Kinematic analysis of thalamic versus subthalamic neurostimulation in postural and intention tremor

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Deep brain stimulation of the thalamus (thalamic DBS) is an established therapy for medically intractable essential tremor and tremor caused by multiple sclerosis. In both disorders, motor disability results from complex interaction between kinetic tremor and accompanying ataxia with voluntary movements. In clinical studies, the efficacy of thalamic DBS has been thoroughly assessed. However, the optimal anatomical target structure for neurostimulation is still debated and has never been analysed in conjunction with objective measurements of the different aspects of motor impairment. In 10 essential tremor and 11 multiple sclerosis patients, we analysed the effect of thalamic DBS through each contact of the quadripolar electrode on the contralateral tremor rating scale, accelerometry and kinematic measures of reach-to-grasp-movements. These measures were correlated with the anatomical position of the stimulating electrode in stereotactic space and in relation to nuclear boundaries derived from intraoperative microrecording.

We found a significant impact of the stereotactic z-coordinate of stimulation contacts on the TRS, accelerometry total power and spatial deviation in the deceleration and target period of reach-to-grasp-movements. Most effective contacts clustered within the subthalamic area (STA) covering the posterior Zona incerta and prelemniscal radiation. Stimulation within this region led to a mean reduction of the lateralized tremor rating scale by 15.8 points which was significantly superior to stimulation within the thalamus \( P < 0.05 \), student’s \( t \)-test. STA stimulation resulted in reduction of the accelerometry total power by 99%, whereas stimulation at the ventral thalamic border (68%) or within the thalamus proper (2.5%) was significantly less effective \( P < 0.01 \). Concomitantly, STA stimulation led to a significantly higher increase of tremor frequency and decrease in EMG synchronization compared to stimulation within the thalamus proper \( P < 0.001 \). In reach-to-grasp movements, STA stimulation reduced the spatial variability of the movement path in the deceleration period by 28.9% and in the target period by 58.4%, whereas stimulation within the thalamus was again significantly less effective \( P < 0.05 \), with a reduction in the deceleration period between 6.5 and 21.8% and in the target period between 1.2 and 11.3%. An analysis of the nuclear boundaries from intraoperative microrecording confirmed the anatomical impression that most effective electrodes were located within the STA.

Our data demonstrate a profound effect of deep brain stimulation of the thalamic region on tremor and ataxia in essential tremor and tremor caused by multiple sclerosis. The better efficacy of stimulation within the STA compared to thalamus proper favours the concept of a modulation of cerebello–thalamic projections underlying the improvement of these symptoms.

Keywords: deep brain stimulation; tremor; ataxia; thalamus; subthalamic white matter; kinematic analysis

Abbreviations: DBS = deep brain stimulation; ET = essential tremor; MS = multiple sclerosis; STA = subthalamic area; TRS = tremor rating scale; VIM = ventral intermedius nucleus

Introduction

Deep brain stimulation of the ventrolateral thalamus (thalamic DBS) is used to treat a wide range of medically intractable tremor syndromes, nowadays mostly severe essential tremor (ET) and tremor caused by multiple sclerosis (MS). In both diseases, motor disability results from the complex interaction of kinetic (postural, action and intention) tremor and ataxia with voluntary movements. The efficacy of thalamic DBS in ET is proven in randomized and controlled trials (Dick, 2003). For MS tremor, no controlled studies are available and the current data is therefore insufficient to support clinical efficacy on an evidence-based level. Nevertheless, results from case series support the clinical impression of a significant symptomatic benefit from thalamic DBS in at least a subpopulation of MS tremor patients (Wishart et al., 2003). Whereas clinical effects of thalamic DBS have been thoroughly assessed, crucial aspects of its neural mechanisms still await further characterization: first, the optimal anatomical target structure for DBS in tremor is still debated and has never been analysed in conjunction with objective measures of different aspects of motor disability in ET and MS patients. Second, the physiological influence of thalamic DBS on the different components of kinetic tremor as well as abnormalities attributed to cerebellar dysfunction in ET and MS have not been completely characterized.

The standard stereotactic coordinates for thalamic DBS are located at the border between the ventral intermediate nucleus (VIM) and the subthalamic white matter (Krack et al., 2002). It is therefore debatable whether tremor reduction is caused by neural elements within the thalamus proper or the subthalamic area. Furthermore, the basic physiological mechanisms of DBS as well as the neural elements influenced by neurostimulation have not yet been conclusively defined. From electrophysiological studies, there is evidence for impact of DBS both on fibre tracts (Ranck, 1975; Holsheimer et al., 2000; Kiss et al., 2003a; Anderson et al., 2004, 2006) and neuronal somata (Beurrier et al., 2001; Kiss et al., 2002; Magarinos-Ascone et al., 2002). It has been proposed that stimulation within the thalamus proper predominantly influences pathological neuronal activity of thalamocortical projection neurons (McIntyre et al., 2004). Alternatively, stimulation of the subthalamic area would primarily impact afferent cerebellothalamic fibres (Anderson et al., 2006). Recent case series have challenged the concept of tremor abolition by neurostimulation of the thalamus proper and located the most effective stimulation site within the subthalamic fibre area (Kitagawa et al., 2000; Murata et al., 2003; Plaha et al., 2004).

Postural and intentional components are essential features of advanced ET (Louis, 2005) and MS tremor (Alusi et al., 2001b). In ET, postural tremor is the most and disease defining symptom (Deuschl et al., 1998).

Thalamic DBS modulates the amplitude, frequency, regularity and tremor-EMG coherence in ET postural tremor (Vaillancourt et al., 2003). In MS, postural tremor is the principal constituent of the broad clinical spectrum of ‘jerky’ movements with a prevalence of 92% and correlates highly with the tremor disability score (Alusi et al., 2001b). The influence of thalamic DBS on electrophysiological properties of MS postural tremor has not yet been investigated.

Intention tremor has a lower prevalence than postural tremor in both diseases. Approximately 15% of ET patients suffer from intention tremor (Biary and Koller, 1987), whereas the proportion among MS tremor patients seems to be even lower (Alusi et al., 2001b). Nevertheless, intention tremor is regarded the predominant source of disability (Tranchant et al., 1995; Liu et al., 1997) and an important factor in considering functional neurosurgery. Clinically clearly defined as a tremor with increasing amplitude during movements towards a target (Deuschl et al., 1998), the electrophysiological assessment of intention tremor is difficult (Frost, 1978; Jankovic and Frost, 1981). Intention tremor is part of atactic (literally: ‘disordered’) movements in cerebellar dysfunction and as such difficult to separate from other features like proximal postural instability or serial dysmetria. One option is the kinematic analysis of visually guided reach-to-grasp movements which allows to measure abnormalities of the movement trajectories during different phases of the motor task. While serial dysmetria is characterized by early correctional movements during the reach, ataxia and intention tremor are most prominent in the deceleration phase of patients with cerebellar disorders (Flament and Hore, 1986; Hallett et al., 1991; Hore et al., 1991; Topka et al., 1998). MS tremor patients with lesions of the cerebellum and infratentorial structures typically share aspects of ataxia with patients suffering from cerebellar deficit of other origin (Feys et al., 2005a). In ET, interestingly, both EMG and kinematic analysis found similar abnormalities in the deceleration period leading to the suggestion of cerebellar dysfunction in a subgroup of ET patients (Britton et al., 1994; Deuschl et al., 2000; Koster et al., 2002). It has been proposed that serial dysmetria in early periods of targeting movements causes delayed compensatory moves which facilitate the occurrence of intention tremor (Elble, 1998). It is therefore important to quantify the effect of thalamic DBS on the different phases of reach-to-grasp movements to elucidate the underlying pathophysiological mechanisms.

The present study aimed at defining fundamental electrophysiological effects of thalamic DBS in severe postural and intention tremor. We investigated the influence of each stimulation contact on the contralateral features of grasp-to-reach movements to elucidate the underlying pathophysiological mechanisms.
### Subjects and methods

#### Subjects

Twenty-one patients (9 females and 12 males) who have been treated with uni- (5) or bilateral (16) thalamic DBS at our centre for a medically intractable tremor according to the diagnostic criteria of the Tremor Investigation Group and the Consensus statement of the Movement Disorder Society Group (Deuschl et al., 1998) caused by MS (11) or ET (10) participated in this study. No patient was taking anti-tremor medication at the time of assessment. Clinical details of the patients are summarized in Table 1. In MS patients (patients no. 11–21), clinical signs in the arms other than tremor and ataxia, symptoms in other parts of the body due to MS as well as the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) are listed in Table 2.

#### Surgical procedure, microrecording

Mounting of the stereotactic ring (Zamoran–Dujovny open ceramic version, Stryker–Leibinger, Freiburg, Germany) was followed by a stereotactic MRI (Magnetom Vision 1.5 tesla, Siemens, Erlangen, Germany) with axial gadolinium-enhanced T1-sequences under general anaesthesia. Target coordinates relative to the midpoint of the anterior and posterior commissure [midACPC] were defined on the T1-images according to the atlas coordinates of the VIM. If the third ventricle exceeded a width of 14 mm, the laterality of the target was adjusted. The trajectories were planned on the gadolinium-enhanced T1-sequences to avoid vessels, sulci and ventricles. For intraoperative microrecording, we used five microelectrodes in a ‘Ben-gun’ configuration (MEAS, Stryker–Leibinger) with one central electrode surrounded by four electrodes situated 2.3 mm anterior, posterior, medial and lateral. Electrodes were simultaneously advanced from 6 mm above the target to 3–4 mm below the target at steps of 0.5 mm. Intraoperatively, we defined the optimal stimulation site by evaluating beneficial and adverse effects of 130 Hz microstimulation at different levels of the five trajectories and then implanted the permanent macroelectrode (model 3387 or 3389, Medtronic, Minneapolis, MN, USA). 43% of all electrodes (16/37) were implanted into the central trajectory, 38% (14/37) into the lateral, 5.5% (2/37) into the posterior trajectory.

Intraoperative microrecordings were monitored online (Leadpoint-system, Medtronic) and stored for offline analysis (CED 1401 system, sampling rate of 25 kHz; Cambridge Electronic Design, Cambridge, UK) with the Spike2 version 5.05 CED software. We defined the neuronal discharge characteristics at each electrode position according to discharge frequency, response to intraoperative cutaneous somatosensory stimulation and rapid active or passive joint movements, as well as the configuration of single unit activity (SUA). Recordings were classified as intrathalamic if SUA had a discharge frequency of at

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>Preoperative total TRS (max 144)</th>
<th>Postoperative total TRS (max 144)</th>
<th>Side of stimulation</th>
<th>Duration after surgery (months)</th>
<th>Stimulation-parameters right electrode (V, µs, Hz)</th>
<th>Stimulation-parameters left electrode (V, µs, Hz)</th>
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<td>ET</td>
<td>69</td>
<td>31</td>
<td>71</td>
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<td>1.2, 60, 130</td>
<td>1.5, 60, 130</td>
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<td>13</td>
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<td>2.2, 60, 180</td>
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</tr>
<tr>
<td>3</td>
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<td>ET</td>
<td>78</td>
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<td>47</td>
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<td>2.3, 60, 130</td>
<td>1.5, 60, 130</td>
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<td>F</td>
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<td>16</td>
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<td>3.5, 90, 180</td>
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<td>MS</td>
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<td>5</td>
<td>79</td>
<td>34</td>
<td>Bilateral</td>
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<td>F</td>
<td>MS</td>
<td>34</td>
<td>15</td>
<td>60</td>
<td>27</td>
<td>Left</td>
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<td>—</td>
<td>2.8, 90, 150</td>
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<tr>
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<td>M</td>
<td>MS</td>
<td>57</td>
<td>13</td>
<td>50</td>
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<td>Left</td>
<td>19</td>
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<td>3.5, 90, 150</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>MS</td>
<td>43</td>
<td>18</td>
<td>56</td>
<td>30</td>
<td>Left</td>
<td>13</td>
<td>—</td>
<td>2.0, 90, 130</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>MS</td>
<td>28</td>
<td>7</td>
<td>58</td>
<td>26</td>
<td>Left</td>
<td>6</td>
<td>—</td>
<td>3.5, 90, 150</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>MS</td>
<td>42</td>
<td>6</td>
<td>98</td>
<td>58</td>
<td>Bilateral</td>
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<td>2.0, 60, 130</td>
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<td>19</td>
<td>F</td>
<td>MS</td>
<td>54</td>
<td>15</td>
<td>77</td>
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<td>Bilateral</td>
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<td>2.0, 90, 130</td>
<td>2.0, 90, 130</td>
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<tr>
<td>20</td>
<td>M</td>
<td>MS</td>
<td>46</td>
<td>15</td>
<td>129</td>
<td>78</td>
<td>Bilateral</td>
<td>6</td>
<td>2.5, 90, 150</td>
<td>3.2, 90, 150</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>MS</td>
<td>23</td>
<td>6</td>
<td>93</td>
<td>28</td>
<td>Bilateral</td>
<td>6</td>
<td>1.5, 60, 130</td>
<td>2.8, 90, 130</td>
</tr>
</tbody>
</table>

Mean ± SME ET: 68.4 ± 3.1, 28.1 ± 4.2, 597 ± 3.6, 218 ± 3.3
Mean ± SME MS: 41.5 ± 3.5, 10.1 ± 1.5, 74.4 ± 8.2, 36.9 ± 5.4

Total: 54.3 ± 3.8, 18.7 ± 2.9, 674 ± 4.8, 297 ± 3.6
Least 15 Hz and/or responded to somatosensory stimulation or joint movements (Kiss et al., 2003b). Recordings from the subthalamic area were defined in the absence of SUA and low background activity or spare SUA below 5 Hz without response to somatosensory stimuli or joint movements (Velasco and Molina-Negro, 1973; Velasco et al., 1976; Eaton and Moss, 1989). If the electrode location could not be definitely classified according to these criteria, the respective trajectory was excluded from further analysis. In 19 finally implanted electrodes, microrecordings allowed to determine the ventral thalamic border (thalamic border) as indicated by a transition from intrathalamic recordings to recordings of the subthalamic area.

### Evaluation of electrode position in stereotactic space

The stereotactic coordinates of each contact of the quadripolar macroelectrode related to midACPC were calculated based on postoperative X-ray radiographies in anteroposterior and lateral projections (Stereoplan plus v.2.3 software, Stryker-Leibinger). If postoperative stereotactic X-rays were unavailable, the coordinates were determined by fusion of the preoperative stereotactic and postoperative MRI.

If microrecordings allowed to define the ventral thalamic border, as described earlier, we calculated the distance of each contact of the macroelectrode to the thalamic border by reconstructing a plane within the commissure-based coordinate system connecting the points of all microelectrodes displaying transition from thalamus to the subthalamic area. The Euclidean distance between the centre of each contact and the reconstructed plane was measured (Fig. 1) using self-written routines in Matlab (MathWorks, Natick, NJ, USA).

### Table 2 Clinical symptoms other than ataxia and tremor as well as Expanded Disability Status Scale (EDSS) of MS tremor patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Clinical symptoms of arms other than tremor and ataxia</th>
<th>Additional clinical symptoms</th>
<th>EDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>–</td>
<td>Paraparesis (mostly wheelchair-bound), sensory dysfunction</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>–</td>
<td>Paraparesis (wheelchair-bound), nystagmus, dysarthria, urinary incontinence</td>
<td>8.0</td>
</tr>
<tr>
<td>13</td>
<td>Mild paresis left arm</td>
<td>Dysarthria</td>
<td>4.5</td>
</tr>
<tr>
<td>14</td>
<td>–</td>
<td>Paraparesis, nystagmus, dysarthria, slight visual disturbance</td>
<td>6.5</td>
</tr>
<tr>
<td>15</td>
<td>–</td>
<td>Paraparesis (wheelchair-bound), nystagmus, dysarthria, slight visual disturbance</td>
<td>7.5</td>
</tr>
<tr>
<td>16</td>
<td>–</td>
<td>Paraparesis, dysarthria, sensory dysfunction, urinary frequency</td>
<td>70</td>
</tr>
<tr>
<td>17</td>
<td>–</td>
<td>Paraparesis (mostly wheelchair-bound), nystagmus, dysarthria</td>
<td>70</td>
</tr>
<tr>
<td>18</td>
<td>Sensory dysfunction both arms</td>
<td>Paraparesis (wheelchair-bound), nystagmus, oculomotoric paresis, dysarthria, urinary incontinence</td>
<td>8.0</td>
</tr>
<tr>
<td>19</td>
<td>–</td>
<td>Paraparesis, nystagmus, oculomotoric paresis, dysarthria</td>
<td>6.5</td>
</tr>
<tr>
<td>20</td>
<td>Sensory dysfunction both arms</td>
<td>Paraparesis (wheelchair-bound) nystagmus, dysarthria, urinary incontinence</td>
<td>8.0</td>
</tr>
<tr>
<td>21</td>
<td>Mild paresis right arm</td>
<td>Paraparesis (wheelchair-bound), nystagmus, oculomotoric paresis, dysarthria, urinary dysfunction</td>
<td>8.0</td>
</tr>
</tbody>
</table>

### Evaluation of neurostimulation effects

All patients underwent a clinical and kinematic assessment of the neurostimulation effects through each contact of the quadripolar stimulation electrode. For standardized comparison, we stimulated each contact with the same parameters used for chronic stimulation in this electrode (Table 1).

### Clinical evaluation

Tremor severity was evaluated using the lateralized TRS, which was calculated from items 5 or 6 (tremor right or left upper extremity), 11 (drawing large Archimedes spiral), 12 (drawing small Archimedes spiral), 13 (drawing straight lines) and 14 (pouring a glass of water) (maximum 28 with higher scores indicating more severe tremor).

### Accelerometry

Patients were comfortably seated on an armchair while holding both arms elevated at the shoulder level in a wing-heatig position with the elbows flexed at 90° and wrists extended in line with the elbows at the level of the patient’s nose. The postural tremor was recorded by a piezoelectric accelerometer attached to the dorsum of each hand 9 cm distal to the processus styloideus ulnae on the distal part of the third metacarpal bone. Simultaneously, surface electromyographic activity of the M. flexor carpi ulnaris and M. extensor carpi ulnaris was recorded with electrodes positioned 2 cm apart, close to the motor point of the respective muscle. The accelerator signals and the EMG channels were sampled over 32 s at a rate of 800 Hz. Tremor activity in DBS OFF as well as in DBS ON with subsequent stimulation of all four contacts was analysed for accelerometer total power \([\log (\text{mg}^2/\mu\text{V}^2)]\) and peak frequency. From the rectified EMG, we determined the...
synchronization between mechanical oscillations and muscle activity accelerometry tremor and EMG (Raethjen et al., 2000).

Kinematic analysis of reach-to-grasp movements
Patients were seated on a comfortable chair with their back supported and the active hand resting with the solum on a small platform located in front. The shoulder was in a neutral position and the elbow flexed at 90°. The target consisted of a cylinder (1 cm diameter, 6 cm length) which was fixed to a heavy support 34 cm above the table at a distance of 50 cm from the body. An acoustic signal instructed the subjects to reach out and grasp the cylinder with their thumb and index. After each movement the hand was returned to the starting position. All patients performed training trials until they were familiar with the task. Twenty trials were sampled in each condition.

The movements were recorded using a magnetic six-degree-of-freedom measurement system, (3SPACE FASTRAK, Polhemus Inc, Colchester, VT, USA). In that system, a low-frequency magnetic field is emanated from a stationary transmitting antenna and sensed with movable receiving antenna at a sampling rate of 40 Hz using LabView-software (National instruments Cooperation, Austin, TX, USA). Markers at a size of 1 × 1 × 1 cm³ containing the receiving antennas were placed on the tip of the thumb and index finger as well as the epicondylus of the wrist. This allowed recording of movement paths of thumb, index and wrist within a 3D-Cartesian coordinate system. Data were analysed by Matlab-software.

For kinematic analysis, the hand transport was divided into acceleration, deceleration and target-period (von Hofsten, 1991; Koster et al., 2002). For definition of the acceleration and deceleration period, we calculated the second derivation of the distance–time function of the wrist sensor and defined the transition from acceleration to deceleration as the zero-crossing of the acceleration–time function (Fig. 2A). From the available literature, the target period has been less precisely defined, however involves the termination of grasping movement of the first and second finger (Deuschl et al., 2000). Based on grip aperture distance between thumb and index finger markers (Fig. 2B), we arbitrarily defined the onset of the target period, when the grip aperture decreased to 20% of the maximal distance between thumb and index finger markers within the trajectory (Fig. 2).

In normal controls, reach-to-grasp movements are characterized by invariant movement trajectories. The deviation from the average path was chosen to quantify ataxia. For quantitative analysis, the path of the wrist sensor was separately evaluated for
the acceleration, deceleration and target period to assign spatial abnormalities to the respective period of the movement. For that purpose, we defined the average path of all available grasping trials in one condition and determined the root mean square (RMS in cm) of each movement trajectory to the average path in a two-dimensional plane perpendicular to the direction of the hand movement (Fig. 2C). Subsequently, we calculated the mean of the RMS of all trajectories from the average path for each of three movement periods. Kinematic analysis was performed in DBS OFF and for each of four contacts with the identical stimulation parameters used in assessment of lateralized TRS and accelerometry. The absolute values for mean deviation from the average path showed a high degree of interindividual variability due to differences in symptom severity. Therefore, the relative change from baseline (DBS OFF) was used to assess the impact of stimulation through the four contacts on the different movement periods.

**Determination of charge of stimulation contact**

We calculated the charge (μC) of each stimulation contact according to the following formula:

\[ \text{Amplitude [V] \times pulse width [μs]/impedance [Ω]} \]

**Statistical analysis**

To describe the relative position of each stimulation contact to the standard target \((x = 13, y = -5.5, z = 0)\), we calculated the difference (in mm) along each axis of the Cartesian stereotactic coordinate system (called ‘coordinate difference’). Based on this calculated difference, each contact was assigned to one of the three categories according to its position on the \(x\), \(y\) and \(z\) axis, respectively. Along the \(x\)-axis, a difference \(< -0.5\) mm was considered ‘medially’ to the standard target, between \(-0.5\) and \(+0.5\) mm ‘at standard coordinates’ and \(+0.5\) mm ‘laterally’ to the standard target. Along the \(y\)-axis, a difference \(< -0.5\) mm was considered ‘posterior’ to the standard target, between \(-0.5\) and \(+0.5\) mm ‘at standard coordinates’ and \(+0.5\) mm ‘anterior’ to the standard target. Along the \(z\)-axis, a difference \(< -0.5\) mm indicated a position ‘below (ventral)’ to standard target, between \(-0.5\) and \(+0.5\) mm ‘at standard coordinates’ and \(+0.5\) mm ‘above (dorsal)’ to standard target.

We used repeated measures of covariance (ANCOVA) with the following dependent variables: change in lateralized TRS, accelerometry total power, tremor frequency and change of spatial deviation in the deceleration and target period and the following covariates: Disease (ET versus MS), stimulation charge and coordinate difference \((x, y, z)\). The ANCOVA results directed measures of variance (ANOVA) and student’s \(t\)-test for individual comparisons.

To describe the position of the stimulation contact in relation to the electrophysiologically determined ventral thalamic border, we calculated the distance of each stimulation contact to that border. In contacts located below the electrophysiologically determined thalamic border, the mean distance to the ventral border was \(1.5 \pm 0.2\) mm (mean ± standard error of the mean). In contacts located above, the mean distance was \(3.3 \pm 0.3\) mm. We used ANCOVA analysis to describe the effect of disease, stimulation charge and distance to ventral thalamic border on change in lateralized TRS, accelerometry total power, change in tremor frequency and change of spatial deviation within the deceleration and target period. To compare the effect of stimulation contacts below and above the thalamic border we used student’s \(t\)-test.

All tests were two-sided with a \(P < 0.05\).

**Results**

**Clinical effect of neurostimulation**

Thalamic DBS using the postoperatively determined chronic stimulation parameters was highly effective in all patients (Table 1). The average reduction of the preoperative TRS in all patients was 55.9 ± 4.4% (mean ± standard error of the mean), in ET patients 64.2 ± 4.4%, and in MS patients 50.4 ± 3.1%.

**Neurostimulation effect on lateralized TRS**

**Correlation of lateralized TRS with stereotactic coordinates**

In DBS OFF, the mean lateralized TRS was 22.3 ± 1.0 for all patients. ANCOVA analysis revealed that the magnitude of change in lateralized TRS in DBS ON depended on the \(z\)-coordinate difference of the stimulation contact \([F(1,148) = 32.1, \ P < 0.001]\). No other covariate or interaction term was associated with a significant difference (Table 3). One-way ANOVA showed a significant difference in change of lateralized TRS between contacts located below, at level of standard target and above \([F(2,145) = 68.0, \ P < 0.001]\). The largest change in lateralized TRS (15.8 ± 1.0) was found for contacts below the standard target, whereas stimulation contacts at level of the standard target or above were significantly less effective (12.1 ± 1.3 and 4.7 ± 0.5) (Fig. 3A).

**Correlation of lateralized TRS with distance of stimulation site to the ventral thalamic border**

In 19 electrodes (76 contacts in 13 patients), electrophysiological recordings allowed to determine the ventral thalamic border. In these cases, the mean lateralized TRS in DBS OFF was 21.5 ± 1.6. In the ANCOVA analysis, only distance to the electrophysiologically determined ventral thalamic border had a significant relation to change in lateralized TRS \([F(1,76) = 63.2, \ P < 0.001]\) (Table 4). Stimulation of contacts below the thalamic border led to a significant larger change of lateralized TRS (15.4 ± 1.3) than contacts above (5.2 ± 0.6, \(P < 0.001, t\)-test) (Fig. 3B).

**Neurostimulation effect on accelerometry in postural tremor**

**Correlation of accelerometry with stereotactic coordinates**

In 33 electrodes (132 contacts in 21 patients), we evaluated the effect of thalamic DBS on accelerometry total
The total power in DBS OFF was 7.9 × 10^2 ± 2.2 × 10^2 [log (mg^2)/μV^2]). ANCOVA analysis showed that the total power depended on the z-coordinate difference of stimulation contacts [F(1,132) = 5.1, P < 0.025], whereas other covariates or interactions did not reveal a significant effect (Table 3). One-way ANOVA showed a significant difference in total power for stimulation contacts below the standard level and above [F(2,145) = 6.8, P < 0.002]. Lowest accelerometry total power was found for contacts located below standard coordinate (7.7 × 10^2 ± 5.2 × 10^2), whereas stimulation at level of standard coordinates (7.8 × 10^3 ± 5.3 × 10^3) and above (2.5 × 10^2 ± 4.8 × 10^3) was significantly less effective (Fig. 3C).

In DBS OFF, tremor frequency differed between ET (3.9 ± 0.1 Hz) and MS patients (3.2 ± 0.2 Hz) (P < 0.001, t-test). ANCOVA analysis revealed significant impact on change of tremor frequency by DBS for disease [F(1,132) = 4.8, P < 0.031], x-coordinate difference [F(1,132) = 24.6, P < 0.001], z-coordinate difference [F(1,132) = 8.6, P < 0.003] as well as the interaction terms [disease × x-coordinate difference] [F(1,132) = 4.0, P < 0.047] and [x-coordinate difference × z-coordinate difference] [F(1,132) = 4.3, P < 0.041] (Table 3). In ET, stimulation contacts below the standard z-coordinate led to an increase of tremor frequency by 0.78 ± 0.12 Hz, at level of standard z-coordinate by 0.60 ± 0.19 Hz and above by 0.13 ± 0.05 Hz. In MS, effect on tremor frequency was less pronounced with an increase by 0.39 ± 0.13 Hz below standard z-coordinate, 0.03 ± 0.03 Hz at standard coordinate and 0.01 ± 0.04 Hz above (Table 5). With respect to the x-coordinate, in ET patients, stimulation contacts located medially to the standard x-coordinate led to an increase by 0.95 ± 0.09 Hz, at standard x-coordinate by 0.43 ± 0.15 Hz and laterally by 0.12 ± 0.06 Hz. In MS, there was no significant difference in change of the tremor frequency in relation to the x-coordinate difference (Table 5).

In DBS OFF, we found synchronization between EMG and accelerometry in 92% of contacts. Synchronization was significantly less frequent (P < 0.001, chi square test) with contacts below the standard z-coordinate (33%) compared to the standard target and above (70.5 and 96%).

### Correlation of accelerometry with distance to the ventral thalamic border

In 17 electrodes (68 contacts from 12 patients), electrophysiological recordings allowed to determine the ventral thalamic border. In these cases, the mean total power was 5.5 × 10^2 ± 3.2 × 10^2 in DBS OFF. The change in total power was significantly related to the distance of the contact from the ventral thalamic border [ANCOVA, F(1,68) = 5.7, P < 0.020] (Table 4). Stimulation below the thalamic border reduced total power to 1.6 × 10^2 ± 5.6 × 10^-1 but stimulation above only to 2.2 × 10^2 ± 6.1 × 10^3 (P < 0.01, t-test) (Fig. 3D).

In DBS OFF, tremor frequency differed significantly between ET (3.94 ± 0.11 Hz) and MS patients (3.1 ± 0.07 Hz) (P < 0.001, t-test). ANCOVA analysis showed a significant influence on the change of tremor

<table>
<thead>
<tr>
<th>Power</th>
<th>Change in lateralized TRS</th>
<th>Accelerometry total power</th>
<th>Change in tremor frequency</th>
<th>Percentage change of spatial deviation (deceleration period)</th>
<th>Percentage change of spatial deviation (target period)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F (1,148) P</td>
<td>F (1,132) P</td>
<td>F (1,132) P</td>
<td>F (1,96) P</td>
<td>F (1,96) P</td>
</tr>
<tr>
<td>1: Disease</td>
<td></td>
<td></td>
<td>4.765 0.031</td>
<td>0.631 0.429</td>
<td>0.071 0.790</td>
</tr>
<tr>
<td>2: Stimulation charge</td>
<td></td>
<td></td>
<td>0.263 0.609</td>
<td>0.792 0.376</td>
<td>0.133 0.716</td>
</tr>
<tr>
<td>3: x-coordinate difference</td>
<td></td>
<td></td>
<td>24.613 0.001</td>
<td>0.401 0.528</td>
<td>3.292 0.073</td>
</tr>
<tr>
<td>4: y-coordinate difference</td>
<td></td>
<td></td>
<td>0.364 0.547</td>
<td>0.899 0.346</td>
<td>0.681 0.412</td>
</tr>
<tr>
<td>5: z-coordinate difference</td>
<td>32.071 0.001</td>
<td>5.136 0.025</td>
<td>8.647 0.003</td>
<td>6.233 0.015</td>
<td>13.352 0.001</td>
</tr>
<tr>
<td>Interaction term [1 × 2]</td>
<td>0.560 0.455</td>
<td>0.402 0.527</td>
<td>0.004 0.951</td>
<td>2.457 0.121</td>
<td>0.243 0.623</td>
</tr>
<tr>
<td>Interaction term [1 × 3]</td>
<td>3.217 0.070</td>
<td>3.340 0.070</td>
<td>1.137 0.288</td>
<td>0.578 0.449</td>
<td>0.016 0.899</td>
</tr>
<tr>
<td>Interaction term [1 × 4]</td>
<td>0.000 0.983</td>
<td>0.460 0.499</td>
<td>1.137 0.288</td>
<td>0.578 0.449</td>
<td>0.016 0.899</td>
</tr>
<tr>
<td>Interaction term [1 × 5]</td>
<td>0.800 0.373</td>
<td>1.247 0.266</td>
<td>2.129 0.147</td>
<td>0.129 0.721</td>
<td>0.199 0.657</td>
</tr>
<tr>
<td>Interaction term [3 × 4]</td>
<td>0.150 0.699</td>
<td>2.578 0.111</td>
<td>0.544 0.462</td>
<td>0.372 0.544</td>
<td>0.525 0.471</td>
</tr>
<tr>
<td>Interaction term [3 × 5]</td>
<td>0.251 0.617</td>
<td>0.319 0.573</td>
<td>2.428 0.041</td>
<td>0.029 0.865</td>
<td>0.119 0.731</td>
</tr>
<tr>
<td>Interaction term [4 × 5]</td>
<td>0.052 0.820</td>
<td>0.548 0.461</td>
<td>1.999 0.160</td>
<td>0.356 0.552</td>
<td>1.932 0.168</td>
</tr>
<tr>
<td>Interaction term [3 × 4 × 5]</td>
<td>3.297 0.72</td>
<td>0.464 0.497</td>
<td>0.170 0.681</td>
<td>0.044 0.834</td>
<td>2.262 0.136</td>
</tr>
</tbody>
</table>

Note: Measures of covariance (ANCOVA) with following dependent variables: change in lateralized TRS, accelerometry total power, change in tremor frequency and percentage deviation in the deceleration and target period of reach-to-grasp movements. Disease, stimulation charge, x-/y-/z-coordinates of stimulation contacts and respective interaction terms represent covariates. Significant impact of covariates and interaction terms are bold typed printed.
frequency for disease \[ F(1,68) = 16.1, \ P < 0.001 \] and distance of stimulation contacts to the thalamic border \[ F(1,68) = 9.6, \ P < 0.003 \] (Table 4). In ET, stimulation of contacts below thalamic border led to a significantly greater increase of tremor \( 0.71 \pm 0.12 \) Hz compared to stimulation above \( 0.21 \pm 0.07 \) Hz \( (P < 0.001, \ t\text{-test}). \]

In MS, there was no significant increase of tremor frequency (Table 6).

Stimulation below the thalamic border reduced the occurrence of EMG synchronization from 90 (DBS OFF) to 20%, whereas stimulation above did not (93%) \( (P < 0.001, \ \text{chi square test}) \).
Table 4 Effect of disease, stimulation charge and position of stimulation contact in relation to the ventral thalamic border on ET and MS tremor

<table>
<thead>
<tr>
<th></th>
<th>Change in lateralized TRS</th>
<th>Accelerometry total power</th>
<th>Change in tremor frequency</th>
<th>Percentage change of spatial deviation (deceleration period)</th>
<th>Percentage change of spatial deviation (target period)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F (1,76) P</td>
<td>F (1,68) P</td>
<td>F (1,68) P</td>
<td>F (1,52) P</td>
<td>F (1,52) P</td>
</tr>
<tr>
<td>1: Disease</td>
<td>3.747 0.57</td>
<td>0.126 0.724</td>
<td>16.11 0.001</td>
<td>0.756 0.389</td>
<td>0.404 0.528</td>
</tr>
<tr>
<td>2: Stimulation charge</td>
<td>0.090 0.765</td>
<td>1.297 0.259</td>
<td>2.580 0.113</td>
<td>0.163 0.688</td>
<td>2.028 0.161</td>
</tr>
<tr>
<td>3: Distance to VIM border</td>
<td>63.182 0.001</td>
<td>5.732 0.020</td>
<td>9.682 0.003</td>
<td>10.383 0.002</td>
<td>25.596 0.001</td>
</tr>
<tr>
<td>Interaction term [1 × 2]</td>
<td>3.821 0.054</td>
<td>0.022 0.884</td>
<td>2.455 0.109</td>
<td>0.989 0.325</td>
<td>0.001 0.978</td>
</tr>
<tr>
<td>Interaction term [1 × 3]</td>
<td>0.031 0.861</td>
<td>0.039 0.844</td>
<td>2.465 0.122</td>
<td>0.021 0.884</td>
<td>0.978 0.328</td>
</tr>
</tbody>
</table>

Note: Measures of covariance (ANCOVA) with following dependent variables: change in lateralized TRS, accelerometry total power, change in tremor frequency and percentage deviation in the deceleration and target period of reach-to-grasp movements. Disease, stimulation charge, position of stimulation contacts relative to the ventral thalamic border and respective interaction terms represent covariates. Significant impact of covariates and interaction terms are bold type printed.

Table 5 Effect of position of stimulation contact within the stereotactic space on increase of tremor frequency

<table>
<thead>
<tr>
<th>z-coordinate relative to standard value</th>
<th>Below</th>
<th>Standard</th>
<th>Above</th>
<th>x-coordinate relative to standard value</th>
<th>Medial</th>
<th>Standard</th>
<th>Lateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET</td>
<td>0.78 ± 0.12</td>
<td>0.60 ± 0.19</td>
<td>0.13 ± 0.05</td>
<td>0.95 ± 0.09</td>
<td>0.43 ± 0.15</td>
<td>0.12 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>0.39 ± 0.13</td>
<td>0.03 ± 0.03</td>
<td>0.01 ± 0.04</td>
<td>0.19 ± 0.07</td>
<td>0.16 ± 0.04</td>
<td>0.12 ± 0.09</td>
<td></td>
</tr>
</tbody>
</table>

Note: Mean change of tremor frequency (Hz) (±standard error of the mean) in DBS ON compared to DBS OFF. Since ANCOVA revealed a significant influence of disease, analysis has been performed separately for ET and MS. Stimulation contacts have been divided into three groups according to the difference of coordinate of the stimulated contact to the standard y-value and x-value, respectively. Student’s t-test was used for comparison of values at standard coordinates and above/laterally with values located below/medially to standard values. Significant differences are bold type printed.

Neurostimulation effect on reach-to-grasp movements

Correlation of change in kinematic parameters with stereotactic coordinates

Kinematic analysis was available for 24 electrodes (96 contacts in 17 patients). In the other cases tremor in DBS OFF was too severe to complete the task.

Thalamic DBS had no consistent influence on the acceleration period of reach-to-grasp-movements. However, we found significant improvements in the variability of the movement trajectories during the deceleration and target period in ET (Fig. 4A–C) and MS patients (Fig. 4D–F). Z-coordinate difference from the standard target was the only significant predictor of improvement in the deceleration period [ANCOVA, F(1,96) = 6.2, P < 0.015]. The highest percentage improvement was found for contacts located below standard z-coordinate (29.9 ± 4.5%), whereas contacts located at standard z-coordinates (6.5 ± 7.5%) and above (1.3 ± 4.4%) were significantly less effective (P < 0.05, t-test) (Fig. 5A).

Likewise, improvement in the target period was significantly related only to the z-coordinate difference [ANCOVA, F(1,96) = 13.4, P < 0.001] (Table 3). The relative improvement in the target period was greatest for contacts below standard z-coordinate (58.4 ± 3.3%), whereas contacts located at level of standard z-coordinates (21.7 ± 10.1%) and above (11.3 ± 3.2%) were significantly less effective [ANOVA, F(2,95) = 8.4, P < 0.01] (Fig. 5B).

Table 6 Effect of position of stimulation contact in relation to the ventral thalamic border on tremor frequency

<table>
<thead>
<tr>
<th>Position relative to electrophysiologically determined ventral thalamic border</th>
<th>Below</th>
<th>Above</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET</td>
<td>0.71 ± 0.12</td>
<td>0.21 ± 0.07</td>
</tr>
<tr>
<td>MS</td>
<td>0.14 ± 0.09</td>
<td>0.04 ± 0.06</td>
</tr>
</tbody>
</table>

Note: Mean change of tremor frequency (Hz) (±standard error of the mean) in DBS ON compared to DBS OFF. Since ANCOVA revealed a significant influence of disease, analysis has been performed separately for ET and MS. Stimulation contacts have been divided according to their position below and above the electrophysiologically determined thalamic border. Student’s t-test was used for comparison of values above with values below ventral thalamic border. Significant changes are bold type printed.
The stereotactic coordinates of the most effective contacts in reducing the spatial variability in the target period projected onto the prelemniscal radiation and posterior part of the Zona incerta in the Schaltenbrand–Wahren atlas (Fig. 6).

Correlation of change in kinematic parameters with distance to the ventral thalamic border
In 14 electrodes (56 contacts in 9 patients), electrophysiological recordings allowed to determine the thalamic border and to relate the electrode location to the performance in reach-to-grasp movements. In both, the deceleration and the target period, the vertical distance from the thalamic border had a significant bearing on the relative improvement of spatial variability [ANCOVA, $F(1,52) = 10.3$, $P < 0.002$] and [$F(1,52) = 25.6$, $P < 0.001$] (Table 4). Stimulation of contacts below the thalamic border was significantly more effective than above as displayed in Fig. 5C and D.

Discussion
We observed pronounced effects of thalamic DBS on fundamental electrophysiological features of MS and essential tremor which strongly depended on the anatomical site of stimulation. Thalamic DBS significantly reduced pathological features of postural tremor and also improved
unsteadiness in the terminal phase of goal-directed movements, which is a typical feature of atactic movements in cerebellar dysfunction. These effects were markedly stronger for electrode contacts below the AC–PC line as compared to stimulation at the standard VIM target within the ventrolateral thalamus. The ventrodorsal location of stimulation (stereotactic z-axis) was the only significant covariate of the change in tremor and movement parameters, with the exception of the change in tremor frequency, which was also related to the location of the electrode along the x-axis.

Methodical considerations
The level of the AC–PC line defines the ventral thalamic border in most stereotactic reference systems (Guiot et al., 1976; Schaltenbrand and Wahren, 1977). We therefore argue that the most effective contacts were probably located...
within the subthalamic white matter and not within thalamic nuclei. Before interpreting this data, some potentially confounding factors have to be considered: our anatomical interpretation is based on superimposition of landmark-based stereotactic coordinates on a standard brain atlas. Especially in MS patients, due to atrophy of grey and white matter, the thalamic region may show a significant atrophy in MRI-based quantification of parenchyma volume (Wylezinska et al., 2003; Carone et al., 2006) and therefore not match the standard anatomical atlas. We did not correlate the postoperative location of the electrode on MRI to the ventral border of the thalamus, which may be difficult to identify. Based on microelectrode recordings, which enables discrimination between grey and white matter signals, we confirmed our observation of a better stimulation efficacy below the ventral thalamic border in a subset of patients. However, accuracy of the position of the macroelectrode position relative to the electrophysiologically determined thalamic boundary may be impaired by different factors. First, there may be a mismatch between the position of the trajectory used for microrecording and the finally implanted macroelectrode. According to the available literature, the difference between the calculated target and the implanted electrode for the z-axis is in the range of 0.8 mm (Dormont et al., 1997; Ferroli et al., 2004). In our analysis of contacts considered to be located within the subthalamic area, the mean distance to the electrophysiologically determined ventral thalamic border was 1.5 mm. Therefore, we cannot exclude a potential imprecision for few contacts located in close vicinity to ventral thalamic border as determined by microrecording. In the majority of contacts, however, the vertical spacing between contact and electrophysiologically determined thalamic border was clearly larger. Second, intraoperative brain shift due to leakage of cerebrospinal fluid and re-shifting during the postoperative period have to be considered. Although there is no systematic quantitative study available on the magnitude of brain shifting following DBS, it may introduce uncertainties when postoperative imaging is used for electrode location.
The effect of brain shift in the target area, however, is likely to be small given the very accurate match between stereotactic planning and actual electrode location on postoperative stereotactic imaging in most cases. Third, simultaneously advancing of five microelectrodes as in our surgical approach may push forward the adhering brain tissue. This may lead to the impression that the recorded activity is deeper than it actually is when the brain tissue has resettled around the chronic macroelectrode. This location error is probably small, because the microelectrodes in our setup are sharp tipped and have a diameter of only 125 μm, which enables them to penetrate the tissue with little resistance.

Influence of thalamic neurostimulation on postural tremor

We analysed accelerometry total power, EMG synchronization and tremor frequency during a postural task and found that stimulating the subthalamic area reduced the total power of tremor by nearly three dimension scales approaching the range of physiological tremor (Deuschl et al., 2001). In contrast, stimulating the thalamus proper reduced postural tremor only within the range of pathological values. The synchronization between EMG and mechanical tremor oscillations—reflecting the central driving oscillator—was disrupted by stimulation through most of the contacts within the subthalamic area, but was still present with stimulation within ventrolateral thalamus. Moreover, stimulation of contacts in the subthalamic area significantly increased tremor frequency, which also reflects a reduced contribution of a pathological central tremor oscillator (Deuschl and Bergman, 2002). This effect was stronger in ET than in MS tremor, but still present in MS patients. The similar effects of neurostimulation in the two patient groups, underline the symptomatic efficacy of thalamic DBS in postural tremor in general, irrespective of the underlying disease.

A previous study has characterized the neurophysiological consequences of thalamic DBS on postural tremor in ET (Vaillancourt et al., 2003). The main finding was a marked reduction of tremor amplitude comparable to values of physiological tremor in control subjects. Additionally, effective thalamic DBS resulted in reduced tremor-EMG coherence and an increase of tremor frequency by ~1 Hz. In general, these observations are in good agreement with our results. Some differences in analysing tremor data, patient characteristics and study design, however, have to be considered in comparing both studies. In contrast to our approach, the former study investigated the root mean square displacement from the dominant tremor frequency and the degree of entrainment for determination of tremor strength and EMG-tremor coherence, respectively. Based on our qualitative method of analysing EMG-tremor coherence, we cannot completely exclude a shift of EMG activity to higher frequencies with a lower and broader coherence peak. Despite these differences, both studies support the view that effective thalamic DBS suppresses central tremor oscillations and allow mechanical-reflex factors, represented by a desynchronization and an increase of tremor frequency, to play a larger role. Basic characteristics of ET patients were different in both studies, most notably for tremor frequency in DBS OFF. Although disease duration in the former study was not stated, the markedly lower frequency of 3.8 Hz in our study suggests that our patients probably had been operated in a more advanced stage of disease. As a major difference, the previous study did not correlate the clinical and electrophysiological effects of thalamic DBS to the anatomical site of stimulation. It was therefore not possible to conclude which anatomical part of the central tremor oscillator was affected by thalamic DBS.

ET is thought to arise from abnormal oscillatory activity within the olivo–cerebellar–thalamic circuit. In the animal model of harmaline-induced tremor (Lamarre and Mercier, 1971; Elble, 1998), resembling ET in some aspects, the cerebellar cortex and the deep cerebellar nuclei synchronously show similar oscillations (Wilms et al., 1999). Cerebellar information is relayed from the deep cerebellar nuclei to thalamic nuclei and consecutively to motor cortical areas (Steriade et al., 1997). Along this pathophysiological model, thalamic DBS may act by interrupting the transfer of pathologic oscillations in the olivo–cerebellar circuit to the motor cortex (Benabid et al., 1996; Kiss et al., 2002; Anderson et al., 2003). Based on electrophysiological findings with approximately 40 times lower thresholds for fibres of passage and axonal terminals than for cell somata (Holsheimer et al., 2000; Kiss et al., 2003a; Anderson et al., 2004, 2006), it has been suggested that the targeted neuronal elements in thalamic DBS are predominantly axonal. However, despite a higher excitability for fibre tracts (Ranck, 1975), it cannot be excluded that DBS also exerts some somatodendritic effects within the volume of current spread, which may contribute to the clinical benefit. Based on PET studies demonstrating a stimulation-associated increase of regional blood flow in the primary motor cortex (Ceballos-Baumann et al., 2001) and supplementary motor area (Perlmutter et al., 2002), it has been hypothesized that effective thalamic DBS excites thalamocortical projections. By high-frequency excitation, thalamic DBS may mask the abnormal input of synchronous oscillations to the motor cortex and therefore cancel the rhythmic entrainment of spinal motoneurons and muscles (Elble, 1996; Hua et al., 1998). However, magnetoencephalographic experiments have challenged the idea of a primary role of the thalamocortical circuit in development of ET (Halliday et al., 2000). Our finding with most effective stimulation in the subthalamic area is neither consistent with the concept of modulating the thalamocortical efferent outflow for tremor suppression. Instead it favours the idea that presynaptic stimulation of cerebellar input to the thalamus may be
more appropriate to disrupt oscillatory activity. Recent electrophysiological studies in brain slices and intraoperative microrecordings in ET patients (Anderson et al., 2006) support that elimination of oscillatory input to thalamic tremor cells might be most accountable for stopping tremor propagation. Nevertheless, more effective stimulation by affecting cerebello–thalamic projections does not necessarily conflict the findings of the aforementioned PET studies. Since cerebello–thalamic projections are excitatory by nature, high-frequency stimulation within the subthalamic area could drive downstream thalamic neurons resulting in activation of cortical areas in PET imaging. A problem in interpreting the present PET data is the lack of information on the stereotactic localization of the effective electrode contacts. Further imaging studies focusing on the differential effect of the stimulation site may therefore improve our understanding of whether stimulation within the subthalamic area leads to a different activation pattern compared to stimulation within thalamus proper.

To our knowledge, no study has assessed the impact of thalamic DBS on electrophysiological parameters of postural tremor in MS. Similar to ET, stimulation of subthalamic white matter was most effective in reducing tremor power and EMG-tremor coherence. The less pronounced change in tremor frequency may reflect additional cerebellar symptoms of MS such as proximal postural instability which may contribute to low-frequency mechanical oscillations and prevent the dominance of higher-frequency mechanical-reflex oscillations.

Despite the widespread lesions in MS, action tremor seems to be specifically related to damage of the cerebellum or its connections (Liu et al., 1999). There is supporting evidence from animal experiments showing that sufficient myelination of the olivocerebellar connection is crucial for generating synchronous and exactly timed complex spike activity in the cerebellum (Lang and Rosenbluth, 2003). In myelin-deficient rats, disturbance of myelination in the olivocerebellar system results in abnormal cerebellar activity and is associated with the appearance of tremor. In MS patients, CNS myelin deficiency of the olivocerebellar system may similarly contribute to tremor activity which is conveyed to the thalamus and the thalamocortical system. Similar to ET, presynaptic blocking of the abnormal afferent input to thalamic neurons appears to be most effective in reducing postural tremor.

So far no study had assessed the impact of thalamic DBS on kinematic parameters of visually guided reach-to-grasp movements in ET. However, increasing experimental evidence suggests the evolution of cerebellar dysfunction in advanced stages of the disease, which is typically reflected by imprecise targeting during goal-directed movements. In a tracking paradigm moving a horizontal manipulandum either with the wrist (Britton et al., 1994) or elbow (Koster et al., 2002), the second agonist burst was significantly delayed in ET resulting in an abnormal deceleration profile, movement overshoot and intention tremor (Berardelli et al., 1996). One study (Zackowski et al., 2002) studied the effect of thalamic DBS on the agonist-antagonist-pattern in a sudden stretch load, but did not find a change in the timing relationship between the initial agonist and antagonist burst. Since, however, the load was applied in the hold position of the wrist, the experimental settings does not meet the criteria of a goal-directed movement but rather of a postural task. The inaccuracy of goal-directed hand movements was related to intention tremor and hypermetria in the target period and slowing during the deceleration period in a three-dimensional kinematic analysis of ET patients (Deuschl et al., 2000).

The aetiology of cerebellar dysfunction in ET is presently under discussion (Louis, 2005). It is unlikely to result from structural cerebellar damage, but may rather reflect interference with the feed-forward function of the cerebellum caused by abnormal timing signals from a dysfunctional olivocerebellar circuitry. In animal studies, complex spike activities of olivocerebellar climbing fibres have been correlated with tracking direction, amplitude and speed (Ebner et al., 2002). In combination with simple spike activity carried by mossy fibres from the spinal cord, brainstem and cerebral cortex, they probably provide the basis for a ‘velocity command signal’ essential for the control of limb movement (van Kan et al., 1993; Ebner, 1998). In the harmaline model of ET, there is enhanced rhythmic activity of complex spikes and simultaneously elimination of simple spikes (Llinas and Volkind, 1973; De Montigny and Lamarre, 1975), most likely causing disintegration of sensory and olivary input on the level of Purkinje neurons. This misarranged activation may perturb the feed-forward function of the cerebellum (Allen and Tsukahara, 1974) leading to disturbances in the deceleration and target period resembling ataxia in primary cerebellar disease. Support for this hypothesis comes from the effect of ethanol which decreases complex spikes and increase of single-spike activity in the animal model (Sinclair et al., 1982) and significantly improves cerebellar-like gait ataxia in ET (Klebe et al., 2005). However, experimental evidence for the beneficial effect of ethanol and subsequent normalisation of the olivocerebellar pathway on limb ataxia is lacking. A possible alternative to a primary cerebellar dysfunction underlying imprecise targeting in ET could be the massive interference of tremor itself with the proprioceptive feedback signal necessary to

**Influence of thalamic neurostimulation on reach-to-grasp movements**

Thalamic DBS significantly reduced the spatial variability in the target and deceleration period of visually guided reach-to-grasp movements. The improvement of these two kinematic parameters was only observed with stimulation of the subthalamic area.
control the reaching movement. Presently, it is not known which pathophysiological mechanism is improved by thalamic DBS. However, modulating the cerebello-thalamic fibre system appears to be most effective in improving ataxia. This again favours a direct impact of thalamic neurostimulation on the propagation of pathological cerebellar outflow signals and not the interruption of a reverberating tremor oscillation within the thalamocortical loop.

In MS patients, reach-to-grasp movements are severely compromised by overshoot in the deceleration period as well as intention tremor in the target period (Deuschl et al., 2000). Also abnormalities in the acceleration period of elbow flexion movements have been described (Hallett et al., 1991). In MS patients suffering from cerebellar ataxia, infratentorial lesions in the brainstem and cerebellum are commonly found on MRI (Nakashima et al., 1999). Intention tremor, in particular, is more frequently associated with lesions in the cerebellar peduncles and the pons than in the cerebellar hemispheres (Feys et al., 2005b). Lesions in these areas would mainly affect the afferent pathways of the cerebellum, the rubroolivary and the corticoolivary pathway, which could impair cerebellar activation. Neurostimulation of the cerebello–thalamic projections may disrupt pathological efferent neural activity within the cerebello–thalamo–cortical loop and thereby improve ataxia. MS lesions, however, could also disturb ascending projections within the cerebello–thalamic pathways. Additionally, disabled coordination in MS patients has been correlated with supratentorial lesions in the commissural fibres tracts (Charil et al., 2003). Thalamic DBS is unlikely to restore deficient efferent cerebellar activity or to alleviate ataxia of cortical origin. This might explain the lower efficacy on ataxia in MS patients compared to ET patients.

Thalamic neurostimulation reduced the spatial variability already in the deceleration period of reach-to-grasp movements in both MS and ET patients. This is probably related to a reduced movement overshot which has been described in previous studies of ET and MS tremor. In our study, we did not compare kinematic parameters of controls and patients. However, previous studies in normal controls demonstrated the regularity of movement trajectories with only minimal deviations from the average wrist path (Bastian et al., 1996). The reduced deviation in the deceleration period by subthalamic area stimulation probably reflects improvement of dysmetria, another feature of ataxia. The extent of improvement in the deceleration period is not as high as in the target period. However, poor accuracy already in the deceleration period may lead to subsequent agonist bursts as a compensatory mechanism with the end result of intention tremor (Berardelli et al., 1996). Therefore, even moderate improvement in the deceleration period may be causative for the much higher improvement in the target period.

Clinical effect of thalamic DBS

On the clinical TRS our ET patients improved by 64% and our MS patients by 50%, which is in good accordance with previous clinical studies. For ET, the average improvement of extremity tremor was between 50 and 80% and of head and voice tremor between 55 and 95% (Onodo et al., 1998; Limousin et al., 1999; Obwegeser et al., 2001; Sydow et al., 2003). In MS, most studies found a qualitative post-operative improvement in 50 to 100% of patients (Benabid et al., 1996; Geny et al., 1996; Montgomery et al., 1999; Berk et al., 2002; Hooper et al., 2002; Schuler et al., 2003). In the few studies providing quantitative assessment, thalamic DBS reduced the total TRS in a range between 36 and 70% (Berk et al., 2002; Schuler et al., 2003; Bittar et al., 2005).

The lateralized TRS, which was used in our study to specifically assess extremity tremor, was associated with slightly higher reduction in the range of 70 and 80% for ET patients and 62 to 76% in MS patients. This experimental parameter is difficult to compare to previous clinical trials, which typically evaluate tremor after prolonged periods of stimulation, not immediately after a change in stimulation parameters.

In keeping with the objective experimental measures, clinical tremor ratings in ET and MS were markedly better for stimulation within the subthalamic area than within ventrolateral thalamus. This emphasizes that our experimental design captured relevant features of symptom severity.

Characterization of the subthalamic area

Which could be the neural target elements of subthalamic area stimulation in ET and MS tremor? After projection onto the Schaltenbrand–Wahren atlas, the most effective electrode contacts localized onto the prelemniscal radiation which is the posterior extension of field H of Forel. From labelling and degeneration studies in animals, the course of fibres from deep cerebellar nuclei to the cerebellar thalamus has been accurately defined (Mehler and Nauta, 1974; Stanton, 1980; Illinsky and Kultas-Ilinsky, 1984). After leaving the dentate nucleus and crossing to the contralateral side, fibres form a distinct bundle which ascends rostrally and passes through and around the lateral portion of the red nucleus. The bulk of fibres continuing in the rostro-lateral direction passes through the field H of Forel and enters the thalamus, notably the VIM, through its ventral aspects. Stimulation within the subthalamic area, therefore, probably takes advantage of an anatomical ‘bottle neck’ where a large proportion of cerebellothalamic afferents can be affected by a small volume of current spread, before the fibres spread out to innervate the entire VIM nucleus (Sakai et al., 1996). Three previous clinical case series of DBS in ET also described a more effective tremor reduction by stimulation of subthalamic targets.
including the field of Forel, prelemniscal radiation and Zona incert a (Kitagawa et al., 2000; Murata et al., 2003; Plaha et al., 2004). There is no data so far on the clinically optimal stimulation site in MS tremor, but in a series of 13 MS tremor patients treated by thalamotomy the best results were obtained in patients where the lesion was confined to the subthalamic area (Alusi et al., 2001a). This observation corroborates the concepts of ‘subthalamotomy’ or ‘cam-

the subthalamic area (Alusi et al., 2001b). A direct comparison of our findings to the results of lesonal surgery, however, may be difficult for two reasons: first, localizations of lesions have not always been exactly determined due to lack of modern imaging techniques in historical studies. Second, in both procedures the underlying neural mechanism leading to tremor reduction is clearly distinct. In contrast to lesioning, DBS does not silence neuronal activity but rather acts by modulating pathological information transfer without the need for destroying brain tissue.

Conclusion

Thalamic neurostimulation does not only reduce clinical and electrophysiological measures of postural tremor in ET or MS. It is also highly effective in decreasing the spatial variability in the deceleration and target period of goal-directed movements, which are kinematic features of cerebellar ataxia. This effect on target-oriented movements may underlie the clinically impressive improvement of intention tremor in both conditions. The more pronounced tremor reduction when stimulating the subthalamic area favours the concept of modulating cerebello–thalamic projections.

References

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