Physiological and anatomical decomposition of subthalamic neurostimulation effects in essential tremor

Sergiu Groppa, Jan Herzog, Daniela Falk, Christian Riedel, Günther Deuschl and Jens Volkmann

Postural tremor is the leading symptom in essential tremor, but in some cases intention tremor and limb ataxia emerge and can become highly disabling features. Deep brain stimulation of the thalamus or subthalamic white matter improve tremor and ataxia; however, the underlying network mechanisms are enigmatic. To elucidate the mechanisms of deep brain stimulation in essential tremor, we pursued a multimodal approach combining kinematic measures of reach-to-grasp movements, clinical assessments, physiological measures of neuronal excitability and probabilistic tractography from diffusion tensor imaging. Seven patients with essential tremor (age 62.9 ± 10.3 years, two females) received thalamic deep brain stimulation and a clinical examination of severity of limb tremor and ataxia at off stimulation, using therapeutic and supratherapeutic stimulation parameters. A reach-to-grasp task based on acoustic cues was also performed. To examine the electrical properties of target structures, we determined the chronaxie of neural elements modulated. A control group of 13 healthy subjects (age 56 ± 7.6 years, five females) underwent whole-brain diffusion tensor imaging at 3 T. Probabilistic tractography was applied in healthy subjects from seeds in cerebellum and midbrain to reconstruct the connectivity pattern of the subthalamic area. The positions of stimulation electrodes in patients were transferred into probability maps and connectivity values were correlated to clinical outcome measures. Therapeutic stimulation improved ataxia and tremor mainly during the target period of the reaching paradigm (63% reduction compared with off stimulation). Notably the acceleration (29%) and deceleration periods (41%) were improved. By contrast, supratherapeutic stimulation worsened ataxia during the deceleration period with a 55% increase of spatial variability, while maintaining near complete suppression of tremor. Chronaxie measures were in the range of rapidly-conducting myelinated fibres with significantly different values for the anti-tremor effect of therapeutic stimulation (27 s) and the pro-ataxic effect of supratherapeutic stimulation (52 s). The degree of connectivity to the dentato-thalamic tract at the stimulating electrode correlated significantly with the reduction of tremor in the therapeutic condition. Our data suggest that stimulation induced tremor reduction and induction of ataxia by supratherapeutic stimulation are mediated by different fibre systems. Probabilistic tractography identified the dentato-thalamic tract as a likely target of tremor suppression. Stimulation-induced
ataxia may be caused by additional recruitment of adjacent fibre systems at higher amplitudes. Stimulation with short pulse duration may help to increase the therapeutic window and focus on the anti-tremor effect.

Keywords: deep brain stimulation; essential tremor; ataxia; cerebellum; tractography
Abbreviations: DBS = deep brain stimulation; ICARS = International Cooperative Ataxia Rating Scale

Introduction

Deep brain stimulation (DBS) has become a mainstay treatment for severe and medically intractable tremors. Frequent indications are severe essential tremor and tremor caused by multiple sclerosis. In both disorders, motor disability results from the complex interaction of postural-, action-, intention tremor and ataxia with voluntary movements. In a previous publication we used kinematic analysis to show that, in a group of patients with essential tremor, high-frequency stimulation of the subthalamic area is more effective in alleviating postural and intention tremor than stimulation of the ventro-intermediate thalamic nucleus, the preferred target for thalamotomy (Herzog et al., 2007). The term ‘subthalamic area’ in this context refers to the white matter space just below the thalamus, and specifically below the ventro-intermediate thalamic nucleus, and must not be confused with the subthalamic nucleus.

Interestingly, subthalamic neurostimulation or thalamotomy may relieve cerebellar symptoms such as intention tremor, while at the same time impairing motor adaptation during reaching indicating a negative impact on cerebellar outflow function (Chen et al., 2006). This dichotomy becomes particularly evident at high stimulation voltages, where neurostimulation induces clinically apparent gait or limb ataxia, whereas tremor remains suppressed (Chen et al., 2006; Fasano et al., 2010, 2012).

Ataxia describes a dysfunction in temporal and spatial coordination significantly interfering with the execution of voluntary goal-directed movements. Signs of limb ataxia are manifold and include asynmetry, dysmetria, dysdiadochokinesia or intention tremor. Another prominent feature of ataxia is dysmetria leading to movement over or undershoot during reaching (Flament and Hore, 1986; Hallett et al., 1991). Ataxia is now viewed as a circuitry disorder and typically attributed to functional disruption of cerebello-thalamo-cortical networks (Levesque and Fabre-Thorpe, 1990; Garcia et al., 2003, 2005; Fasano et al., 2010), because either cerebellar, cortical (Blangero et al., 2009) or thalamic (Solomon et al., 1994) lesions may cause the typical symptoms.

Postural or kinetic tremor are the defining symptoms of essential tremor, but ~10–15% of patients additionally share typical features of ataxia (Deuschl et al., 2000a; Stolze et al., 2001; Brennan et al., 2002; Helmchen et al., 2003; Elble, 2009). The exact neural mechanisms of ataxia in essential tremor are not completely known, but probably involve pathological oscillatory activity interfering with normal cerebellar timing function (Elble, 1998, 2009; Deuschl et al., 2000b).

Why subthalamic neurostimulation reduces tremor and ataxia in essential tremor at lower voltages, but induces ataxia without tremor at supra-effective amplitudes remains enigmatic. Furthermore, it is unclear why DBS improves certain aspects of ataxia in multiple sclerosis, such as intention tremor, whereas other aspects of cerebellar dysfunction such as dysmetria remain unaffected. The clinical effects of deep brain stimulation resemble those of lesioning the target structure. The cellular mechanisms, however, are far more complex (McIntyre et al., 2004; Zheng et al., 2011). It has been suggested that the high frequency required for the beneficial effects of neurostimulation acts universally and might cause a reversible suppression of neuronal activity or interfere with the spread of abnormal oscillatory activity within the cerebellothalamic or thalamocortical networks. The proposed functional silencing of pathological oscillations might be achieved through non-synaptic mechanisms, e.g. depolarization block of Na⁺ channels (Beurrer et al., 2001), antidromic effects (Li et al., 2007), adenosinergic inhibition (Bekar et al., 2008) or through synaptic mechanisms such as activation of inhibitory thalamic interneurons (Strafella et al., 1997). However, the electrical stimulus is more likely to act upon axons than dendrites or cell somata (Holsheimer et al., 2000a) and a number of electrophysiological or neurochemical studies have revealed activation of projection neurons deriving from the stimulated target (Hashimoto et al., 2003; Maurice et al., 2003; Galati et al., 2006; Li et al., 2012). We have recently proposed that driving axons at high-frequency could result in a temporary transmission block, which could act as a filter or ‘masking’ mechanism for pathological activity (Zheng et al., 2011).

Based on clinical and anatomical findings we have speculated that the anti-ataxic effect of subthalamic DBS might be a result of masking of abnormal oscillatory activity within cerebellothalamic projections (Plaha et al., 2004; Hamel et al., 2007; Herzog et al., 2007), whereas the pro-ataxic effect of supratherapeutic DBS could result from an enlarged electrical field and current spread into anatomically neighbouring structures. However, the effects on ataxia within the target region of ventro-intermediate thalamic nucleus-DBS have never been examined in more detail and evidence for the abovementioned hypotheses is lacking. A recent study using diffusion tensor imaging and probabilistic tractography reconstructed a network of motor cortical, brainstem and cerebellar sites forming the anatomical basis for remote effects of ventro-intermediate thalamic nucleus stimulation in essential tremor (Klein et al., 2012), but it did not dissociate beneficial and adverse effects. Neither did this study discriminate the exact contribution of the cerebellothalamic or thalamocortical networks to the effects of ventro-intermediate thalamic nucleus stimulation in essential tremor.

In the present study we aimed to further elucidate the mechanism of subthalamic neurostimulation in essential tremor using a multimodal anatomical and physiological approach. For
characterizing DBS effects during therapeutic and supratherapeutic stimulation we performed a quantitative kinematic analysis of reach-to-grasp movements. This motor task has been previously found suitable for investigating ataxia and tremor in patients with essential tremor (Deuschl et al., 2000; Herzog et al., 2007). A neurophysiological measure, the chronaxie of tremor suppression and ataxia induction, was used to characterize the type of neural elements underlying DBS effects (Holsheimer et al., 2000). Finally, diffusion tensor imaging and tractography added information about the connectivity pattern of subthalamic neurostimulation effects.

Materials and methods

Patients and control subjects

Seven patients (two females) with pharmacologically intractable essential tremor were included in this study. Two patients were treated with unilateral thalamic DBS contralateral to the more affected hand; five patients were treated with bilateral DBS. Mean age of patients (± standard deviation) was 62.9 ± 10.3 years, disease duration 27.4 ± 16.5 years and mean duration of DBS treatment was 19.7 ± 14.4 months (Table 1). No patient received anti-tremor medication at the time of assessment.

Entry criteria for this study were diagnosis of essential tremor according to the criteria of the Tremor Investigation Group (Deuschl et al., 1998), a stable clinical response to thalamic DBS for at least 6 months, and exclusion of other neurological symptoms. All patients underwent a preoperative high resolution MRI (T1, T2, T2*, FLAIR) to exclude morphological anomalies. A connectivity map of the subthalamic area was reconstructed from diffusion tensor images of 13 healthy controls (five females, mean age of 56 years ± 7.6, range 47–66 years) selected from the hospital staff relatives. To exclude a significant brain atrophy in patients potentially interfering with the projection of stimulation contacts onto the tractography map of healthy controls we performed a further automatic post-processing and volumetric group comparison of the T1 data sets (see below).

Table 1 Age, disease duration and duration after implantation of DBS electrodes

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Disease duration (years)</th>
<th>Time after surgery (months)</th>
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<tr>
<td>Mean ± SD</td>
<td>62.9 ± 10.3</td>
<td>27.4 ± 16.5</td>
<td>19.7 ± 14.4</td>
</tr>
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</table>

Surgical procedure and evaluation of electrode position

The surgical procedure has been previously described in detail (Schrader et al., 2002; Herzog et al., 2007). The stereotactic coordinates of each contact of the quadripolar macroelectrode related to the midpoint of the line between anterior and posterior commissure were calculated based on fusion of the preoperative stereotactic and postoperative MRI (Ludwig et al., 2007). To allow a pooled data analysis we only considered absolute x-values, thus projecting left electrodes onto the right hemisphere. The mean coordinates of active contacts were: x: 12.9 ± 1.6 mm, y: 6 ± 1.3 mm, z: 1.8 ± 0.7 mm.

Evaluation of neurostimulation effects

Clinical evaluation

The severity of limb tremor was evaluated by the Fahn-Tolosa-Marin Rating Scale, from which we calculated a lateralized tremor score by summing 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 score of 28 with higher scores indicating more severe tremor.

Severity of limb ataxia was rated using item 10 of the International Cooperative Ataxia Rating Scale (ICARS) with higher scores indicating more severe decomposition and dysmetria of proximal limb movements (Trouillas et al., 1997).

Evaluation of reach-to-grasp movements

Assessment of reach-to-grasp movements was carried out as described in our previous publication (Herzog et al., 2007). Briefly, patients performed repetitive hand movements from a starting platform to a cylindrical object that was fixed to a heavy support 34 cm above the table and ~50 cm from the body. They were instructed to reach out after an acoustic starting signal and grasp the object between thumb and index finger at self-chosen speed.

The movements were recorded using a magnetic six degrees-of-freedom measurement system (3SPACE FASTRAK, Polhemus Inc.) with a sampling frequency of 40 Hz. Markers at a size of 1 × 1 × 1 cm containing the receiving antennas were attached to the nails of the thumb and index finger and the lateral epicondylus of the wrist. This allowed recording of the movement paths of thumb, index and wrist within a 3D Cartesian coordinate system. Data were analysed in Matlab (MathWorks).

For kinematic analysis, the hand transport was divided into acceleration, deceleration and target-period (von Hofsten, 1991; Deuschl et al., 1996; Koster et al., 2002; Herzog et al., 2007). The acceleration and deceleration periods were defined according to the acceleration profile of the wrist sensor. The onset of the target period was defined within the final part of the movement path when the grip aperture (measured by the distance of the thumb and index marker) decreased to 20% of its maximal value.

To quantify the amount of ataxia we determined the deviation (root mean square in cm) at each time point of a given movement from the average path of all reaching movements. Subsequently, we calculated the average root mean square of all trajectories during each of the three movement periods. We considered the root mean square during the target period as a correlate of intention tremor and during the acceleration or deceleration period as a marker of dysmetria.

The absolute root mean square values showed a high degree of interindividual variability in relation to symptom severity. Therefore,
we used the relative change from baseline (DBS off) to assess the individual impact of stimulation and as a clinical correlate for the diffusion tensor imaging analysis (see below).

Change of stimulation intensity for normal and supratherapeutic stimulation

Patients with essential tremor were assessed in the following three stimulation conditions: no stimulation (off stimulation), stimulation with the clinically optimized and chronically used stimulation parameters (on stimulation) and supratherapeutic stimulation. The intensity threshold for supratherapeutic stimulation was determined by gradually increasing voltage and pulse width, if needed until dysmetria of pointing movements became clinically apparent during contralateral finger to nose testing. Other adverse effects, e.g. dysarthria or muscle contractions because of current diffusion into the internal capsule were clinically excluded. Mean stimulation parameters for ‘on stimulation’ were 2.4 ± 0.6 V, 62.5 ± 8.6 μs, 134.2 ± 14.4 Hz; and for supratherapeutic stimulation 2.9 ± 0.4 V, 95.0 ± 11.7 μs, 134.2 ± 14.4 Hz (Table 2). To avoid any interhemispheric interference we deactivated stimulation ipsilateral to the active hand in patients with bilateral DBS.

Clinical assessments (lateralized Fahn-Tolosa-Marin Rating Scale and ICARS) were carried out using monopolar stimulation of each of the four contacts of the quadripolar electrode in the on stimulation and supratherapeutic stimulation conditions. For standardized comparison, stimulation parameters remained the same as determined for the chronically used contact in the two conditions. The stimulation device was controlled by a clinical research assistant and the examiner was blinded to the stimulation condition and chosen contact.

Kinematic assessments of the reach-to-grasp movements were carried out during off stimulation, on stimulation and supratherapeutic stimulation using monopolar stimulation of the chronically stimulated cathode. The order of stimulation conditions was balanced among patients. A waiting period of at least 30 min between the stimulation conditions was observed to reduce carry over effects.

Evaluation of chronaxie

To further characterize the neural elements influenced during tremor suppression in on stimulation and the induction of ataxia in supratherapeutic stimulation we determined the chronaxie for each clinical effect. The chronaxie or strength-duration-time constant is a biophysical parameter of the excitability of neural elements (Ranck, 1975). Chronaxie was calculated from the threshold voltages (Vth) for suppression of tremor and induction of ataxia at pulse widths of 60, 90, 120, 150, 180, 210, 300 and 450 μs and a frequency of 130 Hz as outlined below. During the test session we increased the pulse amplitude in 0.1 V steps until tremor vanished completely (Vth-tremor). We then increased amplitude further until dysmetria became apparent in the finger-to-nose test or the patient failed to target the nose repeatedly. Pulse widths (PWs) were applied in a random order. Each next stimulation (with a different pulse width) was only started when the tremor had fully recovered.

The relationship between the threshold charge (Qth) and the pulse duration required to excite a nerve fibre is described by the following empirical equation, which is known as Weiss’s law (Weiss, 1901):

\[ Q_{th} = I_{rh}(PW + \tau_{sd}) \]  

(1)

where \( I_{rh} \) is the rheobase current, defined as the minimal current needed at infinitely long pulse duration. The charge delivered during a stimulus pulse is equivalent to the area under the current curve, which allows to substitute \( Q_{th} \) by \( I_{rh} \) * PW:

\[ I_{rh} \times PW = I_{rh} \times PW + I_{rh} \times \tau_{sd} \]  

(2)

As outlined by Holsheimer et al. (2000) one can reasonably assume an approximately constant load of the constant voltage pulse generator (Kinetra®, Medtronic Inc.) during the stimulus sessions, in which case our determined threshold voltages (Vth) become proportional to \( I_{rh} \):

\[ V_{th} \times PW = V_{th} \times PW + V_{th} \times \tau_{sd} \]  

(3)

When plotting \( V_{th} \) * PW against PW and fitting a linear regression line to the data, equation (3) can be graphically solved, because \( V_{th} \) corresponds to the intercept and \( \tau_{sd} \) to the slope of the linear fit.

Magnetic resonance imaging

Acquisition

We acquired diffusion tensor images in healthy subjects on a 3 T Philips Achieva with an echo planar sequence covering the whole brain (echo time/repetition time = 59/11 855 ms, field of view

<p>| Table 2 Stimulation parameters during therapeutic (on stimulation) and supratherapeutic stimulation |
|-----------------------------------------------|-----------------|------------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
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<th>Stimulation contact</th>
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<td>Amplitude (V)</td>
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<td>62.5 ± 8.6</td>
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<td>134.2 ± 14.4</td>
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224 × 224 mm, 60 axial slices, 2 mm slice thickness without interslice gap, resulting in an isotropic voxel size of 2 × 2 × 2 mm). Diffusion gradients applied along 32 evenly distributed directions with a b-value of 1000 s/mm², and five non-diffusion weighted image (b = 0 s/mm²).

To increase the signal to noise ratio, the diffusion tensor imaging sequence was repeated three times. T₁ structural images were acquired for volumetric analysis. We used a standard MP-RAGE sequence with an isotropic voxel resolution of 1 mm³ and sagittal slice orientation (repetition time 7.7 ms, echo time 3.6 ms, flip angle 8°, 160 slices). The scan time was 35 min. The preoperative 3D-T₁ MRI for surgical planning was used to perform the volumetric T₁ analysis in patients.

Analysis

The data were transformed to nifti format (dcm2nii, http://www.sph.sc.edu) and introduced into the further analysis using FSL 4.1 (http://www.fmrib.ox.ac.uk/fsl/). Study relevant details will be briefly presented.

Volumetric comparison

We used SIEANAX (implemented in FSL, run with default options) to exclude global atrophy changes in patients with essential tremor and compared the total brain, grey matter and cortical spinal fluid volumes between patients with essential tremor and healthy subjects included in the diffusion tensor imaging analysis (Smith, 2002). A Mann-Whitney U-test was used for a two-group comparison for the volumes of the each of the abovementioned compartments.

Probabilistic tractography

Correction of eddy-current distortions was performed using the included algorithms and the three scans were averaged thereafter. Subsequently the data were processed to determine the diffusion behaviour on a voxel-by-voxel basis (Basser et al., 1994). The probabilistic tractography algorithm that we used is described in detail elsewhere (Behrens et al., 2003; Groppa et al., 2013). The aim of our tractography analysis was to generate a voxel-based connectivity index map in the region of the DBS electrodes. To allow bias-free definition of seed and target areas unaffected by subjective judgements about anatomical correspondences, we used all voxels in the basal ganglia and midbrain structures as generated by the MNI atlas and defined this region as target region (Lancaster et al., 2000). Different seeds were used in this study for generating the probability maps. All voxels in the ipsilateral internal pallidum, red nucleus as well as the contralateral dentate nucleus, nucleus fastigius and nucleus interpositus as derived from the MNI and cerebellum atlases were used as seed masks for separate tract reconstruction (Diedrichsen et al., 2010). The analysis was run in MNI space. Here, we processed 5000 streamline samples from our seeded voxels through to generate a probability distribution of connections to every targeted voxel (Behrens et al., 2003). For the elimination of spurious connections, tractography in individual subjects was thresholded to include only voxels through which at least 5% samples had passed. The probability of connection to the target mask was obtained from the proportion of samples that reached each of the voxel. The individual maps were then normalized to produce a probability map of the target region for each tract. From the voxels (including the interpolated values of the neighbouring voxels) at the DBS electrode coordinates the tract probability estimation values were extracted and included into a regression analysis with clinical (lateralized Fahn-Marin Rating Scale score) or kinematic measures (spatial variability during the target phase of the grasping task) of the contralateral stimulation effect.

A Bonferroni correction was applied for the one tailed multiple correlation distributions and considered significant at \( P < 0.05 \).

Results

Clinical effects of thalamic stimulation

Evaluation of the lateralized Fahn-Tolosa-Marin Rating Scale demonstrated a significant (\( P < 0.001 \)) tremor reduction in ‘on stimulation’ through the most distal contact (contact 0), which was superior compared with contacts 1–3 (\( P < 0.01 \)) (Fig. 1). This was in keeping with contact 0 being used for chronic stimulation in all patients except one (Table 2).

Evaluation of ICARS item 10 showed that the supratherapeutic stimulation condition led to significantly increased limb dysmetria compared with off stimulation when using contact 0 (\( P < 0.0001 \)), but not when stimulating contacts 1–3 (Fig. 1). Stimulation-induced ataxia became also apparent in supratherapeutic stimulation of contact 0 by a worsening of spiral drawing causing a small, but significant increase of the lateralized Fahn-Tolosa-Marin Rating Scale compared with on stimulation (\( P < 0.05 \), Table 3). Supratherapeutic stimulation through contacts 1–3 had no significant bearing on the lateralized Fahn-Tolosa-Marin Rating Scale (data not shown).

Effects of thalamic stimulation on reach-to-grasp movements

On stimulation and supratherapeutic stimulation using the chronically activated contact had a marked impact on the trajectories of the ICARS compared with off stimulation and stimulation of the quadripolar electrode. Contact 0 led to a significant reduction of the lateralized Fahn-Tolosa-Marin Rating Scale compared with the off stimulation condition (STIM-OFF) and the other three stimulation contacts (**\( P < 0.01 \)). Supratherapeutic stimulation of contact 0 led to a significant increase of item 10 of the ICARS compared with off stimulation and stimulation of the other three contacts (#\( P < 0.01 \)).
reach-to-grasp movements (Fig. 2). Quantitative analysis revealed the most prominent effect of on stimulation in the target period of the reach with a reduction of the root mean square of the mean deviation from the average path from 0.99 cm (off stimulation) to 0.36 cm \((P < 0.005)\). Furthermore, on stimulation decreased spatial variability in the acceleration \((P < 0.05)\) and deceleration period \((P < 0.01, \text{Fig. 3 and Table 4})\). The relative improvements of the mean deviation are provided in Table 4. Supratherapeutic stimulation led to a significant increase of spatial variability in the deceleration period compared to on stimulation \((0.45–1.16, P < 0.001)\) whereas we did not observe any significant changes in the other movement periods (Fig. 3 and Table 4).

### Determination of chronaxie

From the strength-duration curves we determined a chronaxie of 27.0 ± 13.4 μs for the suppression of intention tremor and 52.1 ± 15.6 μs for the induction of ataxia. Both values were significantly different \((P < 0.05)\) as also indicated by the divergent slope of the linearized strength-duration curves in Fig. 4.

### Volumetric comparison

The automatic outputs of SIENAX were visually checked to ensure the correct segmentation and presented a valid segmentation of into global brain, grey matter and CSF masks. Applying the Mann-Whitney U-test for the two-group comparison with the variable of interest including the entire brain volumes, cortical grey, white matter and CSF volumes, we found no significant differences \((P < 0.05)\) between patients with essential tremor and the group of studied healthy control subjects.

### Probabilistic tractography

When visually inspecting the averaged tract probability maps we found the electrode locations with higher connectivity values centred within the fibre path generated by seeding the dentate nucleus, whereas the tract generated by seeding the red nucleus took a parallel but more medial and dorsal course (Fig. 6). The correlation analysis between the kinematic measure of intention tremor in the target period of the reach to grasp-movement and

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stimulation site</th>
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<td>5.6 ± 3.8</td>
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Table 3: Effect of therapeutic and supratherapeutic stimulation on tremor and limb ataxia

Effect of therapeutic (on stimulation) and supratherapeutic stimulation of the chronically used contact on the lateralized tremor rating scale (Fahn-Tolosa-Marin Rating Scale) and International Cooperative Ataxia Rating Scale (ICARS) compared to stimulation switched off (off stimulation).

Figure 2: Examples of reach-to-grasp movements with stimulation switched off (STIM-OFF), therapeutic (STIM-ON) and supratherapeutic stimulation (STIM-ST). (A) Patient 3, right hand; (B) Patient 7, right hand; and (C) Patient 4, right hand.
the connectivity values at the electrode position revealed a significant relation between the anti-tremor effect and the connectivity of the electrode site to fibres originating from the dentate nucleus ($r = 0.660; t = 2.78; P < 0.05$, Fig. 5). The corresponding analyses for fibre tracts originating from red nucleus, globus pallidus, fastigial nucleus or interposed nucleus did not reveal any significant correlations between connectivity and measures of tremor reduction (Table 5).

### Discussion

Kinematic features of upper limb movements in patients with advanced essential tremor closely resemble abnormalities found in patients suffering from cerebellar ataxia, as targeted hand movements show delayed deceleration, target overshoot and intention tremor (Deuschl et al., 2000; Herzog et al., 2007).

In keeping with these previous observations, our patients did not only exhibit increased temporospatial variability in the target phase of reaching movements after deactivating neurostimulation, which is reflective of the intention tremor, but also in the acceleration and deceleration period of the reach. Although we cannot entirely dismiss the possibility that superimposed action tremor may have contributed to the quantitative changes in the acceleration and deceleration period, the typical oscillatory tremor path was almost exclusively seen during the target period of the reach as illustrated by the movement trajectories in Fig. 2.

The key clinical finding of our study is that suppression of tremor with therapeutic stimulation (on stimulation) is associated with an improvement of ataxia and that ataxia returns without recurrence of tremor when stimulating excessively (supratherapeutic stimulation) the exact same contact. However, stimulation-induced ataxia is kinematically distinct from essential tremor-related ataxia, because spatiotemporal variability of the

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**Figure 3** Spatial deviation in the (A) acceleration, (B) deceleration and (C) target period of reach-to-grasp movements. The charts contain data from individual patients as well as mean values of each condition (bold line).
movement path increased only in the deceleration phase of the reach. Clinically the movement disorder observed at supratherapeutic stimulation intensity was characterized by dysmetria and corrective movements when approaching the target in the finger chase or finger-to-nose test.

The strength-duration-curves of tremor alleviation and dysmetria induction helped us to further characterize the neural elements underlying these phenomena. Voltage-derived strength duration curves are systematically biased and underestimate the true chronaxie by \(\frac{30-40}{C24}\%\) (Holsheimer et al., 2000b). Nevertheless, the observed chronaxies of 27 ms (corrected 38 ms) for tremor reduction and 52 ms (corrected 73 ms) for dysmetria induction are well within the known limits of 5200 ms for fast conducting, myelinated axons, whereas smaller axons have values between 200 and 700 ms and cell bodies, dendrites or unmyelinated axons have chronaxies \(\frac{3}{1}\) ms. The assumption that stimulation acts preferentially upon fast conducting, myelinated fibre tracts fits well to our previous observation, that the most effective stimulation contacts for intention tremor were located within the white matter of the subthalamic area, where several large fibre bundles deriving from the cerebellum and basal ganglia intersect (Herzog et al., 2007). A likely candidate for the anti-ataxic effects in our patients was the dentate-thalamic tract, which fans out in the subthalamic area before entering the ventrolateral thalamus.

### Role of the dentate-thalamic tract in improving ataxia of patients with essential tremor

The assumption that dentate-thalamic fibres play a prominent role in mediating the beneficial effects of neurostimulation is supported by the following observations: First, stereotactic coordinates of the most effective stimulation contacts were located \(\sim 2\) mm below the anterior commissure–posterior commissure line, which corresponds to the subthalamic fibre tract area. More specifically, this site falls within the prelemniscal radiation, which is a main transition zone of cerebellar fibres from the brachium conjunctivum to the ventrolateral thalamus (Vogt, 1909; Mehler and Nauta, 1974; Stanton, 1980; Ilnisky and Kultas-Ilnisky, 1984; Krack et al., 2002). Second, measurements of chronaxie revealed values typical of thick

### Table 4  Percentage change of spatial variability during the acceleration, deceleration and target period as a result of therapeutic stimulation of the chronically-used stimulation contacts

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Stimulation site</th>
<th>Acceleration period (%)</th>
<th>Deceleration period (%)</th>
<th>Target period (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left</td>
<td>-75</td>
<td>-74.8</td>
<td>63.6</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>-66.4</td>
<td>-60.8</td>
<td>-82.9</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>-74.2</td>
<td>-67.8</td>
<td>-68.8</td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>-30.6</td>
<td>-17.3</td>
<td>-45.4</td>
</tr>
<tr>
<td>5</td>
<td>Right</td>
<td>-36.5</td>
<td>-30.8</td>
<td>-79.8</td>
</tr>
<tr>
<td>6</td>
<td>Left</td>
<td>72.3</td>
<td>-21.6</td>
<td>-57.9</td>
</tr>
<tr>
<td>7</td>
<td>Right</td>
<td>-75</td>
<td>-74.8</td>
<td>-73.8</td>
</tr>
<tr>
<td>8</td>
<td>Left</td>
<td>66.4</td>
<td>33.8</td>
<td>-44.4</td>
</tr>
<tr>
<td>9</td>
<td>Right</td>
<td>26.7</td>
<td>0</td>
<td>-70.6</td>
</tr>
<tr>
<td>10</td>
<td>Left</td>
<td>33.3</td>
<td>0</td>
<td>-41.7</td>
</tr>
<tr>
<td>11</td>
<td>Right</td>
<td>-35.4</td>
<td>-52.1</td>
<td>-76.7</td>
</tr>
<tr>
<td>12</td>
<td>Left</td>
<td>-21.9</td>
<td>-54.8</td>
<td>-46.7</td>
</tr>
</tbody>
</table>

Mean ± SD: -29.3 ± 44.9, -40.7 ± 27.2, -62.7 ± 15.0

### Figure 4 Time-strength duration curves depicting the relationship between pulse width and amplitude necessary for tremor suppression and the induction of ataxia. The data were linearized by plotting pulse width against the product of amplitude and pulse width, which allows to infer the rheobase current from the intercept and the chronaxie from the slope of the linear curve fit.

### Figure 5 Correlation analysis of the connectivity with the dentate nucleus at the DBS electrode position and the improvement of spatial variability in the target period of the reach as an objective measure of intention tremor severity.
myelinated axons that might correspond to the dentate-thalamic tract. Third, we correlated kinematic measures of ataxia with the connectivity maps from the dentate nucleus as revealed by probabilistic tractography. We found a significant relation between the improvement of ataxia and the connectivity of the target region to the dentate nucleus, but not to other studied cerebellar or basal ganglia nuclei interconnected with the subthalamic area.

The dentate-thalamic tract is the main output pathway of the lateral cerebellum to the motor cortex by way of the ventrolateral thalamus. The dentate nucleus is mainly involved in voluntary movements of the extremities such as single-joint and multi-joint goal-directed movements toward a fixed or moving target (Schwartz et al., 1987; Marple-Horvat et al., 1998; Marple-Horvat and Criado, 1999; Cooper et al., 2000). Dentate lesioning in monkeys disrupts the spatial aspects of goal-directed movements resembling limb ataxia in humans (Goldberger and Growdon, 1973). Temporary inactivation of the dentate nucleus by muscimol injection is associated with deficits in the aiming of reach movements and stability of the arm (Mason et al., 1998; Goodkin and Thach, 2003), whereas the execution of less complex movements with support of wrist and elbow is only slightly impaired by dentate lesions (Thach et al., 1992; Martin et al., 2000). Our reach-to-grasp paradigm conforms to the criteria of a complex and freely performed aiming task that likely involves the dentate nucleus. Hence, the improvement of ataxia by neurostimulation may be explained by blocking the spread of abnormal timing signals in essential tremor to thalamic and cortical regions through the dentate-thalamic tract.

Table 5 Correlation between normalized connectivity ratios and reduced spatial variability during the target phase as an objective measure of intention tremor

<table>
<thead>
<tr>
<th>Seeds</th>
<th>n</th>
<th>r (x,y)</th>
<th>r^2</th>
<th>t</th>
<th>P-corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus ruber</td>
<td>12</td>
<td>0.35</td>
<td>0.12</td>
<td>1.17</td>
<td>n.s.</td>
</tr>
<tr>
<td>Nucleus dentatus</td>
<td>12</td>
<td>0.67</td>
<td>0.44</td>
<td>2.78</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nucleus interpositus</td>
<td>12</td>
<td>0.08</td>
<td>0.28</td>
<td>0.92</td>
<td>n.s.</td>
</tr>
<tr>
<td>Nucleus fastigii</td>
<td>12</td>
<td>0.06</td>
<td>0.2</td>
<td>−0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>12</td>
<td>0.40</td>
<td>0.16</td>
<td>1.38</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. = not significant.

**The mechanisms of supratherapeutic stimulation**

Supratherapeutic stimulation worsened the deceleration period but left the targeting period of reaching intact, which was associated with clinically apparent dysmetria. This stimulation effect was therefore distinct from the anti-ataxic effect of therapeutic DBS at lower amplitude and may involve a separate myelinated fibre tract. This was supported by a significantly longer chronaxy as compared to the chronaxy of tremor suppression. The increased stimulation intensity at supratherapeutic stimulation leads to an enlarged volume of tissue activated; hence, the recruited fibres are likely to be located in close vicinity to the therapeutic target. We were not able to relate the induction of dysmetria to a particular fibre bundle in the subthalamic area by means of
probabilistic tractography. Anatomical and physiological reasoning, however, suggest afferent or efferent axons of the red nucleus as a possible substrate. The dentate-thalamic tract forms the lateral border of the red nucleus and an enlarged electrical stimulation field will inevitably encroach upon this structure.

Early inactivation studies in cats and non-human primates have revealed marked dysmetria of reaching movements after lesioning the red nucleus (Ranish and Soechting, 1976; Sybirska and Gorska, 1980). The symptoms were less pronounced when fibre sparing methods were used (Levesque and Fabre-Thorpe, 1990). However, these findings may not directly apply to humans, as anatomical differences exist in the organization of the red nucleus between lower mammals and primates. In humans, the red nucleus forms a part of the cerebello-rubrospinal system, which is thought to complement the motor functions of the cerebello-thalamo-cortical loop. It is composed of a caudally located magnocellular division and a more rostrally located parvcellular division. The two divisions have completely different input and output connections: the magnocellular division receives afferents mainly from the cerebellar interposed nucleus, whereas the parvcellular division receives input predominantly from the cerebral cortex. The magnocellular part gives rise to the rubrospinal tract, which innervates several contralateral brainstem nuclei and all spinal segments. The sole projection of the parvcellular division is to the ipsilateral inferior olive, that sends information to the cerebellum by way of climbing fibre input (Nieuwenhuys et al., 2008). A striking physiological feature of the cerebello-rubrospinal system is the remarkable sensory-to-motor transformation that occurs over relatively few synapses and is particularly important for the cerebellar control of goal-directed movements.

We have recently proposed, that tremor reduction from subthalamic area DBS could result from interrupting the deleterious oscillatory entrainment of the cerebello-thalamo-cortical loop in essential tremor (Herzog et al., 2007; Fasano et al., 2010). However, the interruption of physiological information flow within this loop would need to be compensated for to allow normal motor function. We like to suggest that the cerebello-rubrospinal system could subserve this function and failure of this second cerebellar outflow system by suprathreshold stimulation could cause the reappearance of cerebellar motor deficits without tremor. Support for this hypothesis comes from the observation that reaching movements are only transiently impaired by experimental lesions to either the cerebello-rubrospinal or cerebello-thalamo-cortical loop, but remain permanently dysmetric when disrupting both systems (Lorincz and Fabre-Thorpe, 1997). Nevertheless, other mechanisms such as interference of
therapeutic and supratherautic DBS with different cerebellar outflow pathways, the thalamocortical loop or adjacent fibre systems (i.e. the pyramidal tract) could be plausible and should be considered.

Limitations

A drawback of our study is the reconstruction of the subthalamic connections from probabilistic tractographies of normal controls, because no preoperative diffusion tensor imaging data were available in our patients. We nevertheless consider this approach justified because previous studies did not find evidence for brain atrophy in patients with essential tremor or other macroanatomical variations of essential tremor brains from healthy controls (Rajput et al., 1991, 2004; Daniels et al., 2006), despite some subtle neurodegenerative changes on a microscopic level (Louis et al., 2007). In our patients with essential tremor, the volumes of the global brain, cortical grey and white matter and CSF, which are important markers for brain atrophy, were all in the range of healthy control subjects.

Moreover, we did not model the volume of tissue activation, which depends on voltage and other stimulus parameters, tissue impedance and tissue anisotropy (McNeal, 1976; Butson and McIntyre, 2006). On the other hand, these models depend on a priori assumptions about the membrane properties of stimulated axons, which may yet have to be further refined by human experimental data such as the chronaxie measurements in our study. Finally, we did not reconstruct the connectivity profile of the electrode regions to cortical structures. We cannot completely rule out that some anti-ataxic effect could be related to modulation of thalamocortical network activity. This should be clarified in further studies. The methods used in this study were directed at reconstructing the anatomical network of subthalamic DBS effects. However, they do not allow one to discern the exact functional role of the described networks, nor the mode of action of neurostimulation, which might act on pathological or physiological activity within these loops.

Clinical implication

Our study corroborates the assumption of a close relationship between DBS effects and the modulation of particular fibre pathways within functional brain networks. Because these fibre tracts may run in close vicinity or even intersect, spatial shaping of the electrical field may not be sufficient to enhance the selectivity of DBS effects. Our chronaxie data demonstrate that rather temporal parameters of the stimulus pulse may help with focusing neurostimulation effects in such ‘bottleneck’ structures. The internal pulse generators used in this study (KINETRA or ACTIVA PC, Medtronic Inc) were not capable of producing pulses shorter than 60 µs. However, one would like to stimulate with a pulse width close to the chronaxie of tremor suppression, which was estimated between 30 and 40 µs in our study, to focus on the excitation of the corresponding fibre pathway. At longer pulse widths, the therapeutic window between tremor suppression and the induction of ataxia will diminish, leading to the risk of inducing both effects at nearly the same threshold. This may explain the high prevalence of balance problems and incoordination as ataxic adverse effects in a DBS study of essential tremor, which stimulated with pulse durations ~120 µs (Pahwa et al., 2006), as compared to others using shorter pulse width (Limousin et al., 1999; Rehncrona et al., 2003).

The trend to target fibre pathways rather than brain nuclei in deep brain stimulation entails the necessity for better individual visualization of white matter structures (Coenen et al., 2011). Probabilistic MRI tractography could be a promising aid for direct stereotactic targeting and visualization software-assisted programming in tremor patients. The method allows for depicting complete and branching pathways and estimating statistical confidence limits for connectivity. Furthermore, it is resistant to noise and does not underestimate the size of fibre tracts like deterministic tractography (Yamada et al., 2009). Probabilistic tractography has previously shown accurate display of fibre tracts within the brainstem and cerebellum (Habas and Cabanis, 2007), but the method has limitations in regions where fibres cross in multiple directions within a single voxel. Future studies will need to establish prospectively that refining the target for electrode implantation by probabilistic tractography will improve surgical outcome.

Conclusion

Neurostimulation of the subthalamic area is highly effective in improving tremor and appendicular ataxia in essential tremor. Chronaxie measures indicate that this effect is mediated by stimulating fast conducting axons, which are most likely part of the dentate-thalamic tract according to the present tractography study. Suprathreshold stimulation causes dysmetria, while still preserving tremor control due to possible inadvertent stimulation of neighbouring fibre pathways. In clinical practice, a short pulse width (if technically possible even lower than 60 µs) should be chosen to allow for the largest therapeutic window between tremor suppression and the induction of dysmetria.

Funding

This study was funded by a research grant of Christian-Albrechts-University to Dr. Groppa and within the ERANET. NEURON scheme (grant #01EW0902).

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