scan itself (that is, when the 'head count' began to rise; see below), the appropriate learning discrimination was presented to the subject. In this way, we ensured that the acquisition of the count data corresponded precisely to the different types of learning manipulated in the experiment.

The exact sequence of discriminations for one typical run is described below.

Discrimination Performance

Prior to the commencement of the first rCBF measurement, the subject was asked to acquire an initial discrimination, D_1, consisting of two exemplars from each of the three dimensions (for example, white and green, one and six, and arrow and square). However, the correct stimulus was specified by one particular exemplar from one dimension—for example, the colour green—so that this dimension was relevant while the two remaining dimensions—shape and value—were irrelevant. All 12 subjects were able to learn D_1 to criterion within a maximum of a dozen or so trials, and continued to respond by choosing the correct stimulus up until the start of, and *throughout* the entire duration of, the rCBF measurement itself. Once this measurement was completed, the screen was cleared and the subject asked to rest for approximately 5 min before the next scan. Thus, in this *performance* scan, the subject merely performed an *already-learnt* discrimination. We assumed that the amount of new learning occurring during the scan itself was minimal and, therefore, constituted a good baseline against which to compare the rCBF associated with the three specific learning discriminations.

Reversal

Before the second scan commenced, the subject was shown D_1 and asked to relearn this discrimination. Once criterion had been reached, a new discrimination, D_2, was presented which consisted of entirely new exemplars from each of the stimulus dimensions (for example, red and blue, three and seven, and circle and triangle). In this discrimination, the correct stimulus was specified by an exemplar from the previously relevant dimension—for example, the color red—and constituted an ID shift in which attending to the previously relevant dimension facilitated learning. All 12 subjects were able to learn D_2 quickly and continued to respond to the correct stimulus right up until the beginning of the rCBF measurement. At this point, the reward valences of the exemplars for D_2 were reversed so that the previously incorrect stimulus—blue—was correct while the previously correct stimulus—red—was now incorrect. Once the subject learnt this reversal to criterion, D_2 was reversed again, so that the original stimulus-reward relations were restored. When the scan finished, the screen cleared, and the subject asked to rest. We assumed that the rCBF collected in this *reversal* scan, reflected learning that the previously acquired stimulus-reward relationships no longer held and that the opposite relationships were now in force.

ID Shift

Prior to the third rCBF measurement, the subject reacquired D_2 to criterion, and was then given a further ID discrimination, D_3, in which all stimulus exemplars were again novel but in which colour remained relevant. As expected, all 12 subjects learnt D_3 to criterion easily and continued to choose the correct stimulus in this discrimination right up until the beginning of the PET scan. At this point, the subject was shifted to a fourth discrimination with new exemplars, D_4, and scanned while acquiring this discrimination. Crucially, the relevant dimension in D_4—colour—was also unchanged from that previously and constituted another ID shift. Any acquired attentional bias to that dimension on the part of the subject (Mackintosh, 1965; Sutherland & Mackintosh, 1971 for review; Zeaman & House, 1963) would facilitate acquisition of this discrimination. Once the subject had learnt D_4 to criterion, a further ID shift discrimination, again with novel exemplars, was given in the form of D_5. Once the scan had finished, the screen was cleared and the subject rested for approximately 5 min. We assumed that the rCBF acquired in this *ID shift* scan was influenced by the previously acquired *attentional* bias towards the relevant dimension.

ED Shift

Before the fourth rCBF measurement, the subject reacquired D_5 to criterion before being given another discrimination with all new exemplars in which colour was relevant, D_6. Once the subject had learnt this discrimination, he/she continued to respond to the correct stimulus right up until the start of the rCBF measurement at which point a final discrimination with new exemplars, D_7, was given. However, now the correct stimulus was no longer specified by one of the colours but rather by one of the values. Thus, D_7 constituted an ED shift in that the subject had to attend to a different stimulus dimension from that which was previously relevant in order to learn the discrimination. We assumed that, since by this stage the subject had learnt no fewer than six colour discriminations, and two reversals within that dimension, he/she would have acquired a reasonably strong 'attentional-set' for the stimulus dimension of colour. Insofar as this attentional bias persists in this ED shift condition, learning should be retarded relative to learning in earlier ID shift discriminations. Once D_7 had been acquired, a second ED shift from value to shape was given in the form of the final discrimination, D_8. After the scan had finished, the screen was cleared and the subject was asked to rest. We assumed that the rCBF collected in this *ED shift* scan was influenced by the requirement to override or modulate in some way a previously acquired attentional bias towards a now-irrelevant stimulus dimension.

Design

Four subjects completed the sequence described above in which colour was the relevant dimension in the first run of the study. For these subjects, value was relevant in the second run, and shape was relevant in the third. For four different subjects, the ordering of relevant dimensions across the three runs was value, shape, and colour, and for the remaining four subjects, the ordering was shape, colour, and value. In this way, each dimension was relevant an equal number of times in each of the first, second, and third runs.

Controlling Motor Responding

One important design issue involved the number of motor responses, or, equivalently, the number of trials across the different conditions of the study. For example, in discriminations in which learning is relatively rapid, frequency of responding will tend to be high because the subject needs little time in which to deliberate about which stimulus is correct. By contrast, in discriminations in which learning is slowed, frequency of responding may be relatively decreased to the extent that the subject thinks longer before making his/her response. In this case, comparisons of rCBF associated with these conditions may be contaminated by changes due simply to gross differences in the amount of motor movement. We wished to control for such effects, and implemented a controlled frequency of responding across scans. Specifically, each display was presented on the screen for 1 sec before a brief auditory tone (frequency: 700 Hz; duration: 165 msec) sounded to indicate that the subject was to respond immediately. He/she was instructed to use this tone as a cue to respond (even when unsure about the correct stimulus), and, thus, to develop an even rate of responding across all the scans. Once the subject made his/her response, the screen was cleared before the next display was presented 1 sec later. The program that presented the sequences of discriminations to the subject, and collected latency and error data across the scans, also counted the number of responses in the scan windows. To reiterate the results presented above, the frequency of responding was tightly controlled across all four types of scans, and it is extremely unlikely that the rCBF differences described here are due to gross differences in motor activity.

PET Scanning

Measurements of rCBF were obtained using a CTI model 953B PET scanner (CTI, Knoxville, TN, USA). Collimating septa were retracted in order to increase the sensitivity of the PET camera and increase the number of recorded true counts from the administered radiation (Bailey, Jones, Friston, Colebatch, & Frackowiak, 1991). A 10-min transmission scan was obtained using a retractable external source of $^{68}Ge/^{68}Ga$ to correct for attenuation of gamma radiation by the brain and skull. Twelve dynamic images were acquired at 10-min intervals to allow for the decay of radioactive tracer. ^{15}O has a half life of 2.04 min. Approximately, 9.4 mCi of $H_2{}^{15}O$ were administered as a slow bolus infusion per subject.

In each of the learning scans, the shift to a new discrimination was initiated as the head count started to rise. Typically, subjects achieved at least two shifts in the 45 sec corresponding to the rise and peak of the head count. For each of the 12 scans, emission data were collected for 90 sec.

Data Analysis

Image analysis was performed with SPM software (Wellcome Department of Cognitive Neurology; http://www/fil.ion.ac.uk/spm) within MATLAB (Mathworks, Natick, MA, USA). Realignment and normalisation used the current working version of SPM (SPM 99 beta), while statistical analysis was performed with SPM 96 (Ashburner, Neelin, Collins, Evans, & Friston, 1997).

Image Normalisation

Following reconstruction, the images were realigned using the mean of all 12 scans as a reference (Friston et al., 1995a), and transformed into standard space corresponding to the MNI brain (Evans, Collins, & Milner, 1992). Stereotactic standardisation of PET images allows comparison of scan data in identical voxels across different subjects and scans. Finally, the images were smoothed using a Gaussian filter of 16-mm full width half maximum (FWHM) in order to remove high-frequency noise and to accommodate differences in gyral anatomy between individual subjects.

Statistical Analysis

Conditions and covariates for each subject were specified in an analysis of covariance (ANCOVA) that removed the confounding effect of differences in global activity (radioactive counts) across scans and normalized global activity to a notional mean rCBF of 50 ml dl^{-1} min^{-1} (Friston et al., 1990). Effects at each and every voxel were estimated according to the general linear model (Friston et al., 1995b). Condition effects at each voxel were compared using linear contrasts. The resulting set of voxel t statistics for each contrast constitute a statistical parametric map (SPM $\{t\}$). SPM $\{t\}$ maps were transformed to the unit normal distribution SPM $\{Z\}$ for display and thresholded at 3.09 or $p = .001$ uncorrected. The resulting foci were then characterized in terms of spatial extent (k) and peak height (u). The significance of each region was estimated using distributional approximations from the theory of Gaussian fields. This

characterisation is in terms of the probability that the peak height observed (or higher) could occur by chance $PZ_{max}>u$ over the entire volume analyzed (that is, a corrected p-value).

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Reprint requests should be sent to Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, OX3 75T, UK or via e-mail: robert.rogers@psychiatry.oxford.ac.uk

REFERENCES

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organisation of functionally-segregated circuits linking the basal ganglia and cortex. *Annual Reviews of Neuroscience*, *9*, 357–381.

Anderson, S. W., Damasio, H., Dallas Jones, R., & Tranel, D. (1991). Wisconsin Card Sorting Test performance as a measure of frontal damage. *Journal of Clinical and Experimental Neuropsychology*, *13*, 909–922.

Anderson, T. J., Jenkins, I. H., Brooks, D. J., Hawken, M. B., Frackowiak, R. S. J., & Kennard, C. (1994). Cortical control of saccades and fixation in man. A PET Study. *Brain*, *117*, 1073–1084.

Ashburner, J., Neelin, P., Collins, D. L., Evans, A., & Friston, K. (1997). Incorporating prior knowledge into image registration. *Neuroimage*, 344–352.

Baddeley, A. D. (1986). *Working Memory*. Oxford: Oxford University Press.

Bailey, D. L., Jones, T., Friston, K. J., Colebatch, J. G., & Frackowiak, R. S. J. (1991). Physical validation of statistical parametric mapping [abstract]. *Journal of Cerebral Blood Flow and Metabolism*, *11* (Suppl. 2), S150.

Berman, K. F., Randolph, C., Gold, J., Goldberg, T. E., Coppola, R., Ostrem, J. L., Carson, R. E., Herscovitch, P., & Weinberger, D. R. (1986). Physiological activation of a cortical network of the Wisconsin Card Sorting Test: A positron emission tomography study. *Neuropsychologia*, *33*, 1027–1046.

Berman, K. F., Zee, R. F., & Weinberger, D. R. (1995). Physiologic dysfunction of dorsolateral-prefrontal cortex in schizophrenia: II. Role of neuroleptic treatment, attention and mental effort. *Archives of General Psychiatry*, *43*, 126–135.

Bowen, F. P., Kamienny, R. S., Burns, M. M., & Yahr, M. D. (1975). Parkinsonism: Effects of levodopa on concept formation. *Neurology*, *25*, 701–704.

Bushnell, M. C., Goldberg, M. E., & Robinson, D. L. (1981). Behavioural enhancement of visual responses in the monkey cerebral cortex: I. Modulation in posterior-parietal cortex related to selective visual attention. *Journal of Neurophysiology*, *46*, 755–772.

Chelazzi, L., Miller, E. K., Duncan, J., & Desimone, R. (1993). A neural basis for visual search in inferior-temporal cortex. *Nature*, *363*, 345–347.

Cohen, J. D., Peristein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., & Smith, E. E. (1997). Temporal dynamics of brain activation during a working-memory task. *Nature*, *386*, 604–608.

Colebatch, J. G., Deiber M.-P., Passingham, R. E., Friston, K. J., & Frackowiak, R. S. J. (1991). Regional cerebral blood flow during voluntary arm and hand movements in human subjects. *Journal of Neurophysiology*, *65*, 1392–1401.

Corbetta, M., Meizin, F. M., Dobmeyer, S., Shulman, G. L., & Petersen, S. E. (1991). Selective and divided attention during visual discriminations of shape, color, speed: Functional anatomy by positron emission tomography. *Journal of Neuroscience*, *11* (8), 2383–2402.

Corbetta, M., Meizin, F., Shulman, G. L., & Petersen, S. E. (1993). A PET study of visuospatial attention. *Journal of Neuroscience*, *13* (3), 1202–1226.

Corbetta, M., Shulman, G. L., Meizin, F., & Petersen, S. E. (1995). Superior-parietal cortex activation during spatial attention shifts and visual feature conjunction. *Science*, *270*, 802–805.

Cowey, A., & Gross, C. G. (1970). Effects of prestriate and inferotemporal lesions on visual discrimination by rhesus monkeys. *Experimental Brain Research*, *11*, 128–144.

Daum, I., Schugens, M. M., Channon, S., Polkey, C. E., & Gray, J. A. (1991). T-maze discrimination and reversal learning after unilateral-temporal or frontal-lobe lesions in man. *Cortex*, *27*, 613–622.

Deiber, M.-P., Colebatch, J. G., & Friston, K. J. (1991). Cortical areas and the selection of movement: A study with positron emission tomography. *Experimental Brain Research*, *84*, 393–402.

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selctive visual attention. *Annual Review of Neuroscience*, *18*, 193–122.

Dias, R., Robbins, T. W., & Roberts, A. C. (1996a). Dissociation in prefrontal cortex of affective and attentional shifts. *Nature*, *380*, 69–72.

Dias, R., Robbins, T. W., & Roberts, A. C. (1996b). Primate analogue of the Wisconsin Card Sorting Test: Effects of excitotic lesions of the prefrontal cortex in the marmoset. *Behavorial Neuroscience*, *110*, 872–886.

Dias, R., Robbins, T. W., & Roberts, A. C. (1997). Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sorting Test: Restriction to novel situations and independence from ''on-line'' processing. *Journal of Neuroscience*, *17* (23), 9285–9297.

Divac, I., Rosvold, H. E., & Szwarcbart, M. K. (1967). Behavioural effects of selective ablation of the caudate nucleus. *Journal of Comparative Physiological Psychology*, *63*, 184–190.

Downes, J. J., Roberts, A. C., Sahakian, B. J., Evenden, J. L., Morris, R. G., & Robbins, T. W. (1989). Impaired extradimensional-shift performance in medicated, and unmedicated, Parkinson's disease: Evidence for a specific attentional dysfunction. *Neuropsychologia*, *27*, 1329–1343.

Drewe, E. A. (1974). The effect of type and area of brain lesion on Wisconsin Card Sorting Test performance. *Cortex*, *10*, 159–170.

Eslinger, P. J., & Damasio, A. R. (1985). Severe disturbances of higher cognition after bilateral frontal lobe ablation: Patient EVR. *Neurology*, *35*, 1731–1741.

Evans, A. C., Collins, D. L., & Milner, B. (1992). An MRI-based stereotactic atlas from 250 young normal subjects. *Society for Neuroscience (Abstract)*, *18*, 408.

Fox, P. T., Raichle, M. E., & Thach, W. T. (1985). Functional mapping of the human cerebellum with positron emission tomography. *Proceedings of the National Academy of Science*, *82*, 7462–7466.

Friston, K. J., Frith, C. D., Liddle, P. F., Dolan, R. J., Lammertsma, A. A., & Frackowiak, R. S. J. (1990). The relationship between global and local changes in PET scans. *Journal of Cerebral Blood Flow and Metabolism*, *10*, 458–466.

Friston, K. J., Ashburner, J., Frith, C. D., Poline, J.-B., Heather, J. D., & Frackowiak, R. S. J. (1995a). Spatial registration and normalisation. *Human Brain Mapping*, *2*, 1–25.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-B., Frith, C. D., & Frackowiak, R. S. J. (1995b). Statistical parametric maps in functional imaging: A general approach. *Human Brain Mapping*, *2*, 189–210.

Gaffan, D. (1996). Memory, action, and the corpus striatum: Current developments in the memory-habit distinction. *Seminars in the Neurosciences*, *8*, 33–38.

Goldberg, T. E., Berman, K. F., Randolph, C., Gold, J. M., & Weinberger, D. R. (1996). Isolating the mnemonic components in spatial-delayed response: A controlled PET 15O-labelled water regional cerebral blood flow study in normal humans. *Neuroimage*, *3*, 69–78.

Goldman-Rakic, P. S. (1987). Circuitry of primate prefrontal cortex and regulation of behaviour by representational knowledge. In F. Plum & V. B. Mountcastle (Eds.), *Handbook of physiology* (pp. 373–417).

Goldman-Rakic, P. S. (1991). Prefrontal cortical dysfunction in schizophrenia: The relevance of working memory. In B. J. Carroll & J. E. Barret (Eds.), *Psychopathology and the brain* (pp. 1–23). New York: Raven.

Goldman-Rakic, P. S. (1994). The issue of memory in the study of prefrontal functions. In A. M. Thiery, J. Glowinski, P. S. Goldman-Rakic, & Y. Christen (Eds.), *Motor and cognitive functions of the prefrontal cortex* (pp. 112–122). Berlin: Springer-Verlag.

Goldman-Rakic, P. S. (1995). Architecture of the prefrontal cortex and the central executive. *Annals of the New York Academy of Sciences*, *769*, 71–83.

Grafman, J., Jonas, B., & Salazar, A. (1990). Wisconsin Card Sorting Test performance based on location, and size, of neuroanatomical lesion in Vietman with penetrating head injury. *Perceptual and Motor Skills*, *71*, 1120–1122.

Grant, D. A., & Berg, E. A. (1948). A behavioural analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. *Journal of Experimental Psychology*, *38*, 404–411.

Gross, C. G. (1973). Inferotemporal cortex and vision. In E. Stellar & J. M. Sprague (Eds.), *Progress in physiological psychology*, *5* (pp. 77–123). New York: Academic Press.

Haber, S. N., Kunishio, K., Mizobuchi, M., & Lynd Balta, E. (1995). The orbital amd medial prefrontal circuit through the basal ganglia. *Journal of Neuroscience*, *15*, 4851–4867.

Haxby, J. V., Grady, C. L., Horwitz, B., Ungerleider, L. G., Mishkin, M., Carson, R. E., Herscovitch, P., Schapiro, M. B., & Rapoport, S. I. (1991). Dissociation of object and spatial visual processing pathways in human-extrastriate cortex. *Proceedings of the National Academy of Science*, *88*, 1621–1625.

Heck, E. T., & Bryer, J. B. (1986). Superior sorting and categorizing ability in a case of bilateral-frontal atrophy: An exception to the rule. *Journal of Clinical and Experimental Neuropsychology*, *8*, 313–316.

Hedreen, J. C., & Folstein, S. E. (1995). Early loss of neostriatal striosome neurones in Huntington's disease. *Journal of Neuropathology and Experimental Neurology*, *54*, 105–120.

Hermann, B. P., Wyler, A. R., & Richey, E. T. (1988). Wisconsin Card Sorting Test performance in patients with complex partial seizures of temporal lobe origin. *Journal of Clinical and Experimental Neuropsychology*, *10*, 467–476.

Issacs, D., & Duncan, I. D. (1962). Reversal and nonreversal shifts within and between dimensions in concept formation. *Journal of Experimental Psychology*, *64*, 580–585.

Iversen, S. D., & Mishkin, M. (1970). Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Experimental Brain Research*, *11*, 376–386.

Iwai, E., & Mishkin, M. (1969). Further evidence on the locus of the visual area in the temporal lobe of the monkey. *Experimental Neurology*, *25*, 585–594.

Jones, B., & Mishkin, M. (1972). Limbic lesions and the problem of stimulus-reinforcement associations. *Experimental Neurology*, *36*, 362–377.

Jones, E. G., & Powell, T. P. S. (1970). An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain*, *93*, 793–820.

Josiassen, R. C., Curry, L. M., & Mancall, E. L. (1983). Development of neuropsychological deficits in Huntington's disease. *Archives of Neurology*, *40*, 791–796.

Kohler, S., Kapur, S., Moscovitch, M., Winocur, G., & Houle, S. (1995). Dissociation of pathways for object and spatial vision: A PET study in humans. *NeuroReport*, *6*, 1865–1868.

Konishi, S., Nakajima, K., Uchida, I., Kameyama, M., Nakahara, K., Sekihara, K., & Miyashita, Y. (1998). Transient activation of inferior-prefrontal cortex during cognitive set shifting. *Nature Neuroscience*, *1*, 80–84.

Kruschke, J. K. (1996). Dimensional relevance shifts in category learning. *Connection Science*, *8*, 225–247.

Lange, K. W., Sahakian, B. J., Quinn, N. P., Marsden, C. D., & Robbins, T. W. (1995). Comparison of executive and visuospatial memory function in Huntington's disease and dementia of Alzheimer type matched for degree of dementia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *58*, 598–606.

Lawrence, A. D., Sahakian, B. J., Hodges, J. R. , Rosser, A. E. , Lange, K. W., & Robbins, T. W. (1996). Executive and mnemonic functions in early Huntington's disease. *Brain*, *119*, 1633–1645.

Mackintosh, N. J. (1965). Selective attention in animal discrimination learning. *Psychological Bulletin*, *64*, 124–150.

Martin, D. J., Oren, Z., & Boon, K. (1991). Major depressives' and dysthymics' performance on the Wisconsin Card Sorting Test. *Journal of Clinical Psychology*, *47*, 684–690.

Martin, A., Wiggs, C. L., Ungerleider, L. G., & Haxby, J. V. (1996). Neural correlates of category-specific knowledge. *Nature*, *379*, 649–652.

Maunsell, J. H. R. (1995). The brain's visual world: Representation of visual targets in cerebral cortex. *Science*, *270*, 764–768.

McCarthy, G., Puce, A., Constable, R. T., Krystal, J. H., Gore, J. C., & Goldman-Rakic, P. S. (1996). Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. *Cerebral Cortex*, *6*, 600–611.

Middleton, F. A., & Strick, P. L. (1996). The temporal lobe is a target of output from the basal ganglia. *Proceedings of the National Academy of Science*, *93*, 8683–8687.

Milner, B. (1963). Effects of different brain lesions on card sorting. *Archives of Neurology*, *9*, 100–110.

Milner, B. (1964). Some effects of frontal lobectomy in man. In J. M. Warren & K. Akert (Eds.), *The frontal granular cortex and behaviour* (pp. 410–444). New York: McGraw-Hill.

Mishkin, M. (1964). Perseveration of cerebral sets after frontal lesions in monkeys. In J. M. Warren & K. Akert (Eds.), *The frontal granular cortex and behaviour* (pp. 219–241). New York: McGraw-Hill.

Mishkin, M., Malamut, B., & Bachevalier, J. (1984). Memories and habits: Two neural systems. In G. Lynch, J. L. McGaugh, & N. M. Wenberger (Eds.), *Neurobiology of learning and memory* (pp. 65–77). New York: Guilford.

Moscovitch, M., Kapur, S., Kohler, S., & Houle, S. (1995). Distinct neural correlates of visual long-term memory for spatial location and object identity: A positron emission tomography study in humans. *Proceedings of the National Academy of Science*, *92*, 3721–3725.

Motter, B. C. (1994). Neural correlates of attentive selection for color or luminance in extrastriate areas V4. *Journal of Neuroscience*, *14*, 2176–2189.

Mountcastle, V. B., Lynch, J. C., Georgopoulos, A., Sakata, H., & Acuna, C. (1975). Posterior parietal association cortex of the monkey: Command functions for operations within extrapersonal space. *Journal of Neurophysiology*, *38*, 871–908.

Nelson, H. E. (1982). National Adult Reading Test (NART), Test Manual. Windsor (UK): NFER-Nelson.

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex*, *12*, 313–324.

Nobre, A. C., Sebestyen, G. N., Gitelman, D. R., Mesulam, M. M., Frackowiak, R. S. J., & Frith, C. D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. *Brain*, *120*, 515–533.

Nolan, J. D., Stoneking, B. C., & Hatch, S. A. (1978). Test–retest evaluations of attention and rigidity. *American Journal of Psychology*, *91* (2), 275–288.

Oscar-Berman, M., & Zola-Morgan, S. M. (1980). Comparative neuropsychology and Korsakoff's syndrome: I. Spatial and visual reversal learning. *Neuropsychologia*, *18*, 499–512.

Owen, A. M. (1997). The functional organization of working memory processes within human lateral frontal cortex: The contribution of functional imaging. *European Journal of Neuroscience*, *9*, 1329–1339.

Owen, A. M., Roberts, A. C., Polkey, C. E., Sahakian, B. J., & Robbins, T. W. (1991). Extradimensional versus intradimensional set shifting performance following frontal lobe excision, temporal lobe excision or amygdalo-hippocampectomy in man. *Neuropsychologia*, *29*, 993–1006.

Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E., & Robbins, T. W. (1993). Contrasting mechanisms of impaired attentional shifting in patients with frontal lobe damage or Parkinson's disease. *Brain*, *116*, 1159–1175.

Owen, A. M., Evans, A. C., & Petrides, M. (1996). Evidence for a two-stage model of spatial working memory within the lateral frontal cortex: A positron emission tomography study. *Cerebral Cortex*, *6*, 31–38.

Passingham, R. E. (1993). *The frontal lobes and voluntary action.* Oxford University Press.

Paulesu, E., Frith, C. D., & Frackowiak, R. S. J. (1993). The neural correlates of the verbal correlates of working memory. *Nature*, *362*, 342–344.

Petersen, S. E., Corbetta, M., Miezin, F. M., & Shulman, G. L. (1994). PET studies of parietal involvement in spatial attention: Comparison of different task types. *Canadian Journal of Experimental Psychology*, *48* (2), 319–338.

Petrides, M. (1994). Frontal lobes and working memory: Evidence from investigations of cortical excisions in non human primates. In F. Boller & J. Gratman (Eds.), *Handbook of Neuropsychology,* vol. 9 (pp. 59–82). Amsterdam: Elsevier.

Petrides, M. (1995). Functional organisation of the human frontal cortex for mnemonic processing. *Annals of the New York Academy of Sciences*, *769*, 85–96.

Rafal, R., & Robertson, L. (1985). The neurology of visual attention. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 625–648). Cambridge, MA: MIT Press.

Richmond, B. J., & Sato, T. (1987). Enhancement of inferior temporal neurones during visual discrimination. *Journal of Neurophysiology*, *58*, 1292–1306.

Roberts, A. C., Robbins, T. W., & Everitt, B. J. (1988). The effects of intradimensional and extradimensional shifts on visual discrimination learning in humans and nonhuman primates. *Quarterly Journal of Experimental Psychology*, *40B*, 321–341.

Roberts, A. C., Robbins, T. W., Everitt, B. J., & Muir, J. L. (1992). A specific form of cognitive rigidity following excitotic lesions of the basal forebrain in marmosets. *Neuroscience*, *47*, 251–264.

Roberts, A. C., De Salvia, M. A., Wilkinson, L. S., Collins, P., Muir, J. L., Everitt, B. J., & Robbins, T. W. (1994). 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin Card Sorting Test: Possible interaction with subcortical dopamine. *Journal of Neuroscience*, *14* (5), 2531–2544.

Robinson, A. L., Heaton, R. K., Lehman, R. A. W., & Stilson, D. W. (1980). The utility of the Wisconsin Card Sorting Test in detecting and localizing frontal lobe lesions. *Journal of Consulting and Clinical Psychology*, *48*, 605–614.

Rolls, E. T. (1996): The orbito-frontal cortex. *Philosophical Transactions of the Royal Society of London, Series B*, *351*, 1433–1444.

Rolls, E. T., Hornak, J., Wade, D., & McGrath, J. (1994). Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *Journal of Neurology, Neurosurgery and Psychiatry*, *57*, 1518–1524.

Sandson, J., & Albert, M. L. (1984). Varieties of perserveration. *Neurology*, *22*, 715–732.

Sandson, J., & Albert, M. L. (1987). Perserveration in behavioural neurology. *Neurology*, *37*, 1736–1741.

Shepp, B. E., & Eimas, P. D. (1964). Intradimensional and extradimensional shifts in the rat. *Journal of Comparative and Physiological Psychology*, *57*, 351–361.

Shepp, B. E., & Schrier, A. M. (1969). Consecutive intradimensional and extradimensional shifts in monkeys. *Journal of Comparative and Physiological Psychology*, *67*, 199–203.

Slamecka, N. J. (1968). A methodological analysis of shift paradigms in human discrimination learning. *Psychological Bulletin*, *69*, 423–438.

Smith, E. E., Jonides, J., & Koeppe, R. A. (1996). Dissociating verbal, spatial, and working memory using PET. *Cerebral Cortex*, *6*, 11–20.

Spitzer, H., & Richmond, B. J. (1991). Task difficulty: Ignoring, attending to, and discriminating a visual stimulus yield progressively more activity in inferior temporal neurones. *Experimental Brain Research*, *83*, 340–348.

Sutherland, N. S., & Mackintosh, N. J. (1971). *Mechanisms of animal discrimination learning.* New York: Academic Press.

Teuber, H. L., Battersby W. S., & Bender, M. B. (1951). Performance of complex visual tasks after cerebral lesions. *Journal of Nervous and Mental Disease*, *114*, 413–429.

Thorpe, S. J., Rolls, E. T., & Maddison, S. (1983). Neuronal activity in the orbito-frontal cortex of the behaving monkey. *Experimental Brain Science*, *49*, 93–115.

Ungerleider, L. G. (1995). Functional brain-imaging studies of cortical mechanisms for memory. *Science*, *270*, 769–775.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical-visual systems. In J. Ingle, M. A. Goodale, & R. J. W. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549–586). Cambridge, MA: MIT Press.

van den Broek, M. D., Bradshaw, C. M., & Szabadi, E. (1993). Utility of the modified Wisconsin Card Sorting Test in neuropsychological assessment. *British Journal of Clinical Psychology*, *32*, 333–343.

Watson, J. D. G., Myers, R., Frackowiak, R. S. J., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., Shipp, S., & Zeki, S. (1995). Area V5 of the human brain: Evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cerebral Cortex*, *3*, 79–94.

Webster, M. J., Bachevalier, J., & Ungerleider, L. G. (1993). Subcortical connections of inferior temporal areas TE and TEO in macaque monkeys. *Journal of Comparative Neurology*, *335*, 73–91.

Weinberger, D. R., Berman, K. F., & Zee, R. F. (1986). Physio-

logic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. *Archives of General Psychiatry*, *43*, 114–124.

Yeterian, E. H., & Pandya, D. N. (1995). Cortico-striatal connections of extrastriate visual areas in rhesus monkeys. *Journal of Comparative Neurology*, *352*, 436–457.

Zeaman, D., & House, B. J. (1963). An attention theory of retardate discrimination learning. In N. R. Ellis (Ed.), *Handbook in mental deficiency: Psychological; theory and research* (pp. 159–223). New York: McGraw-Hill.

Zeki, S., Watson, J. D. G., Lueck, C. J., Friston, K. J., Kennard, C., & Frackowiak, R. S. J. (1991). A direct demonstration of functional specialization in the human visual cortex. *Journal of Neuroscience*, *11*, 641–649.