Thalamocingulate Interactions In Performance Monitoring

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Performance monitoring is an essential prerequisite of successful goal-directed behavior. Research of the last two decades implicates the anterior midcingulate cortex (aMCC) in the human medial frontal cortex and frontostriatal basal ganglia circuits in this function. Here, we addressed the function of the thalamus in detecting errors and adjusting behavior accordingly. Using diffusion-based tractography, we found that, among the thalamic nuclei, the ventral anterior (VA) and ventral lateral anterior (VLa) nuclei have the relatively strongest connectivity with the aMCC. Patients with focal thalamic lesions showed diminished error-related negativity, behavioral error detection, and posterror adjustments. When the lesions specifically affected the thalamic VA/VLa nuclei, these effects were significantly pronounced, which was reflected by the complete absence of the error-related negativity. These results reveal that the thalamus, particularly its VA/VLa region, is a necessary constituent of the performance-monitoring network, anatomically well connected and functionally closely interacting with the aMCC.

Introduction
Human goal-directed behavior requires a flexible system evaluating behavioral progress and adjusting behavior as needed. The error-related negativity (ERN), an event-related brain potential (ERP) associated with response errors (Falkenstein et al., 1990; Gehring et al., 1993), is used to study the function of this performance-monitoring system (Ullsperger, 2006). ERN is assumed to be generated in the anterior midcingulate cortex (aMCC) (Debener et al., 2005) and to reflect a discrepancy or conflict of erroneous and competing correct response tendencies (Falkenstein et al., 1990; Coles et al., 2001; Yeung et al., 2004). The aMCC overlaps with the rostral cingulate zone (Picard and Strick, 1996), the human homolog of the monkey’s rostral and dorsal cingulate motor areas. Neuroimaging and invasive studies in humans and monkeys showed that the aMCC is part of a larger network signaling the need for behavioral change (Shima and Tanji, 1998; Ridderinkhof et al., 2004), thereby taking into account outcome history (Kennerley et al., 2006; Rushworth and Behrens, 2008; Jocham et al., 2009). Studies in patients with focal lesions (Gehring and Knight, 2000; Ullsperger et al., 2002; Hogan et al., 2006; Ullsperger and von Cramon, 2006a), Parkinson’s disease (Falkenstein et al., 2001; Frank et al., 2004, 2007; Willemsen et al., 2008), and Huntington’s disease (Beste et al., 2006, 2008) provide strong evidence that interactions of the aMCC with the lateral prefrontal cortex and the basal ganglia (BG) are necessary for functional integrity of performance monitoring. Presumably, the BG play a key role in monitoring and adjusting performance—ranging from immediate motor adjustments via action selection to learning from action outcomes (Holroyd and Coles, 2002; Frank, 2005). In the BG circuits relevant for performance monitoring, the thalamus seems to enable information flow from the prefrontal cortex to the more motor-related areas via nonreciprocal corticothalamic connections (Haber, 2003). Moreover, the ventral anterior (VA) and ventralateral anterior (VLa) thalamus appears to mediate the interaction of cerebellar inputs with the BG loops to “adaptively adjust basal ganglia activity on the basis of some internal model and error signal” (Hoshi et al., 2005). Here, we investigate the role of the thalamus in human performance monitoring by studying its anatomical connectivity with the aMCC and examining functional impairments related to focal thalamic lesions.

Evidence from nonhuman primates suggests that the aMCC receives inputs from the adjacent pre-supplementary motor area, dorsal premotor cortex, and the thalamic VA and VLa nuclei (Van Hoesen et al., 1993; Hatanaka et al., 2003). These nuclei, in turn, are termination sites of pallidal efferents (Dum and Strick, 1993). Thus, the aMCC receives input from BG predominantly via the thalamic VA/VLa region. In addition, mediiodorsal (MD), anterior, and intralaminar nuclei connect to aMCC (Vogt et al., 1979; Baleydier and Mauguier, 1980; Barbas et al., 1991). Using diffusion-based tractography, we tested whether fiber connections between aMCC and thalamus originate in the VA/VLa region in humans. In addition, the functional role of the thalamus and its subregions to performance monitoring were tested in an ERP study with patients suffering from focal thalamic lesions.

Materials and Methods
Diffusion-based imaging
Participants. Sixteen healthy participants (five female; mean age, 29.6 years; age range, 25–38 years) took part in the diffusion data acquisition, which was performed at the Max-Planck-Institute for Human Cognitive and Brain Sciences in Leipzig, Germany. Subjects had no history of neurological, psychiatric, or other major medical disorder. The experiments were conducted in accordance with the Declaration of Helsinki and the study was approved by the local ethics committee of the University of
Leipzig (Leipzig, Germany). Participants gave written informed consent. Data were handled anonymously.

Data acquisition and preprocessing. Diffusion-weighted data and high-resolution three-dimensional (3D) T1- and T2-weighted images were acquired on a Siemens 3T Trio scanner with an eight-channel array head coil and maximum gradient strength of 40 mT/m. The diffusion-weighted data were acquired using twice-refocused spin-echo echo planar imaging (repetition time = 1000 ms, 72 axial slices, resolution 1.72 × 1.72 × 1.7 mm). We used a GRAPPA technique (reduction factor 2.0) for parallel imaging. Diffusion weighting was isotropically distributed along 60 directions (Jones et al., 1999) with a b value of 1000 s/mm². The high angular resolution of the diffusion-weighting improves the robustness of probability density estimation by increasing the signal-to-noise ratio and reducing directional bias. Additionally, seven datasets with no diffusion weighting (b0) were acquired initially and interleaved after each block of 10 diffusion-weighted images as anatomical reference for motion correction. To further increase signal-to-noise, we acquired three consecutive scans, which were subsequently averaged together. The entire data acquisition protocol lasted ~45 min. Motion correction for the diffusion-weighted images was applied to all images using seven-parameter global rescale registration (Jenkinson et al., 2002) as implemented in the FSL software (http://www.fmrib.ox.ac.uk/fsl/). All baseline b0 images were aligned to a reference b0 image and the resulting linear transformation matrices were then applied to the diffusion-weighted images following each baseline b0 image. The gradient direction for each volume was corrected using the rotation parameters, and then the three scan repetitions were averaged to improve the signal-to-noise-ratio.

Tractography. We applied the tractographic approach as outlined by Anwander and colleagues (Friederici et al., 2006; Anwander et al., 2007). This approach is ultimately a 3D-extension of the random walk method proposed by Koch and colleagues (2002) and estimates a spatial probability distribution of connectivity from the seed regions.

Seed regions. All tractography was done in each subject’s native space data (interpolated to 1 × 1 × 1 mm isotropic voxels), and resulting maps were warped into standard space (using the Montreal Neurological Institute 1 mm isotropic brain as reference) for cross-subject averaging and comparison. To ensure that the computed tractograms were dominated by long-range connections, seed points were placed at the gray matter/white matter interface (white matter, fractional anisotropy > 0.15). The seed and target areas were determined based on the high-resolution T1-weighted anatomical scans. The aMCC as well as the thalamic regions of interest was outlined manually by an expert (S.S.) using MRicro and verified by an independent rater (M.U.). Based on prior metaanalyses of performance monitoring (Ridderinkhof et al., 2004), the aMCC seed region was chosen on the left hemisphere such that it was located at the dorsal bank of the cingulate sulcus ~20 mm anterior to the coronal plane through the anterior commissure and had a diameter of ~8 mm. The mean volume of the aMCC seed mask was 231.43 ± 41.60 mm³. The thalamic target masks were drawn on the left thalamus according to an atlas (Jones, 2007). Because the goal was to investigate the relative connectivity of the aMCC to the ventral anterior and ventrolateral anterior nuclei of the thalamus, the region comprising these structures formed the VA/VLa target region (943.93 ± 66.90 mm³). For comparison, all other thalamic regions formed the non-VA/VLa target region (2445.31 ± 164.57 mm³). For each voxel in the aMCC seed masks, the number of samples reaching a particular thalamic target was recorded.

Connectivity measure. Considering all the nerve fibers originating in the source region A (aMCC for this study), the structural connectivity may be defined in terms of the proportion of those fibers that intersect the target region B while running within the brain white matter, yielding a number in the interval between zero (none of the fibers intercept B) and one (all fibers starting in A reach B). This quantity gives no information about the absolute number of connections between two regions, but reflects the degree of connectedness or the relative connection density. The connectivity of A with B is direction-dependent, thus generally not identical to that of B with A (not to be mixed up with the direction of signal exchange, i.e.,afferent and efferent fibers). To remove this dependency on the seed region, we computed the connectivity metric using each region as a seed region once and then averaging the result. If the area...
or volume of A approaches a point, this measure reduces to the existence formulation proposed by Behrens et al. (2003), which only takes values on the discrete subset \([0,1]\) (for further details, see Kaden et al., 2007).

**Patient study**

**Participants.** Fifteen patients with chronic thalamic lesions (mean age, 44.7 years; range, 19–65 years; mean education, 10.8 years; range, 10–13 years; mean time since lesion, 3.9 years; range, 0.5–9 years) and a control group of healthy participants (mean age, 44.4 years; range, 19–65 years; mean education, 10.9 years; range, 10–13 years) who were matched to patients with respect to age and education participated in the study. Demographic data and lesion descriptions are shown in Table 1 and a lesion overlay plot is shown in Figure 1.

To specify the results, we divided the patients into two groups, depending on the anatomical differences of their thalamic lesions. Therefore we defined a region of interest (ROI) as being comprised of the VA nucleus and the VLa nucleus of the thalamus, according to the atlas by Jones (2007). A group of six patients (one female) showed substantial lesion overlap with the ROI (VA/VLa group; mean age, 46.7 years; range, 27–66; mean education, 10.9 years; range, 10–13 years; mean time since lesion, 4.7 years; range, 1–9 years). Only one patient from this group had an additional lesion in the MD nucleus of the thalamus. In comparison, the lesions of a second group of nine patients (four females) did not affect the ROI (non-VA/VLa group; mean age, 43.4 years; range, 19–65 years; mean education, 10.7 years; range, 10–13 years; mean time since lesion, 3.4 years; range, 0.5–8 years). In seven of these nine non-VA/VLa patients, the MD was clearly affected (Table 1). Age, sex, and education were matched between each patient subgroup and its control subgroup; however, patient subgroups could not be matched to each other with respect to sex. Figure 2 shows an ROI plot and the lesion overlap with the ROI and outside the ROI.

**Procedure.** A speeded modified flanker task known to elicit the ERN and to be suitable for patient studies was used in the study (Ullsperger and von Cramon, 2006b). Participants were instructed to respond to a target arrow, which had an onset delayed by 80 ms from the onset of four flanker arrows (two above and two below the target arrow) and which occurred for 110 ms on the screen. In 50% of trials (960 trials, divided into four sets), the flankers pointed in the same direction as the target (compatible trial), and in the other half of the trials, the arrows pointed in the opposite direction (incompatible trial). Participants had to respond with maximal speed and accuracy to the target arrow with the hand...
indicated by its direction. If they noticed an error response, participants were instructed to press a third button in the center of the keyboard within 1400 ms after target onset (Ullsperger and von Cramon, 2006a). Additionally, we made use of an adaptive algorithm that dynamically adjusted the response-time pressure based on the participants’ performance, and aimed at an optimization of error rate by 20% on incompatible errors (Fiehler et al., 2005).

**Electrophysiological recordings.** The participants were seated comfortably in a dimly lit, electrically shielded chamber. The electroencephalogram (EEG) was recorded with Ag/AgCl electrodes from a 64-channel EEG system (BrainAmps MR+; BrainProducts), referenced to left mastoid and offline re-referenced to the arithmetic mean of both mastoids. Channel impedance was kept <5 kΩ. The vertical electrooculogram (EOG) was recorded from electrodes placed above and below the right eye. To monitor horizontal eye movements, the EOG was collected from electrodes placed on the outer canthus of the left and right eye. EEG and EOG were recorded continuously with a low pass filter of 70 Hz, and analog-to-digital converted with 16-bit resolution at a sampling rate of

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**Figure 4.** Results of the performance-monitoring study in patients with thalamic lesions. Top, Response-locked grand mean average waveforms of the event-related potentials to errors (solid line) and correct responses (dotted line) shown for patients (left) and controls (right) at two midline electrodes. Middle, Topographical distribution of the error-related negativity over the scalp shown for patients (left) and controls (right). Bottom, Grand mean waveforms at ocular electrodes after artifact correction. EOGH, Horizontal electrooculogram; EOGV, vertical electrooculogram.
Diffusion-based magnetic resonance imaging has been used to analyze the diffusion properties of water molecules in the brain. This method has been shown to be effective in detecting white matter lesions and identifying areas of fiber tract overlap. Seifert et al. (2013) used this technique to investigate the effects of white matter lesions on performance monitoring in patients with thalamic lesions.

**Results**

### Lesion overlap analyses

Lesion data analysis was performed to determine the extent of overlap between the lesion data of the patients. The lesion data of patients with lesions in the right hemisphere (patient IDs: P789, P845, P1082, P1298) were flipped to allow for a more accurate comparison with the left hemisphere. The rotational and translational parameters were estimated using a linear regression method as described previously (Gratton et al., 1983).

### Functional role of the thalamus in performance monitoring

Fifteen patients with chronic focal lesions of the thalamus and a matched healthy control group underwent electroencephalography while performing a speeded flanker task suited for patient studies and known to elicit a sufficient number of errors (Ullsperger and von Cramon, 2006b). Behaviorally, both patients and controls showed equivalent flanker interference effects typical for flanker tasks, i.e., longer response times and higher error rates for incompatible trials than for compatible trials (main effect of compatibility, reaction times, $F(1,28) = 692.41$, $p < 0.0001$; error rates, $F(1,28) = 118.45$, $p < 0.0001$; no group effect, $p > 0.37$) (Tables 2 and 3). Importantly, resulting from individual adjustments of time pressure, the rate of incompatible errors, i.e., the number of errors in incompatible trials, was higher in the patient group than in the control group.

### Table 4. Results of ERP amplitude analyses for the ERN and Pe

<table>
<thead>
<tr>
<th>Variance</th>
<th>GRP</th>
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<th>f</th>
<th>p</th>
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<td></td>
<td></td>
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<td>Group</td>
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<td>Group × Resp</td>
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<td>0.14</td>
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<td>Group × AP</td>
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<td>2.56</td>
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<td>2.56</td>
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<td>Group × AP × Lat</td>
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<td>Incompatible correct response</td>
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<td>0.12</td>
<td>&gt;0.7</td>
<td>1.28</td>
<td>0.14</td>
<td>&gt;0.72</td>
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<tr>
<td>Group × AP × Lat</td>
<td>4.112</td>
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<td>1.14</td>
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<td>2.28</td>
<td>12.3</td>
<td>&lt;0.005</td>
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<td>4.56</td>
<td>6.37</td>
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<td>Thalamic patient group</td>
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<td>Resp</td>
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<td>1.14</td>
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<td>&lt;0.01</td>
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<td>5.18</td>
<td>&lt;0.01</td>
<td>4.56</td>
<td>1.86</td>
<td>&gt;0.17</td>
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Note: The upper part of the table shows the results of the omnibus ANOVA, below that, the results of planned comparisons are broken down by the factors response and group. Effects and interactions not listed are not significant. Resp, Response factor; AP, anterior–posterior factor; Lat, lateral factor; df, degrees of freedom.
events under investigation, did not differ significantly between groups (patients, 17.0 ± 1.8%, vs controls, 15.8 ± 1.8%; p > 0.64). Compared with the controls, the thalamic patients generally had prolonged reaction times (F(1,28) = 15.20, p < 0.001).

To test error detection, participants were instructed to indicate encountered errors by pressing an error-signaling button (Ulssperger and von Cramon, 2006a). Error signaling was significantly diminished and delayed in the patients (mean ± SEM, 39.1 ± 10.7%, 972 ± 128 ms) compared with the controls (85.1 ± 6.9%, t(28) = 3.83, p < 0.001; 708 ± 56 ms, t(28) = 2.16, p < 0.05). In contrast, spontaneous error-correction time and spontaneous correction rate for both groups did not differ significantly (patients, 266 ± 48 ms, 30.3 ± 8.4%; controls, 183 ± 23 ms, 20.7 ± 4.3%; p > 0.21), supporting the notion that error correction is not a sensitive measure of error processing (Rabbit, 2002; Ulssperger and von Cramon, 2006a). In 42.3 ± 10.4% of erroneous responses, no second key press was recorded for the patients at all, compared with the control group (8.4 ± 5.9%, t(28) = 2.82, p < 0.01). This verifies that the patients responded less accurately to errors than their controls.

The control group showed significant slowing of reactions on trials subsequent to errors (F(1,14) = 7.90, p < 0.05), which was accompanied by posterior improvement in accuracy (F(1,14) = 5.08, p < 0.05). In contrast, the patients’ reduced error-detection ability was accompanied by abolished posterior slowing (p > 0.91) (Tables 2 and 3). Moreover, the patients showed no significant change in error likelihood on posterior trials (p > 0.39). These results show that patients with thalamic lesions were impaired in detecting errors and adjusting behavior accordingly.

These behavioral findings were accompanied by significant group differences in the ERN (Fig. 4). In the control group, errors elicited a typical ERN, reaching a trough-to-peak amplitude of −11.5 ± 0.9 µV at FCz, and a posteriorly located Pe 300–500 ms after the erroneous response. In contrast, patients showed a significantly reduced ERN amplitude of −6.6 ± 0.8 µV and a diminished Pe (for detailed statistical results, see Table 4). No group difference was found between ERP waveforms and correct responses (p > 0.47).

To test the specific functional contribution of the VA/VLa nuclei to performance monitoring, the ERP data were analyzed for two patient subgroups, the VA/VLa group (comprised of six patients in whom lesions affected the VA/VLa region of the thalamus) and the non-VA/VLa group (comprised of nine patients in whom these nuclei remained unaffected) (Fig. 5). Patients from the non-VA/VLa group showed a significant ERN (main effect of response, F(1,009) = 33.65, p < 0.001; interaction response × topographical factors, F(4,32) = 6.62, p < 0.01), though of reduced amplitude compared with the controls (interaction response × topographical factors × group, F(4,64) = 3.43, p < 0.05). In contrast, in VA/VLa patients, no significant amplitude difference between the ERPs for correct and incorrect trials were found at the ERN latency range (p > 0.43). Compared with their controls, there was a significant difference between ERPs in the
entiate the functional significance of the MD in performance monitoring, we compared the ERN data of all VA/VLa patients without additional MD lesion (five of six patients) (Table 1) and all non-VA/VLa patients with clear MD lesion (seven of nine patients) with each other and to their healthy controls. This restriction of the patient groups specified that VA/VLa lesions were associated with a loss of the ERN, whereas this component was present and only somewhat smaller in thalamic lesions affecting the MD but sparing VA/VLa (for detailed statistics, see Tables 5 and 6).

Specificity of lesion effect to performance monitoring

To test whether thalamic lesions have a general detrimental effect on ERPs, we investigated the P300 for patients and controls in a visual oddball task in which participants had to press a response button whenever a rare visual target stimulus was presented in a sequence of standard visual stimuli. For target responses, the waveform of both groups showed a clear centroparietal P300 (Fig. 6). Neither amplitude nor topography differed significantly between thalamic patients and healthy controls or between thalamic subgroups and their controls ($p > 0.33$), suggesting that thalamic lesions did not have a general effect on cognitive ERPs.

Discussion

These data show that the ventral anterior and ventrolateral anterior thalamus is anatomically and functionally closely connected with the aMCC. Diffusion-based tractography confirms the notion based on anatomical studies in animals that, among the thalamic nuclei, the VA/VLa nuclei have relatively strong connectivity with the aMCC in humans. Notably, diffusion-based connectivity measures provide neither direction information nor an absolute number of fiber connections, but they are highly useful for the comparison of relative connectivity strength between cortical and subcortical regions. Furthermore, it should be noted that the ROI encompassing VA/VLa may have included small portions of adjacent anterior nuclei and the internal capsule, such that some connections from anterior thalamic nuclei might have contributed to the findings. Moreover, the data also suggest relatively strong connections from the MD to aMCC, which is in line with previous findings in monkeys (Vogt et al., 1979; Baleydier and Mauguiere, 1980; Barbas et al., 1991; Hatanaka et al., 2003).

The patient data suggest that the thalamus, particularly its VA/VLa region, is functionally necessary for performance monitoring. Thalamic lesions are associated with an impairment of ERN generation. The subgroup data suggest a gradient in impairment ranging from slight amplitude reduction in posterior and medial lesions affecting the MD to complete loss of the ERN in ventrolateral anterior and ventral anterior lesions. In contrast to previous patient studies, in which an absent ERN was not always accompanied by unequivocal behavioral deficits (in part because less sensitive measures than error detection, such as error correction, were examined) (Ullsperger and von Cramon, 2006a), here the patients showed clear behavioral performance-monitoring impairment. In particular, conscious error detection, as indicated by the error-signaling procedure, was reduced in the patients, showing that they were aware of less than half of the committed errors, whereas healthy controls noticed almost all errors. In addition, in contrast to the controls, patients showed no trial-by-trial adjustments, such as posterror slowing (Rabbitt, 1966) and posterror improvement in accuracy. The concomitant abolishment of the ERN and posterror behav-

Figure 6. A, B, Stimulus-locked grand mean average waveforms for target (solid line) and standard (dotted line) stimuli in the oddball task shown at two midline electrodes separately for the thalamic patients (A) and control group (B). C, D, Data for the VA/VLa (C) and non-VA/VLa subgroups (D).
Thalamus and Performance Monitoring

It should be noted that, in many patients, the lesions were not completely confined to the thalamus, but also affected neighboring structures, such as the internal capsule and the putamen. Striatal lesions have been shown to affect the ERN (Ullsperger and von Cramon, 2006b). Notably, the region-of-interest analysis of the VA/VLa area shows that the electrophysiological findings are specific to the frontostriato-thalamocortical circuits connected via these predominantly motor-related thalamic nuclei. Importantly, all behavioral and ERP findings remained significant when a patient with an additional lesion of the lateral prefrontal cortex (P325) was excluded from analysis, further supporting the specificity of the results to the thalamus.

This study particularly focused on the thalamic VA/VLa nuclei, as this region connects motor-action-related striatal and cerebellar inputs with the motor-related rostral cingulate zone in aMCC (Van Hoesen et al., 1993; Hatanaka et al., 2003; Hoshi et al., 2005), monitoring of which, according to current models of performance, should be relevant for detecting deviations in action outcomes (Holroyd and Coles, 2002). Notably, other regions of the thalamus are connected with the aMCC as well, in particular the MD and anterior and intralaminar nuclei, implicated in pain processing (Vogt et al., 1993; Vogt, 2005), arousal, and attention (Van der Werf et al., 2002). This is reflected in two findings of the present experiments. First, diffusion-based tractography revealed substantial, though relatively less, connectivity of the aMCC and the thalamic areas not captured by the VA/VLa region, in particular the MD. Second, patients with thalamic lesions not affecting the VA/VLa nuclei still show a somewhat reduced ERN amplitude, suggesting that input from other thalamic areas to the aMCC are of importance as well. In addition, their ability to consciously perceive errors appears similarly impaired as in the VA/VLa patients, which may have to do with the role of the MD and intralaminar nuclei in arousal and awareness.

In summary, in humans, the thalamus closely interacts with the aMCC. This interaction is of great functional importance for performance monitoring and subsequent adjustments. The performance-monitoring function appears to be represented more in the ventral anterior and ventrolateral anterior than in medial and posterior regions of the thalamus. The VA/VLa nuclei seem to modulate aMCC activity and to integrate inputs from the striatum, the lateral prefrontal cortex (via nonreciprocal corticothalamic fibers), and the cerebellum. An important aim for future research is to examine the relative contributions of these inputs for performance monitoring and cognitive control. The present findings may also be of potential clinical interest as deep brain stimulation (DBS) in nearby thalamic regions has recently been used for the treatment of Tourette’s syndrome (Servello et al., 2008, 2009). It will be important to see whether and how the impaired performance monitoring in this disorder (Johannes et al., 2002; Müller et al., 2003), reflected in increased ERN amplitudes, is modulated by DBS in the thalamus; moreover, the implantation of depth electrodes may allow direct recording of electrical activity in these regions (Marceglia et al., 2010) and link it to performance monitoring and other cognitive functions.

References


