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The role of the ventrolateral frontal cortex in inhibitory oculomotor control

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It has been proposed that the inferior/ventrolateral frontal cortex plays a critical role in the inhibitory control of action during cognitive tasks. However, the contribution of this region to the control of eye movements has not been clearly established. Here, we describe the performance of a group of 23 frontal lobe damaged patients in an oculomotor rule switching task for which the association between a centrally presented visual cue and the direction of a saccade could change from trial to trial. A subset of 16 patients also completed the standard antisaccade task. Ventrolateral damage was found to be a significant predictor of errors in both tasks. Analysis of the rate at which patients corrected errors in the rule switching task also revealed an important dissociation between left and right hemisphere damaged patients. Whilst patients with left ventrolateral damage usually corrected response errors with secondary saccades, those with right hemisphere lesions often failed to do so. The results suggest that the inferior frontal cortex forms part of a wider frontal network mediating inhibitory control over stimulus elicited eye movements. The critical role played by the right ventrolateral region in cognitive tasks may arise due to an additional functional specialization for the monitoring and updating of task rules.

Keywords: executive control; eye tracking; antisaccades; task switching; frontal lobe

Abbreviations: DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye fields; VLF = ventrolateral frontal

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Introduction

The ability to inhibit stimulus elicited action is a faculty that has long been associated with the frontal lobes of the cerebral cortex (e.g. Holmes, 1938). Perhaps the most straightforward test of volitional inhibitory control in neurological patients is the antisaccade task, in which a saccadic eye movement has to be executed in the direction opposite to the location of a peripheral stimulus onset (Hallett and Adams, 1980; Leigh and Kennard, 2004). Yet even in the case of this relatively simple test, for which the neural control centres are well-charted in animal models (Munoz and Everling, 2004), there is considerable disagreement between studies concerning the critical frontal lesion site that leads to an impairment in humans. Research in the domain of oculomotor control also rests uncomfortably with the wider literature on response inhibition in cognitive tasks which posits a role for the inferior frontal region in inhibitory control processes (see Aron *et al.*, 2004*a*, *b* for review).

The performance of frontal lobe damaged patients in the antisaccade task was first studied by Guitton *et al.* (1985). These authors contrasted performance of patients with frontal lobe lesions to those with temporal lobe damage. The frontal lobe group made a significantly increased number of errors in which the target stimulus was fixated. It was speculated that these patients had impaired volitional inhibitory control due to damage affecting the frontal eye fields (FEF). However, later studies suggested that it was the adjacent dorsolateral prefrontal cortex (DLPFC) which was the critical lesion site leading to an impairment

(Pierrott-Deseilligny *et al.*, 1991; Rivaud *et al.*, 1994). Together with evidence from neurophysiological studies in monkeys, these patient studies imply a role for the DLPFC region in the volitional suppression of reflex saccades (Goldman-Rakic, 1987; Funahashi *et al.*, 1989, 1993; Pierrot-Deseilligny *et al.*, 2005).

Other evidence can be used to argue against a critical role for the DLPFC in the antisaccade task. Functional activation and transcranical magnetic stimulation studies have shown that in humans the FEF lies at the intersection of the superior frontal sulcus and the precentral sulcus, just anterior to the hand and face representation in the motor strip (Paus, 1996; Ro *et al.*, 1999). One study which used this precise anatomical criterion found that patients with chronic FEF lesions made increased contralesional errors in the task (Machado and Rafal, 2004). The same report also describes two patients with lesions which appear to spare the FEF that performed antisaccades normally. Lesion reconstructions suggest that both these patients had relatively small lesions confined to the dorsal aspect of the lateral prefrontal surface (i.e. the DLPFC).

Another report that runs contrary to a critical role for the DLPFC in inhibitory oculomotor control is that of Paus *et al.* (1991). These authors used a different procedure in which patients viewed a series of pictures/abstract patterns presented at fixation whilst irrelevant stimuli appeared without warning to the left and right of fixation. Lesions were carefully plotted onto standardized templates and categorized according to whether they had dorsal, ventral or medial prefrontal damage. Comparisons between the groups revealed that it was the ventrolateral (rather than dorsolateral) frontal damaged group who made increased distractibility errors.

An important single case report which also implicates the ventrolateral region in inhibitory oculomotor control was described by Walker *et al.* (1998). These authors describe a patient with right ventrolateral frontal damage of a type that is common following middle cerebral artery (MCA) stroke (Finley *et al.*, 2003; Naidich *et al.*, 2003). The patient made close to 100% antisaccade errors, a deficit which had not resolved a year or more after his stroke. He was also found to be impaired on a number of other cognitive tasks, including tests of spatial working memory, problem solving and attentional set shifting. The lesion was confined almost entirely to the inferior frontal gyrus, including the ventral prefrontal region and anterior insula cortex, approximating to the homologue of Broca's area in the right hemisphere. Although the authors' discussion focused largely on the implications of the case for hypothesized modal (i.e. spatial versus object) processing dichotomies in prefrontal cortex (Goldman-Rakic, 1996), the lesion location and pattern of deficits are clearly also consistent with the proposed specialization of the inferior frontal region for response inhibition across a range of cognitive tasks (Garavan *et al.*, 1999; Aron *et al.*, 2003, 2004a, b; Swainson *et al.*, 2003; Konishi *et al.*, 1999).

One potential explanation for the inconsistencies in the literature on antisaccades and frontal lobe damage is the criterion used to select patients. Many studies have set out with the aim of testing existing neural models of oculomotor control derived from animal neurophysiological investigations. Patients have therefore been selected and classified into groups based on whether they have a lesion that is judged to include (or exclude) a particular structure implicated in existing models (e.g. Periott-Deseilligny *et al.*, 1991; Rivaud *et al.*, 1994; Machado and Rafal, 2004). Regions of maximal lesion overlap in these studies reflect patient selection criterion rather than the existence of a functionally critical 'hot-spot'. The alternative is to use a more inclusive selection criterion in which all consenting neurological patients with frontal lobe damage are selected regardless of a priori assumptions concerning lesion regions of interest. Individuals can then be classified according to their behavioural performance—whether or not they show an impairment—and the statistical likelihood of a particular type of damage being associated with the functional deficit can be assessed.

Another concern is the relative lack of complexity of the antisaccade task compared to other tests of cognitive inhibitory control. It might be argued that other paradigms place much greater demands on cognitive control. Go/No-go, stop signal tasks (Logan, 1994; Aron *et al.*, 2003), as well as task switching procedures such as the Wisconsin card sorting test (Konishi *et al.*, 1999, 2002), require suppression of motor responding only on a subset of trials. Ventrolateral frontal cortex may only be engaged during tasks for which the demand to inhibit a response varies from trial to trial. Consistent with this explanation, a recent combined ERP/fMRI study suggests that the region is activated by the demand to switch into a response suppression mode, rather than mediating response inhibition per se (Swainson *et al.*, 2003). It is possible therefore that the antisaccade task may be relatively insensitive to the consequences of ventrolateral frontal damage.

To examine these issues, we tested a randomly selected group of patients with various types of frontal lobe lesions using a 'rule switching' task in which saccades have to be executed based on changing cue-saccade mappings. This task tests the inhibitory control of saccades under conditions of intermittent rule conflict, as well as the ability to monitor and correct errors with secondary corrective saccades (Husain *et al.*, 2003; Hodgson *et al.*, 2004). Patients were first classified as being impaired/unimpaired in their performance of the task relative to a group of age-matched controls. The distribution and characteristics of lesions in both groups were then compared using the voxel-based analysis of lesions technique (Rorden and Karnath, 2004). Additional behavioural analysis was also carried out in which patients were grouped on the basis of lesion location (left and right ventrolateral/non-ventrolateral) rather than performance.

For control purposes we also tested a subset of the patient group on the conventional pro and antisaccade tasks.

Materials and methods

Experimental subjects

Rule switching task

Twenty-three patients (5 females) with lesions involving the frontal lobe participated in the rule switching task. All were recruited from neurology and neurosurgery services at Charing Cross Hospital, London, UK and the Royal Devon and Exeter Hospital, Exeter, Devon, UK (Table 1). Candidate patients for the study were those who had sustained isolated focal lesions (i.e. not multiple infarcts) that included the frontal lobe, who were not undergoing chemotherapy or suffering from comorbid neurological conditions such as dementia and with no history of psychiatric illness. All patients who took part in the study gave their informed consent and the research was approved by the Riverside Regional Ethical Committee and North and East Devon Local Research Ethics Committee. The mean age of the patient group was 54 years, ranging from 27 to 76 years (SD = 16.4). An age-matched control group of 21 individuals (6 females) was recruited from employees of Charing Cross Hospital and the University of Exeter. The mean age of the control group was 53 years, ranging from 25 to 78 years (SD = 18.6).

Pro/antisaccades

Sixteen of the patients also completed the pro and antisaccade tasks. The mean age of the patient group was 55 years, ranging between 35 and 76 years (13 males). All but one of these patients also completed the rule switching task (Table 1). An age-matched control group of 16 subjects also completed the pro/antisaccade tasks. The mean age of the control group was 52 years ranging between 34 and 75 years.

Eye movement recording

Eye movements were recorded using an EyeLink II system (SR Research Ltd), a video-based pupil tracker with head movement compensation system sampling at 250 Hz. Subjects were seated 60 cm in front of a 22 inch CRT computer display monitor. Pupil position was monitored via two miniature infrared CCD video cameras mounted on an adjustable headband. The head movement compensation system meant that no active restraint of head movements was required to obtain sufficiently accurate gaze position recordings. Eye movements were recorded and visualized off line, saccades were identified and artefacts removed using custom software programs developed within the LabVIEW visual programming environment (National Instruments Inc.).

Table 1 Patient details

Patient	Age	Sex	Aetiology	Scan	Side	Lesion age	Lesion vol (cc)
1[b]	66	M	Middle cerebral artery infarct	CT	R	6 m	16.4
2[b]	56	F	Middle cerebral artery infarct	CT	R	1 m	68.4
3[b]	68	M	Middle cerebral artery infarct	MRI	R	3 y	105.6
4[b]	27	M	Excised frontal pole tumour	MRI	L	2 y	9.1
5[b]	28	F	Saggital sinus thrombosis	MRI	R	6 m	21.9
6[b]	33	F	Excised sub-frontal tumour	CT	L + R	6 m	67.8
7[b]	30	M	Excised medial frontal tumour	MRI	R	6 m	7.6
8[b]	67	M	Middle cerebral artery infarct	MRI	R	3 y	47.6
9	36	F	Middle cerebral artery infarct	MRI	R	8 w	4.8
10	38	M	Excised frontal pole tumour	MRI	L	6 m	5.8
11	43	F	Excised dorsomedial frontal tumour	MRI	R	2 m	19.8
12	35	M	Excised dorsolateral frontal tumour	MRI	R	1 y	2.4
13	63	M	Middle cerebral artery infarct	MRI	R	4 y	65.7
14	66	M	Middle cerebral artery infarct	MRI	R	4 y	83.9
15	45	M	Anterior cerebral artery infarct	MRI	R	4 m	14.1
16	63	M	Anterior cerebral artery infarct	MRI	R	5 m	2.8
17	58	M	Middle cerebral artery infarct	MRI	L	7 y	114
18	63	M	Middle cerebral artery infarct	MRI	L	7 y	141.5
19	72	M	Middle cerebral artery infarct	CT	L	12 y	13.1
20	72	M	Localised trauma frontal pole	MRI	R	50 y	6.6
21	76	M	Middle cerebral artery infarct	CT	L	11 y	16.7
22	60	M	Anterior cerebral artery infarct	MRI	L	2 m	1.4
23	76	F	Middle cerebral artery infarct	MRI	R	4 m	70.8
24[a]	79	M	Middle cerebral artery infarct	MRI	L	6 m	67.1

[a]No data available for rule switching task.
[b]No data available for antisaccades.

Task and procedure

General

Three boxes, outlined in black on a dark grey coloured background, were presented in the centre and 9° to the left and right of the screen. Each box subtended 3° of visual angle. Following eye tracker set-up and calibration, participants were given verbal instructions and completed a short practice block of 10 experimental trials.

Rule switching task

Each trial was triggered to start when the subject had been continuously fixating the central location for a period >800 ms. A coloured circle (cue) was then presented in the central box. The colour of the cue (red/blue) instructed the subject whether to look left or right. The next fixation longer than 800 ms on either the left or the right box was taken as the subject's response on that trial, such that an eye fixation of shorter duration could be made towards the alternate location before the subject made their final decision. Once the viewer had selected one of the boxes by fixating it for >800 ms, feedback was given to indicate if the choice was correct or incorrect in the form of a happy/sad face displayed within the selected box, accompanied by a high- or low-pitched tone. Subjects were made aware that the rule linking the colour of the cue and direction of saccade would reverse at several points during the test. Rule changes were indicated by unexpected errors following runs of between 9 and 13 correct response trials. Each subject completed two blocks of 100 trials, comprising a maximum of 16 possible rule reversals. They were instructed to perform the task as quickly and as accurately as possible and to respond on the basis of the rule they knew to be correct at that time, without anticipating the occurrence of a rule change (Fig. 1).

Pro/antisaccades

Each trial started with the presentation of a white spot (0.5° diameter) in the centre of the screen. After a period of 500 ms the spot was extinguished and simultaneously reappeared in either the left or the right response box. In prosaccade blocks, participants were instructed to fixate the target stimulus and in antisaccade blocks, they were asked to saccade to the location directly opposite to the target stimulus. Once either the left or right location had been fixated for a period longer than 800 ms feedback was given to indicate that a correct movement had been executed. Following a delay of a further 1500 ms the next trial commenced with the onset of the fixation stimulus. A total of 60 trials were presented in each block.

Lesion analysis

High resolution ($1 \times 1 \times 1\,mm^3$ voxel size), T1 weighted structural MRI scans were acquired using either the 1.5T Siemens scanner at Charing Cross Hospital or the 1.5T Phillips scanner at the Peninsula MR Research Centre, University of Exeter. Lesion regions of interest (ROI) were digitized directly from scan images using MRIcro software (Chris Rorden, University of South Carolina). For patients for whom only clinical CT scans were available, ROIs were traced onto transverse view slices of a standard T1 MRI template from the CT scan films, taking care to correct the orientation of the transverse slicing of the template image to that of the CT scan, based upon anatomical landmarks visible in lowest slices of the CT scans (Damasio and Damasio, 1989). All lesion ROIs were then normalized into standardized MNI/Talarach coordinate space using SPM2 software using the cost function masking technique described elsewhere (Brett *et al.*, 2001). Figure 2 presents all patients ROIs displayed on a standard 1 mm resolution T1 template image.

Results

Lesion analysis

Rule switching task

Performance of the age-matched control group was used to estimate the expected range of error rates/response times for the rule switching task in the wider population of neurologically normal subjects. Patients were classified as impaired in the task if either their *uncorrected* error rates (i.e. excluding *corrected* errors, see Fig. 1B) or reaction times fell more than two standard deviations above the mean of control group performance (an uncorrected response error rate >10% of trials or mean saccadic response time/latency >638 ms). Ten of the 23 patients were classified as impaired in the rule switching task according to this criterion.

Lesion overlap plots for the impaired patient group revealed a region of maximal overlap within the right anterior insula cortex (Fig. 3A). None of the unimpaired patients had lesions inside this region (Fig. 3B). Correlation analyses were also carried out to determine whether lesion volume was related to performance in the task. This showed a significant correlation between lesion size and response latency (person coeff' = 0.505, $P < 0.05$), but no correlation between lesion size and error rates.

MRIcro software was used to carry out a voxelwise χ^2 analysis in which the statistical likelihood of observed versus expected numbers of impaired/unimpaired patients was assessed for patients sharing damage to a given voxel for each and every voxel in the brain (Rorden and Karnath, 2004). The resulting plot (Fig. 3C) shows regions for which the χ^2 statistic reached statistical significance in white, yellow and ochre (critical value = 3.84, df = 1, $P = 0.05$). The peak χ^2 value was located within a small region of the anterior insula cortex corresponding to BA47, although more dorsal/anterior regions extending along the inferior frontal gyrus including BA44 and BA45 also reached statistical significance.

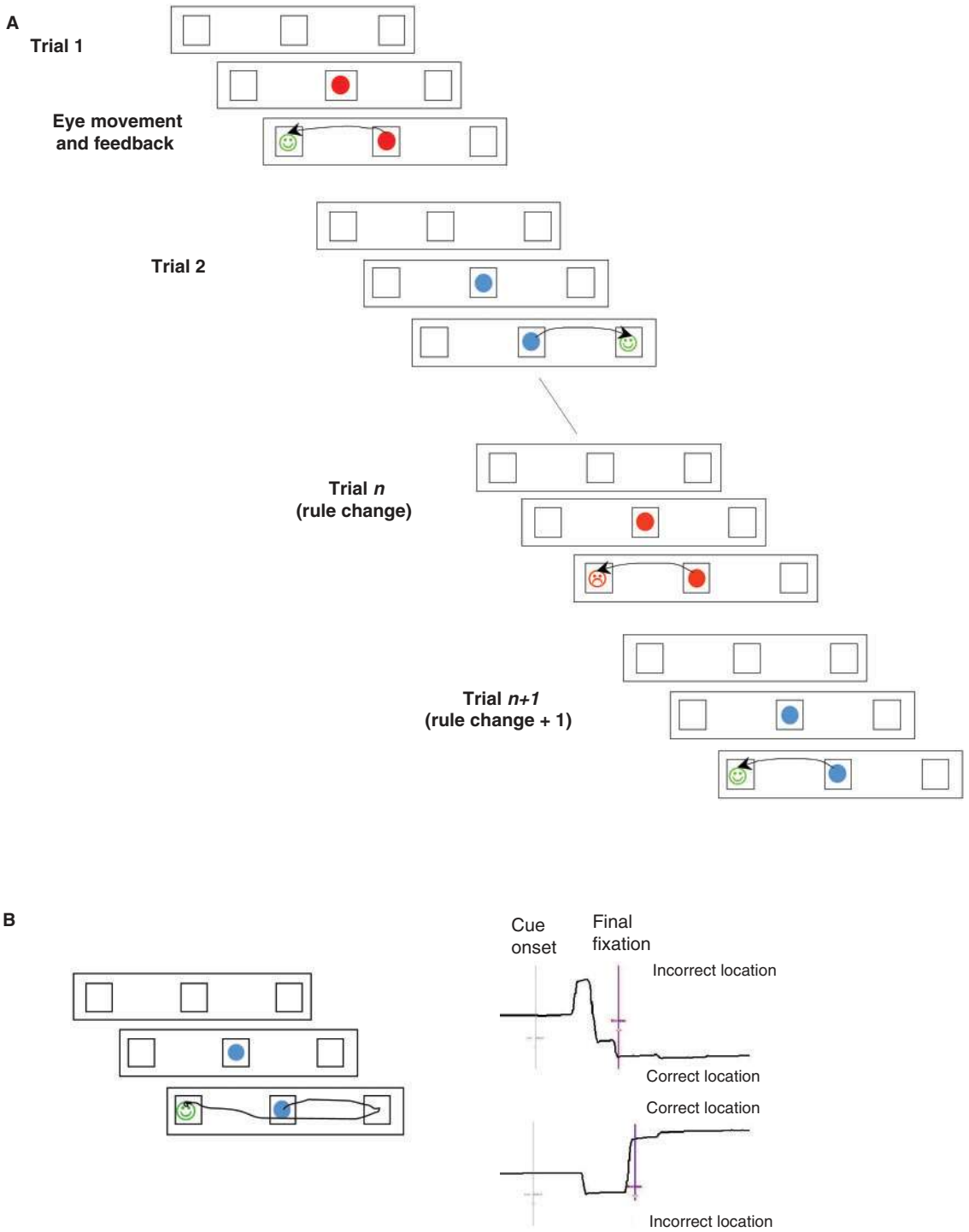

Fig. 1 (**A**) Schematic of oculomotor rule switching task. Successive stages of the task are illustrated from top left to bottom right. Subjects make saccades based on a rule linking a coloured shape with a movement to either the left or the right. Feedback is given following a fixation >800 ms on one of the response boxes allowing several eye movements to be made before a decision is recorded and feedback is given to the subject. After a random number of trials ('*n*') feedback indicated that the rule had reversed. (**B**) Saccades directed to the incorrect location were often followed by secondary corrective movements ('corrected errors'). This is shown schematically alongside eye position against time traces for corrected error trials. Both example eye position traces show trials for which an initial saccade is directed towards the incorrect location followed by a secondary saccade which brings the eye onto the correct location.

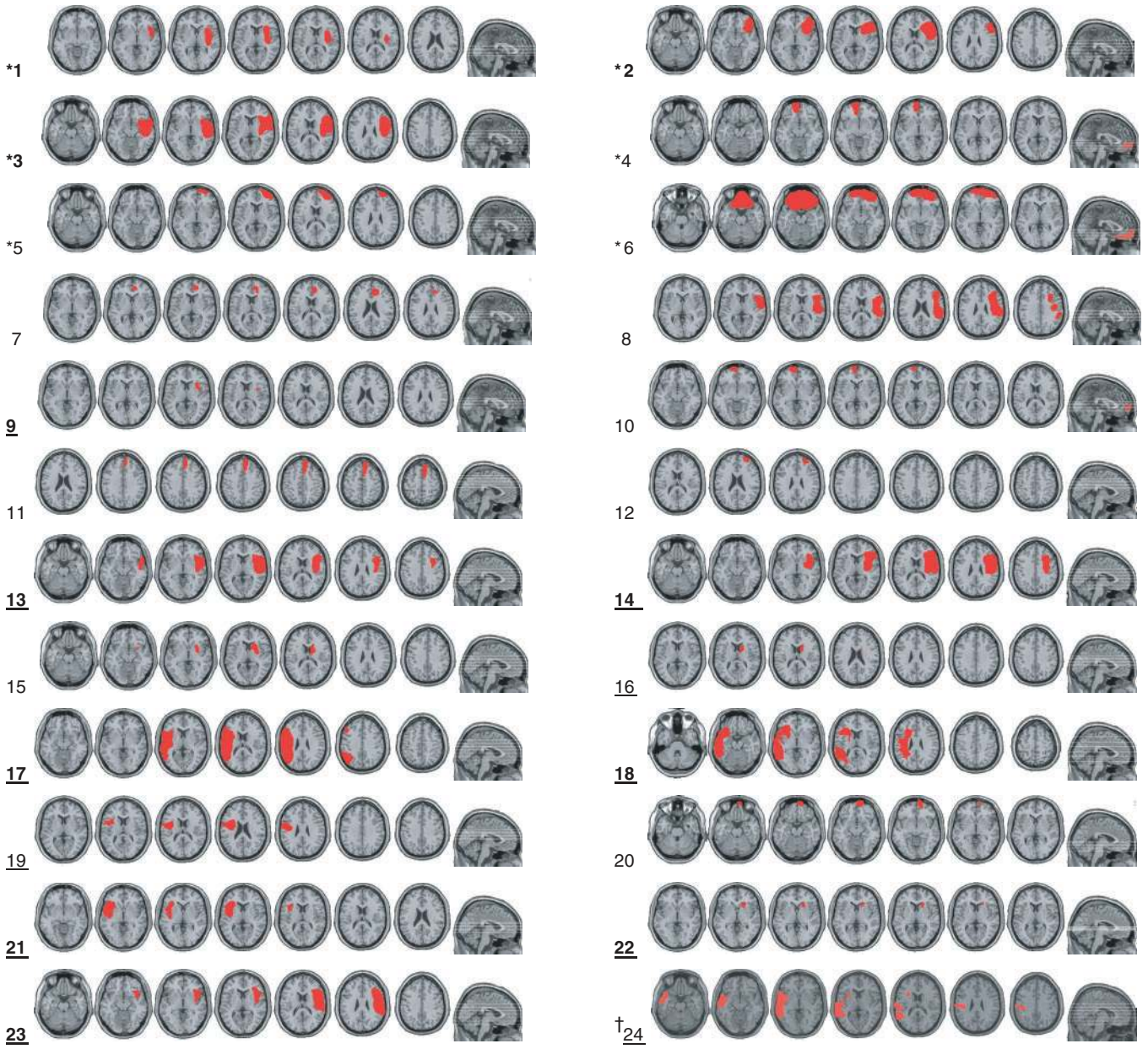

Fig. 2 Lesion regions of interest displayed on a transverse view of a standard TI MRI template image. Bold numerals indicate patients who were impaired at the rule switching task. Underscored numerals indicate impairment in antisaccade task. †No data available for rule switching. *No data available for antisaccades.

Antisaccade task

The same approach was used to analyse the association between antisaccade impairments and lesion location. For the control subject group, the mean proportion of saccade errors in the antisaccade block was 11% of trials ranging between 0 and 45%. The upper band of the 95% confidence intervals of control performance was 20.7% and the standard deviation of control subject error rates was 14.9%. A criterion of two standard deviations above the mean of control group performance (40.8% errors) was used to classify patients into impaired/unimpaired groups. Eleven out of the 16 patients tested were classified as being impaired according to this criterion. We also examined the distribution of saccadic latency (i.e. reaction time) in the patient group relative to the control group. Only two patients had mean antisaccade latencies which lay more than two standard deviations above the mean of control performance (725 ms). Both of these patients were also classified as impaired based on their rate of errors in the antisaccade task.

Lesion overlap analysis revealed two loci of maximal overlap in the impaired group within homologous regions of white and grey matter of either the right or left ventrolateral frontal (VLF) cortex (Fig. 4A). All unimpaired

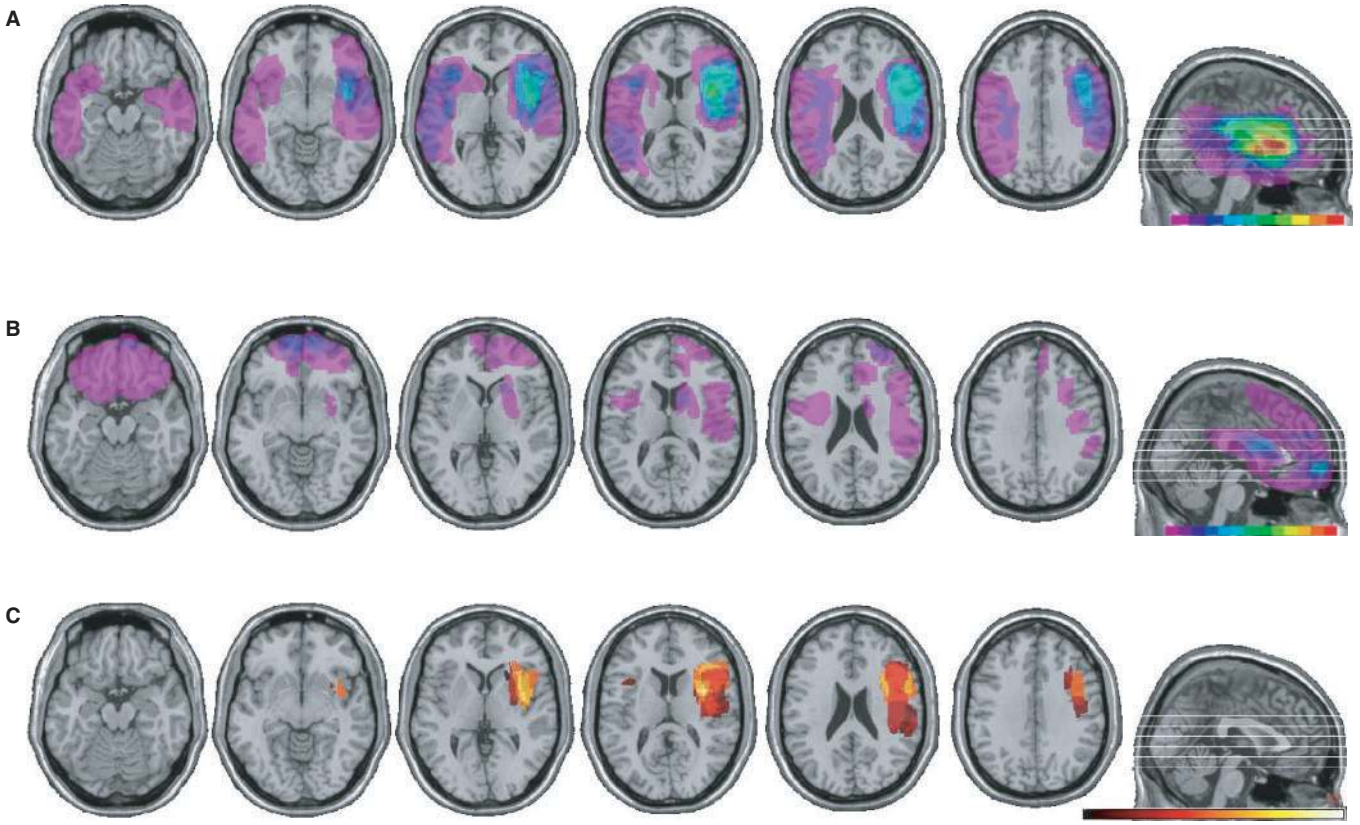

Fig. 3 (**A**) Lesion overlap plot for impaired patients in the rule switching task. Colour indicates number of overlapping lesion ROIs at each voxel. (**B**) Lesion overlap plot for unimpaired patients. (**C**) Chi-squared (χ^2) statistic plot indicating the likelihood of observed lesion overlap occurring by chance. Regions exceeding the critical value of 3.84 ($P < 0.05$, df = 1) are indicated by ochre, yellow and white regions.

patients had lesion ROIs which fell outside of this region (Fig. 4B), whilst only one of the impaired patient group had damage outside this region (head of caudate nucleus, patient 16). There was no significant correlation between lesion volume and error rates.

As the lesion overlap plots suggested that damage to homologous regions of either left or right hemisphere led to increased saccade errors, lesions were remapped onto a single hemisphere in the voxelwise χ^2 analysis. The peak χ^2 value was once again located within a small region of the anterior insula cortex corresponding to BA47. Other VLF regions within BA44 and BA45 also reached statistical significance (Fig. 4C).

Lesion analysis summary

In summary, lesions affecting the right VLF cortex were predictive of impairments in the rule switching task. Impaired antisaccade performance was also associated with damage to the same region of VLF cortex, although patients classified as impaired in this task were equally likely to have lesions in homologous regions of the left and right hemisphere.

Subsequent detailed behavioural analysis classified patients according to lesion type: left/right and VLF/non-VLF frontal (regardless of impairments). Twelve of the 24 patients were judged to have lesions that included the VLF region (5 left: patients 17, 18, 19, 21 and 24; 7 right hemisphere: patients 1, 3, 8, 9, 13, 14 and 23, see Fig. 2).

Behavioural analysis: rule switching task

Response errors

Two-way analyses of variance (ANOVAs) were carried out on error rates using subject group (patient type or control/patient) and trial after rule change (one to six with trial 1 being the first trial after the feedback which instructed each change in rule mappings) as factors. Errors were classified according to whether or not they were *corrected* with a secondary saccade prior to the feedback or *uncorrected* resulting in 'actual' errors (Fig. 1B).

Corrected saccade errors occurred more frequently on trials immediately following a rule change [significant effect of trial: $F(5,105) = 4.01$, $P < 0.005$] but there was no significant difference in corrected errors between the control and patient groups. However, there was a significant increase in the number of *uncorrected* errors between the VLF and non-VLF patient groups [$F(1,21) = 11.72$, $P < 0.025$] as well as between VLF patients and controls [$F(1,30) = 18.26$, $P < 0.001$]. Consistent with the results of the lesion analysis (see above), this effect was due predominantly to an increase in uncorrected error rates

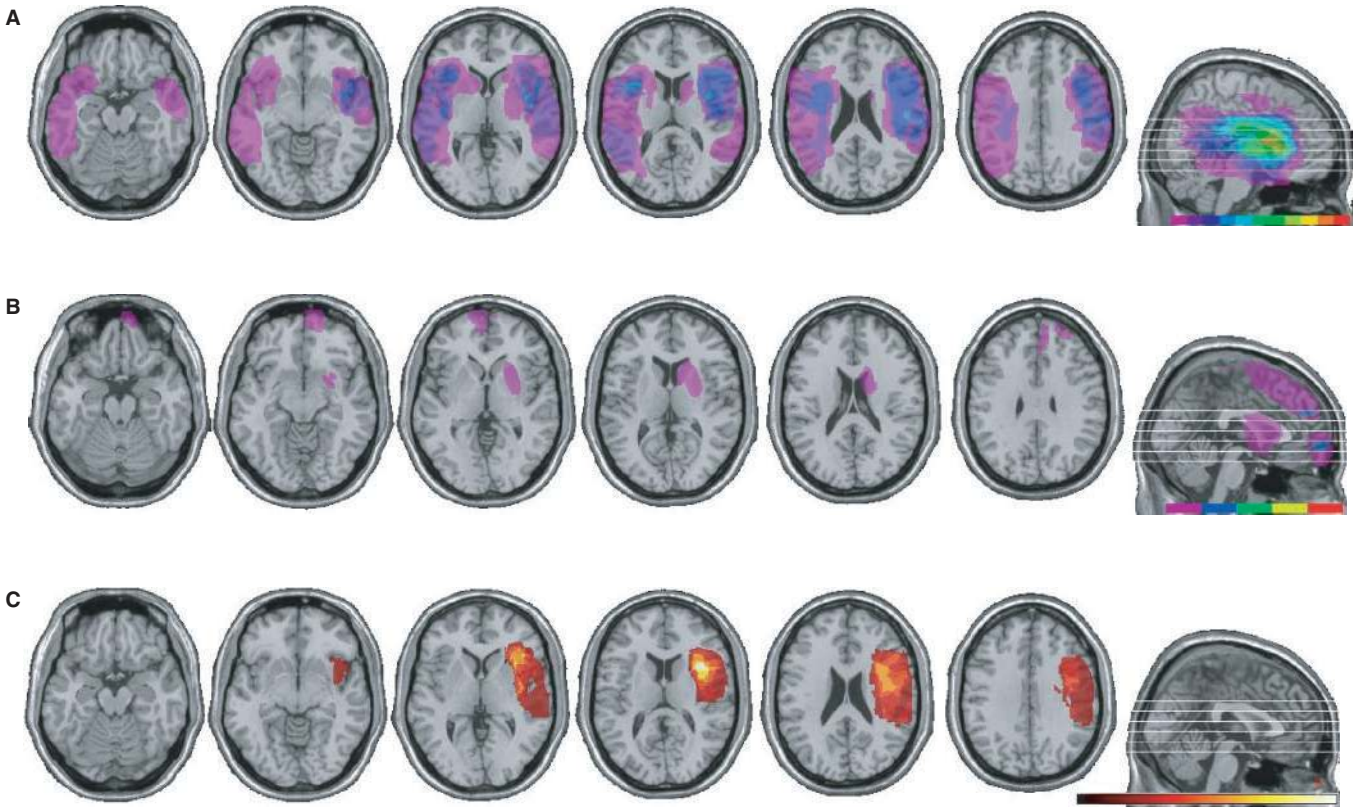

Fig. 4 (**A**) Lesion overlap plot for patients classified as impaired in the antisaccade task. (**B**) Equivalent plot for unimpaired group. (**C**) χ^2 analysis for antisaccade task (as the lesion overlap plots indicated that damage to homologous regions of the left and right hemisphere were associated with increased antisaccade errors, left- and right-sided lesions were mapped onto a single hemisphere in this χ^2 analysis).

in the *right* VLF patients, as evidenced by a significant difference between uncorrected errors in the right VLF group and controls [$F(1,26) = 16.97$, $P < 0.001$] with no significant difference in uncorrected errors between left VLF patients and controls [$F(1,22) = 0.28$]. An ANOVA directly comparing right and left VLF patients also revealed an interaction between trial after rule change and subject group, with the difference in uncorrected errors between groups being most marked on the first trial following a rule change [$F(1,10) = 7.82$, $P < 0.02$] (Fig. 5). When data from the first trial after a rule change was excluded, the difference between left and right VLF groups did not reach significance, although the right VLF patients were still impaired relative to the non-VLF patient group [$F(1,17) = 7.15$, $P < 0.02$] and healthy controls [$F(1,26) = 12.89$, $P < 0.001$].

Error direction

We also examined the direction of patients' errors relative to the damaged/undamaged hemisphere. Patients overall made significantly more corrected errors into the contralesional relative to ipsilesional field [$F(1,20) = 17.44$, $P < 0.001$]. However, there was also an interaction between side of lesion and direction of error, such that left hemisphere patients were more likely to correct contralesional errors and right hemisphere patients made overall fewer corrected errors. This interaction only reached significance for the VLF group [$F(1,10) = 16.05$, $P < 0.005$]. When the same analysis was carried out for *uncorrected* (i.e. actual) errors, there was no significant effect of direction (ipsi versus contralesional) [$F(1,20) = 0.71$, n.s.] or interaction between side and lesion [$F(1,20) = 0.82$, n.s.] (Fig. 6).

In summary, analysis of error direction reveals an important difference in the behaviour of left and right hemisphere VLF patients. Although left VLF patients made contralesional response errors, 68% of these errors were corrected with secondary saccades. In contrast, patients with right VLF damage made an equal number of contralesional and ipsilesional errors and only corrected around 30% of these errors (Fig. 6).

Latencies

Latencies of correct responses were analysed using 2-way ANOVAs with subject group (patient/control or VLF/non-VLF) and trial after rule change as factors (trials 1 to 6).

This analysis confirmed a significant main effect of trial after rule change, with latencies being greatly increased on

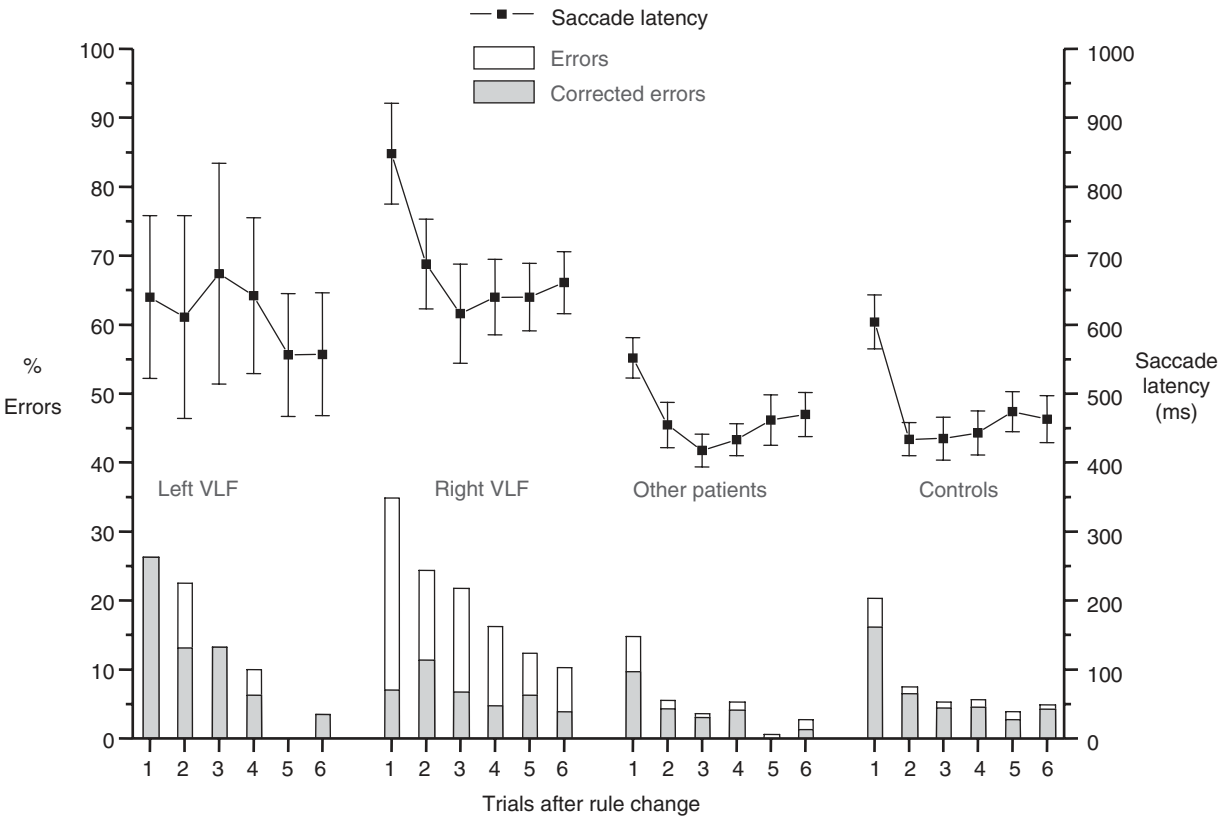

Fig. 5 Saccadic latency and error rates in the rule reversal task for left/right VLF damaged patients, other frontal damaged patients and control group in the rule reversal task plotted against trial after rule change (trial 1 being the first trial following the feedback which instructed a change in rule). The height of bars represents the total percentage of trials on which the initial saccade was directed in the wrong direction, whilst the filled segment represents the number of saccade errors which were corrected. The number of uncorrected errors is therefore represented by the size of the remaining unfilled segment of the bar plots.

the first trial after a change in rule mappings [$F(5,105) = 5.52$, $P < 0.0001$] as well as a significant difference overall between VLF and non-VLF frontal patients [$F(1,21) = 10.97$, $P < 0.005$] and VLF patients versus control subjects [$F(1,31) = 22.22$, $P < 0.0001$]. Both left and right VLF patients showed increased response latencies [left VLF versus controls: $F(1,21) = 6.27$, $P < 0.025$; right VLF versus controls: $F(1,27) = 27.23$, $P < 0.0001$]. However only in the case of left VLF patients there was a significant interaction between this effect and trial after rule change [$F(5,105) = 3.14$, $P < 0.025$] reflecting the absence of a strong effect of trial after rule change on response latencies for the left VLF group (Fig. 5).

Behavioural analysis: anti/prosaccade task

Errors

In contrast to the rule reversal task, almost all errors were corrected with a secondary saccade in the antisaccade task (>99%) and no errors (i.e. spontaneous antisaccades) were made by any of the patients or control subjects in the prosaccade task blocks. Comparison between the performance of patients with VLF and non-VLF damage in the antisaccade task showed a significant increase in the rate of erroneous saccades directed towards contralesional targets (paired sample t-test, $t = 3.87$, $P < 0.001$, one-tailed; means: contralesional 56%; ipsilesional 41%). However, interestingly the antisaccade 'unimpaired' group (whose lesions lay entirely outside the VLF region) nevertheless showed a small but significant increase in errors towards contralesional targets ($t = 2.36$, $P < 0.05$, one-tailed; contralesional 13.4%; ipsilesional 6.6%).

Latencies

A 2-way, one within, one between factor ANOVA with direction (contra/ipsilesional) and patient group (antisaccade impaired/unimpaired) was used to analyse mean saccadic latency on correct antisaccade trials. No significant effect of direction [$F(1,11) = 0.049$ n.s.] or patient group was found, although there was a tendency overall towards slower response latencies in the antisaccade impaired group [$F(1,11) = 3.25$, $P = 0.09$]. A similar analysis was carried out on the latency of error saccades in the antisaccade task and revealed no significant difference between groups [$F(1,15) = 0.46$, n.s.]. However, the antisaccade impaired group had significantly longer prosaccade latencies than the age-matched control group (independent samples t-test:

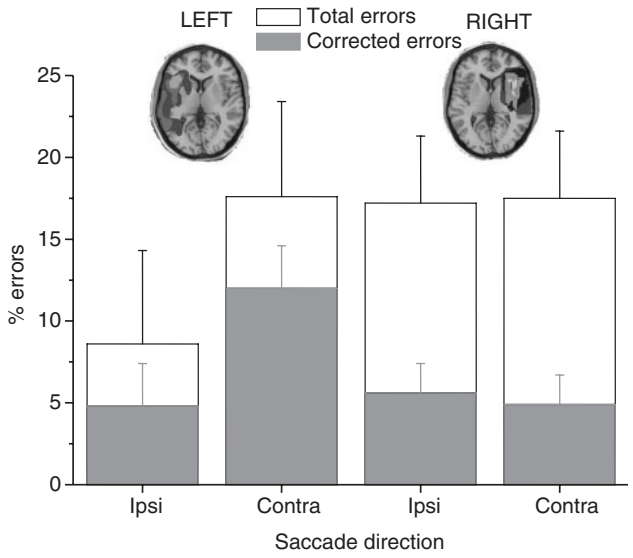

Fig. 6 Relative direction of corrected and uncorrected saccade errors in the rule reversal task for patients with either left or right VLF lesions. Unfilled segment of bar plots indicate uncorrected errors as in Fig. 5.

latency $t = 2.62$, $P < 0.02$; patients 276 ± 63 ms; controls 211 ± 50 ms).

Discussion

The results of this study are consistent with a role for the VLF cortex in inhibitory oculomotor control. VLF damage was found to be a significant predictor of impaired performance in an oculomotor rule switching task as well as the standard antisaccade test. In the case of the rule switching task it was right VLF patients who were most likely to show a clear impairment relative to controls. Patients with left VLF damage made increased contralesional saccade errors in the task, but they corrected these errors on 68% of trials. In contrast, right VLF damaged patients were more likely to leave errors uncorrected (correcting only 30% of errors) (see *Rule Switching Task*, *Error Direction* earlier; Fig. 6). Left and right VLF patients were equivalently impaired in the standard antisaccade task, but importantly patients with other types of frontal damage also made increased contralesional errors (see *Anti/prosaccade task*, *Errors* earlier).

These findings support the hypothesis that the VLF cortex mediates inhibitory control across multiple effector modalities, including eye movements (Aron *et al.*, 2004*a*, *b*). Along with other patient-based studies (e.g. Aron *et al.*, 2004*a*), the importance of the inferior frontal region in cognitive control is also emphasized by a large number of neuroimaging studies in healthy subjects. Duncan and Owen (2000) examined the loci of frontal activations in 20 studies using various cognitive tasks. The same regions of the medial and lateral frontal cortex were found to be activated across studies, including a cluster of activations extending along the frontal operculum and into the anterior insula. More recently, Dosenbach *et al.* (2006) has described sustained (block related) and transient (trial/event related) activity within bilateral VLF areas across several tasks which utilized different sensory input and motor output modalities. These findings emphasize the domain generality of processing in frontal regions, consistent with the possibility that VLF cortex constitutes part of a general 'task set' control system (Braver and Barch, 2006).

On superficial inspection, many fMRI studies that have directly studied the antisaccade task do not highlight the inferior frontal region as being an important component in a network for oculomotor control. However, it should be noted that many of these studies have used region of interest analyses in which areas not implicated in standard models of the oculomotor system are excluded from detailed analysis (e.g. Desouza *et al.*, 2003; Connolly *et al.*, 2004). Several studies which have taken a more inclusive approach have found VLF activity during antisaccades. Matsuda *et al.* (2004) showed strong bilateral activity in the posterior section of the inferior frontal gyrus for contrasts of both antisaccades relative to rest and antisaccades relative to proscaccades. Connolly *et al.* (2000) describe ventral frontal activity associated with both antisaccades and 'anti pointing' tasks which they label as 'ventral premotor'. The authors describe the area as 'situated ventral to the inferior frontal sulcus and immediately anterior to the precentral gyrus' i.e. the posterior inferior fontal gyrus. Most recently, Chikazoe *et al.* (2007) have shown activity in the right inferior frontal gyrus during a task in which antisaccade trials occur with reduced frequency and the length of the preparatory/instruction period prior to target onset is reduced.

Whilst consistent with the wider literature on cognitive control, our results are problematic for accounts which argue for a critical and exclusive role for the DLPFC or FEF in the inhibitory control of stimulus driven saccades (Goldman-Rakic, 1987; Funahashi *et al.*, 1989, 1993; Pierrott-Deseilligny *et al.*, 1991, 2005; Rivaud *et al.*, 1994). Although many of the VLF patients tested here had large lesions affecting other cortical areas, one of the patients classified as impaired in both tasks had a very small region of damage confined to the posterior part of the right inferior frontal gyrus (Patient 9). Furthermore, the finding that patients classified as 'unimpaired' (based on norms derived from a group of age-matched controls) showed a significant increase in contralesional (relative to ipsilesional) antisaccade errors indicates that damage to other parts of the frontal lobe can impair inhibitory control to a degree (e.g. frontal pole, patients 10 and 12). Therefore, whilst the present results are unequivocal in demonstrating that the DLPFC and FEF are not the only frontal lesion sites that result in increased antisaccade errors, our findings do not directly contradict the results of previous studies which have reported deficits in these patients (e.g. Pierrott-

Deseilligny *et al*., 1991; Machado and Rafal, 2004). Rather than being localized to a particular subregion, aspects of inhibitory control may be distributed throughout the structure of the frontal cortex.

As well as response inhibition, efficient performance of the rule switching task requires current task rules to be maintained on line, current motor output (and/or preparatory motor signals) to be monitored and corrective action taken when intended and actual motor output come into conflict. The most unexpected but important finding of the present study was an apparent dissociation in such self-monitoring/control functions between right and left VLF damaged patients. It is possible in the light of these findings that the specialization of the *right* inferior frontal lobe for cognitive inhibition reported in many previous patient studies (Aron *et al*., 2004*a*, *b*) may in fact be a consequence of its role in the representation or monitoring of arbitrary stimulus response associations (Passingham *et al*., 2000). Several neuroimaging studies have shown that activity in this area increases as stimulus response mappings are learned or recalled (Passingham *et al*., 1998). Furthermore, surgical removal of the ventral prefrontal region severely impairs learning of novel stimulus response mappings in macaque monkeys (Murray *et al*., 2000). Other lesion studies in monkeys (Heilman *et al*., 1995) and neuropsychological reports in humans (Butter *et al*., 1988; Husain and Kennard, 1996) have linked lateral frontal damage with attentional neglect. Impairments suffered by right VLF damaged patients in cognitive tasks might also reflect motor inattention to response errors, or a deficit in engaging attention to action following stimuli which indicate that task rules have changed.

It is interesting to contrast the performance of left and right VLF damaged patients in the current study with that of a single patient with an unusually focal left supplementary eye field (SEF) lesion who has been described elsewhere (Patient 'JR', Husain *et al*., 2003; Parton *et al*., 2007). This patient made close to 100% errors on trials following a change in mappings in the rule reversal task, yet was able to correct the great majority of these errors with a secondary saccade. As in the case of left VLF damaged patients described here, JR's ability to correct errors suggests that whilst suppression of stimulus cued saccades is disrupted, his representation of task rules is intact. JR also had an increased 'stop signal' or 'countermanding' saccade reaction time, as measured by a task in which a secondary cue instructed him to redirect a preprogrammed saccade on a proportion of trials (see also Schall, 2002; Leigh and Kennard, 2004; Nachev *et al*., 2005). However, he performed within normal limits in the antisaccade test (for which the demand to inhibit responding is constant from trial to trial) and his deficits were specific to saccades, such that they were not apparent on a manual version of the rule switching task. In contrast, VLF damage leads to an impairment in antisaccade performance (Butter *et al*., 1988; Walker *et al*., 1998; present study) and causes deficits in cognitive inhibitory control across multiple effector modalities (Aron *et al*., 2004*a*, *b*). Taken together, these findings suggest that the supplementary motor complex (within which the SEF lies) has a motor-modality-specific organization and engages inhibitory control under conditions for which the demand to exert control varies unpredictably. In contrast, VLF damage leads to more general impairments in inhibitory control which span effector modalities.

Finally, as well as having implications for the functional neuroanatomy of cognitive control, the present results also have important implications for our understanding of the human consequences of neurological damage. Impaired representations of task rules and deficits in inhibitory control over saccades could have potential consequences for patients in the real world, where many tasks require us to ignore attentionally salient stimuli and implement complex gaze shifting strategies to achieve arbitrary task goals (Land and Furneax, 1997; Land *et al*., 1999; Hodgson *et al*., 2000; Hodgson and Golding, 2003; Kennard *et al*., 2005). Future research might profitably assess the extent to which such deficits impact on the everyday lives of patients and what compensatory strategies and rehabilitative measures may be beneficial in such cases.

Conclusions

Our results show that VLF damage causes impairments in the inhibitory control of saccadic eye movements. Damage to this region in both the left and right hemisphere results in failures to suppress stimulus cued saccades in the antisaccade task as well in a rule switching task in which responses are executed based on changing stimulus response rules. Patients with right VLF damage often fail to correct saccade errors during rule switching, whilst left-sided patients make more corrective movements and less actual errors following a rule change. The results are consistent with a role for bilateral VLF cortex in inhibitory oculomotor control, with the right VLF region playing an additional role in the monitoring and control of behaviour based on arbitrary task rules.

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References

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 2003; 6: 115–6.

Aron AR, Monsell S, Sahakian BJ, Robbins TW. A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. Brain 2004*a*; 127: 1561–73.

Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 2004*b;* 8(4): 170–7.

Braver TS, Barch DM. Extracting core components of cognitive control. Trends Cogn Sci 2006; 10(12); 529–532.

Brett M, Leff AP, Rorden C, Ashburner J. Spatial normalization of brain images with focal lesions using cost function masking. Neuroimage 2001; 14: 486–500.

Butter CM, Rapcsak S, Watson RT, Heilman KM. Changes in sensory inattention, directional motor neglect and ''release'' of the fixation reflex following a unilateral frontal lesion: a case report. Neuropsychologia 1988; 26: 253–545.

Chikazoe J, Konish S, Asari T, Jimura K, Miyashita Y. Activation of right inferior frontal gyrus during response inhibition across response modalities. J Cogn Neurosci 2007; 19: 69–80.

Connolly JD, Goodale MA, Desouza JFX, Menon RS, Vilis TA. Comparison of fronto-parietal fMRI activation during anti-saccades and anti-pointing. J Neurophysiol 2000; 84: 1645–55.

Connolly JD, Melvyn A Goodale, Goltz HC, Munoz DP. fMRI activation in the human frontal eye field is correlated with saccadic reaction time. J Neurophysiol 2004; 94: 605–11.

Damasio AR, Damasio H. Lesion analysis in neuropsychology. Oxford, UK: Oxford University Press; 1989.

Desouza JFS, Menon RS, Everling S. Preparatory set associated with pro-saccades and anti-saccades in humans investigated with event-related fMRI. J Neurophysiol 2003; 89: 1016–23.

Dosenbach NUF, Visscher KN, Palmer ED, Miezin FM, Wenger KK, Kang HC, et al. A core system for the implementation of task sets. Neuron 2006; 50: 799–812.

Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Cogn Sci 2000; 23: 475–83.

Finley A, Saver J, Alger J, Pregenzer M, Leary M, Ovbiagele B, et al. Diffusion weighted imaging assessment of insular vulnerability in acute middle cerebral artery infarctions [abstract]. Stroke 2003; 34: 259.

Funahashi S, Charles BJ, Goldman-Rakic PS. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J Neurophysiol 1989; 61: 331–49.

Funahashi S, Chafee MV, Goldman-Rakic PS. Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. Nature 1993; 365: 753–6.

Garavan H, Ross TJ, Stein EA. Right hemisphere dominance of inhibitory control: an event-related magnetic resonance imaging study. Proc Natl Acad Sci USA 1999; 96: 8301–6.

Goldman-Rakic P. Circuitry of primate prefrontal cortex and regulation of behaviour by representational knowledge. In: Plum F, Mountcastle V, editors. Handbook of physiology Vol. 5; 1987. p. 373–417.

Goldman-Rakic PS. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. Philos Trans R Soc Lond B Biol Sci 1996; 351: 1445–53.

Guitton D, Buchtel HA, Douglas RM. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generation of goal directed saccades. Exp Brain Res 1985; 58: 455–72.

Hallet PE, Adams BD. The predictability of saccadic latency in a novel voluntary oculomotor task. Vision Res 1980; 20: 329–39.

Heilman KM, Valenstein R, Day A, Watson R. Frontal lobe neglect in monkeys. Neurology 1995; 45: 1205–10.

Hodgson TL, Bajwa A, Owen AM, Kennard C. Strategic control of gaze direction during the tower of London task. J Cogn Neurosci 2000; 12: 894–907.

Hodgson TL, Golding C, Mort D, Molyva D, Rosenthal C, Kennard C. Eye movements during task switching: reflexive, symbolic and affective contributions to response selection. J Cogn Neurosci 2004; 16: 318–30.

Hodgson TL, Golding C. Executive contributions to saccade control. In: Hyönä J, Radach R, Deubel H, editors. The mind's eyes: cognitive and applied aspects of eye movements. Oxford: Elsevier Science; 2003. p. 49–64.

Holmes G. The cerebral integration of the ocular movements. Br Med J 1938; 16: 107–12.

Husain M, Kennard C. Visual neglect associated with frontal lobe infarction. J Neurol 1996; 243: 652–7.

Husain M, Parton A, Hodgson T, Mort D, Rees G. Self-control during response conflict by human supplementary eye field. Nat Neurosci 2003; 6: 117–8.

Kennard C, Mannan SK, Nachev P, Parton A, Mort DJ, Rees G, et al. Cognitive processes in saccade generation. Clinical and basic oculomotor research: in honor of David S. Zee. Ann NY Acad Sci 2005; 1039: 176–83.

Konishi S, Nakajima K, Uchida I, Kikyo H, Kameyama M, Miyashita Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. Brain 1999; 122: 981–91.

Konishi S, Hayashi T, Uchida I, Kikyo H, Takahashi E, Miyashita Y. Hemispheric asymmetry in human lateral prefrontal cortex during cognitive set shifting. Proc Natl Acad Sci 2002; 99: 7803–8.

Land MF, Furneax S. The knowledge base of the oculomotor system. Philos Trans R Soc Lond 1997; 352: 1231–9.

Land MF, Mennie N, Rusted J. The roles of vision and eye movements in the control of activities of daily living. Perception 1999; 28: 1311–28.

Leigh RJ, Kennard C. Using saccades as a research tool in the clinical neurosciences. Brain 2004; 127: 460–77.

Logan G. On the ability to inhibit thought and action. In: Dagenbach D, Carr TH, editors. Inhibitory processes in attention, memory and language. San Diego, CA: Academic Press; 1994. p. 189–239.

Machado L, Rafal RD. Control of fixation and saccades during an anti-saccade task: an investigation in humans with chronic lesions of oculomotor cortex. Exp Brain Res 2004; 156: 55–63.

Matsuda T, Matsuura M, Ohkubo T, Ohkubo H, Matsushima E, Inoue K, et al. Functional MRI mapping of brain activation during visually guided saccades and antisaccades: cortical and subcortical networks. Psychiatry Res: Neuroimaging 2004; 131: 147–55.

Munoz DP, Everling S. Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci 2004; 5: 218–28.

Murray EA, Bussey T, Wise SP. Role of the prefrontal cortex in a network for arbitrary visuomotor mapping. Exp Brain Res 2000; 133: 114–29.

Nachev P, Rees G, Parton A, Kennard C, Husain M. Volition and conflict in human medial frontal cortex. Curr Biol 2005; 15: 122–8.

Naidich TP, Firestone MI, Blum JT, Abrams KJ. Zonal frequency analysis of the gyral and sulcal extent of cerebral infarcts. Part III: middle cerebral artery and watershed infarcts. Neuroradiology 2003; 45: 785–92.

Parton A, Nachev P, Hodgson TL, Mort D, Thomas D, Ordrige R, Morgan PS, Jackson S, Rees G, Husain M. Role of the human supplementary eye field in the control of saccadic eye movements. Neuropsychologia 2007; 45(5): 997–1008.

Passingham RE, Toni I, Schluter N, Rushworth MFS. How do visual instructions influence the motor system? In: Goode J, Glickstein M, editors Sensory guidance of movement. Chichester: Wiley; 1998. p. 129–41.

Passingham RE, Toni I, Rushworth MFS. Specialisation within the prefrontal cortex: the ventral prefrontal cortex and associative learning. Exp Brain Res 2000; 133: 103–13.

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

Paus T, Kalina M, Patockova L, Angerová Y, Cerná R, Mecir P, et al. Medial vs lateral frontal lobe lesions and differential impairment of central-gaze fixation maintenance in man. Brain 1991; 114: 2051–67.

Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y. Cortical control of reflexive visually-guided saccades. Brain 1991; 114: 1473–85.

Pierrot-Deseilligny C, Muri RM, Nyffeler T, Milea D. The role of the human dorsolateral prefrontal cortex in ocular motor behavior. Clinical and basic oculomotor research: in Honor of David S. Zee. Ann NY Acad Sci 2005; 1039: 239–51.

Rivaud S, Müri RM, Gaymard B, Vermasch AI, Pierrot-Deseilligny C. Eye movement disorders after frontal eye field lesions in humans. Exp Brain Res 1994; 102: 110–20.

Ro T, Cheifet S, Ingle H, Shoup R, Rafal R. Localization of the human frontal eye fields and motor hand area with transcranial magnetic stimulation and magnetic resonance imaging. Neuropsychologia 1999; 37: 225–31.

Rorden C, Brett M. Stereotaxic display of brain lesions. Behav Neurol 2000; 12: 191–200.

Rorden C, Karnath H-O. Using human brain lesions to infer function: a relic from a past era in the fMRI age? Nat Neurosci 2004; 5: 813–19.

Schall JD. The neural selection and control of saccades by the frontal eye field. Philos Trans R Soc Lond B Biol Sci 2002; 357: 1073–82.

Swainson R, Cunnington R, Jackson GM, Rorden C, Peters A, Morris PG, et al. Cognitive control mechanisms revealed by ERP and fMRI: evidence from repeated task-set switching. J Cogn Neurosci 2003; 15: 785–99.

Walker R, Husain M, Hodgson TL, Harrison J, Kennard C. Saccadic eye movement and working memory deficits following damage to human prefrontal cortex. Neuropsychologia 1998; 36: 1141–59.