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The role of the human thalamus in processing corollary discharge

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Summary

Corollary discharge signals play an important role in monitoring self-generated movements to guarantee spatial constancy. Recent work in macaques suggests that the thalamus conveys corollary discharge information of upcoming saccades passing from the superior colliculus to the frontal eye field. The present study aimed to investigate the involvement of the thalamus in humans by assessing the effect of thalamic lesions on the processing of corollary discharge information. Thirteen patients with selective thalamic lesions and 13 healthy age-matched control subjects performed a saccadic double-step task in which retino-spatial dissonance was induced, i.e. the retinal vector of the second target and the movement vector of the second saccade were different. Thus, the subjects could not rely on retinal information alone, but had to use corollary discharge information to correctly perform the second saccade. The amplitudes of first and second saccades were significantly smaller in patients than in controls. Five thalamic lesion patients showed unilateral deficits in using corollary discharge information, as revealed by asymmetries compared with the other patients and controls. Three patients with lateral thalamic lesions including the ventrolateral nucleus (VL) were impaired contralaterally to the side of damage and one patient with a lesion in the mediodorsal thalamus (MD) was impaired ipsilaterally to the lesion. The largest asymmetry was found in a patient with a bilateral thalamic lesion. The results provide evidence for a thalamic involvement in the processing of corollary discharge information in humans, with a potential role of both the VL and MD nuclei.

Keywords: saccades; thalamus

Abbreviations: CC = control condition; CM-Pf = centromedian-parafascicular complex; FEF = frontal eye field; IAA = indices of absolute asymmetry; IML = internal medullary lamina; MD = mediodorsal nucleus; PPC = posterior parietal cortex; RDC = retino-spatial dissonance condition; RT = reaction time; SC = superior colliculus; VL = ventrolateral nucleus

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Introduction

Despite frequent eye and head movements that cause motion of the retinal image, we maintain perceptual stability. Visual and motor signals seem to interact to construct a constantly updated internal representation of space (Colby and Goldberg, 1999). Extraretinal information about an ongoing saccade is presumably provided by an efference copy or, more generally, corollary discharge of the motor command to move the eyes (von Holst and Mittelstaedt, 1950; Sperry, 1950; Thiele *et al*., 2002).

Retinal and extraretinal information is integrated in the posterior parietal cortex (PPC) to update visual space perception (Duhamel *et al*., 1992; Heide and Kompf, 1998; Tobler *et al*., 2001).

In the monkey brain, a pathway from the superior colliculus (SC) via the mediodorsal nucleus of the thalamus (MD) to the frontal eye field (FEF) conveys signals that are thought to represent corollary discharge information of upcoming eye movements (Sommer and Wurtz, 2004*a*). Consistent with this view, lesioning MD in monkeys was found to impair updating of visual space (Sommer and Wurtz, 2004*b*).

So far, few studies have addressed the question whether thalamic lesions in humans affect the use of corollary discharge information of eye movements and it is as yet unclear which regions of the thalamus play a critical role. Two patients with thalamic lesions affecting the internal medullary

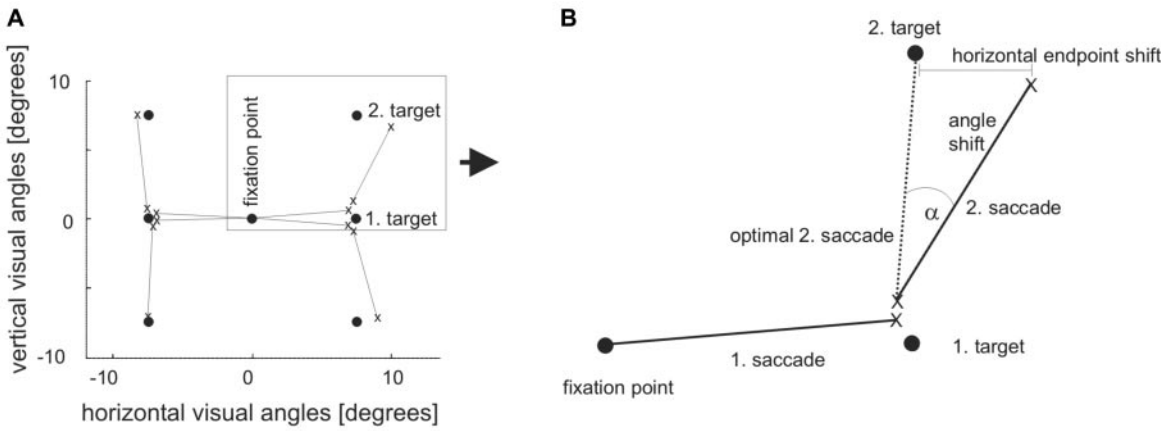

Fig. 1 (**A**) Pattern of first and second saccades to all possible target locations. Every trial starts with a fixation point in the middle of the display. The first target appears either right or left of the fixation point. The second target appears either above or below the first target. The three stimuli appear successively; the subject's task is to perform two successive saccades to the locations of first and second targets. The only difference between the RDC and the CC is in timing of the first target (see Methods). Due to small fixational drifts in the intersaccade-interval the endpoint of the first saccade is not identical to the starting point of the second saccade. (**B**) Hypothetical pattern of first and second saccades on a particular trial and illustration of the variables angle shift and horizontal endpoint shift of second saccades. The second saccade shifts away from the display centre.

lamina (IML) were impaired when taking into account eye position displacement between the presentation of a visual stimulus and the execution of a saccade (Gaymard *et al*., 1994). In a further study, hypometric auditory-guided saccades ipsilateral to the damage in three patients with medial thalamic lesions were interpreted in terms of deficient monitoring of eye position produced by inadequate corollary discharge signals (Versino *et al*., 2000). However, the data from these studies need to be corroborated in larger samples before firm conclusions can be reached.

The aim of the present study was to further investigate the role of the thalamus in updating visual space in humans by studying the effect of specific thalamic lesions on performance of saccade tasks. To explore which part of the human thalamus conveys corollary discharge information, patients with different thalamic lesions performed a double-step task. While anatomical studies as well as single-cell recordings in monkeys provide evidence that the SC projects to the FEF via MD (Harting *et al*., 1980; Sommer and Wurtz, 2004*a*), the pathway may be different in humans. In their review, Tehovnik *et al*. (2000) suggested that the pathway may lead through more lateral parts of the thalamus in humans, possibly through the ventrolateral nucleus (VL). The intralaminar nuclei of the central thalamus might also play a role. Similar to the neurons described by Sommer and Wurtz (2004*a*) in MD, the discharge properties and connections of single cells in the monkey IML make this region a candidate for supplying the cortex with information about ongoing eye movements (Benevento and Fallon, 1975; Schlag-Rey and Schlag, 1984, 1989; Wyder *et al*., 2003, 2004).

A double-step task was used in which subjects had to perform two successive saccades (Hallett and Lightstone, 1976) and which was conceptually similar to the task used in monkeys by Sommer and Wurtz (2004*b*). Since both saccade targets have already disappeared before the first saccade is executed, the task induces retino-spatial dissonance, i.e. the retinal vector of the second target differs from the movement vector necessary to reach the target. In the retino-spatial dissonance condition (RDC), therefore, corollary discharge information about the first saccade's metrics is required to perform a spatially precise second saccade because no other sources of information are available. A comparable task not involving retino-spatial dissonance serves as a control condition (CC; see Fig. 1A for an illustration of the location of stimuli; for details on stimulus timing see Methods).

Healthy human subjects as well as monkeys are able to perform accurately variants of saccadic double-step tasks (Hallett and Lightstone, 1976; Mays and Sparks, 1980). In the present study, deficits in monitoring the first saccade manifest themselves in horizontal shifts of second saccades' endpoints and directions away from the centre of the display (Fig. 1B). As most of the patients participating in this study had unilateral lesions, analyses focused on asymmetries in performance. The patients also underwent comprehensive neuropsychological screening to rule out unrelated impairments, which might influence performance in the saccade task, and to elucidate the potential association between saccade-related spatial constancy and visuo-spatial abilities, which has been described for patients with parietal cortex lesions (see Heide and Kompf, 1998).

Methods

Subjects

Thirteen patients with focal ischemic lesions of the thalamus and 13 healthy control subjects participated in this study. Eleven patients had unilateral and two patients had bilateral lesions. Patients and controls were matched according to age, sex and intelligence

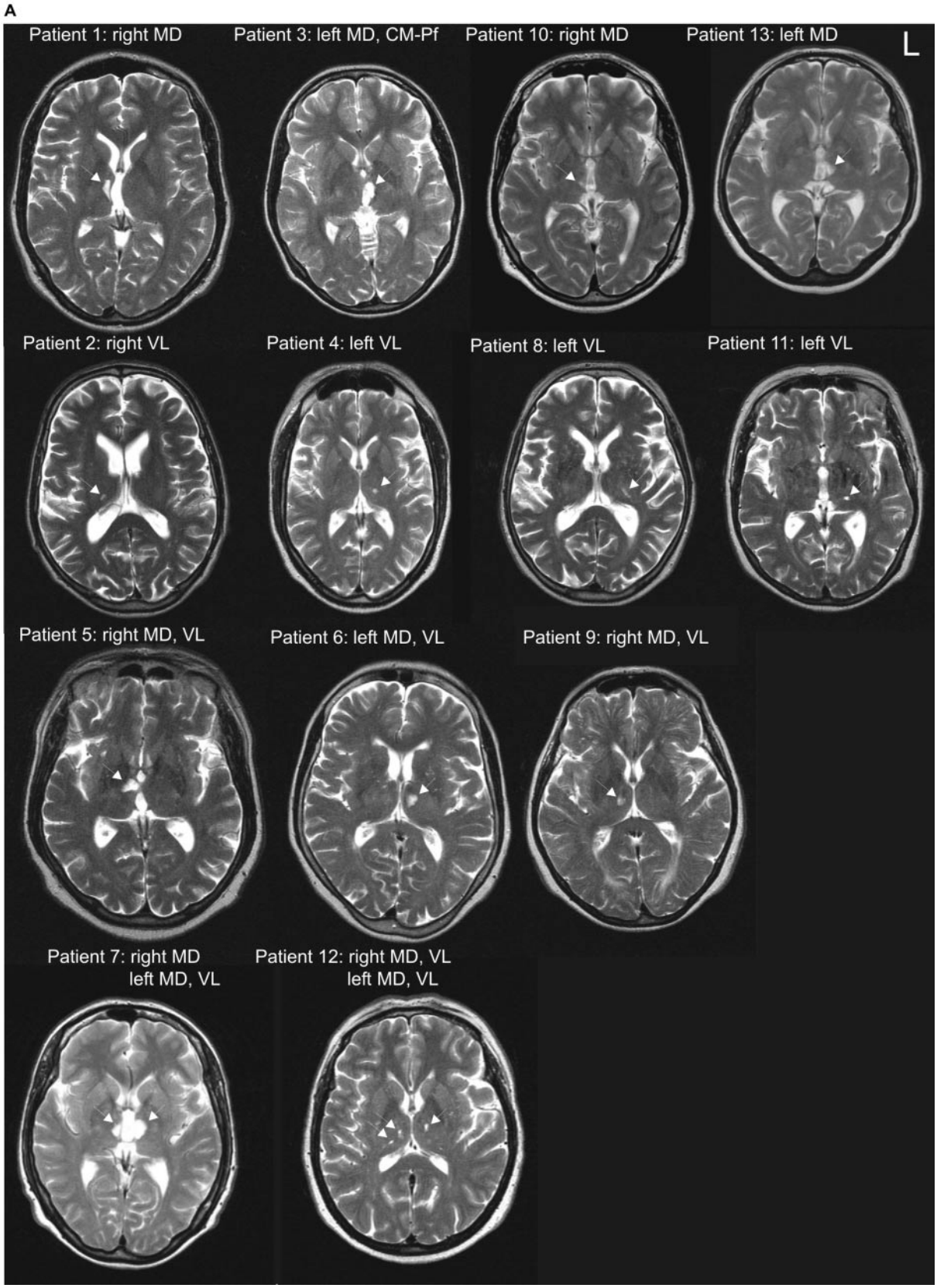

Fig. 2 (**A**) T2-weighted, transverse MR-images of lesion locations for all patients. White arrows indicate lesion locations. (**B**) T1-weighted, coronal MR-images of lesion locations for the 11 patients who entered quantitative saccade analysis. Lesions are indicated by black arrows (L – left side).

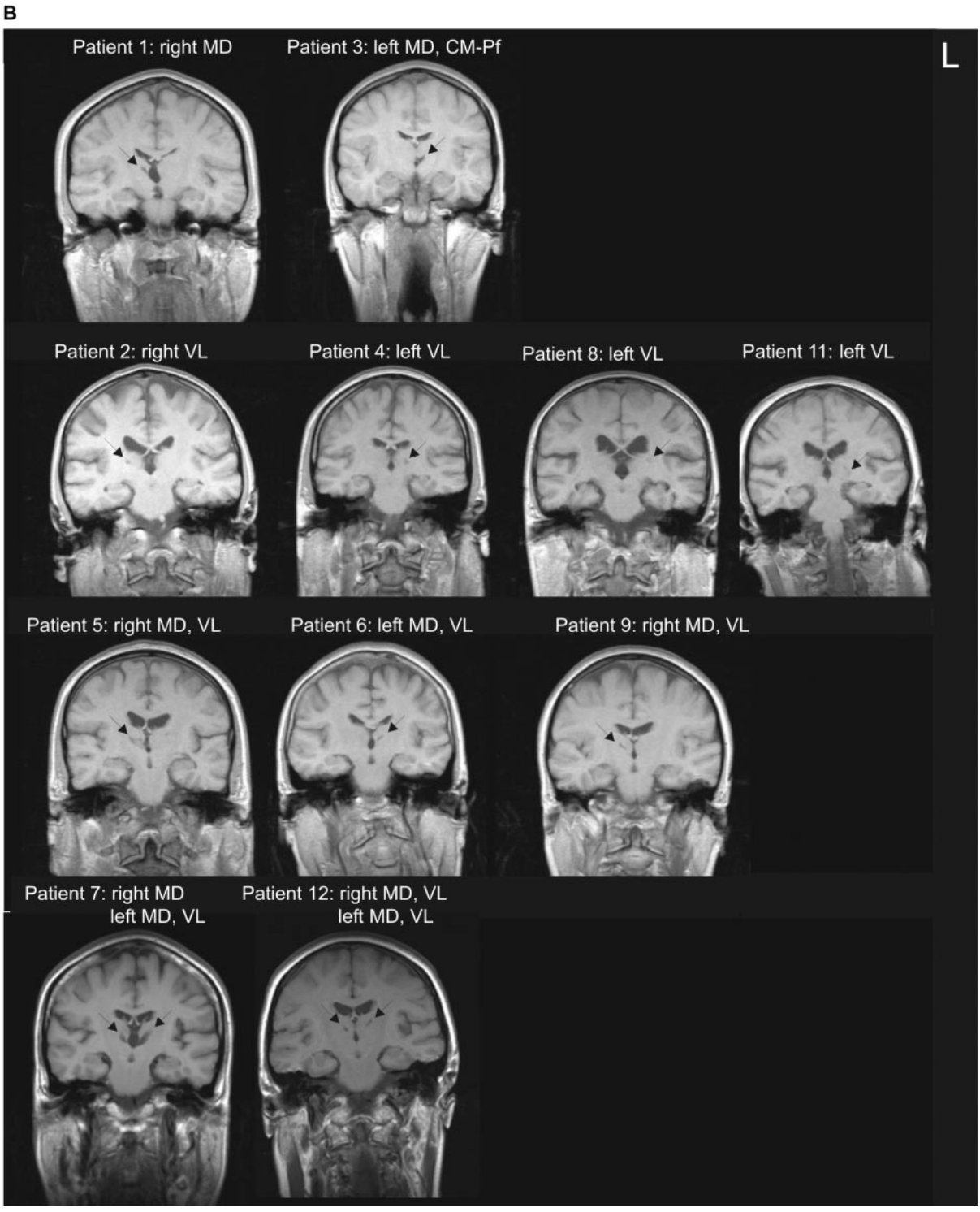

Fig. 2 *Continued*.

quotient (IQ). All participants had normal or corrected to normal vision. Two patients and two control subjects were left-handed; all other subjects were right-handed. All patients and control subjects gave written informed consent. The study was approved by the Ethics Committee of the Medical Faculty of the Ruhr-University of Bochum.

The patients were outpatients of the Klinikum Dortmund, Germany. Thalamic lesions were documented with MRI using a standard three-dimensional T2-weighted sequence for transverse sections and a standard three-dimensional T1-weighted sequence for coronal sections (1 mm × 5 mm × 5 mm voxel size; see Fig. 2A and B). Images were obtained at a neurological

Table 1 *Time since lesion, affected thalamic nuclei, additional lesions and neurological deficits at follow-up for every patient*

Patient	Time since lesion (months)	Affected nuclei	Additional lesions	Neurological deficits
1	75	Right MD	None	None
2	49	Right VL	None	Light somatosensory deficits in the face and in the left hand
3	87	Left MD, CM-Pf	None	None
4	57	Left VL	None	Light somatosensory deficits in the right hand
5	36	Right MD, VL	None	None
6	56	Left MD, VL	Small cerebellar infarct	None
7	40	Right MD, Left MD, VL	None	None
8	78	Left VL	None	None
9	68	Right MD, VL	None	None
10	24	Right MD	None	None
11	76	Left VL	None	Light somatosensory deficits in the right hand
12	13	Right MD, VL, Left MD, VL	None	None
13	4	Left MD	None	None

follow-up examination, which was performed on average ~1 year before testing. On the basis of the MRI, the affected nuclei were determined for each individual patient using an established atlas (Mai *et al*., 1997). Table 1 lists time since lesion, affected thalamic nuclei, additional lesions and neurological status for each patient. There were no psychiatric disorders in any of the patients.

Healthy control subjects were chosen to match the patient group from a large pool of healthy volunteers at the Department of Neuropsychology. Exclusion criteria were history of neurological or psychiatric disorder and alcohol or substance abuse.

The patient group consisted of seven females and six males, and the control group of six females and seven males. The mean age of patients was 54.2 years (SD=12.7) and of controls 51.9 years (SD=13.5).

Patient groups

Although there is much interindividual variability with respect to lesion location and size, unilaterally lesioned patients can be divided into three groups.

The lesions of Patients 1, 3, 10 and 13 affect MD, clearly sparing VL. The lesion in Patient 3 differs from the lesions of Patients 1, 10 and 13 in that it also affects the centromedian-parafascicular complex (CM-Pf), located inferior of MD. It should also be noted that, in Patients 10 and 13, additional lesions could be seen in the initial images, obtained at the time of the infarct: Patient 10 had a bilateral thalamic oedema. At follow-up, only a unilateral lesion could be seen on MRI. Similarly, in Patient 13, the initial MRI showed an oedema in the midbrain, near the nucleus ruber on the left side. At follow up, MRI showed only the thalamic lesion.

In Patients 2, 4, 8 and 11, MRI suggests exclusive VL involvement. Given the mild somatosensory deficits in Patients 2, 4 and 11 at follow-up, it might be possible that lesions in these patients extended slightly into the posterolateral and posteromedial ventral nuclei, which are associated with sensory deficits (Caplan *et al*., 1988; Combarros *et al*., 1991). According to Caplan *et al*. (1988), sensory deficits may also be the result of VL lesions.

In Patients 5, 6 and 9, lesions affect the IML. The lesions of Patients 5 and 9 are clearly not restricted to MD or VL. In Patient 9, the lesion is located near the IML, extending into lateral MD as well as medial VL. In Patient 5 mainly MD is affected, but the lesion extends laterally into the IML and into VL. The coronal MRI section of the lesion in Patient 6 suggests selective MD-involvement. However, the transverse MRI shows that the lesion also extends laterally, into the IML.

Finally, Patient 7 and Patient 12 show bilateral lesions. In Patient 7, the right-sided lesion is restricted to MD, whereas the left sided lesion affects MD and medial VL. In Patient 12, the lesion on the left side affects parts of MD and VL, and thus the IML in between. On the right side, there are two small lesions (in the coronal section only the more medial lesion can be seen); one affecting MD, the other VL.

Eye movement recording

Eye movements were recorded from both eyes with an EyeLink video system (SMI, Sensorimotor Instruments, Germany). The signal was sampled with 250 Hz. Subjects were seated 57 cm in front of a computer monitor with an LCD display, on which the visual stimuli were presented. A chin rest was used to stabilize head position. Small head movements were corrected for by the EyeLink system. To reduce external reference information, a circular frame was put in front of the screen.

Saccadic double-step task

In the saccadic double-step task, a central fixation point on a screen disappeared after an unpredictable delay (range: 1000–1650 ms) and two targets were presented successively. Red dots of 0.5° visual angle served as stimuli.

Subjects were required to perform two successive saccades to the screen locations of the targets. In the control condition, presentation times for the two targets were 1000 ms (first target) and 50 ms (second target). To ensure that, on one hand, enough trials in the

experimental condition fulfilled the criterion of retino-spatial dissonance and that, on the other hand, the task was not too difficult, two different presentation times for the first target were used in this condition. On half of the trials, the first target was presented for 100 ms and, on the other half, it was presented for 150 ms. As in the control condition, the second target was always presented for 50 ms. The first target appeared either in the right or left hemifield (relative to the central fixation point) with an eccenticity of 7.5°. The second target appeared either above or below the first target with a distance of 7.5° between the targets (Fig. 1A).

Subjects performed six blocks of 40 trials each. Each block consisted of 20 CC trials and 20 RDC trials. Conditions and target locations were presented in random order. In Patient 10, longer presentation times needed to be used for presentation of the first target in the RDC trials due to a general slowing of responses (150 ms and 200 ms, respectively).

Saccade analysis

Saccades were detected online by the EyeLink-system when velocity exceeded 30°/s and acceleration exceeded 800°/s^2. All data were recorded in screen coordinates. As a first step in the analysis, maximally two saccades per trial were determined off-line whose amplitudes were >2.5° visual angle and which appeared in response to the visual stimuli, i.e. after the onset of the first and second target stimuli, respectively.

The saccades were then examined in more detail. Trials were excluded from further analysis if: (i) the first saccade was anticipatory (earlier than 80 ms after onset of the first target); (ii) no or only one saccade occurred on the trial; (iii) the first saccade was directed directly towards the second target; or (iv) the first or the second saccade did not reach predefined circular areas around the target location. These areas were very wide (5° for target 1 and 10° for target 2) and served to exclude trials in which subjects did not manage to follow the instruction due to slips of attention. The proportion of trials excluded on the basis of these criteria was determined for each subject. In addition, only trials with evidence of retino-spatial dissonance entered the analysis of the experimental condition, i.e. the first saccade had to start after the second target had already disappeared. Due to a very high number of trials meeting the exclusion criteria, two patients were excluded from subsequent quantitative saccade analysis.

For quantitative analysis, the following variables were defined for both saccades—latency and amplitude as well as horizontal and vertical shifts of saccade endpoints with respect to target location. For the shift measures, positive scores indicate shifts away from the centre of the display, whereas negative scores indicate shifts towards the centre.

The angle of the shift of second saccades was also determined. The optimal direction of the second saccade aiming at the second target depends on the starting point of the saccade. For each trial, the deviation of the second saccade from the optimal direction was computed (Fig. 1B). Again, positive scores indicate direction shifts away from the centre of the display, whereas negative scores indicate shifts towards the centre. Although information from both variables (horizontal endpoint shift versus angle shift) appears to be closely related, the data do not completely overlap (see Fig. 1B for illustration). If, for example, the second saccade is very short and not accurately directed towards the second target, a large shift of the angle away from the centre results—but not necessarily a large deviation of the saccade endpoint.

As most of the patients of the present study had unilateral lesions and were thus expected to show unilateral deficits, indices of absolute asymmetry (IAA) were computed for the variables of quantitative saccade analysis. Therefore, data for rightward trials (i.e. trials with a rightward first saccade) were pooled irrespective of the location of the second target (above or below the first target). The same analysis was performed for leftward trials. For each variable, median scores were determined separately for the RDC and CC on rightward and leftward trials. The IAA was then computed according to the following formula (RDC = median value in the retino-spatial dissonance condition, CC = median value in the control condition, L = leftward trials and R = rightward trials):

$$\mathrm{IAA} = \left| (\mathrm{RDC_L} - \mathrm{CC_L}) - (\mathrm{RDC_R} - \mathrm{CC_R}) \right|$$

Large values on IAA scores indicate large asymmetries in performance.

The results reported below are based on data from the right eye; the pattern of findings was identical for data from the left eye.

Neuropsychological screening

Patients and control subjects completed a neuropsychological assessment to detect potential confounding as well as associated impairments. An estimate of general intellectual abilities was derived from the Similarities and Picture Completion subtests of a short German version of the Wechsler Adult Intelligence Scale (Dahl, 1972).

Attention was screened by means of the 'Alertness' subtest of the TAP, a computerized test battery (Zimmermann and Fimm, 1993). In this simple reaction time (RT) task, subjects are asked to press a key in response to a visual stimulus. In 50% of the trials, a tone precedes the visual stimulus. RTs on these trials represent phasic alertness, i.e. the ability to increase attention in response to a warning stimulus.

To screen visual field deficits, the Visual Field subtest of the TAP was administered. Subjects were asked to press a button when they noticed a particular visual target stimulus that appeared on different peripheral locations while they fixated a central point.

Verbal and visual short-term and working memory were assessed using the Digit span and Block span subtests of the Wechsler Memory Scale (Wechsler, 1987). In these tasks, subjects are asked to reproduce correctly digit sequences (Digit span) or sequences of spatial positions (blocks on a wooden board; Block span) of increasing length in forward or backward order. Forward reproduction is considered as a measure of short-term memory and backward reproduction as a measure of working memory. Visuo-constructive ability and visual long-term memory were assessed by copy and free recall of a complex geometrical figure (Osterrieth, 1944).

Procedure

Subjects were told the study aimed to assess the accuracy of eye movements and that they would see a central fixation point on the screen, followed by a first and then a second red dot. They were asked to make two successive eye movements to match the target positions as precisely as possible. The eye movement task would be followed by a number of memory and concentration tests. It was emphasized that subjects could stop participating at any time.

Statistical analysis

Group comparisons on single variables such as the IAA scores were evaluated, as appropriate, by *t*-tests or Mann-Whitney *U*-tests. General group differences (patients versus controls) with respect

to performance on the RDC and CC trials were evaluated by repeated measures ANOVA (analysis of variance) with the factors GROUP and CONDITION.

Results

Analysis of general saccade performance in patients and control subjects

To test for general performance differences between groups and/or experimental conditions irrespective of the direction of the first saccade (ipsilateral or contralateral with respect to lesion side), analyses with the factors GROUP and CONDITION were performed on the proportions of trials not fulfilling the inclusion criteria as well as on medians of saccade latencies, amplitudes, horizontal and vertical endpoint shifts of both saccades and angle shifts of second saccades. All patients and controls were included in the analyses of proportions of trials meeting exclusion criteria, whereas Patients 10 and 13 were excluded from quantitative analyses, because too many trials met the exclusion criteria.

Trials meeting exclusion criteria

For the RDC, only those trials entered quantitative analysis in which the first saccade started after the second target had already disappeared—because only then retino-spatial dissonance is given. With 76.6% (SD = 17.1) of trials in control subjects and 73.0% (SD = 16.3) of trials of in patients meeting this criterion, there was no significant group difference ($P = 0.479$).

All the other exclusion criteria for quantitative saccade analysis refer to RDC and CC trials. The proportions of trials meeting these criteria are listed in Table 2.

On the number of omissions of second saccades [$F(1,24) = 7.182$, $P = 0.013$] and the number of trials with inadequate second saccades [$F(1,24) = 4.432$, $P = 0.046$], there were significant main effects of the factor GROUP (patients versus controls), with patients scoring higher than controls.

Some effects of the factor CONDITION also emerged (RDC versus CC trials). On RDC trials, first saccades were directed to the second target more often than on CC trials [$F(1,24) = 13.750$, $P = 0.001$]. There were also significantly more inadequate first saccades [$F(1,24) = 8.218$, $P = 0.008$] and a tendency towards more inadequate second saccades on RDC relative to CC trials ($P = 0.059$). On CC trials, anticipatory saccades could be observed, whereas there were no such saccades on RDC trials. This difference was significant [$F(1,24) = 6.618$, $P = 0.017$].

None of the interactions between GROUP and CONDITION approached significance (all $P > 0.274$), indicating that retino-spatial dissonance had no differential effect on the number of trials meeting exclusion criteria in patients and controls.

Latencies, amplitudes and saccade accuracy

Patients performed the first saccade on average after 219 ms (SD = 41 ms) on CC and after 232 ms (SD = 51 ms) on RDC trials. The corresponding latencies in the control subjects were 216 ms (SD = 30 ms) and 223 ms (SD = 31 ms), respectively. Latencies were significantly shorter on CC relative to RDC trials [$F(1,22) = 17.515$, $P < 0.001$]. There was no significant effect of GROUP and no interaction between GROUP and CONDITION (all $P > 0.208$).

Figure 3 illustrates the results for amplitudes, horizontal and vertical endpoint shifts of first and second saccades, and angle shifts of second saccades for patients and control subjects on RDC and CC trials. For first saccades, analysis of amplitudes and horizontal endpoint shifts revealed main effects of GROUP and CONDITION; first saccades were shorter in patients compared with controls [$F(1,22) = 8.281$, $P = 0.009$]. Saccades of controls were well matched to the target location, whereas patients showed significantly larger shifts of first saccade endpoints towards the centre in both conditions [$F(1,22) = 8.454$, $P = 0.008$].

Saccades were also shorter on RDC compared with CC trials [$F(1,22) = 4.357$, $P = 0.049$], with horizontal shifts of first saccade endpoints towards the centre being significantly larger on RDC compared with CC trials [$F(1,22) = 5.970$, $P = 0.023$]. Analysis of amplitudes and horizontal endpoint shifts did not yield significant interactions (all $P > 0.644$), showing that the factor CONDITION had no differential effect on first saccades in patients and controls. There were no significant

Table 2 *Means (SDs) of percentages of trials excluded due to different exclusion criteria for patients and controls in the RDC and CC*

Exclusion criteria	Controls		Patients		
	RDC	CC	RDC	CC	Effects
Saccade 1 anticipatory	0.0 (0.0)	0.7 (1.5)	0.0 (0.0)	1.3 (2.4)	‡
Saccade 1 omitted	0.0 (0.0)	0.4 (0.9)	0.0 (0.0)	1.1 (3.2)	
Saccade 2 omitted	1.7 (3.5)	0.5 (0.8)	6.8 (8.4)	8.8 (13.3)	*
Inadequate 1 saccade	3.8 (4.0)	1.0 (1.3)	6.7 (8.1)	2.0 (2.4)	‡
Inadequate 2 saccade	1.9 (1.5)	1.0 (1.9)	5.0 (5.5)	3.1 (4.1)	* (‡)
1. Saccade directed to 2. target	4.0 (3.1)	0.1 (0.3)	7.9 (10.3)	0.6 (0.7)	‡

See Methods section for an exact description of exclusion criteria. inadequate 1.saccade: distance to 1.target >5°; inadequate 2.saccade: distance to 2.target >10°; *Main effect GROUP: $P < 0.05$; ‡Main effect CONDITION: $P < 0.05$; (‡)Tendency main effect CONDITION: $P < 0.10$.

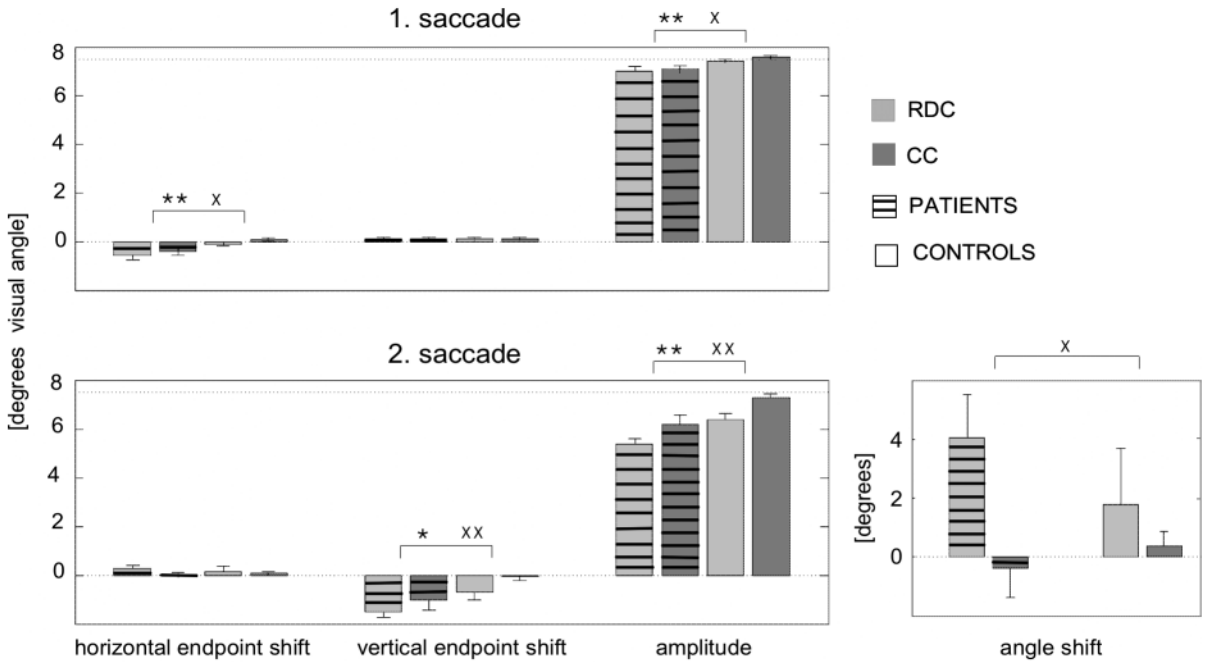

Fig. 3 Means and standard errors (SE) of amplitudes, horizontal and vertical endpoint shifts of first and second saccades and of second saccades' angle shifts for patients and controls (∗∗—main effect GROUP, $P < 0.01$; ∗—main effect GROUP, $P < 0.05$; XX—main effect CONDITION, $P < 0.01$; X—main effect CONDITION, $P < .05$).

GROUP or CONDITION effects for vertical endpoint shifts (all $P > 0.447$).

Because of the differences in stimulus timing on RDC and CC trials (see Methods), the latencies between appearance of the second target and execution of the second saccade were much longer on RDC than on CC trials. Therefore, no between conditions comparison was conducted for this measure.

Patients performed the second saccade on average 498 ms (SD = 151 ms) after presentation of the second target on RDC trials. On CC trials, the mean latency was 270 ms (SD = 58 ms). The latencies for control subjects were 528 ms (SD = 165 ms) on RDC and 241 ms (SD = 43 ms) on CC trials. The two groups did not differ on the latency measures (both $P > 0.303$).

Amplitude analysis of second saccades yielded a similar pattern as in first saccades. Amplitudes were generally smaller in patients than in controls [$F(1,22) = 9.528$, $P = 0.005$], which was reflected in greater vertical endpoint shifts towards the centre [$F(1,22) = 5.956$, $P = 0.023$]. Saccades were generally shorter on RDC compared with CC trials [$F(1,22) = 27.447$, $P < 0.001$], with larger vertical shifts of saccade endpoints towards the centre [$F(1,22) = 9.649$, $P = 0.005$]. Again, there were no significant interactions between GROUP and CONDITION (both $P > 0.654$). Analysis of horizontal endpoint shifts did not yield any significant effects (all $P > 0.211$).

Second saccades' angle shifts differed significantly between conditions, with larger shifts away from the centre of the display on RDC relative to CC trials [$F(1,22) = 5.780$, $P = 0.025$]. The overall GROUP difference and the interaction did not reach significance on this measure (both $P > 0.228$).

Asymmetry analysis

For two reasons, IAA between leftward and rightward trials were determined for latencies, amplitudes, horizontal and vertical endpoint shifts of first and second saccades, as well as angle shifts of second saccades.

First, pilot screening of healthy subjects revealed high interindividual variability with respect to saccade accuracy on RDC and CC trials. Virtually all subjects did, however, show a clear symmetrical pattern, with differences between RDC and CC trials being very similar for rightward and leftward trials. Therefore, we expected unilateral lesion patients to show a more asymmetrical pattern than controls. Unilateral deficits in using corollary discharge information should become obvious in horizontal endpoint shifts and/or angle shifts of second saccades in the RDC on one side, leading to large IAAs on these measures.

Secondly, introducing the IAA allows for comparing the performance of control subjects to patients as a group, irrespective of the side of lesion. In subsequent case analysis, the performance of single patients is related to the lesion location and the side of the lesion.

Figure 4 illustrates the mean IAA scores for patients and controls in the variables mentioned. As for the quantitative analysis of general saccade performance, two patients were excluded from asymmetry analysis, because too many trials met the exclusion criteria.

The only significant differences between groups were found in two measures of the second saccade: Patients showed significantly larger asymmetries than controls in horizontal endpoint shifts [$U = 29.00$, $P = 0.013$] and angle shifts

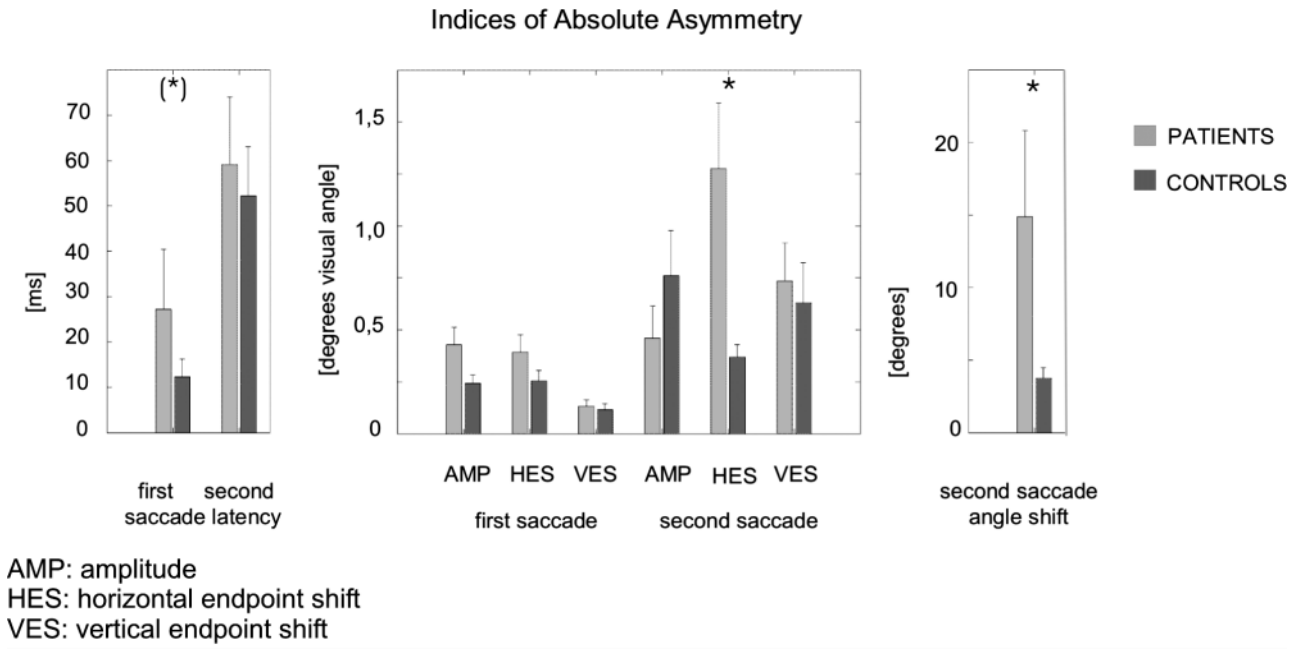

Fig. 4 Means and SEs of indices of absolute asymmetry (IAA) of latencies, amplitudes, horizontal and vertical endpoint shifts of first and second saccades and of second saccades' angle shifts (∗—main effect GROUP, $P < 0.05$; (∗)—tendency main effect GROUP, $P < 0.10$).

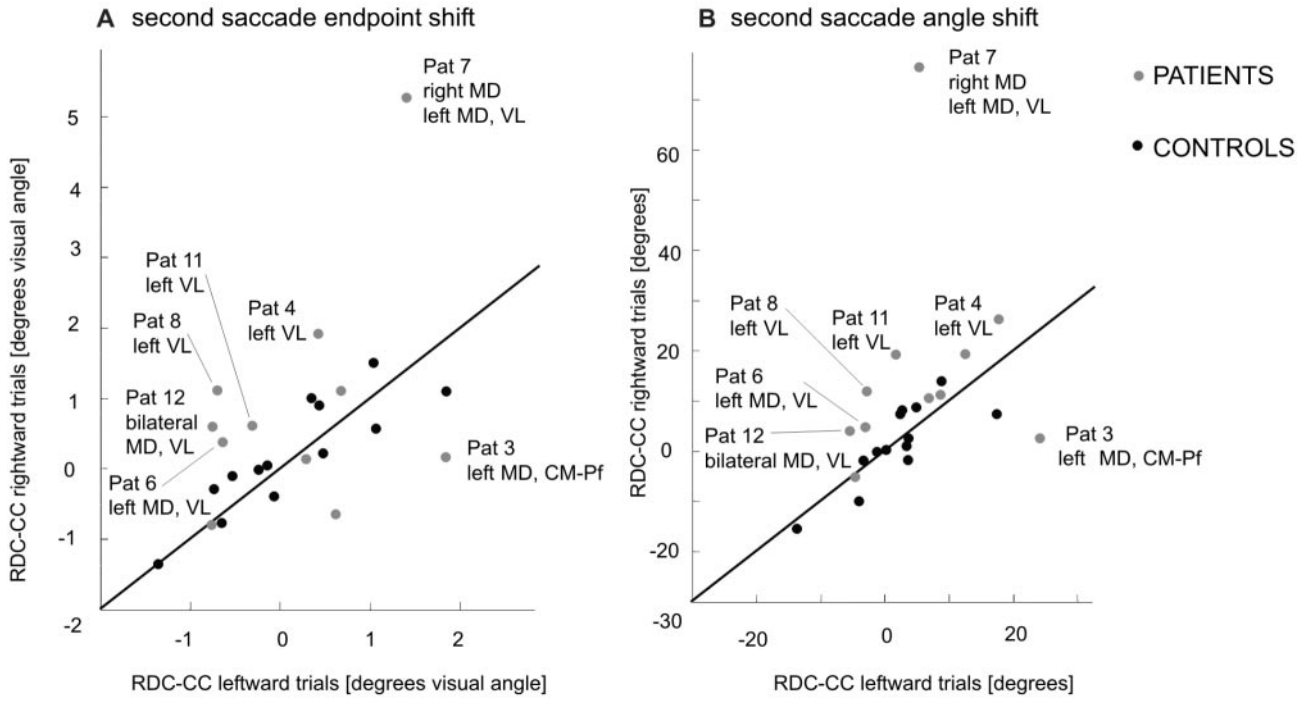

Fig. 5 Asymmetries in performance for individual subjects. The figures show differences in performance between the RDC and the CC, separately for rightward and leftward trials for (**A**) second saccade endpoint shifts and (**B**) second saccade angle shifts. The diagonal line represents perfect symmetry of performance. Black circles show the performance of individual control subjects, grey circles represent the performance of single patients. See Methods for further explanation of asymmetry measures.

[$U = 30.00$, $P = 0.015$]. GROUP differences in asymmetry of first saccade amplitude approached significance ($P = 0.072$), with patients showing larger asymmetries than controls. In none of the other variables' asymmetry scores were there significant group differences (all $P > 0.252$).

Selective case analysis

In the next stage of the analysis, the patients showing the largest asymmetries were identified. Figure 5 shows individual asymmetries for every subject in the two variables,

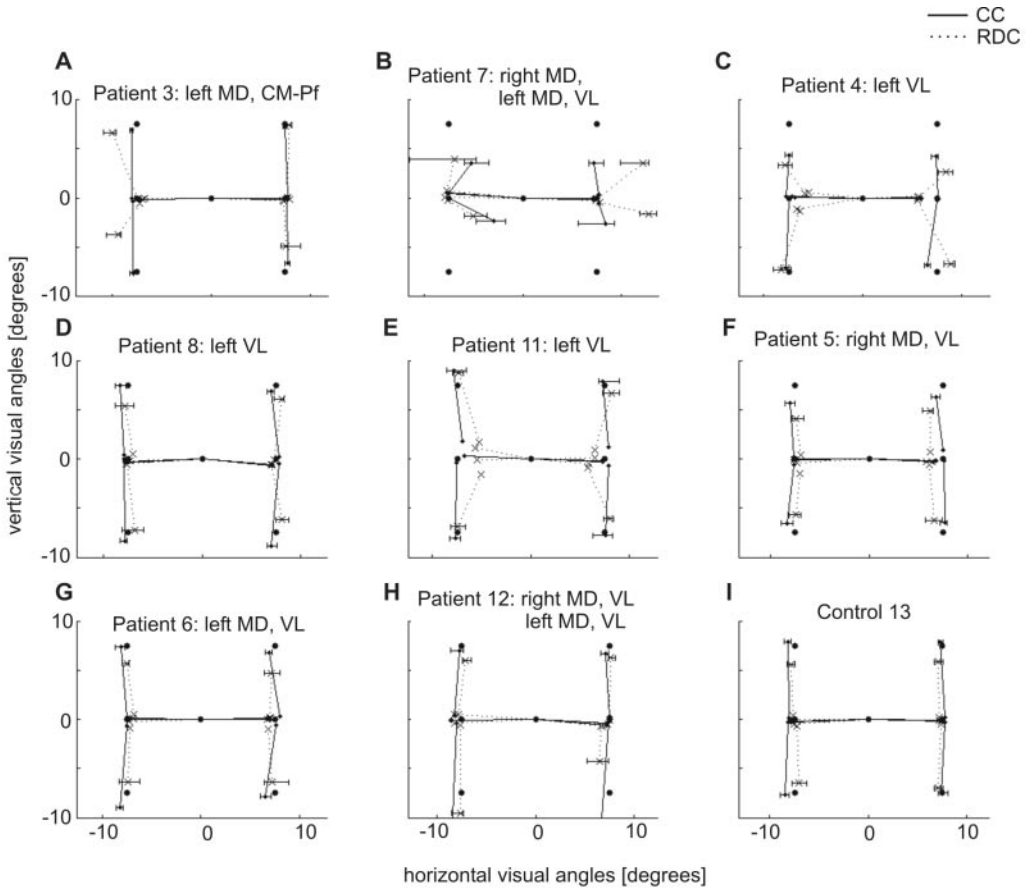

Fig. 6 Medians of saccade directions and amplitudes for all possible target locations in the RDC and CC. Error bars indicate 25% iles of horizontal endpoint shifts of second saccades. Due to small fixational drifts in the intersaccade-interval first saccades' endpoints and second saccades' starting points are not identical. Note that for asymmetry analysis of second saccades' angle shifts RDC- and CC-trials were not compared directly. In both conditions angles were compared to the optimal angle necessary to reach the second target.

for which patients and controls differed significantly—horizontal endpoint shifts (Fig. 5A) and angle shifts of second saccades (Fig. 5B).

For single case analysis, z-scores for individual patients relative to the control group were computed for the asymmetry indices of both variables.

Two patients with MD lesions showed evidence of a deficit in updating visual space. Patient 3 with a unilateral left-sided lesion scored high on both asymmetry measures with z-scores of 6.2 (endpoint shift) and 6.4 (angle sift). As can be seen in the saccade pattern of this Patient (Fig. 6A), she showed very accurate second saccades in both conditions on rightward, i.e. contralateral trials (trials with a first saccade directed contralateral with respect to the lesion side); on ipsilateral trials; the second saccades showed deviations away from the centre only on RDC trials.

In both variables, the largest asymmetry of all patients was shown by the bilaterally lesioned Patient 7 (z = 24.3 for asymmetries on angle shifts and z = 16.7 for asymmetries on endpoint shifts). On leftward trials, the second saccades were directed towards the centre on both RDC and CC trials. On rightward trials, the patient frequently showed a second horizontal saccade directed away from the centre, but only on RDC trials. On CC trials, the second saccades, although very short, were directed more clearly towards the second target (see Fig. 6B for the saccade pattern of Patient 7).

Three of the four patients of the present study with unilateral lesions affecting VL, Patients 4, 8 and 11 showed large asymmetries in the endpoint shift measure and/or the angle shift measure. In the endpoint shift measure, Patients 4 and 8 showed the largest asymmetries (z-scores of 5.3 and 6.9, respectively), whereas in the angle shift measure Patients 8 and 11 scored highest (z = 3.9 and z = 5.0, respectively). They all had left-sided lesions and asymmetries were caused by a shift of second saccades away from the display centre in the RDC in rightward and thus contralateral trials (see Fig. 6C–E).

Second saccades to targets at the top of the display were generally quite inaccurate in Patient 4. However, it is obvious that second saccades' endpoints showed a greater shift away from the display centre in the RDC on contralateral trials compared with ipsilateral trials.

Patients 8 and 11 were able to direct second saccades quite accurately towards second targets on ipsilateral trials. Patient 11 was even able to compensate for too short first saccades by adjusting the second saccade. On contralateral trials,

however, second saccades were too oblique in both patients, leading to shifts away from the display centre.

None of the unilaterally lesioned patients whose lesions extended into the IML showed evidence of a unilateral deficit. In Patient 5, for example, second saccades in both conditions were directed towards the targets very accurately (Fig. 6F).

Asymmetries in performance do not necessarily indicate a unilateral deficit in monitoring the first saccade. Patients 6 and 12, for example, showed a quite large asymmetry in the endpoint shift measure (Fig. 5A). However, the asymmetries were not caused by a shift of second saccades away from the display centre in the RDC on one side compared with the other. Instead, they were caused by unilateral shifts towards the display centre in the CC (Patient 6) and the RDC (Patient 12). The saccade patterns of these patients are shown in Fig. 6G and H; Fig. 6I shows an example of one control subject.

In summary, one patient with a unilateral MD lesion seemed to be impaired in monitoring saccades directed ipsilateral to her lesion, whereas three patients with a unilateral VL lesion seemed to have deficits contralateral to their lesion. The largest asymmetries were shown by a bilaterally lesioned MD patient.

Neuropsychological screening

Means and SDs for the cognitive data are presented in Table 3. The mean IQ estimate was 105.1 (SD = 10.2) for patients and 112.8 (SD = 7.3) for controls; this difference was not significant.

Patients and controls did not differ significantly on the short term memory measures (digit span and block span forward, $P > 0.10$), but patients produced shorter spans for backward reproduction (digit span: $P = 0.029$; block span: $P = 0.022$). There were no GROUP differences in copying a geometrical figure ($P = 0.240$), but the patients recalled fewer details about the figure after a delay than the controls ($P = 0.003$).

The following analyses are based on those subjects included in the quantitative saccade analysis (11 patients and 13 control subjects), because the measures served to assess deficits possibly affecting saccade performance.

Analysis of RTs in the two alertness conditions did not yield a significant overall GROUP difference or a differential effect of the warning stimulus (all $P > 0.170$). In the Visual Field task, patients tended to respond more slowly than controls ($P = 0.055$), but did not show more omissions ($P = 0.649$). The RT differences to visual stimuli appearing ipsilateral and contralateral to the side of lesion in

Table 3 *Means (SDs) of results in neuropsychological tests for patients and controls*

Tests	Controls	Patients	Effects
Geometrical figure copy	35.0 (1.1)	31.5 (8.4)	
Geometrical figure recall	21.9 (6.6)	12.5 (7.4)	**
Digit span forward	7.8 (1.6)	7.1 (1.9)	
Digit span backward	7.5 (1.6)	6.1 (1.8)	*
Block span forward	8.6 (1.6)	7.5 (1.3)	
Block span backward	8.6 (1.9)	7.1 (1.8)	*
Alertness without acoustic warning (ms)	258.0 (27.5)†	280.8 (48.5)†	
Alertness with acoustic warning (ms)	254.5 (42.2)†	274.8 (40.0)†	
Visual field (ms)	502.3 (77.7)†	580.2 (121.9)†	(*)

†Means and SDs are based on the 11 patients included into quantitative saccade analysis. *Main effect GROUP: $P < 0.05$; **Main effect GROUP: $P < 0.01$; (*)Tendency main effect GROUP: $P < 0.10$

Table 4 *Individual patients' z-scores for five neuropsychological measures*

Patient	Affected nuclei	Geometrical figure recall	Digit span forward	Digit span backward	Block span forward	Block span backward
1	Right MD	−0.22	1.40	0.91	0.24	1.83
2	Right VL	−0.75	0.15	−0.95	−1.63	−1.41
3	Left MD, CM-Pf	1.08	0.15	0.91	0.86	−0.87
4	Left VL	−2.04	0.15	−0.95	0.24	−0.87
5	Right MD, VL	−1.21	−0.48	−0.95	0.24	−1.41
6	Left MD, VL	−2.19	0.77	−0.95	−1.00	−0.33
7	Right MD, left MD, VL	−1.97	0.15	−1.57	−1.63	−0.33
8	Left VL	−0.37	−1.74	−1.57	−1.63	−1.41
9	Right MD, VL	−2.73	−2.37	−2.19	−1.00	−0.33
10	Right MD	−1.74	−2.37	0.91	−1.00	−0.87
11	Left VL	−1.59	0.15	−1.57	−1.00	−1.95
12	Right MD, VL, left MD, VL	−1.89	−1.11	−1.57	−1.00	−1.41
13	Left MD	−3.03	−0.48	−2.19	−0.38	−1.41

unilateral lesion patients did not approach significance ($P = 0.340$).

Neuropsychological performance of individual patients

Impairments in visuo-spatial function and/or (visual) short-term and working memory may be related to performance in the saccadic double-step task. Table 4 lists individual patient's *z*-scores relative to control subjects for these measures. There are no obvious deficit patterns related to specific lesion sites. Patient 13, who was not included in the quantitative saccade analysis due to frequent omissions of second saccades, was most severely impaired in reproduction of a geometrical figure. Her scores on working memory measures were also low. Of the remaining patients, those with bilateral lesions (Patients 7, 12) showed a general tendency towards lower scores compared with the unilateral patients.

Discussion

The present study aimed to further elucidate the role of the thalamus in processing corollary discharge information in humans by investigating the effect of focal thalamic lesions on the accuracy of saccades in a double-step task.

The results suggest that patients with lateral thalamic lesions are impaired in using corollary discharge information. Three of the four patients with lesions of lateral VL showed large asymmetries in angle shifts and/or horizontal endpoint shifts of second saccades. In all of these patients, the effects were due to larger shifts away from the centre on RDC trials contralateral to the side of the lesion. In contrast, there was no evidence of a unilateral deficit in the three patients with IML involvement. Their lesions were caused by paramedian or tuberothalamic artery infarction, which may affect both lateral MD and medial VL (Schmahmann, 2003). One patient with a unilateral MD lesion showed a very marked, unilateral impairment in monitoring the first saccade but, unlike the other patients with unilateral deficits, her impairment is ipsilateral to the side of the lesion. The largest asymmetry was shown by a patient with a bilateral lesion.

Human lateral thalamus and corollary discharge information

Anatomical analyses in monkeys have shown that the deep layers of the SC project to MD as well as to central thalamic nuclei (Benevento and Fallon, 1975; Harting *et al*., 1980). The neurons in MD that receive afferents from SC project to the FEF (Harting *et al*., 1980; Sommer and Wurtz, 2004*a*) and relay information about impending eye movements from SC to FEF (Sommer and Wurtz, 2004*a*). Although anatomical evidence is sparse, it has been suggested that this pathway may pass through more lateral parts of the thalamus in humans, probably through VL (Tehovnik *et al*., 2000). This assumption is consistent with the results of the present study: The deficits of the three patients with focal lesions of lateral VL resemble the deficits observed in monkeys with MD lesions (Sommer and Wurtz, 2004*b*). In both studies, thalamic lesions caused only a relatively small shift of second saccades away from the display centre, indicating a considerable amount of information about first saccades' metrics which is relayed despite of the thalamic lesion. In monkeys, the average shift of second saccades' endpoints—in the cases with a significant shift—was 19% of the first saccade amplitude (Sommer and Wurtz, 2004*b*). The asymmetry of second saccades' endpoints in the three contralaterally impaired patients of the present study amounted to 20.6% of the amplitude of the first saccade.

Possible reasons for the partial deficit in patients

There are several possible reasons for the fact that disruption of the transthalamic SC–FEF pathway only leads to a partial deficit. According to Sommer and Wurtz (2004*b*), the lesion induced in the monkeys of their study might not have inactivated all thalamic relay neurons. This might also be true for the patients of the present study.

As only four different target arrangements were used in the present study, one explanation may also be that subjects performed pre-planned saccade sequences, possibly not requiring corollary discharge information. In fact, there are differences in the cortical networks involved in familiar compared with new saccade sequences (Grosbras *et al*., 2001). However, the subjects were not trained prior to the experiment, so at the beginning the saccade sequences were new to them. If saccade sequencing was responsible for the partial deficit, one would expect to find a larger deficit at the beginning of the experiment and more accurate performance in later trials. Inspection of raw data indicated that there was no evidence of such a pattern in the patients of the present study. Furthermore, the size of the deficit in the present study is comparable to that reported by Sommer and Wurtz (2004*b*), who used multiple target arrangements in monkeys.

Alternative pathways possibly relaying corollary discharge information

The most reasonable explanation for the small deficit is that pathways other than the SC–MD–FEF pathway contribute to the updating of visual space by conveying corollary discharge information. There are, for example, other transthalamic fibres connecting oculomotor subregions of the cerebellar dentate nucleus or the substantia nigra to the FEF (Lynch *et al*., 1994), which might also relay information about ongoing eye movements. Additionally, corollary discharge information might originate in the FEF itself. As the FEF sends motor commands for saccadic eye movements to the SC (Segraves and Goldberg, 1987), it is possible that corollaries of these commands are sent to other cortical areas.

Although lesion studies in humans have failed to find a crucial role of the FEF in updating visual space (Rivaud *et al*., 1994; Heide *et al*., 1995; Gaymard *et al*., 1999), updating on a single cell level seems to occur: Some cells in the monkey FEF show predictive remapping, i.e. they anticipate the retinal consequences of upcoming saccades by reacting to visual stimuli in their future receptive field (Umeno and Goldberg, 1997). In addition, in humans transcranial magnetic stimulation (TMS) applied over the FEF impairs performance of a saccadic double-step task (Tobler and Muri, 2002).

It is widely accepted that the PPC is recruited in the integration of visual and oculomotor information (Heide and Kompf, 1998; Colby and Goldberg, 1999; Heide *et al*., 2001; Medendorp *et al*., 2003; Sapir *et al*., 2004). Thus, in addition to pathways from subcortical structures to the FEF, direct pathways from the thalamus to the PPC might also relay eye movement related information. For example, the lateral intraparietal area (LIP) is the target of disynaptic output of the SC, probably relayed in the lateral pulvinar nucleus of the thalamus. A small percentage of these afferents originates in the intermediate layers of the SC (Clower *et al*., 2001) and may thus relate to oculomotor function.

The central thalamus might also play a role in the updating process. In the monkey, the SC deep layers project to many intralaminar nuclei (Benevento and Fallon, 1975), which in turn project to the FEF as well as the PPC, at least in the cat (Kaufman and Rosenquist, 1985). When monkeys perform delayed saccades to visual targets, the vast majority of central thalamic neurons is active in conjunction with saccade execution, with a proportion of these cells possibly carrying corollary discharge information (Wyder *et al*., 2003).

Gaymard *et al*. (1994) observed deficits in two patients with IML lesions in conditions where information about initial eye displacement had to be used for a subsequent saccade. As lesions also affected the lateral thalamus in both patients, the saccade impairments could also be attributed to lateral rather than IML damage. It should also be pointed out that the present findings do not support the assumption that the IML plays a critical role in processing eye movement-related information. Lesions involving the IML did not cause deficits.

It is important to note that corollary discharge may arise from different levels of the neuronal circuitry, representing information about ongoing eye movements with different degrees of accuracy. The SC, for example, does not only send information about ongoing eye movements to the FEF, but it also receives feedback information from the brainstem (Soetedjo *et al*., 2002). Some cells in the SC intermediate layers even show predictive remapping (Walker *et al*., 1995).

The role of medial thalamic nuclei

The saccade performance of two patients of the present study (Patients 3 and 7) suggests that the human medial thalamus might be involved in relaying corollary discharge information. The most surprising result was the ipsilateral impairment of Patient 3. The lesion of this patient mainly affects MD, but extends caudally to the CM-Pf complex.

Sommer and Wurtz (2004*a*) described neurons in MD firing nearly exclusively before contraversive saccades. However, in the few studies investigating humans with thalamic lesions, ipsilateral deficits have also been observed (Gaymard *et al*., 1994; Versino *et al*., 2000). Interestingly, the lesions of the patients in the study of Versino and colleagues (2000) also affected the medial thalamus. In the literature on monkey studies, there are also some suggestions that the thalamus does not only relay information about contralateral saccades. Postsaccadic activity in the FEF has been found to represent the last saccade made and many cells with postsaccadic activity show the strongest responses after ipsilateral saccades (Goldberg and Bruce, 1990). Additionally, Sommer and Wurtz (2004*b*) observed that lesioning MD in monkeys can lead to an ipsilateral impairment in single cases.

On the other hand, MD lesions do not necessarily lead to impairments in using corollary discharge information. The lesions of Patients 5 and 6 mainly affect MD and these patients did not show evidence of a deficit. In MD-lesioned Patient 1, saccade performance was generally poor, such that a potential deficit in processing corollary discharge signals might have been masked.

In general, it cannot be excluded that the involvement of the CM-Pf complex is somehow related to the deficits of Patient 3. Literature on the involvement of this complex in eye movements is sparse. Although it has been shown that neurons in CM discharge during different phases of a delayed saccade task (Wyder *et al*., 2003), neither anatomical nor physiological data suggest an involvement of the CM-Pf complex in processing corollary discharge information of ongoing eye movements (Sadikot *et al*., 1992*a*,*b*; Van der Werf *et al*., 2002; Wyder *et al*., 2003, 2004).

Patient 7, who showed the largest asymmetry in saccade performance, had bilateral lesions of the medial thalamus, with the left-sided lesion extending into lateral parts of the thalamus. First saccades were quite accurate, but the patient had great difficulty in performing second (i.e. vertical) saccades. While the performance on leftward trials might reflect a general deficit in saccade performance, the pattern on rightward trials could indicate a deficit in using corollary discharge information. On RDC trials, the patient performed two successive horizontal saccades in the same direction, often followed by a vertical saccade. It is possible that this pattern reflects an impairment associated with a strategy to perform saccade sequences. The patient may have had difficulty in monitoring the horizontal saccade and may therefore have performed it twice. It cannot be decided, on the basis of the data, whether the deficit is related to the ipsilateral or the contralateral thalamic lesion or both.

General impairments of saccade performance

In addition to the impairments in updating visual space we found in some patients, the results of the present study

indicate that thalamic lesions in humans disrupt some aspects of saccade performance in general, irrespective of retinospatial dissonance requirements and lesion side. The deficits mainly affected second (i.e. vertical) saccades in the double-step task: Patients performed more inadequate second saccades and omitted second saccades more frequently than controls—even if Patients 10 and 13, who showed the most omissions and were therefore excluded from quantitative saccade analysis, were not considered. This is in line with the findings of Sommer and Wurtz (2004*b*), who reported a bilateral increase of omissions resulting from unilateral thalamic inactivation. Furthermore, saccades in the patients of the present study were hypometric, particularly the second—vertical—saccade. This finding is surprising because, in earlier studies, hypometria was not generally observed in patients with thalamic lesions (Gaymard *et al*., 1994; Versino *et al*., 2000). It has been shown that lesions of nucleus VL of the thalamus lead to impaired saccade adaptation (Gaymard *et al*., 2001), probably because this nucleus receives cerebellar afferents (Leichnetz and Goldberg, 1988; Lynch *et al*., 1994; Barash *et al*., 1999). According to Barash *et al*. (1999), saccade adaptation might reflect a mechanism to overcome fatigue. However, there is no evidence that the saccadic hypometria observed in the patients of the present study can be attributed to fatigue, as saccades were hypometric from the start of the experiment. Similarly, the deficits in performing the second saccade cannot be caused by attentional or visual field deficits, since patients did not differ from control subjects on these measures. The most likely explanation for the general hypometria is therefore that thalamic lesions in the patients of the present study damaged passing fibres involved in saccade generation.

Relation between saccade performance and neuropsychological deficits

Neuropsychological assessment partly corroborated the findings of previous research. Deficits in verbal and visual working memory and in visual long-term memory were observed in patients relative to control subjects. These results are in line with reports of memory dysfunction after unilateral thalamic lesions (Van der Werf *et al*., 2000; Zoppelt *et al*., 2003). The findings do, however, not support the idea of an association of impairments in using corollary discharge information and of visuo-spatial abilities, as suggested by Heide and Kompf (1998). Patients were not impaired in copying, but only in recalling visuo-spatial stimuli, thus indicating a visuo-spatial memory deficit rather than visuo-spatial processing deficits *per se*. Furthermore, the individual patients with evidence of problems in updating visual space did not show inferior performance on copy or reproduction of visuospatial material compared with the patients with relatively intact saccades.

However, there may be an association between general saccade performance and neuropsychological measures of visuo-spatial function and/or short term or working memory. The only patient with consistently low performance in these measures (Patient 13) was excluded from quantitative saccade analysis due to frequent omissions of the second saccade. Neuropsychological and saccadic deficits in this patient may be due to the very short post-lesion time, which was 4 months at the time of testing. Patient 10, who also omitted many second saccades, scored low on the geometrical figure recall and on verbal short-term memory. In this patient, deficits in general saccade performance are likely to be caused by a general slowing of cognitive processes, which was reflected in his very long reaction times in the alertness task.

Effect of lesion-test interval

Although the time since lesion varied between 4 and 87 months in the present study, the severity of deficits in using corollary discharge information is comparable to the impairments described by Sommer and Wurtz (2004*b*) in monkeys after acute deactivation as well as to the deficits found in humans 14–45 days after the infarct (Gaymard *et al*., 1994; Versino *et al*., 2000). While there are no longitudinal studies of the course of cognitive changes after thalamic lesions (Schmahmann, 2003), deficits have been described for lesion-test intervals ranging from 2 months to 24 years (Buttner *et al*., 1991; Van der Werf *et al*., 2003; Zoppelt *et al*., 2003) and there is, so far, no evidence of a significant effect of time since lesion.

Conclusion

Taken together, both VL as well as MD lesions may lead to deficits in using corollary discharge information about ongoing eye movements in humans. The role of the human VL appears to be similar to the role of MD in the monkey brain, relaying information about impending eye movements directed contralaterally from SC to the FEF. It is likely that other pathways are also involved in relaying this information, as a disruption of the SC-FEF pathway does not cause complete loss of information about ongoing eye movements. As far as the involvement of the medial thalamus in humans is concerned, the MD seems to have access to information about ipsilateral eye movements, at least in single cases. The exact role of MD in programming eye movements in primates needs to be further elucidated by future research.

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