

# Impact of frontal white matter lesions on performance monitoring: ERP evidence for cortical disconnection

Alexandra M. Hogan,<sup>1</sup> Faraneh Vargha-Khadem,<sup>1</sup> Dawn E. Saunders,<sup>2</sup> Fenella J. Kirkham<sup>3</sup> and Torsten Baldeweg<sup>1</sup>

<sup>1</sup>Developmental Cognitive Neuroscience Unit, <sup>2</sup>Department of Radiology and <sup>3</sup>Neurosciences Unit, Institute of Child Health, University College London, Great Ormond Street Hospital for Children NHS Trust, London, UK

Correspondence to: Dr Alexandra Hogan, Developmental Brain-Behaviour Unit, School of Psychology, University of Southampton, Highfield, Southampton, SO17 1BJ, UK  
E-mail: a.hogan@soton.ac.uk

**We examined the impact of discrete white matter lesions in the frontal lobes on event-related potential (ERP) correlates of performance monitoring. We tested the hypothesis that abnormal performance monitoring may result from injury to white matter without evidence of injury to grey matter in the frontal lobes. It was predicted that such lesions may result in disconnection of the lateral and medial frontal cortices. The close interaction of these two areas has been implicated in performance monitoring. Two fast-choice response tasks were administered to patients with MRI-confirmed frontal white matter lesions due to sickle cell disease (SCD) vasculopathy ( $n = 11$ ; age = 11–23 years; 6 unilateral left lesions and 5 bilateral lesions) and two control groups: SCD patients without brain lesions and non-sickle cell sibling controls ( $n = 11$  each). Stimulus-locked ERP components N2 and P3 were not significantly affected by presence of lesions. The difference between response-locked components to correct trials (correct-response negativity—CRN) and erroneous trials (error-related negativity—ERN) was diminished in patients with unilateral and bilateral frontal white matter lesions. This finding was due to a significantly attenuated ERN amplitude in lesion patients compared with both sibling and non-lesion control groups. These ERP findings were not due to performance differences between groups and hence reflect a compromised neural substrate underlying performance monitoring. The latter may also contribute to the deficits in executive function tasks observed in these patients. As disruption to ERP markers of error processing was found in the absence of lesions to the lateral or medial frontal cortex, we conclude that a functional connection between these areas facilitates performance monitoring, possibly implemented via tracts traversing the deep frontal white matter.**

**Keywords:** performance monitoring; white matter injury; sickle cell disease; event-related potentials; executive functions

**Abbreviations:** ACC = anterior cingulate cortex; CRN = correct-response negativity; CRT = choice-response task; DLFC = dorsolateral frontal cortex; ERN = error-related negativity; ERP = event-related potential; pmFC = posterior medial frontal cortex; SCD = sickle cell disease; SOPT = Self-Ordered Pointing Test; WCST = Wisconsin Card Sort Test

Received January 26, 2006. Revised May 4, 2006. Accepted May 5, 2006. Advance Access publication June 30, 2006

## Introduction

Goal-directed behaviour requires the continuous evaluation of performance and the initiation of appropriate self-correcting actions in the event of an error. The dorsolateral frontal cortex (DLFC) and posterior medial frontal cortex (pmFC) have been implicated in two performance monitoring systems, namely error detection and conflict monitoring (see reviews by Botvinick *et al.*, 2004; Ridderinkhof *et al.*, 2004a; Ullsperger and von Cramon,

2004). Electrophysiological recordings in monkeys, as well as functional imaging (fMRI) studies in humans, have consistently shown error-related activation within an extended region of the pmFC, including the dorsal anterior cingulate cortex (ACC). This region has been termed the rostral cingulate zone, the human homologue of the rostral cingulate motor area (rCMA) in the monkey (Picard and Strick, 1996). Furthermore, there is emerging evidence for the role of the

DLFC in implementing cognitive control operations, such as adjustments in response mode and in resolving response conflict (Carter *et al.*, 1998; Kerns *et al.*, 2004). This has led to the hypothesis (Botvinick *et al.*, 2001) that the pMFC serves as a monitor of ongoing performance while the DLFC acts in a more executive capacity, integrating information about task demands and accuracy of performance. The implication is that the close interaction of these two regions is critical for adaptive behaviour (Ridderinkhof *et al.*, 2004b).

Neural functions associated with error detection have been investigated using event-related potential (ERP) recordings (Falkenstein, 2004, for review). Errors are associated with a short-latency (<100 ms post-response) vertex negative component called the Ne (Falkenstein *et al.*, 1990), also termed the error-related negativity (ERN) (Gehring *et al.*, 1993). The ERN is typically of greater amplitude than a negative deflection associated with correct responses (CRN) (Ford, 1999). The CRN may reflect a degree of response uncertainty (Falkenstein *et al.*, 2000; Allain *et al.*, 2004). It is hypothesized that the significant difference between the ERN and CRN magnitudes represents a mismatch between intended and executed response (Falkenstein *et al.*, 1990) or different degrees of post-response conflict (Carter *et al.*, 1998; see Falkenstein, 2004, for review). ERP source localization studies suggest that the ERN is generated in the pMFC, most likely in the ACC (Dehaene *et al.*, 1994; van Veen and Carter, 2002; Herrmann *et al.*, 2004). In support of this view, error-related fMRI activity was found in the cingulate sulcus (Ullsperger and von Cramon, 2001, 2004), and patients with medial frontal lesions show diminished ERN activity (Swick and Turken, 2002; Stemmer *et al.*, 2004).

ERP studies in patients with frontal lobe lesions have indeed suggested that error detection depends on the interaction of the DLFC and medial frontal error-detection networks (pMFC generators of ERN) (Gehring and Knight, 2000). A study of adults with infarct lesions of the lateral frontal cortex (LFC) revealed diminished ERP amplitude difference between correct and error responses (Gehring and Knight, 2000). A similar finding was reported by Ullsperger *et al.* (2002) in patients with LFC lesions compared with a normal ERN in patients with bilateral frontopolar and unilateral temporal lobe lesions. A diminished ERN was also found in a more recent study of adults with LFC and basal ganglia lesions (Ullsperger and von Cramon, 2006). These studies often included patients with extensive cortical and sub-cortical lesions, mostly due to infarction in the territory of the middle cerebral artery, with frequent involvement of the insular and premotor cortex. The possibility of remote effects, either secondary to disconnection or to more widespread perfusion deficits (*see e.g.* Hillis *et al.*, 2002), cannot be excluded in these cases. A more direct test of the disconnection hypothesis put forward by Gehring and Knight (2000) would be to identify patients with discrete lesions affecting only the white matter of the frontal lobes.

Here, we report on a group of patients with sickle cell disease (SCD)—a disorder of haemoglobin, affecting people

of Afro-Caribbean descent—who often show discrete lesions in the deep frontal white matter between the DLFC and medial frontal cortices. These lesions are considered to be infarcts, commonly not associated with overt neurological signs (Prengler *et al.*, 2002 for review). We hypothesized that if performance monitoring critically depends on connectivity between the DLFC and ACC, ERP markers of error detection would be vulnerable to disruption. Specifically, we predicted a diminished amplitude difference between error (ERN) and correct responses (CRN), even in the absence of damage to the cortex. In addition, we tested if the presence of lesions also disrupts performance on neuropsychological tests of executive functions, which place high demand on performance monitoring.

## Methods

Ethical approval for this study was obtained from the Research and Ethics Committee of the Great Ormond Street Hospital NHS Trust. All participants underwent ERP recording and neuropsychological testing on the same day. In addition, all SCD patients underwent MRI scanning.

## Participants

A group of 11 patients with MRI evidence of frontal lobe infarction due to SCD vasculopathy (SCD-FL:  $M = 18.3$  years, range = 11:11–23:7) were identified from a larger cohort ( $n = 50$ ) of children, adolescents and young adults with SCD. The majority of participants with SCD were part of a longitudinal study of neuropsychological outcome, some of whom were originally described by Watkins *et al.* (1998). Two control groups consisted of equal numbers of SCD patients without infarcts (SCD-C:  $n = 11$ ,  $M = 18.2$  years, range = 13:6–25:0) and sibling controls (controls:  $n = 11$ ,  $M = 17.7$  years, range = 12:2–21:0; two with haemoglobin AS, six with haemoglobin AA, remainder with unknown haemoglobin status) of similar age.

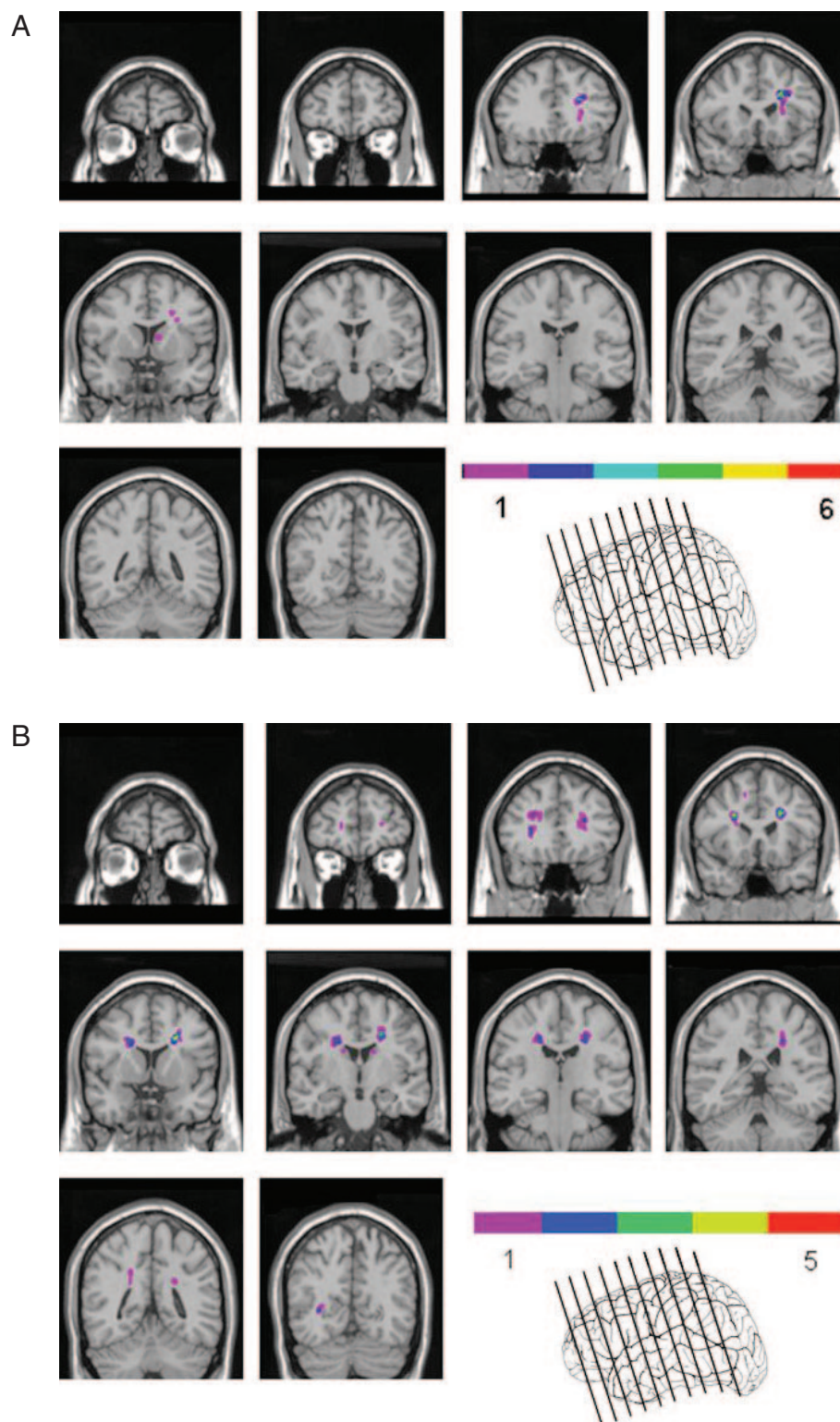
## MRI investigations

MRI studies ( $T_1$ - and  $T_2$ -weighted images, fluid-attenuated inversion recovery (FLAIR) images, magnetic resonance angiography (MRA) were evaluated by a consultant paediatric neuroradiologist (D.E.S.), blind to the clinical characteristics of each participant. All MR images of SCD cases without lesions (no-lesion group) were reviewed a second time, jointly with another neuroradiologist, in order to confirm the accuracy of the initial evaluation.

For the illustration of lesion sites in the SCD-FL group, lesion overlap maps were created using MRIcro software (C. Rorden, www.mricro.com) (Fig. 1). For this purpose, location and approximate size of lesions were transcribed manually (as volumes of interest) from individual axial and coronal  $T_2$ -weighted images onto standard coronal slices of the MNI single subject  $T_1$  image.

## Neuropsychological measures of executive function

- (i) *Test of Everyday Attention (TEA—adults)/Test of Everyday Attention in Children (TEA-Ch—children)* (Robertson *et al.*, 1994): Three subtests from the TEA/TEA-Ch were administered to measure attention processes. Selective attention was



**Fig. 1** Location and extent of overlap across patients with unilateral (A) and bilateral (B) white matter lesions. The density of overlap is indicated by the colour bar.

measured by visual target detection: 'Map Search' in the TEA or 'Map Mission' in the TEA-Ch. Sustained attention was measured by an auditory stimulus-monitoring task ('Lottery'—TEA; 'Code Transmission'—TEA-Ch). Switching

attention was measured by the 'Visual Elevator' and 'Creature Counting' subtests, respectively. Both involve switching between the direction of counting according to stimulus cues. For each subtest the individual receives a scaled

score (mean = 10, SD = 3), based on standardized normative data.

- (ii) *Wisconsin Card Sort Test (WCST)*: The WCST requires the individual to sort cards according to three dimensions shown on cue cards (colour, form, number). The maximum number of categories that can be obtained is six, that is, colour, form and number, each sorted to a criterion of 10 correct in a row and then repeated. The sorting rule is known only to the examiner who informs the participant whether they are 'right' or 'wrong' after they place each card. The participant must try and learn the current correct sorting category only from this information. The WCST procedure is described in greater detail by Milner (1963). The WCST provides a number of qualitative and objective measures of sorting behaviour, but three scores are of particular interest: (a) The number of categories obtained (maximum 6); (b) Perseverative errors, defined as the number of cards sorted to the rule of a previously rewarded category despite examiner feedback indicating that the card has been placed incorrectly; (c) 'Failure-to-maintain-set' errors occur when the participant correctly sorts three cards in a row with positive feedback and then switches to another sorting category on the next card. The number of sorting categories obtained, perseverative errors and the number of 'failure-to-maintain-set' errors were recorded for each individual.
- (iii) *Self-Ordered Pointing Test (SOPT)*: On the basis of the original version of the SOPT (Petrides and Milner, 1982) an adapted version using abstract line drawings was designed for children and adolescents (F. Vargha-Khadem, A. Incisa della Rocheta, and S. Taylor, unpublished data). The SOPT was administered and scored according to the procedures described by Petrides and Milner (1982). Total error rate and time taken (cumulative across all five test blocks: 4, 6, 8, 10 and 12 stimuli) to complete the task were recorded for each participant.

## ERP paradigm

Stimuli were horizontal arrows pointing to the left or right, presented centrally on a black background (17 cm in length and 5 cm in width), modified after a study by Kaiser *et al.* (1997). Stimulus-onset asynchrony was 1500 ms; duration of presentation was 100 ms. Participants were asked to sit as still as possible and focus on a screen 50 cm in front of them. Instructions were given to hold a computer mouse in their hands and to rest the thumbs of the left and right hands on the corresponding mouse buttons. No practice trials were administered, but participants were familiarized with the stimuli and given an opportunity to ask questions. Speed and accuracy were equally stressed for all participants, but no instructions were given requiring the self-correction of errors. For both the 2-CRT and 4-CRT tasks, two blocks consisting of 100 stimuli each were presented with a short break in between. (i) 2-choice response task (2-CRT): green arrow stimuli were randomly presented pointing either to the left or right with equal probability. Participants were asked to press the left mouse button on presentation of a left-pointing arrow, and the right mouse button on presentation of a right-pointing arrow. (ii) 4-choice response task (4-CRT): participants were shown green arrows (compatible stimuli: probability of occurrence: 75%) and red arrows (incompatible stimuli: 25%) that randomly pointed to the left and right with equal probability. Participants were

instructed to respond to the green arrows as before (compatible trials), but to press the opposite mouse button (i.e. right button to left-pointing arrow, and vice versa) in response to red arrows (incompatible trials). Although participants had to choose between only two response buttons, there were four possible stimulus-response combinations. The 4-CRT condition was administered after the 2-CRT in all cases.

## ERP recording

Twenty-one silver/silver chloride electrodes were individually positioned at midline and lateral sites of the 10–20 system. Continuous EEG data were recorded at a sampling rate of 500 Hz (band-pass of 0.05–70 Hz) using a Cz reference and re-referenced offline to averaged mastoid electrodes. Vertical EOG was recorded from bipolar electrodes attached separately above and below the right eye, and horizontal EOG was recorded from bipolar electrodes positioned next to the lateral canthi. Impedance was kept <15 k $\Omega$ .

## Data analysis

- (i) *Behavioural responses*: The percentage of errors, the percentage of corrected errors and the mean correct/error response time (RT) were recorded for each participant. Post-error slowing was calculated as the difference in mean RT in correct trials immediately following an error and mean RT from all other correct trials.
- (ii) *ERP analysis*: Automatic blink reduction was performed in all participants according to the algorithm of Semlitsch *et al.* (1986). EEG data were segmented into epochs centred on both stimulus presentation and response onset (button press). Stimulus-locked epochs were baseline-corrected at –200 to 0 ms before stimulus onset, automatically artefact-rejected ( $\pm 100$   $\mu$ V), and then averaged separately for compatible (green arrows: 2-CRT) and incompatible (red arrows; 4-CRT) trials. The ERP data for the 4-CRT compatible stimuli were not included because the ERN amplitude was small and difficult to detect in most participants (Hogan *et al.*, 2005). The amplitude of the stimulus-locked P3 complex was measured at electrode Cz, where both the P3a and P3b subcomponents could be readily identified, and defined as the maximum positive peaks between 250 and 450 ms (P3a), and between 450 and 800 ms (P3b), respectively. The N2 component (correct trials) was measured at electrode FCz between 190 and 310 ms post-stimulus. On the basis of an earlier report that measured the N2 at latencies up to 400 ms (Yeung *et al.*, 2004), and evidence of early and late N2 subcomponents ('N2b' and 'N2c': Kopp *et al.*, 1996), we also measured such late negative component activity present between 380 and 520 ms at frontocentral electrodes Fz and FCz (termed here N4) in stimulus-locked ERPs to 4-CRT stimuli. Response-locked epochs were baseline-corrected at –100 to 0 ms before button press, automatically artefact-rejected ( $\pm 100$   $\mu$ V) and averaged separately for correct responses (CRN) and error responses (ERN). CRN and ERN peak amplitude and latency were measured at FCz after band-pass filtering (1–20 Hz). These components were defined as the maximum negative peak between 0 and 200 ms post-response onset. The Pe component was measured for error averages only, defined as the maximum positive peak between 200 and 500 ms. On the basis of data from a previous study

**Table 1** Mean scores for measures of full-scale IQ, attention and executive function across study groups

	Control (n = 11)	SCD-C (n = 11)	SCD-FL (n = 11)	Group main effect
Full-scale IQ (SD)	100.5 (16.3)	90.3 (16.7)	83.9 (10.2)	$F(2,30) = 3.58$ , $P = \mathbf{0.040}^*$
Attention (scaled scores)				
Selective	11.1 (1.9)	10.6 (3.2)	7.8 (3.2)	$F(2,30) = 4.34$ , $P = \mathbf{0.022}^*$
Sustained	10.1 (2.7)	8.9 (3.9)	7.7 (3.2)	$F(2,30) = 1.45$ , $P = 0.250$
Switching	7.4 (2.1)	7.4 (5.0)	4.7 (2.7)	$F(2,30) = 2.15$ , $P = 0.133$
WCST				
Number of categories <sup>†</sup>	6.0 (0)	5.8 (0.4)	4.3 (1.7)	$\chi^2(2) = 13.94$ , $P = \mathbf{0.001}^{* \#}$
Number of perseverative errors	7.0 (5.7)	6.5 (7.2)	23.8 (15.9)	$F(2,30) = 9.32$ , $P = \mathbf{0.001}^{* \#}$
Number of 'failure-to-maintain set' errors	0.6 (0.6)	0.6 (1.2)	2.4 (2.5)	$F(2,30) = 4.44$ , $P = \mathbf{0.020}^{* \#}$
SOPT				
Number of errors	15.1 (6.2)	15.4 (6.3)	17 (4.9)	$F(2,30) = 0.31$ , $P = 0.735$
Time taken (s)	409 (44)	436 (56)	615 (244)	$F(2,30) = 6.11$ , $P = \mathbf{0.006}^{* \#}$

Standard deviation is shown in brackets. *Post hoc* tests (Tukey/Mann–Whitney) revealed significant differences between the control and SCD-FL groups ( $P < 0.05$ )\*, and between the SCD-C and FL-Lesion groups ( $P < 0.05$ )#. <sup>†</sup>Kruskal–Wallis Test. Bold values indicate significant *P* values.

(Hogan *et al.*, 2005), the ERN and CRN data for the 2-CRT condition (compatible stimuli) and the 4-CRT incompatible condition were compared across all groups.

### Statistical analyses

Neuropsychological data were analysed by one-way ANOVA (analysis of variance), with group (controls, SCD-C, SCD-FL) as the independent variable. *Post hoc* test results (Tukey) are reported for significant comparisons. Additional planned comparisons investigated the possibility that patients with bilateral frontal lobe lesions were more impaired than those with unilateral lesions using non-parametric Mann–Whitney tests.

Group differences in behavioural and ERP data were assessed using a mixed-design ANOVA, using the factors of group (three levels) and condition (two levels—2-CRT versus 4-CRT). Self-correction scores were log-transformed in order to permit parametric analysis. In order to investigate the integrity of the performance-monitoring system (CRN–ERN differences), response-locked CRN and ERN amplitudes and latencies were subjected to a mixed-design ANOVA using the factors of group (three levels), condition (two levels), and ERP component (two levels—CRN versus ERN). Planned group comparisons on all behavioural and ERP measures were performed using one-way ANOVA. Task performance and ERP measures in the bilateral and unilateral SCD-FL subgroups were compared using Mann–Whitney tests.

## Results

### MRI data

There was no evidence of structural abnormality or atrophy in the SCD-C group. In the SCD-FL group, six patients had left-sided lesions and five had bilateral lesions. Cortical atrophy was not detected in any of the participants with a unilateral lesion. In patients with bilateral lesions, however, only one did not show atrophy, while two had mild (focal sulcal enlargement alone) and another two had moderate atrophy (sulcal enlargement and white matter loss). Atrophy was confined to the right frontal lobe and posterior bilateral parietal lobes in the two cases with mild atrophy. Moderate atrophy was global in the third case and present throughout

the left hemisphere and at the MCA/PCA watershed region in the fourth case. One unilateral case had an additional infarct in the left basal ganglia (caudate head). Four bilateral cases had additional infarct lesions: one small left temporal lobe white matter infarct; one left and one right parietal lobe white matter infarct; one left caudate head infarct; and one left and one right caudate head and one left and one right parietal lobe white matter infarct. A benign choroidal fissure cyst, of no clinical significance, was found in one unilateral case. The neuroanatomical location of lesions in SCD-FL patients is shown in Fig. 1. These lesion overlap maps show the average lesion location in the dorsal frontal white matter for unilateral and bilateral SCD-FL patients (Fig. 1A and B, respectively).

### Neuropsychology

Significant group differences were found in all three measures of executive function (Table 1). In each case, the performance of the SCD-FL group was significantly impaired compared with controls, and, additionally, compared with the SCD-C group in WCST and SOPT measures. In contrast, mean scores did not differ between the control and SCD-C groups. Performance was not significantly different in patients with bilateral compared with unilateral frontal lobe lesions.

### ERP paradigm

*Behavioural data:* The increase in task demand between 2-CRT and 4-CRT significantly (all  $P < 0.001$ ) affected all behavioural outcome measures (Table 2); however, there were no main effects of group or interaction effects with group for any of these variables. The absence of significant group differences was supported by the results of planned comparisons reported in Table 2. There were also no significant differences in performance between unilateral and bilateral lesion groups. In summary, the ERP task

**Table 2** Behavioural data (SD)

	Control <i>n</i> = 11	SCD-C <i>n</i> = 11	SCD-FL <i>n</i> = 11	Univariate group main effect
2-CRT compatible				
Correct RT (ms)	350 (28)	363 (54)	376 (54)	$F(2,30) = 0.77, P = 0.473$
Error RT (ms)	264 (36)	281 (41)	269 (39)	$F(2,30) = 0.56, P = 0.576$
Error rate (%)	8.1 (5.8)	8.1 (4.7)	10.9 (13.1)	$F(2,30) = 0.39, P = 0.681$
Self-corrected errors (%)	44.9 (41.8)	46.9 (39.6)	42.4 (32.8)	$F(2,30) = 0.04, P = 0.962$
Post-error slowing (ms)	14 (40)	26 (77)	26 (53)	$F(2,30) = 0.15, P = 0.863$
4-CRT incompatible				
Correct RT (ms)	546 (44)	541 (68)	560 (142)	$F(2,30) = 0.12, P = 0.886$
Error RT (ms)	372 (43)	423 (92)	442 (112)	$F(2,30) = 1.91, P = 0.164$
Error rate (%)	19.3 (12.0)	18.3 (7.6)	16.8 (10.5)	$F(2,30) = 0.16, P = 0.852$
Self-corrected errors (%)	20.2 (20.6)	34.1 (39.7)	29.3 (32.8)	$F(2,30) = 0.54, P = 0.590$
Post-error slowing (ms)	95 (61)	73 (70)	133 (95)	$F(2,30) = 1.68, P = 0.202$

**Table 3** Stimulus-locked ERP amplitudes and latencies

	Control <i>n</i> = 11	SCD-C <i>n</i> = 11	SCD-FL <i>n</i> = 11	Univariate group main effect
Compatible				
N2				
Amplitude	−3.5 (5.3)	−5.1 (5.5)	−.3 (3.9)	$F(2,30) = 2.61, P = 0.090$
Latency	253 (26)	262 (34)	263 (40)	$F(2,30) = 0.28, P = 0.753$
P3a				
Amplitude	16.4 (5.8)	12.0 (4.1)	12.8 (7.9)	$F(2,30) = 1.56, P = 0.227$
Latency	346 (33)	384 (33)	373 (48)	$F(2,30) = 2.77, P = 0.079$
P3b				
Amplitude	7.3 (2.9)	8.0 (4.8)	7.5 (8.3)	$F(2,30) = 0.04, P = 0.959$
Latency	491 (78)	471 (39)	507 (97)	$F(2,30) = 0.61, P = 0.549$
Incompatible				
N2				
Amplitude	−.75 (8.7)	−2.68 (8.5)	0.62 (5.0)	$F(2,30) = 0.52, P = 0.599$
Latency	263 (28)	250 (37)	259 (21)	$F(2,30) = 0.48, P = 0.619$
P3a				
Amplitude	21.8 (7.9)	16.1 (7.1)	18.8 (7.8)	$F(2,30) = 1.57, P = 0.223$
Latency	349 (19)	368 (35)	388 (45)	$F(2,30) = 3.28, P = 0.051$
N4				
Amplitude	−.66 (8.1)	−1.79 (8.7)	5.57 (9.2)	$F(2,30) = 2.27, P = 0.120$
Latency	448 (27)	476 (32)	485 (40)	$F(2,30) = 2.83, P = 0.075$
P3b				
Amplitude	16.8 (7.7)	13.2 (7.8)	17.7 (10.7)	$F(2,30) = 0.75, P = 0.478$
Latency	547 (52)	576 (93)	554 (91)	$F(2,30) = 0.375, P = 0.691$

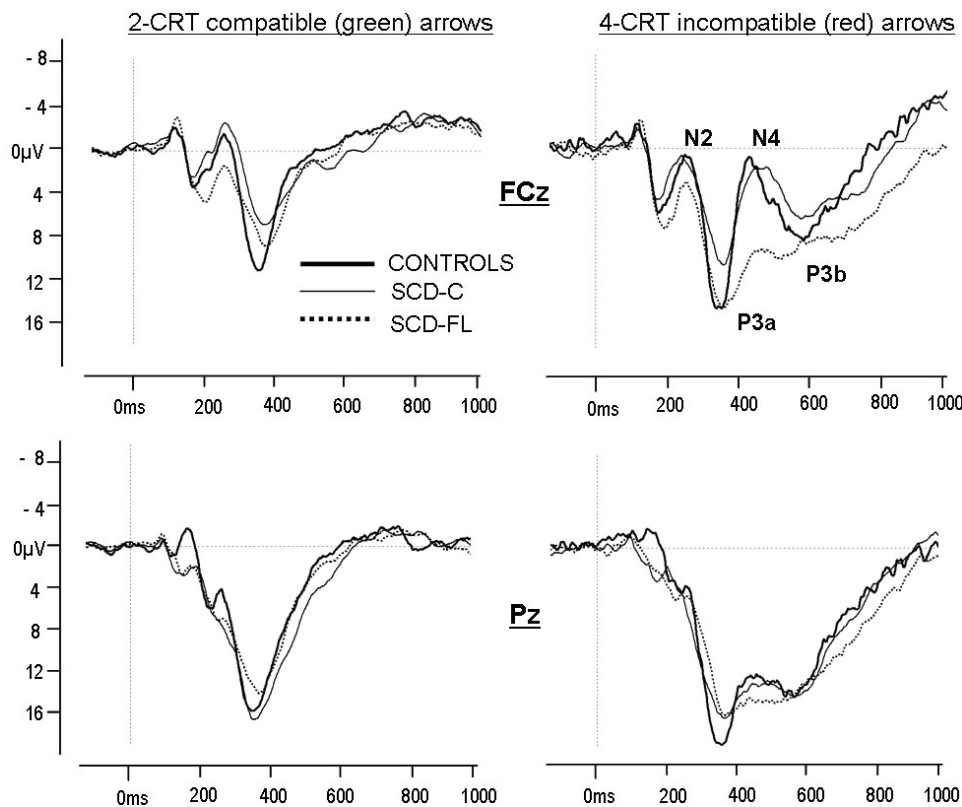
performance of the SCD-FL group did not differ from that of the SCD-C or control groups.

## ERP components

**Stimulus-locked ERP components:** The amplitude of N2, P3a and P3b components, and P3b latency were significantly modulated by an increase in task demand between 2-CRT and 4-CRT conditions (all  $P < 0.05$ ; see also Table 3). A main effect of group for P3a latency [ $F(2,30) = 3.5, P = 0.043$ ] indicated a small latency prolongation in both SCD groups compared with controls, but planned comparisons failed to reach conventional levels of significance (Table 3). A slight N2 amplitude reduction visible in the SCD-FL group

compared with both controls (Fig. 2) also failed to reach significance ( $P = 0.09$ ). Similarly, the N4 was less pronounced and slightly delayed in the SCD-FL group, but these differences were not significant. There were no further group differences and no group interaction effects for any of the ERP components. Furthermore, there were no significant differences between unilateral and bilateral frontal lobe lesion groups for any of these variables.

Stimulus–response compatibility is known to modulate stimulus-locked frontal negative waves such as the N2 (Kopp *et al.*, 1996). We examined such pre-response stimulus–response compatibility effects within the 4-CRT condition by measuring the amplitudes of N2 and N4 components to compatible (green arrows) and incompatible



**Fig. 2** Stimulus-locked ERP waveforms obtained from controls and SCD-C and SCD-FL groups.

stimuli (red arrows). This effect was examined first in both control groups using a mixed ANOVA with the factors stimulus (4-CRT green arrow, 4-CRT red arrow), electrode (Fz, FCz) and group (controls, SCD-C). While the N2 component was not modulated by stimulus compatibility [ $F(1,20) = 0.14$ ,  $P = 0.712$ ], such effect was found for the later N4 wave at  $\sim 470$  ms, which was larger for incompatible compared with compatible stimuli in both control groups [ $F(1,20) = 4.88$ ,  $P = 0.039$ ] (compatible  $-0.3$   $\mu\text{V}$ , incompatible  $-3.1$   $\mu\text{V}$ ). This N4 pattern was not found in the SCD-FL group (compatible:  $-0.1$   $\mu\text{V}$ , incompatible:  $+3.6$   $\mu\text{V}$ ), supported by a significant stimulus by group interaction effect [ $F(2,30) = 3.90$ ,  $P = 0.031$ ].

**Response-locked ERP components:** As shown in Fig. 3, CRN as well as ERN/Pe responses were elicited in all three groups by correct and error trials, respectively; CRN, ERN and Pe amplitudes were significantly modulated by task complexity in all groups (all  $P < 0.05$ ). As predicted, the performance-monitoring system was significantly affected by the presence of frontal white matter lesions, evident in the diminished difference between ERN and CRN components in the SCD-FL group compared with both control groups. This is supported by a significant interaction effect of group and component [ $F(2,30) = 10.5$ ,  $P < 0.001$ ]. Importantly, a *post hoc* analysis including only the SCD-C and SCD-FL groups also revealed a significant group by component interaction [ $F(1,20) = 9.7$ ,  $P = 0.005$ ], indicating that the

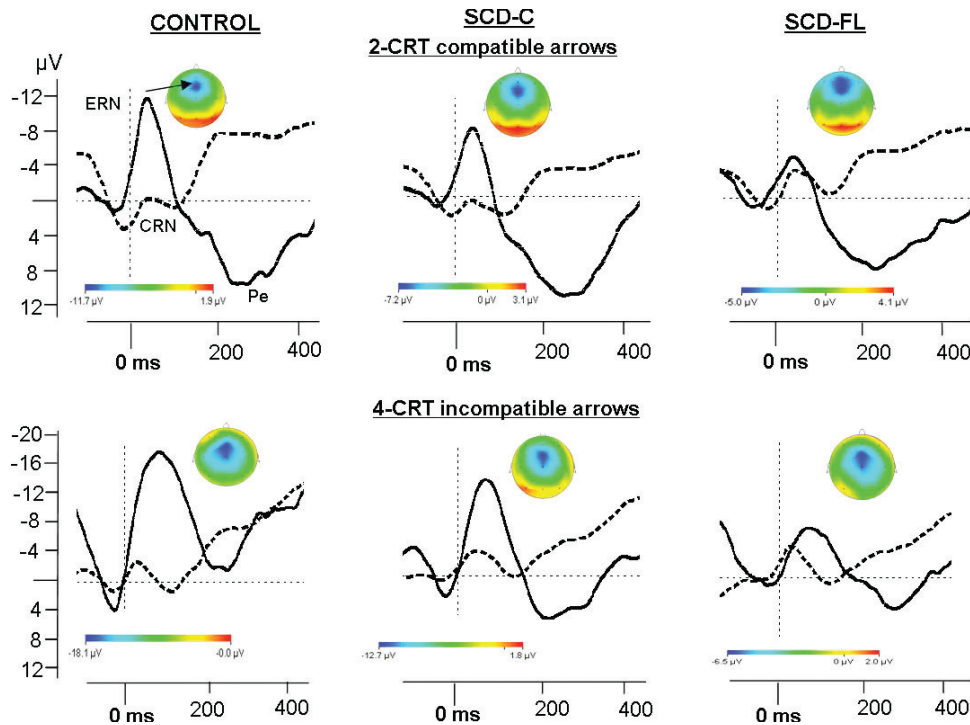
performance-monitoring system was affected by the presence of lesions, not SCD *per se*.

The diminished CRN–ERN difference was due to a significant reduction of ERN in the SCD-FL group [ $F(2,30) = 8.0$ ,  $P = 0.002$ ], while the small increase in CRN was not significant (Table 4). This ERP difference was further investigated within each group using paired *t*-tests. The differentiation between CRN and ERN was significant in the control group [compatible:  $t(10) = 5.8$ ,  $P < 0.001$ ; incompatible:  $t(10) = 4.7$ ,  $P = 0.001$ ], and in the SCD-C group [compatible:  $t(10) = 5.2$ ,  $P < 0.001$ ; incompatible:  $t(10) = 3.7$ ,  $P = 0.004$ ], but not in the SCD-FL group [compatible:  $t(10) = 1.5$ ,  $P = 0.176$ ; incompatible:  $t(10) = 1.3$ ,  $P = 0.222$ ].

Again, there were no significant differences between unilateral and bilateral lesion groups for the CRN, ERN or Pe in either condition, suggesting that left-sided lesions were sufficient to significantly disrupt error processing.

## Discussion

ERP components associated with error detection were elicited using two different choice-response tasks in patients with frontal white matter lesions due to SCD vasculopathy, and in two control groups: SCD patients without lesions and non-SCD sibling controls. As predicted, patients with frontal white matter lesions showed a diminished response-locked



**Fig. 3** Response-locked ERP waveforms obtained from controls and SCD-C and SCD-FL groups. ERP to correct trials are shown as dashed lines and error trials as continuous lines.

**Table 4** Response-locked ERP amplitudes and latencies

	Control <i>n</i> = 11	SCD-C <i>n</i> = 11	SCD-FL <i>n</i> = 11	Univariate group main effect
Compatible				
CRN amplitude	−1.2 (3.2)	−0.3 (5.7)	−4.0 (5.7)	$F(2,30) = 1.57, P = 0.224$
Latency	38 (17)	34 (10)	34 (7)	$F(2,30) = 0.47, P = 0.627$
ERN amplitude	−14.1 (6.1)	−10.1 (4.7)	−6.9 (4.2)	$F(2,30) = 5.46, P = \mathbf{0.009^*}$
Latency	37 (9)	41 (14)	44 (21)	$F(2,30) = 0.42, P = 0.657$
Pe amplitude	14.8 (11.3)	10.0 (12.2)	13.3 (10.4)	$F(2,30) = 0.52, P = 0.598$
Latency	233 (56)	231 (67)	206 (65)	$F(2,30) = 0.63, P = 0.538$
Incompatible				
CRN amplitude	−4.2 (2.9)	−4.9 (6.2)	−5.8 (8.2)	$F(2,30) = 0.18, P = 0.829$
Latency	30 (9)	42 (21)	39 (19)	$F(2,30) = 1.4, P = 0.262$
ERN amplitude	−22.4 (12.4)	−14.7 (8.1)	−8.2 (9.1)	$F(2,30) = 5.48, P = \mathbf{0.009^*}$
Latency	61 (25)	69 (23)	51 (22)	$F(2,30) = 1.63, P = 0.212$
Pe amplitude	3.0 (12.4)	10.1 (10.4)	8.3 (12.2)	$F(2,30) = 1.09, P = 0.347$
Latency	231 (33)	257 (39)	239 (65)	$F(2,30) = 0.80, P = 0.456$

A *post hoc* test (Tukey) revealed significant differences between the control and FL-lesion groups ( $P < 0.01$ )\*.

ERP difference between error (ERN) and correct (CRN) responses in both tasks. This finding supports previous studies of adults with frontal lobe pathology (Gehring and Knight, 2000; Swick and Turken, 2002; Ullsperger *et al.*, 2002; Stemmer *et al.*, 2004; Ullsperger and von Cramon, 2006).

The present investigation extends our knowledge on performance monitoring in three important aspects. First, it demonstrates that ERP correlates of performance monitoring may present alongside executive function deficits assessed

by neuropsychology in patients with frontal lobe lesions. Secondly, it shows that frontal lobe lesions acquired in childhood result in physiological (ERP) deficits similar to those previously observed in adult stroke patients. Thirdly, the type and size of lesions were markedly different from those reported in previous studies of the ERN. The lesions in the present study were comparably discrete and restricted to the frontal white matter with a high degree of overlap between subjects, and, in bilateral cases, they were approximately symmetrical. Greatest lesion overlap occurred in the

dorsal white matter of the frontal lobes adjacent to the genu of the corpus callosum. Thus, the present study adds important evidence that frontal lobe lesions that do not directly involve the cortex of either the DLFC or pmFC (ACC) also impact on performance-monitoring pathways. This is consistent with the hypothesis of a functional and anatomical DLFC–ACC interaction during performance monitoring (Gehring and Knight, 2000; Koski and Paus, 2000; Ridderinkhof *et al.*, 2004b).

Importantly, there were no group performance differences on the CRT measures that could confound ERP data, and all groups responded similarly to an increase in task difficulty. We can therefore exclude the possibility that lack of ability, or different strategies, such as speed-accuracy trade-off, could account for the ERP differences. Likewise, there was a lack of consistent group differences in stimulus-locked ERP components. The amplitude of the N2 component at 200 ms, associated with pre-response conflict on correct-response trials (e.g. Kopp *et al.*, 1996; van Veen and Carter, 2002; Nieuwenhuis *et al.*, 2003), was not significantly modulated by stimulus-response compatibility in this study. In contrast, however, the later N4 component at ~470 ms was sensitive to such effect, suggesting that it was similar to the N2c component identified by Kopp *et al.* (1996). This N4 effect may reflect response priming (Kopp *et al.*, 1996) or pre-response conflict (van Veen and Carter, 2002; Nieuwenhuis *et al.*, 2003) [The N4 occurred ~80 ms before the mean RT for incompatible correct trials (*see* Table 2)]. Interestingly, this effect was not evident in the SCD-FL group, suggesting that pre-response stimulus processing was also affected by presence of discrete frontal white matter lesions. The N2 is sensitive to lower stimulus probability in addition to incompatibility in some studies (Braver *et al.*, 2001; Nieuwenhuis *et al.*, 2003) but not others (Bartholow *et al.*, 2005). Because our study did not control for stimulus probability in the 4-CRT task, it remains unresolved if pre-response conflict monitoring or stimulus probability detection were affected in the SCD-FL group.

In SCD-FL patients, the non-significant CRN–ERN differentiation was due to a lowered ERN magnitude. Indeed, the magnitude of ERN attenuation in the SCD-FL group compared with the SCD-C group showed a moderate effect size ( $d = 0.71$  and  $0.75$  for compatible and incompatible conditions, respectively). This is similar to the pattern of results obtained from adults with LFC lesions by Ullsperger *et al.* (2002) and Ullsperger and von Cramon (2006). Interestingly, the opposite pattern of an increased CRN and an unaffected ERN was reported in patients with LFC lesions by Gehring and Knight (2000). Despite this discrepancy, which may partly be explained by the greater working-memory load in the flanker task used in the latter study, a non-significant differentiation between the CRN and ERN in patients compared with controls was a feature of both studies. According to one model (Coles *et al.*, 2001) this finding may result from diminished representation of the correct stimulus–response relationships being accessible to a

‘comparator’ that distinguishes error from correct actions. This notion is compatible with the neuroanatomical substrate that may underlie error monitoring described by Gehring and Knight (2000) and Ullsperger *et al.* (2002), namely that the pmFC (comparator) depends on the DLFC to hold online a template for correct stimulus–response mappings. We infer that SCD-FL patients were able to establish such a template and that it was used successfully to perform the task, evident in comparable performance and error rates between groups. However, it is possible that the communication of stimulus–response representations to the pmFC comparator was impoverished, resulting in a reduced ERN. This ultimately could lead to performance breakdown if an individual has to process a large number of items or complex stimulus–response mappings, such as those required by the executive function tasks used here. Furthermore, the similarity in topographical scalp distribution of ERN across groups indicates that it is unlikely that the SCD-FL patients recruited brain areas other than those in the pmFC in ERN generation, a finding shared with the study of Ullsperger *et al.*, (2002).

The effect of unilateral compared with bilateral frontal lobe lesions has not previously been addressed in ERP studies of performance monitoring. Earlier studies presented data from unilateral cases: in the study by Gehring and Knight (2000) four out of six DLFC patients had unilateral left hemisphere damage; similarly, in the study by Ullsperger *et al.* (2002), five out of the seven DLFC patients had left hemisphere damage. A preponderance of left lesion cases in these studies and in the present study does not permit an investigation of laterality effects. Bilateral symmetrical frontal lobe damage is rare, but in a series of five adults with damage to the medial prefrontal cortex, including the ACC, absent CRN/ERN was observed in three patients (Stemmer *et al.*, 2004). Notwithstanding the limited statistical power of our own study, it is of interest that unilateral and bilateral lesion groups had a comparably small ERN.

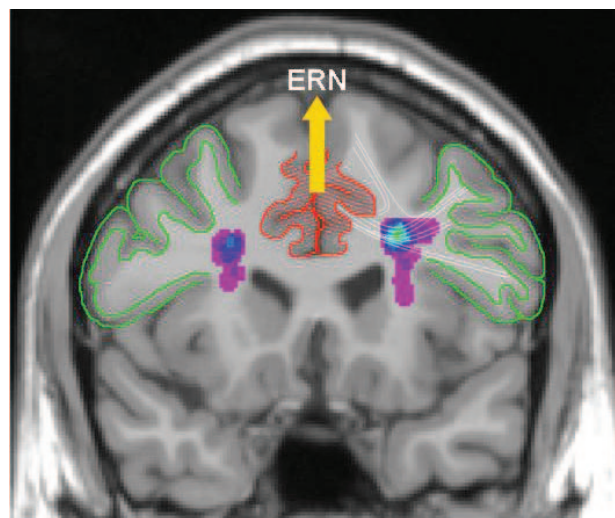
The age at onset of pathology is another important consideration; lesions in our patients were acquired in childhood (the majority at <10 years of age) compared with adult onset in earlier ERN studies. Nevertheless, diminished CRN–ERN amplitude difference is as much a feature in our young frontal lobe lesion patients as it was in adults. In particular, the reorganizational plasticity of the immature brain may have been expected to compensate for unilateral injury, resulting in a normal pattern of ERN activity in unilateral cases compared with a significantly reduced ERN in bilateral cases. This was not confirmed, as both lesion groups had statistically comparable ERN reductions. It is possible that in the left unilateral lesion group the white matter integrity in the right frontal lobes was functionally compromised in a way that was not detected on radiological evaluation. However, those patients in the bilateral group had frank lesions in the right hemisphere but did not demonstrate a statistically greater ERN reduction compared with the unilateral group. Nevertheless, recent evidence from quantitative MRI suggests

that very subtle structural brain abnormalities may be evident from the first year of life in children with SCD (Steen *et al.*, 2004) and persist throughout childhood (Steen *et al.*, 2005). Bilateral constraints on brain function associated with underlying subclinical SCD vasculopathy (Baldeweg *et al.*, 2006) are also indicated by the lowered intelligence scores and executive functions scores, as well as the slightly reduced ERN obtained by the SCD-C group compared with non-SCD controls (*see* Tables 1 and 4, respectively), although these differences were not statistically significant. Alternatively, our findings are also compatible with a previously advanced hypothesis (Gehring and Knight, 2000; Ullsperger *et al.*, 2002) that performance monitoring requires functional connectivity between both frontal lobes.

A limitation of this study is that it was not possible to confirm exactly which white matter tracts were affected in our patients. The knowledge of DLFC–pMFC connectivity in humans is sparse and inferential. These connections are not identified in human diffusion tensor imaging (DTI) and tractography studies (Mori *et al.*, 2005), owing to the problem of crossing fibres of the dominant anterior–posterior fibre bundles connecting the frontal lobes with temporal, parietal and occipital regions (Catani *et al.*, 2002; Jellison *et al.*, 2004). Retrograde tracer studies in monkeys provide the main body of evidence (Picard and Strick, 1996; Rizzolatti and Luppino, 2001). Connections exist between the DLFC (principal sulcus) and premotor areas, including the supplementary motor area (SMA) and rostral and ventral areas of the CMA (Bates and Goldman-Rakic, 1993; Morecraft and van Hoesen, 1993; Lu *et al.*, 1994; Luppino and Rizzolatti, 2000). Reciprocal connections between the DLFC and ACC (Barbas and Pandya, 1989; Preuss and Goldman-Rakic, 1989; Barbas 1992; Petrides and Pandya, 1999) are part of a fronto-limbic network (Arikuni *et al.*, 1994; Barbas 2000).

Moreover, a consistent finding across a large number of functional imaging studies in humans is the co-occurrence of blood flow changes in the DLFC and the ACC, in particular between the middle frontal gyrus and supracallosal ACC e.g. Koski and Paus, 2000. Despite the inference that these regions act in tandem to modulate cortical activity (Bench *et al.*, 1993; Koski and Paus, 2000; Kondo *et al.*, 2004), DLFC–ACC connectivity in humans has not been directly confirmed.

It is hypothesized that the white matter lesions in our patients did not disrupt lateral cortico-cortical connections between premotor and primary motor cortex underpinning selection, preparation for and execution of movement (reviewed in Passingham, 1993). Instead, the lesions may have selectively disrupted more ventromedial DLFC–pMFC connections between structures involved in error processing (Ullsperger and von Cramon, 2001, 2006; *see also* Ullsperger, 2006, for a compatible hypothesis). This hypothesis is summarized in Fig. 4. Ultimately, DTI techniques that enable detection of crossing fibres (Tournier *et al.*, 2004; Wedeen *et al.*, 2005) will be essential for the identification of these tracts in the human brain.



**Fig. 4** A summary of the main study hypothesis: discrete white matter lesions in SCD-FL patients (shown here as lesion overlap; *see* Fig. 1) disrupt hypothetical connections (white lines) between lateral frontal cortex (outlined in green) and the ERN generator (yellow arrow) in the rostral cingulate zone (shaded in red). ERN deficits were previously found in patients with lateral frontal cortex damage (Gehring and Knight, 2000; Ullsperger *et al.*, 2002; Ullsperger and von Cramon, 2006; Ullsperger, 2006). Because no lesions in medial and lateral frontal cortices were identified in SCD-FL patients, it is inferred that the deep frontal lesions disrupt the functional connectivity between those cortical regions during performance monitoring.

The present MRI and ERP data indicate compromised connectivity between DLFC and ACC during performance monitoring. Such diminished connectivity is sufficient to support performance in our stimulus–response tasks. This is evident in the lack of group differences on the CRT measures (*see* Table 2), and perhaps also in some measures of attentional processing (e.g. sustained attention; *see* Table 1). It has been proposed that attention is subserved by widely distributed but interconnected neural networks (Posner and Peterson, 1990; Berger and Posner, 2000). For example, frontoparietal networks are hypothesized to play an important role in selective attention (Kastner and Ungerleider, 2000; Chelazzi and Corbetta, 2000; *see also* Baird *et al.*, 2006), enhancing the processing of goal-relevant information over non-relevant information. This skill may be measured by Stroop-like tasks on which our CRT is based, where the individual is required to ‘facilitate’ a channel for one stimulus and concurrently ‘suppress’ a channel for another stimulus. It is possible that the sparing of sustained and switching attention processes in our patients was due to the lack of damage to other parts of those neural networks hypothesized to subserve attention, such as the parietal cortex and ACC.

The white matter lesions did significantly compromise other executive functions tested in this study. Both the WCST and SOPT have been shown to require efficient functioning of DLFC regions (Milner, 1963; Petrides *et al.*, 1993;

Curtis *et al.*, 2000; Stuss, 2000). For example, Milner (1963) observed a lower number of categories and higher number of perseverative errors in the WCST in adults with DLFC injury compared with patients with temporal and parietal lesions. Successful performance on these tasks relies heavily on the ability to monitor online performance and make behavioural adjustments to errors, and thus may involve DLFC–ACC connectivity as indicated in our patients. We hypothesize that the deficits in the WCST and SOPT measures in SCD-FL patients, in addition to their physiological deficit in ERN generation, were due to disconnection of the DLFC from the ACC. The importance of a DLFC–ACC circuit in executive functioning has also been postulated by D'Esposito *et al.* (1995). Furthermore, efficient interaction between DLFC and medial prefrontal regions is implicated in supporting general intellectual function (Gray *et al.*, 2003). Consistent with this we also found lowered IQ scores in the SCD-FL group.

Our data have implications for the understanding of the neural substrate of performance monitoring and may potentially elucidate a relationship with executive functions. In particular, they may explain executive and intellectual function deficits commonly seen in patients with SCD (e.g. Watkins *et al.*, 1998), in whom lesions of the DLFC are uncommon, but silent infarct lesions in deep frontal watershed areas are frequently found (Pavakis *et al.*, 1988).

## Acknowledgements

The authors gratefully acknowledge the assistance of Dr Paul Telfer (The Royal London Hospital) for permission to recruit patients from his clinic, and the helpful comments during manuscript preparation by Dr Mortimer Mishkin. Research at the Institute of Child Health, UCL, and Great Ormond Street Hospital for Children NHS Trust benefits from Research and Development Funding from the NHS Executive. This work was supported by Action Medical Research, UK.

## References

- Allain S, Carbone L, Burle B, Hasbroucq T, Vidal F. On-line executive control: an electromyographic study. *Psychophysiology* 2004; 41: 113–6.
- Arikuni T, Sako H, Murata A. Ipsilateral connections of the anterior cingulate cortex with the frontal and medial temporal cortices in the macaque monkey. *Neurosci Res* 1994; 21: 19–39.
- Baird A, Dewar BK, Critchley H, Gilbert SJ, Dolan RJ, Cipolotti L. Cognitive functioning after medial prefrontal damage including the anterior cingulate cortex: a preliminary investigation. *Brain Cogn* 2006; 60: 166–75.
- Baldeweg T, Hogan AM, Saunders DE, Telfer P, Gadian DG, Vargha-Khadem F, et al. Detecting white matter injury in sickle cell disease using voxel-based morphometry. *Ann Neurol* 2006; 59: 662–72.
- Barbas H. Architecture and cortical connections of the prefrontal cortex in the rhesus monkey. *Adv Neurol* 1992; 57: 91–115.
- Barbas H. Complementary roles of prefrontal cortical regions in cognition, memory, emotion in primates. *Adv Neurol* 2000; 84: 87–110.
- Barbas H, Pandya DN. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *J Comp Neurol* 1989; 286: 353–75.
- Bartholow BD, Pearson MA, Dickter CL, Sher KJ, Fabiani M, Gratton G. Strategic control and medial frontal negativity: beyond errors and response conflict. *Psychophysiology* 2005; 42: 33–42.
- Bates JF, Goldman-Rakic PS. Prefrontal connections of medial motor areas in the rhesus monkey. *J Comp Neurol* 1993; 336: 211–28.
- Bench CJ, Frith CD, Grasby PM, Friston KJ, Paulus E, Frackowiak RS, et al. Investigations of the functional anatomy of attention using the Stroop test. *Neuropsychologia* 1993; 31: 907–22.
- Berger A, Posner M. Pathologies of brain attentional networks. *Neurosci Biobehav Rev* 2000; 24: 3–5.
- Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. *Psychol Rev* 2001; 108: 624–52.
- Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn Sci* 2004; 8: 539–46.
- Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A. Anterior cingulate cortex and response conflict: effects of frequency, inhibition, and errors. *Cereb Cortex* 2001; 11: 825–36.
- Carter C, Braver T, Barch D, Botvinick M, Noll D, Cohen J. Anterior cingulate cortex, error detection and the online monitoring of performance. *Science* 1998; 280: 747–9.
- Catani M, Howard RJ, Pajevic S, Jones DK. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *Neuroimage* 2002; 17: 77–94.
- Chelazzi L, Corbetta M. Cortical mechanisms of visuospatial attention in the primate brain. In: Gazzaniga MS, editor-in-chief. *The new cognitive neurosciences*. 2nd edition. Cambridge, MA: MIT Press; 2000. p. 667–86.
- Coles MGH, Scheffers MK, Holroyd CB. Why is there an ERN/Ne on correct trials? Response representations, stimulus-related components and the theory of error-processing. *Biol Psychol* 2001; 56: 173–89.
- Curtis C, Zald D, Pardo J. Organization of working memory within the human prefrontal cortex: a PET study of self-ordered object working memory. *Neuropsychologia* 2000; 38: 1503–10.
- D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. *Nature* 1995; 378: 279–81.
- Dehaene S, Posner MI, Tucker DM. Localization of a neural system for error detection and compensation. *Psychol Sci* 1994; 5: 303–5.
- Falkenstein M. ERP correlates of erroneous performance. In: Ullsperger M, Falkenstein M, editors. *Errors, conflicts and the brain. Current opinions on performance monitoring (MPI special issue in human cognitive and brain sciences)*. Vol. 1. Leipzig: MPI for Cognitive Neurosciences; 2004. p. 5–14.
- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L. Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: Brunia CHM, Gaillard AWK, Kok A, editors. *Psychophysiological brain research*. Tilburg: Tilburg University Press; 1990. p. 192–5.
- Falkenstein M, Hoormann J, Christ S, Hohnsbein J. ERP components on reaction errors and their functional significance: a tutorial. *Biol Psychol* 2000; 51: 87–107.
- Ford JM. Schizophrenia: the broken P300 and beyond. *Psychophysiology* 1999; 36: 667–82.
- Gray JR, Chabris CR, Braver TS. Neural mechanisms of general fluid intelligence. *Nat Neurosci* 2003; 6: 316–22.
- Gehring W, Knight R. Prefrontal-cingulate interactions in action monitoring. *Nat Neurosci* 2000; 3: 516–20.
- Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E. A neural system for error detection and compensation. *Psychol Sci* 1993; 4: 385–90.
- Herrmann MJ, Rommner J, Ehrls AC, Heidrich A, Fallgatter AJ. Source localization (LORETA) of the error-related-negativity (ERN/Ne) and positivity (Pe). *Brain Res Cogn Brain Res* 2004; 20: 294–9.
- Hillis AE, Wityk RJ, Barker PB, Beauchamp NJ, Gailloud P, Murphy K, et al. Subcortical aphasia and neglect in acute stroke: the role of cortical hypoperfusion. *Brain* 2002; 125: 1094–104.
- Hogan AM, Vargha-Khadem F, Kirkham FJ, Baldeweg T. Maturation of action monitoring from adolescence to adulthood: an ERP study. *Dev Sci* 2005; 8: 525–34.
- Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, Alexander AL. Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy and tumor imaging patients. *Am J Neuroradiol* 2004; 25: 356–69.

- Kaiser J, Barker R, Haenschel C, Baldeweg T, Gruzelier J. Hypnosis and event-related potential correlates of error processing in a Stroop-type paradigm: a test of the frontal hypothesis. *Int J Psychophysiol* 1997; 27: 215–22.
- Kastner S, Ungerleider LG. Mechanisms of visual attention in the human cortex. *Ann Rev Neurosci* 2000; 23: 315–41.
- Kerns JG, Cohen JD, MacDonald AW, Cho RY, Stenger VA, Carter CS. Anterior cingulate conflict monitoring and adjustments in control. *Science* 2004; 303: 1023–6.
- Kondo H, Morishita M, Osaka N, Osaka M, Fukuyama H, Shibasaki H. Functional roles of the cingulo-frontal network in performance on working memory. *Neuroimage* 2004; 21: 2–14.
- Kopp B, Rist F, Mattler U. N200 in the flanker task as a neurobehavioural tool for investigating executive control. *Psychophysiology* 1996; 33: 282–94.
- Koski L, Paus T. Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Exp Brain Res* 2000; 133: 55–65.
- Lu MT, Preston JB, Strick PL. Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *J Comp Neurol* 1994; 341: 375–92.
- Luppino G, Rizzolatti G. The organization of the frontal motor cortex. *News Physiol Sci* 2000; 15: 219–24.
- Milner B. Effects of different brain lesions on card sorting. The role of the frontal lobes. *Arch Neurol* 1963; 9: 100–10.
- Morecraft RJ, Van Hoesen GW. Frontal granular cortex input to the cingulate (M3), supplementary (M2) and primary (M1) motor cortices in the rhesus monkey. *J Comp Neurol* 1993; 337: 669–89.
- Mori S, Wakana S, Nagae-Poetscher LM, van Zijl PCM. MRI atlas of human white matter. Amsterdam: Elsevier; 2005.
- Nieuwenhuis S, Yeung N, Van Den Wildenberg W, Ridderinkhof KR. Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. *Cogn Affect Behav Neurosci* 2003; 3: 17–26.
- Passingham RE. *The Frontal Lobes and Voluntary Action*. Oxford: Oxford University Press, 1993.
- Pavakis SG, Bello J, Prohovnik I, Sutton M, Ince C, Mohr JP, et al. Brain infarction in sickle cell anemia: magnetic resonance imaging correlates. *Ann Neurol* 1988; 23: 125–30.
- Petrides M, Milner B. Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* 1982; 20: 249–62.
- Petrides M, Pandya DN. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur J Neurosci* 1999; 11: 1011–36.
- Petrides M, Alivisatos B, Evans A, Meyer E. Dissociation of human mid-dorsolateral frontal cortex in memory processing. *Proc Natl Acad Sci USA* 1993; 90: 873–7.
- Picard N, Strick PL. Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* 1996; 6: 342–53.
- Posner MI, Peterson SE. The attention system of the human brain. *Annu Rev Neurosci* 1990; 13: 25–42.
- Pregler M, Pavakis SG, Prohovnik I, Adams RJ. Sickle cell disease: the neurological complications. *Ann Neurol* 2002; 51: 543–52.
- Preuss TM, Goldman-Rakic PS. Connections of the ventral granular frontal cortex of macaques with perisylvian premotor and somatosensory areas: anatomical evidence for somatic representation in primate frontal association cortex. *J Comp Neurol* 1989; 282: 293–316.
- Ridderinkhof KR, van den Wildenberg WP, Segalowitz SJ, Carter CS. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain Cogn* 2004a; 56: 129–40.
- Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. *Science* 2004b; 306: 443–7.
- Robertson IH, Ward A, Ridgeway V, Nimmo-Smith I. *Test of everyday attention*. Bury St Edmunds: Thames Valley Test Company; 1994.
- Rizzolatti G, Luppino G. The cortical motor system. *Neuron* 2001; 31: 889–901.
- Semlitsch HV, Anderer P, Schuster P, Presslich O. A solution for reliable and valid reduction of ocular artefacts, applied to the P300 ERP. *Psychophysiology* 1986; 23: 695–703.
- Steen RG, Hunte M, Traipe E, Hurh P, Wu S, Bilaniuk L, et al. Brain T1 in young children with sickle cell disease: evidence of early abnormalities in brain development. *Magn Reson Imaging* 2004; 22: 299–306.
- Steen RG, Emudianughe T, Hunte M, Glass J, Wu S, Xiong X, et al. Brain volume in pediatric patients with sickle cell disease: evidence of volumetric growth delay? *Am J Neuroradiol* 2005; 26: 455–62.
- Stemmer B, Segalowitz SJ, Witzke W, Schonle PW. Error detection in patients with lesions to the medial prefrontal cortex: an ERP study. *Neuropsychologia* 2004; 42: 118–30.
- Stuss D, Levine B, Alexander M. Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia* 2000; 38: 388–402.
- Swick D, Turken AU. Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *Proc Natl Acad Sci USA* 2002; 99: 16354–9.
- Tournier JD, Calamante F, Gadian DG, Connelly A. Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *Neuroimage* 2004; 23: 1176–85.
- Ullsperger M. Performance monitoring in neurological and psychiatric patients. *Int J Psychophysiol* 2006; 59: 59–69.
- Ullsperger M, von Cramon DY. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage* 2001; 14: 1387–401.
- Ullsperger M, von Cramon DY. Decision making, performance and outcome monitoring in frontal cortical areas. *Nat Neurosci* 2004; 7: 1173–4.
- Ullsperger M, von Cramon DY. The role of intact fronto-striatal circuits in error processing. *J Cogn Neurosci* 2006; 18: 651–64.
- Ullsperger M, von Cramon DY, Muller NG. Interactions of focal cortical lesions with error processing: evidence from event-related brain potentials. *Neuropsychologia* 2002; 16: 548–61.
- van Veen V, Carter CS. The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiol Behav* 2002; 77: 477–82.
- Watkins KE, Hewes DK, Connelly A, Kendall BE, Kingsley DP, Evans JE, et al. Cognitive deficits associated with frontal-lobe infarction in children with sickle cell disease. *Dev Med Child Neurol* 1998; 40: 536–43.
- Wedeen VJ, Hagmann P, Tseng WY, Reese TG, Weisskoff RM. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn Reson Med* 2005; 54: 1377–86.
- Yeung N, Botvinick MM, Cohen JD. The neural basis of error detection: conflict monitoring and the error-related negativity. *Psychol Rev* 2004; 111: 931–59.