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Separate and overlapping functional roles for efference copies in the human thalamus

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ABSTRACT

How the perception of space is generated from the multiple maps in the brain is still an unsolved mystery in neuroscience. A neural pathway ascending from the superior colliculus through the medio-dorsal (MD) nucleus of thalamus to the frontal eye field has been identified in monkeys that conveys efference copy information about the metrics of upcoming eye movements. Information sent through this pathway stabilizes vision across saccades. We investigated whether this motor plan information might also shape spatial perception even when no saccades are performed. We studied patients with medial or lateral thalamic lesions (likely involving either the MD or the ventrolateral (VL) nuclei). Patients performed a double-step task testing motor updating, a trans-saccadic localization task testing visual updating, and a localization task during fixation testing a general role of motor signals for visual space in the absence of eye movements.

Single patients with medial or lateral thalamic lesions showed deficits in the double-step task, reflecting insufficient transfer of efference copy. However, only a patient with a medial lesion showed impaired performance in the trans-saccadic localization task, suggesting that different types of efference copies contribute to motor and visual updating. During fixation, the MD patient localized stationary stimuli more accurately than healthy controls, suggesting that patients compensate the deficit in visual prediction of saccades - induced by the thalamic lesion - by relying on stationary visual references. We conclude that partially separable efference copy signals contribute to motor and visual stability in company of purely visual signals that are equally effective in supporting trans-saccadic perception.

1. Introduction

How our visual system ensures the stability of perception across saccade eye movements is one of the long-standing mysteries in neuroscience. Electrophysiological evidence from the last three decades has demonstrated how saccade related areas in the brain inform frontal areas about the metrics of upcoming eye movements (Wurtz, 2018). Such a neural transmission has been identified in a pathway ascending from the superior colliculus (SC) through the medio-dorsal (MD) nucleus of the thalamus to the frontal eye field (FEF). In their seminal study, Sommer and Wurtz (2002) discovered in monkeys that experimental inactivation of the thalamic MD nucleus leads to impairments in motor tasks that require the monitoring of eye movements. This pathway therefore provides precise knowledge about the vector of the executed eye movement to update the internal representation of space. In humans, lesions involving thalamic regions, likely overlapping with the mediodorsal (MD) or the ventrolateral (VL) nucleus of the thalamus, impaired motor updating (Bellebaum et al., 2005a, 2005b, 2006; Ostendorf et al., 2010, 2013). Classic tests of trans-saccadic perception in MD-lesioned patients (Ostendorf et al., 2010, 2013) and in monkeys whose MD nucleus had been cooled down (Cavanaugh et al., 2016) also revealed deficits in trans-saccadic visual localization attributed to the unavailability of efference copy information, which is needed to trigger the remapping of the coordinates across saccades (Sommer and Wurtz, 2006). It thus seems that information relayed through the thalamus critically contributes to both motor and visual updating, i.e., to trans-saccadic spatial constancy for the purpose of spatially accurate movements as well as perceptual localization. However, the effects of

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thalamic lesions on both visual and motor updating are only partial, with mislocalizations amounting to about 20% of the saccade amplitude, and the conscious impression of visual stability has been reported to be preserved in MD lesion patients (Ostendorf et al., 2013). Here, we tested saccadic and visual localization within the same patients and examined if medial and lateral thalamic lesions differentially contribute to visual and motor updating. Furthermore, we examined if the lesions also lead to deficits in the localization of visual targets in the absence of saccades. This would suggest an important role of efference copies for spatial perception in general. We tested in the same patients, suffering from either a medial (likely involving the MD nucleus) or a lateral (likely involving the VL nucleus) thalamic lesion, motor (experiment 1) and visual (experiment 2) updating across saccades as well as localization accuracy in a pure fixation task (experiment 3). We found deficits in motor updating in single patients with medial or lateral thalamic lesions. However, only the patient with a medial lesion showed impairments in visual updating. In a pure fixation task this patient tended to be more accurate than healthy control participants. These data suggest that medial thalamic lesions likely affecting the MD nucleus impair both visual and motor updating, while the role of the lateral thalamus might be restricted to motor updating. In the absence of efference copy information relayed via the medial thalamus, the sensorimotor system may rely more strongly on visual information.

2. Methods

2.1. Apparatus

In all experiments, subjects were seated 58 cm from an *OK. ODL 32651F-TIW LED* monitor with head stabilized by a chin- and headrest. The visible screen diagonal was 33 in., resulting in a visual field of 74° × 44°. Stimuli were presented on the monitor with a vertical frequency of 60 Hz at a resolution of 1920 × 1080 pixels. The stimuli were presented on a black background. Eye movements were monitored by the EyeLink 1000 system (SR Research), which samples gaze positions with 2000 Hz. Viewing was binocular, but only the dominant eye was recorded. The system detected the start and the end of a saccade when eye velocity exceeded or fell below 22°/s and acceleration was above or below 4000°/s^2.

2.2. Participants

Overall 7 patients with focal thalamic lesions and 18 healthy controls were invited to participate in the study. The aim of the study was not only to compare the performance of patients and healthy control participants in different tasks, but also to explore potentially different deficit patterns in the patients, with impaired performance for some tasks and spared performance in others. We thus decided to include in the analysis of our data only patients and controls who successfully completed all three tasks. The tasks we applied (motor updating, visual updating and visual localization, see below) were quite long and demanding. Due to problems in keeping up attention and alertness over the course of the testing session, four patients and nine healthy controls did not have enough trials in all conditions of each task (see below for details on criteria for exclusion of trials from analysis) and were thus excluded from data analysis. Importantly, these problems occurred in both patients and controls and thus seem to be unrelated to the thalamic damage. Rather it seems that the tasks were generally demanding for an elderly population. For the present study, we thus included data of three patients with focal ischemic thalamic lesions (see below for demographic data), and nine healthy controls (five male, four female, mean age: 63 ± 5 years). The study conformed to the Declaration of Helsinki and was approved by the ethics committee of the Faculty of Mathematics and Natural Sciences at Heinrich Heine University Düsseldorf. The experiment was undertaken with the understanding and written consent of all the subjects. Patients and control subjects were remunerated for the participation.

The patients were outpatients of the Klinikum Dortmund, Germany. Thalamic lesions were diagnosed and localized by magnetic resonance imaging at the time of the lesion event. Fig. 1 displays individual lesion sections, which were obtained by applying the unified segmentation approach as implemented in SPM12 (v7219). To optimize the unified segmentation algorithm, the default regularization settings were rescaled by a factor of 0.1. Scans were normalized to the Montreal Neurological Institute (MNI) space. The voxel dimension of the normalized images was 2 × 2 × 2 mm. For each patient, multiple images were acquired by using different sequences optimized for lesion localization for diagnostic purposes (see Table S1 for a list of the images that were available for each patient and for lesion-test intervals; Fig. S1 displays the lesion location as identified in the different images per participant). The lesion localization, that is, whether the lesion primarily affected the medial (involving MD) or the lateral (involving VL) thalamus, was initially determined by an experienced neurologist (B.K.), who was blind to the behavioral results. Based on all available imaging data per patient, we sought to confirm the MD or VL involvement, respectively (see also Fig. S2, Pergola et al., 2013, and Danet et al., 2015, for a discussion of these procedures). By overlaying the reconstructed lesions on an atlas of the thalamus (Krauth et al., 2010; Jakab et al., 2012), we observed that one patient (male, 69 years, lesion-test interval 75 months) had a lesion that affected the medial part of the right thalamus likely overlapping with the MD (rMD patient), and extended posteriorly as well as inferiorly into the white matter. The other two patients had lesions that mainly affected the lateral nuclei of the thalamus. In one of these patients (female, age = 53 years, lesion test interval 23 months) the lesion seemingly affected the left lateral thalamus also involving the VL (lVL patient), and extended posteriorly. In the other patient (male, age = 68 years, lesion-test interval 21 months), the lesion was in the right thalamus also involving the VL (rVL), and extended more ventrally and laterally. Patient rVL had an additional older lesion that affected the nucleus caudatus and the internal capsule. Furthermore, this patient showed signs of cerebral microangiopathy.

3. Experiment 1: motor updating task

3.1. Stimuli

Fig. 2A shows the placement of the stimuli: A fixation point (FP, 0.75° × 0.75°, red) and two saccade targets (T1, T2), which consisted of rectangles (0.75° × 0.75°, red). In each trial one out of four possible combinations of fixation points and the two saccade targets were shown. Stimulus positions were chosen such that the required first saccade vector was 15° rightwards or leftwards from FP to T1 and the required second saccade vector was 15° upwards or downwards from FP to T1.

3.2. Procedure

A trial started with the presentation of a fixation point in screen center. After a random duration between 1250 and 1750 ms, the fixation point disappeared and T1 was presented. In the updating condition, the first target (T1) disappeared after 50 ms simultaneously with the appearance of the second target (T2), which was also shown for 50 ms. In the no-updating condition both saccade targets were also presented sequentially, but now each one for 500 ms. The participants were required to perform two successive saccades to the positions of the targets as soon as the first target (T1) appeared. Each condition (updating/no-updating) of Experiment 1 consisted of 120 trials with 30 repetitions for each of the four quadrants.

3.3. Data analysis

In the analysis of eye movement data in Experiment 1 we excluded trials if: i) the amplitude of the first saccade was smaller than half of the

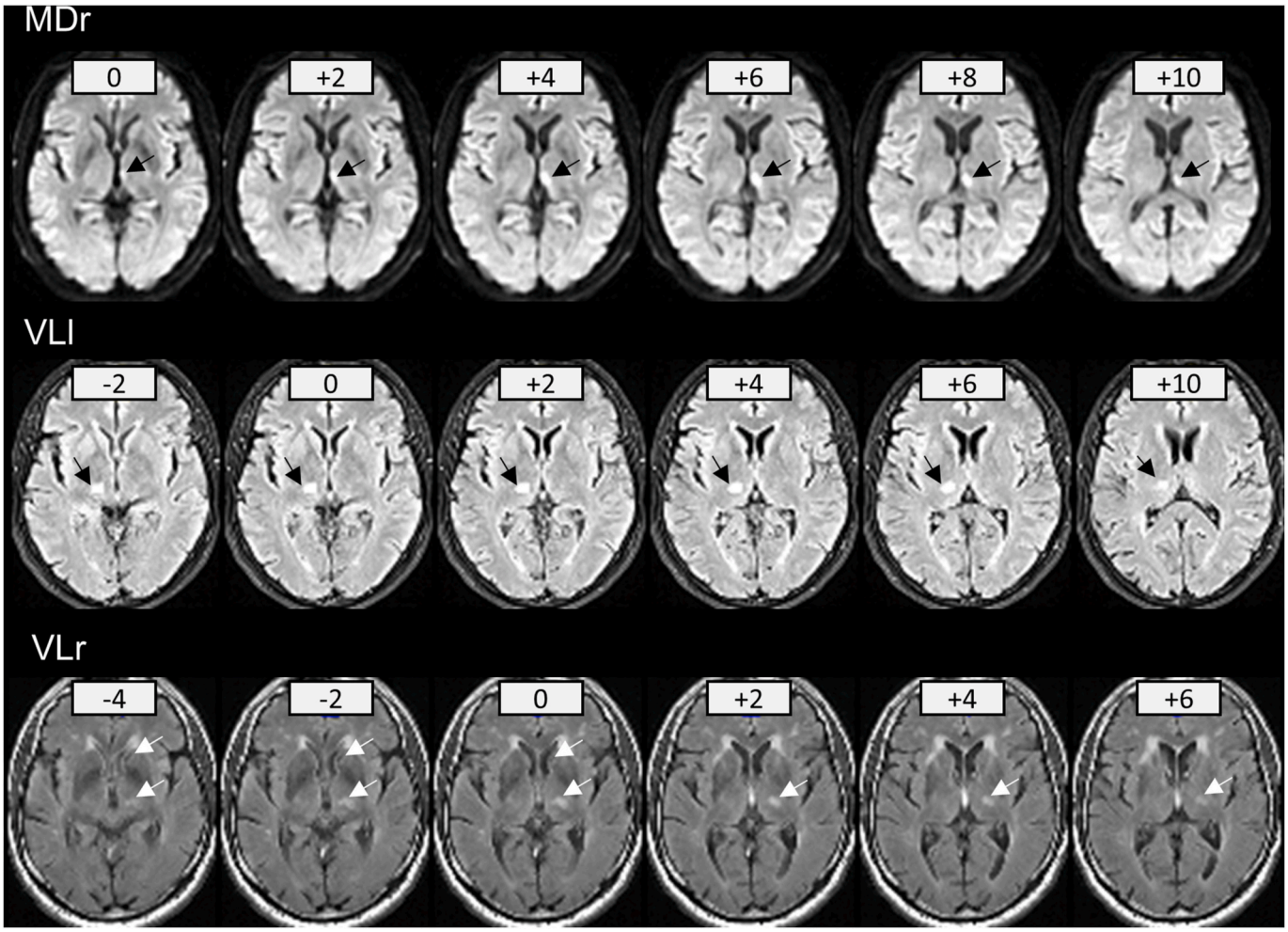

Fig. 1. Individual magnetic resonance images of lesion locations. For each patient (rMD, lVL, rVL), normalized axial sections (z-coordinate levels indicated in mm) displaying the full extent of the lesion are presented. For each participant, we chose images from that one of the acquired sequences (see Table S1 for a list of the images per patient), in which the lesion was most clearly visible. White and black arrows indicate lesion locations.

required distance, i.e. $< 7.5°$, ii) the first saccade had a vertical component larger than 7.5°, iii) the vertical amplitude of the second saccade was smaller than 2°, iv) the latency of the first saccade was <100 ms. These criteria were applied to ensure that both saccades were large enough to reveal a putative deviation of the second saccade. If, for instance, the executed first saccade is much smaller than the required distance, the efference copy should signal a smaller amplitude, thus leading to smaller influences on the direction of the second saccade. In all experiments we included into the analysis only those participants' data sets, which contained at least 9 trials per condition and for leftward and rightward saccades that passed the selection criteria. Table S1 lists the numbers of accepted trials for all participants.

For the statistical analysis we first compared the landing positions of the first saccade between each patient and the control group with a modified *t*-test for single case data, separately for trials with a left- and rightward first saccade and for the updating and the no-updating condition (Crawford and Garthwaite, 2002). This was mainly done to control for basic impairments in saccade generation in the patients. As for each patient four t-tests were conducted, we applied a Bonferroni alpha-correction (adjusted value: $p < 0.0125$). Then, we tested our hypothesis concerning impaired use of efference copy information in the patients by analyzing the direction of the second saccade. Specifically, we determined how far the second saccade deviated from the optimal vector that would have directed the gaze onto the target. We calculated the angle between the second saccade vector and the optimal vector connecting the starting position of the second saccade and the second saccade target. These angles were computed separately for the updating and the no-updating condition. We then calculated separately for each participant and each visual field (left/right) the difference between the angles from the no-updating and the updating condition. We compared these difference values for each patient and the control group again with a modified *t*-test for single case data (Crawford and Garthwaite, 2002). As for each patient now two t-tests were calculated (one for left- and one for right-sided first saccades), the adjusted threshold for statistical significance was $p < 0.025$. Only in case we found a significant deviation of these difference scores between a patient and the control participants we calculated follow-up tests in which we compared saccade direction between single patients and controls for the updating and no-updating conditions separately.

4. Experiment 2: visual updating task

4.1. Procedure

The trial sequence is shown in Fig. 3A. A trial started with the presentation of a fixation point in screen center. After a random duration between 1250 and 1750 ms, the fixation point disappeared and T1 and T2 were presented sequentially, each for 50 ms. Five-hundred ms after the disappearance of the saccade target T2, a reference bar ($0.25° \times 10°$, black) was shown at the same vertical position as T2. Across trials, the

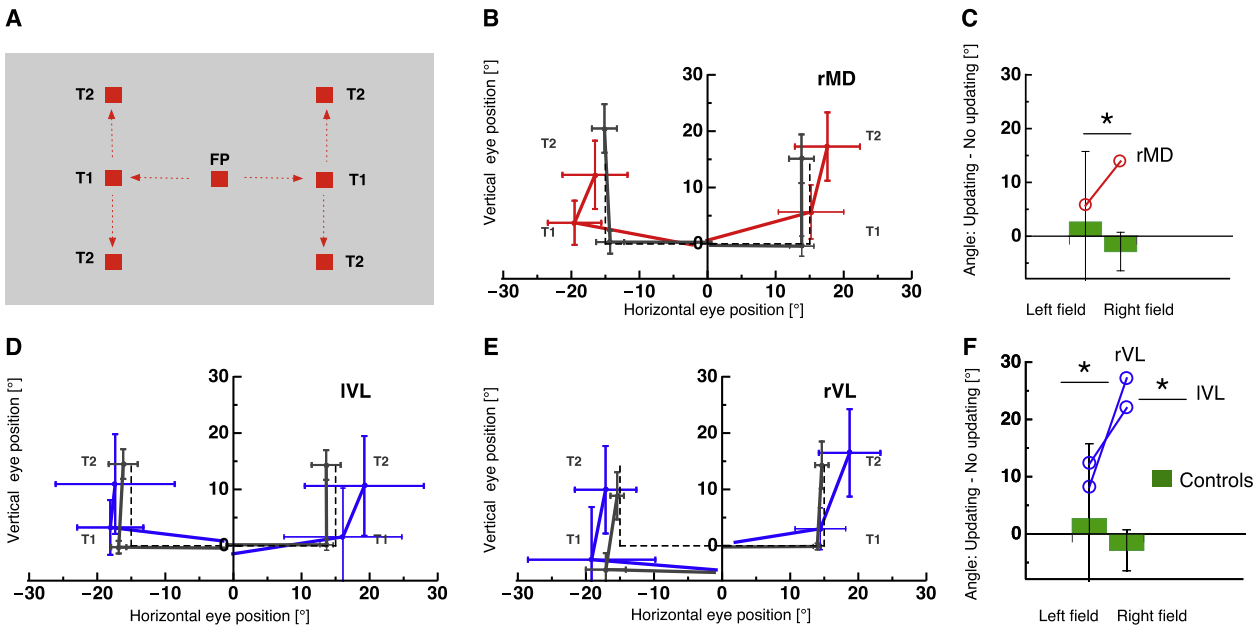

Fig. 2. (A) Experimental setup of the double-step task used to test motor updating. The fixation point (FP) was shown in the screen center. The first saccade target (T1) was presented 15° either to the left or right. From T1 participants had to perform a saccade to the second target (T2) that was shown 15° either above or below T1. (B) Average saccade vectors from FP (0, 0) to T1 (15, 0) and from T1 to T2 (15, 15). Data of the rMD patient are shown from the updating condition (red lines) and the no-updating condition (grey lines). Data from upward and downward second saccades are collapsed. Dashed lines indicate the required saccade path from FP to T1 and from T1 to T2. (C) Angles between the actual second saccade vector and the optimal vector that would have led to the physical target position T2 from the second saccades' starting position: Differences between updating and no-updating condition. Green bars represent data from the control group. Error bars are 95% C.I.s. Data from the rMD patient are shown in red circles. The asterisk indicates statistical significance for the difference between the angles from the no-updating and the updating condition that was tested between the patient and the control group. (D) Average saccade vectors of the lVL patient. Same conventions as in (B). (E) Average saccade vectors of the rVL patient. Same conventions as in (B). (F) Deviations of the second saccade vector from the optimal angle for patients lVL and rVL: Differences between updating and no-updating. Same conventions as in (C). Please note, control data are replotted (as in Fig. 2C) to allow better comparison. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

horizontal positions of the reference bar varied from 12° to 18° (in 6 equidistant and equiprobable steps of 1°) around the horizontal position of T2. Participants were instructed to perform a saccade to the saccade target T1 and then to keep their gaze fixated at that location. They were asked to localize the remembered position of saccade target T2 relative to the position of the reference bar by pressing either the left or the right arrow button on a computer keyboard. Experiment 2 consisted of 240 trials with 60 repetitions for each of the four quadrants.

4.2. Data analysis

In the analysis of eye movement data in Experiment 2 we excluded trials if: i) the amplitude of the first saccade in a trial was smaller than half of the required distance, i.e. $< 7.5°$ and ii) any saccade in a trial went upwards or downwards more than 2.5°, iii) the latency of the saccade was <100 ms. Table S1 lists the numbers of accepted trials for all participants.

We fitted cumulative gaussian functions to the localization data and determined for each subject the 50% value as the point of subjective alignment between references and probe. For the analysis of the perceptual thresholds, we estimated the variance of the gaussian function for each participant. As this task did not entail a no-updating control condition, we statistically compared first saccade landing positions and then the points of subjective alignment from each patient and each visual field side against the healthy control group directly with a modified *t*-test (Crawford and Garthwaite, 2002) (see Experiment 1). Bonferroni alpha-corrections (p-value < 0.025) were applied for each patient to account for multiple testing.

5. Experiment 3: fixation task

5.1. Procedure

All stimuli in Experiment 3 had the same features (0.75° × 0.75°, red) as in the first two experiments. The trial sequence is shown in Fig. 4A. A trial started with the presentation of a fixation point in the center and reference stimuli on the left and right side of the screen. Participants were instructed to fixate on the fixation point throughout the entire session. The reference stimuli were presented in 1 out of 6 possible eccentricities (12°–18° in 6 equidistant and equiprobable steps of 1°, the aligned position at 15° was not included), with the eccentricity being always the same for references on the left and right sides of the screen. After a random duration between 1250 and 1750 ms, a probe target was either flashed for 50 ms or presented stationary for 500 ms, randomly either on the left or the right side of the screen. The probe was shown always at an eccentricity of 15°. Participants had to judge the apparent position of the probe relative to the respective reference. For instance, if the probe was presented on the right side of the screen, participants used the references on the right to indicate the perceived location. Participants were instructed to press the right and the left arrow button on the computer keyboard if they saw the probe to the right and the left of the references, respectively. Experiment 3 consisted of 240 trials with 2 × 60 trials for the flashed and the stationary probes in the left and right visual field, respectively.

5.2. Data analysis

In the analysis of eye movement data in Experiment 3 we excluded trials if saccades were made with a horizontal or vertical amplitude larger than 2.5°. Table S1 lists the numbers of accepted trials for all

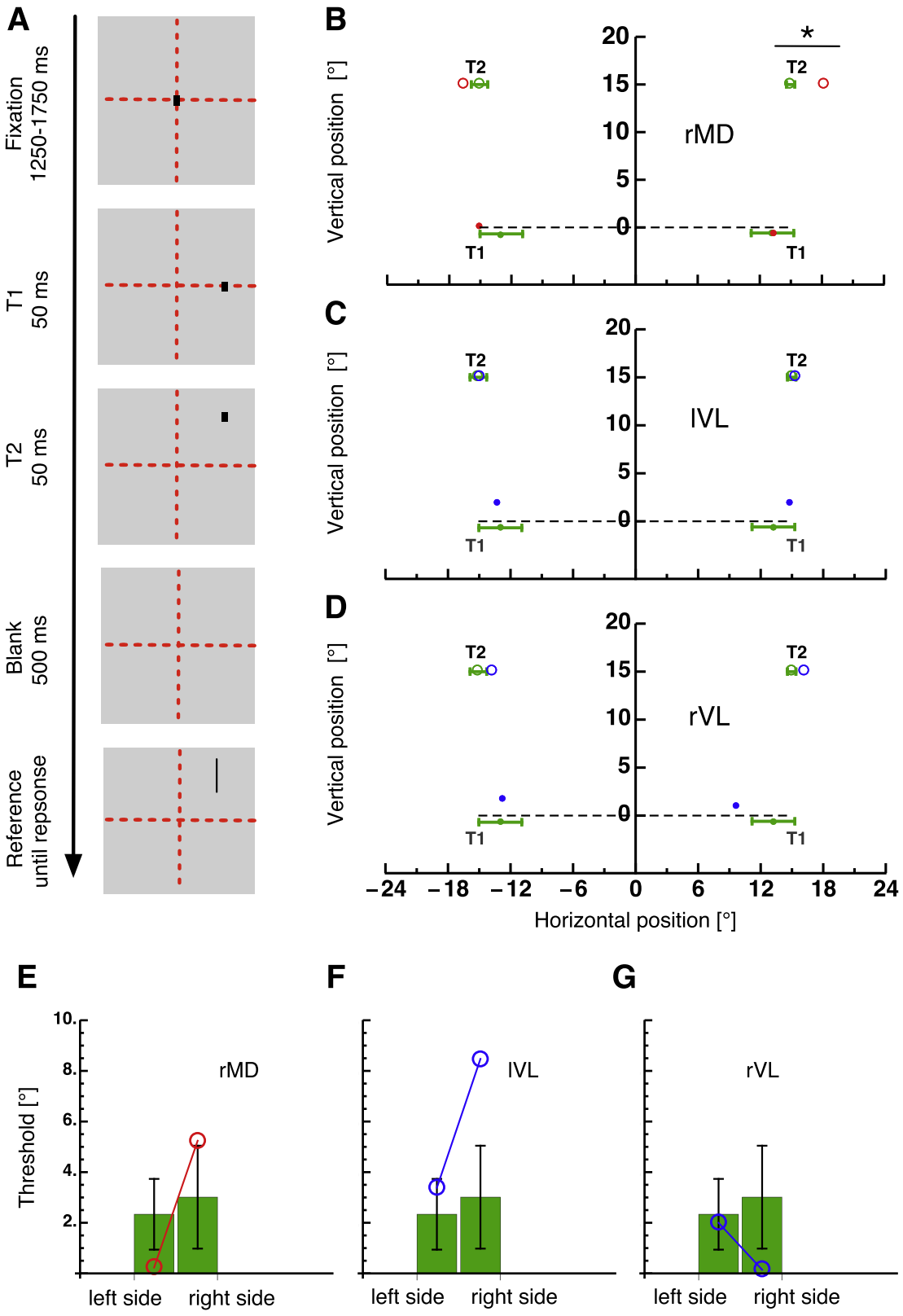

Fig. 3. (A) Example procedure of the task used to test visual updating. The fixation point was shown for a random duration between 1250 and 1750 ms. Then, two targets were flashed sequentially, each for 50 ms. Participants were required to perform a saccade to the first target (T1) and keep their gaze fixated at that position. After the screen was blank for 500 ms a reference bar appeared and participants had to localize the remembered position of target T2. (B–D) Average saccade landing positions (point symbol) and localization data (circle symbol) of the patients (red color: rMD patient, blue color: lVL and rVL patient) and the control group (shown in green). Error bars for the control group are 95% C.I.s. Please note, control data are replotted to allow better comparison. Dashed lines show the required saccade path from the fixation point to saccade target T1. The asterisk indicates statistical significance for the localization difference between the rMD patient and the control group. (E–G) Thresholds derived from the variance of the psychometric functions. Same color conventions as in (B–D). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

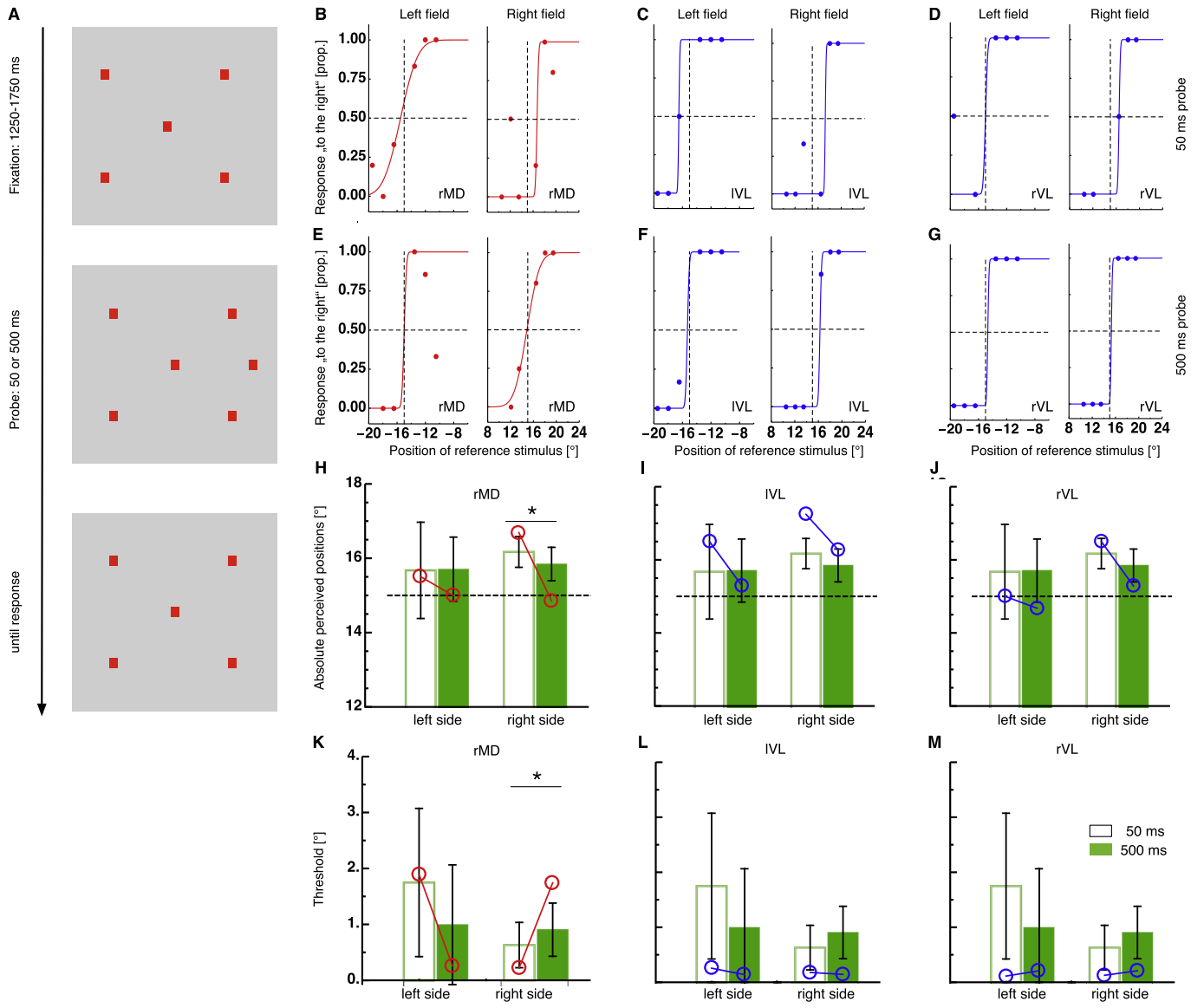

Fig. 4. (A) Example procedure of the task used to test visual localization during fixation. The fixation point together with two references on the left and two on the right side was shown for a random duration between 1250 and 1750 ms. Then a probe was shown either on the left or the right side for 50 ms or 500 ms. Participants had to decide whether the probe appeared to the left or the right of the respective references. (B–G) Psychometric functions for localization after leftward and rightward saccades from the rMD patient (in red) and the VL patients (in blue) for probes presented for 50 and 500 ms. Please note that on the abscissa eccentricity on the left side is shown in negative numbers and on the right side in positive numbers. Thus, on the left side more eccentric localization corresponds to smaller and on the right side to higher numbers. Vertical dashed lines indicate the probe position (15°) and horizontal dashed lines the point where performance was 50%. (H–J) Average absolute positions where participants judged references and probe to be at equal location (red color: rMD patient, blue color: lVL and rVL patient, green color: control group). Note that the probe was always presented at 15° (indicated by the dashed line) and the position of the references varied across trials. Higher numbers correspond to more eccentric localization. Error bars for the control group are 95% C.I.s. Please note, control data are replotted to allow better comparison. The asterisk indicates statistical significance for the localization difference between the rMD patient and the control group. (K–M) Thresholds derived from the variance of the psychometric functions. Same conventions as in (H–J). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

participants. As in Experiment 2, points of subjective alignments were estimated from cumulative gaussian functions. For the analysis of the perceptual thresholds, we estimated the variance of the gaussian function for each participant. We calculated separately for each participant and each visual field (left/right) the difference between the point of subjective alignments from the stationary and the flashed probe condition and compared these difference values of each patient and each visual field side with the values of the healthy control group with a modified *t*-test (see Experiment 1). Again Bonferroni alpha-correction was applied for each patient to account for multiple testing ($p < 0.025$). In analogy to the procedure for Experiment 1, we conducted post-hoc tests of separate comparisons between single patients and controls separately for the two conditions (flashed and stationary probes) only in case of a significant deviation of the difference scores. The identical analysis was performed to compare the variance of the gaussian functions between patients and controls.

6. Results

6.1. Experiment 1: motor updating task

We first asked patients and control participants to perform a classic

double-step task in order to measure the accuracy of motor updating. Given the average latency of 319 ms (95% C.I. = 55 ms) for patients and 297 ms (95% C.I. = 51 ms) for the control group for the first saccade, both targets were off the screen before any of the participants moved their eyes. While the first saccade is directed to the retinal position of the saccade target T1, retrieving the external space coordinates of the second target T2 requires that the intervening first saccade is taken into account.

Fig. 2B shows the average saccade landing positions of the rMD patient in the double-step task for the updating condition (shown in red) and the no-updating condition (shown in grey). For the analysis we distinguished between trials with a leftward or rightward first saccade (ipsi- and contralateral to the lesion in the patients), but we collapsed data from trials with second saccades into the lower and upper visual field.

For statistical analysis we first compared horizontal landing positions of the first saccade for single patients against the control group. In the updating condition, neither leftward (rMD: $t = -1.195$, $p = 0.133$, lVL: $t = -0.622$, $p = 0.276$; rVL: $t = -1.048$, $p = 0.163$) nor rightward saccade landing positions of the patients (rMD: $t = 0.691$, $p = 0.255$, lVL: $t = 1.313$, $p = 0.113$; rVL: $t = 0.691$, $p = 0.255$) deviated significantly from those in the control group. Similarly, In the no-updating condition, neither leftward (rMD: $t = 0.714$, $p = 0.248$, lVL: $t = -1.082$, $p = 0.155$; rVL: $t = -1.242$, $p = 0.125$) nor rightward saccades (rMD: $t = -0.807$, $p = 0.221$, lVL: $t = -0.955$, $p = 0.184$; rVL: $t = -0.651$, $p = 0.267$) deviated significantly from the saccades in the control group. We then calculated the angle between the patient's second saccade vector and the optimal vector that would have led to the physical target position T2 from the second saccades' starting position. We first tested whether the difference in saccade targeting between the updating and the no-updating conditions was significantly larger in the patient than in the control group (see Fig. 2C). While the angles of the control participants were very similar for the updating and the no-updating condition, resulting in a low value for the difference score, the difference between both conditions was significantly larger in the rMD patient, but only for saccades on the right side (modified *t*-test (Crawford and Garthwaite, 2002), $t = 2.902$, $p = 0.01$). No statistical difference between the rMD patient and the controls was found for leftward saccades ($t = 0.142$, $p = 0.445$). Given the descriptively higher variance of the difference measure in the control group on the left side, we performed a post-hoc comparison on the controls' between-subjects variance between the left and the right side and found a significantly higher variance on the left side (F-Test, $t(8) = 0.075$, $p = 0.0014$).

In order to explore whether the larger difference between updating and no-updating condition for trials with rightward first saccades in the patient was specifically associated with a deficit in the updating condition, and thus related to efference copy processing, we conducted post-hoc comparisons of the angles between the rMD patient and the control participants separately for the two conditions. While the patient showed a significantly larger lateral shift than the controls in the updating condition ($t = 3.075$, $p = 0.008$), no significant difference was seen for the no-updating condition ($t = -1.251$, $p = 0.123$).

A comparable deficit pattern in saccade targeting was found for the VL patients (Fig. 2D and E). For both patients the angle difference between updating and no-updating condition was enhanced for rightward (lVL: $t = 4.302$, $p = 0.001$; rVL: $t = 5.201$, $p < 0.001$), but not for leftward saccades (lVL: $t = 0.452$, $p = 0.332$; rVL: $t = 0.262$, $p = 0.400$; see also Fig. 2F). Post-hoc tests revealed that, similar to the rMD patient, both patients with VL lesions showed a clear deficit in saccade targeting in the updating (lVL: $t = 5.073$, $p < 0.001$; rVL: $t = 8.342$, $p < 0.001$) but not in the no-updating condition (lVL: $t = -1.569$, $p = 0.078$; rVL: $t = -0.495$, $p = 0.317$) for rightward saccades. Given the increased variance of the no-updating – updating difference measure for leftward relative to rightward trials in controls (see above), we also compared the variances separately for the two conditions and found a significant difference only in the updating ($t(8) = 10.8$, $p = 0.0029$) but not in the no-updating condition ($t(8) = 4.73$, $p = 0.04$).

6.2. Experiment 2: visual updating task

Next, we wanted to know whether visual updating across saccades was impaired in the patients. Fig. 3B–D shows saccade landing positions (point symbol) and localization data (circle symbol) of the patients (red color: rMD patient, blue color: lVL and rVL patient) and the control group (in green). Neither the horizontal landing positions of rightward (rMD: $t = -0.621$, $p = 0.276$) nor those of leftward saccades (rMD: $t = 0.428$, $p = 0.340$) of the rMD patient, executed to the position of saccade target T1, were significantly different from the landing positions in the control group. Similarly, both VL patients on average did not deviate from the control group for rightward (lVL: $t = 0.217$, $p = 0.417$; rVL: $t = 0.253$, $p = 0.403$) or for leftward saccades (lVL: $t = 0.276$, $p = 0.395$; rVL: $t = -0.314$, $p = 0.381$).

To estimate subjective alignment of the reference bar and T2 we estimated the mean of a psychometric function by fitting a cumulative gaussian distribution to the localization data for all bar positions for each participant. For the control group the localization of the target T2 was virtually veridical. We compared the patients' localization data against the control group separately for each visual field. For the rMD patient, significant mislocalization was found in the right visual field indicated by a more lateral localization of the target T2 ($t = 2.584$, $p = 0.016$), but not in the left visual field ($t = -0.601$, $p = 0.282$), see Fig. 3B. However, no statistical difference with regard to the control group was found in the VL patients (see Fig. 3C and D), neither on the right (lVL: $t = 0.244$, $p = 0.407$; rVL: $t = 1.002$, $p = 0.173$), nor on the left side (lVL: $t = 0.068$, $p = 0.474$; rVL: $t = 0.538$, $p = 0.303$). Fig. 3E–G shows the perceptual thresholds for patients and controls. There were no significant differences in thresholds between patients and healthy controls, neither on the right (rMD: $t = 0.68$, $p = 0.258$; lVL: $t = 1.666$, $p = 0.067$; rVL: $t = -0.875$, $p = 0.204$) nor on the left side (rMD: $t = -0.9333$, $p = 0.189$; lVL: $t = -0.15$, $p = 0.442$; rVL: $t = 0.465$, $p = 0.327$).

6.3. Experiment 3: fixation task

In the fixation task we used a vernier-like arrangement of stimuli to investigate apparent spatial position during fixation. The reference stimuli varied their horizontal positions across trials but were placed such that on average they were shown in the same locations as the second targets in the first two experiments (i.e. eccentricity $x = 15°$, $y = 15°$). The mean of the psychometric function represented the location at which the references and the probe appeared to be horizontally aligned (see Fig. 4B–G). It is well known that localization of stimuli presented in the periphery is biased toward the fovea (Mateeff and Gourevich, 1983). This effect scales with eccentricity (Mateeff and Gourevich, 1983; Müsseler et al., 1999). For the healthy control group, the references had to be presented on average at ~16° to match the position of the probe that was shown at 15° (see Fig. 4H–J, green bars). The control group mislocalized the probe by about the same amount for both presentation durations. Although it has been reported that longer stimulus exposure improves localization accuracy (Aitsebaomo and Bedell, 1992), in our paradigm this factor is likely outbalanced as stimuli are presented far in the periphery. Flashed probes - due to their short presentation duration - only allow to register their absolute position. However, if both, the references and the probe, are presented stationarily, the relative distance between the stimuli might be checked by shifting attention between them or by using their retinal distance as a cue. In the right visual field, the rMD patient perceived stationary probe stimuli much more accurately than flashed probes (see Fig. 4H, red circles). Accordingly, we found a significant difference between the rMD patient and the controls when we compared the difference of localization for flashed and stationary probes on the right side (rMD: $t = 2.247$, $p = 0.027$), which was not found for the patients with VL lesions (lVL: $t = 0.607$, $p = 0.280$; rVL:

t = 1.072, p = 0.157). On the left side, neither the rMD patient nor the VL patients showed larger differences between flashed and stationary probes than the controls (rMD: t = 0.499, p = 0.316; lVL: t = 1.098, p = 0.152; rVL: t = 0.338, p = 0.372).

Finally, we examined the significant effect for rightward probes in the rMD patient further by comparing his localization accuracy with the performance of the control participants separately for flashed and stationary probes. These tests did, however, not yield significant effects, neither for flashed (t = 0.780, p = 0.229) nor for stationary probes (t = −1.366, p = 0.105). The patient's large value in the difference of localization accuracy between stationary and flashed probes was likely caused by the fact that for flashed probes his values were descriptively larger than those of the control participants, while for stationary probes the values were smaller.

Fig. 4K–M shows the perceptual thresholds for patients and controls. We compared the difference between the slopes of the psychometric functions for flashed and stationary targets in the same way as the points of subjective alignment. On the right side the rMD patient differed significantly from the healthy controls (t = 2.394, p = 0.022), but not the patients with VL lesions (lVL: t = 1.772, p = 0.057; rVL: t = 1.525, p = 0.083). On the left side, neither the rMD patient nor the VL patients showed significantly larger differences between flashed and stationary probes than the controls (rMD: t = -1.241, p = 0.125; lVL: t = -0.387, p = 0.709; rVL: t = -1.472, p = 0.09). We chose a wide range (12°–18°) for the placement of probe stimuli, taking into account that our participants might have difficulties with peripheral localization. Applying this procedure, for a few participants and conditions no compari- son stimuli were placed close the point of subjective alignment (see for instance Figure 4G). These psychometric functions have to be interpreted with caution with respect to the estimation of the point of subjective equality and threshold. These psychometric functions might underestimate mislocalization. Since the comparison stimulus positions are evenly spread around the veridical probe position, the point of subjective alignment of a psychometric function that is unconstrained by stimuli around the threshold will be close to 15°. As for the point of subjective alignments, we examined the significant effect for rightward probes in the rMD patient further by comparing his localization precision with the performance of the control participants separately for flashed and stationary probes. These tests did, however, not yield significant effects, neither for flashed (t = −0.609, p = 0.280) nor for stationary probes (t = 1.092, p = 0.153). Similarly to the points of subjective alignments, the enlarged difference between stationary and flashed probes is mostly driven by the results for the stationary probes. The rMD's variance was descriptively higher for the stationary probes compared to the controls.

7. Discussion

We tested patients with unilateral lesions in the medial or lateral thalamus in a saccade motor updating, a saccade visual updating and a fixation localization task. In the saccade motor updating task, the rMD patient and the two VL patients showed characteristic unilateral mislocalization, indicating an impaired transmission of the efference copy signal. The rMD patient also visually mislocalized the remembered position of a stimulus across saccade execution, demonstrating that updating was insufficient also for visual space. Both, the deficits in motor and in visual updating were on the right side of the visual field. Motor and visual targeting were driven outward, towards the periphery.

These findings indicate a single functional dissociation between the medial and lateral thalamus and might suggest that different trans-saccadic pathways contribute to spatial constancy across saccades, which are used for different purposes. The pathway through the lateral thalamus may primarily underlie motor updating, which is in line with a cerebellar source of the saccade related information relayed in this part of the thalamus, as the cerebellum codes the amplitude of the actually performed saccade (Robinson and Fuchs, 2001). The medial thalamus and the MD nucleus may enable spatial constancy for different purposes, visual and motor. There was no clear relationship between lesion side and laterality of the deficit. All patients showed a rightward deficit, although the MD and one of the VL patients were lesioned on the right side and another VL patient lesioned on the left side. Both ipsi- and contralesional efference copy deficits have been reported. Bellebaum et al. (2005a, 2005b) found ipsilesional deficits for an MD patient and contralesional deficits for VL patients. Ostendorf et al. (2013) tested 11 thalamic patients and did not find a systematic relationship between lesion side and deficit. We also found that the between-subject variance in the control group was higher for updating on the left side. One of the authors of the present study found a more pronounced right hemisphere contribution to visual space updating in previous research (Bellebaum et al., 2005a, 2005b), with updating for rightward saccades being supported by both left and right hemispheric processing, while updating for leftward saccades is exclusively driven by the right hemisphere. This right hemisphere dominance for spatial updating is consistent with earlier findings for visuospatial processing and atten- tion (Corballis, 2003; Muri et al., 2002), and might explain why there was higher between- subject variance, i.e. higher inter-subject differences in updating, on the left side.

As already mentioned, efference copies might originate in the cerebellum which is involved in saccade generation. Evidence suggests that the cerebellum predicts the sensory consequences of actions with the help of efference copies from motor commands (for a review, see Wurtz, 2018). Dense projections from the deep cerebellar nuclei reach the VL nucleus (Allen and Tsukahara, 1974) and the intra-laminar nuclei (Kalil, 1981; for a review, see (Jones, 2007), where the most lateral, paralaminar MD portion is attributed to the intralaminar nuclei group[1]). Additionally, the dentate nucleus projects through the VL nucleus to the FEF (Lynch et al., 1994). A role of the VL nucleus for transferring efference copies has been suggested by patient studies showing either deficits in motor updating (Bellebaum et al., 2005a, 2005b) or a reduced capability to monitor and adapt saccade amplitudes in response to systematic targeting errors (Gaymard et al., 2001; Zimmermann et al., 2015), although it is difficult to rule out concurrent damage in the intralaminar nuclei. Indeed, we found deficits in motor updating not only in a patient with a lesion involving the MD but also in two patients with lesions involving the VL nucleus. However, only a lesion in the MD nucleus affected trans-saccadic vision. This evidence from a sensory-motor integration task is consistent with current models that posit a prominent involvement of the MD in cognitive updating (Ouhaz et al., 2018; Rikhye et al., 2018; Pergola et al., 2018). In summary, both the MD and the VL nucleus carry efference copy information relevant for motor updating and only the MD nucleus pathway transfers information for motor and visual updating, suggesting that, at least partially, the medial and lateral thalamus serve separate and overlapping functional roles in updating space across saccades.

In a recent report, Rath-Wilson and Guitton (2015) could demonstrate that previous evidence for a lack of efference copy in patients with a lesioned parietal lobe might be attributable to the high task demands of the classic double-step paradigm. The authors argue that the quick succession of the targets makes it hard for the patients to dissociate them, thereby producing the deficits on the performance of the second saccade. In principle, this critique might also apply to our data since we used the classic double-step paradigm. However, we found that our patients had a deficit only in one hemifield and were able to correctly perform both saccades in the opposite hemifield.

We also asked why patients did not report any changes in visual perception in their every-day life although efference copy transfer is demonstrably limited. Important sources for localization are visual

[1] As this thalamic subregion is attributed to the MD in the atlas used for lesion segmentation in this study, Fig. S2 reports a conservative estimate. The magnocellular and parvocellular MD are likely spared in the VL patients we tested, more than it would appear from Fig. S2.

references. We tested the extent to which patients rely on visual references by asking them to localize objects during fixation relative to stationary comparison stimuli. Healthy participants mislocalized the probe even when it was presented for 500 ms, most probably because of its high eccentricity. Surprisingly, and in contrast to the performance of the controls, the rMD patient localized those probes veridically. For short probe presentations of 50 ms, preventing a benefit through visual references (Aitsebaomo and Bedell, 1992), the rMD patient mislocalized probes as the healthy participants. These data might suggest that visual references are consulted to improve transsacadic updating when the use of efference copy information is impaired as it is the case for the rMD patient of the present study. The usage of a visual reference, especially at that eccentricity, might come at a cost: While the accuracy increases, precision was reduced compared to the healthy controls. This account might explain why patients do not suffer from a breakdown in perception across saccades despite a lesion in the neural pathway that has been shown to control visual stability (Ostendorf et al., 2013).

In conclusion, our findings might suggest that several routes from motor areas through the thalamus to cortical regions transmit saccade related efference copies. These signals are used for updating of either only motor or both, motor and visual space, with a role of the lateral thalamus for the first and of the medial thalamus for both. Deficits in transmitting efference copies for visual space might be compensated by relying more strongly on visual references, as a patient with a lesion likely affecting the MD nucleus was able to localize stimuli more accurately than healthy controls.

CRediT authorship contribution statement

Eckart Zimmermann: Methodology, Formal analysis, Writing - original draft. **Marta Ghio:** Formal analysis, Writing - original draft. **Giulio Pergola:** Formal analysis. **Benno Koch:** Formal analysis. **Michael Schwarz:** Formal analysis. **Christian Bellebaum:** Methodology, Formal analysis, Writing - original draft.

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All experimental data can be viewed under the link: https://osf.io/pfmy5/?view_only=90043fe3fd0a4b1c8dee86a21781fb56.

Appendix A. Supplementary data

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