# Deep brain stimulation in the subthalamic area is more effective than nucleus ventralis intermedius stimulation for bilateral intention tremor

Hamel, Wolfgang; Herzog, Jan; Kopper, Florian; Pinsker, Marcus; Weinert, Dieter; Muller, Dieter; Krack, Paul; Deuschl, Gunther; Mehdorn, Maximilian Hubertus

Acta Neurochir (Wien) (2007) 149: 749–758
DOI 10.1007/s00701-007-1230-1
Printed in The Netherlands

*Acta Neurochirurgica*

*Clinical Article*

# Deep brain stimulation in the subthalamic area is more effective than nucleus ventralis intermedius stimulation for bilateral intention tremor

**W. Hamel[1,3], J. Herzog[2], F. Kopper[2], M. Pinsker[1], D. Weinert[1], D. Müller[3], P. Krack[2,4], G. Deuschl[2], H. M. Mehdorn[1]**

[1] Department of Neurosurgery, Christian-Albrechts-University, Kiel, Germany
[2] Department of Neurology, Christian-Albrechts-University, Kiel, Germany
[3] Department of Neurosurgery, University-Hospital-Eppendorf, Hamburg, Germany
[4] Current address: Department of Neurosciences, University Hospital Grenoble, Grenoble, France

Received 6 October 2006; Accepted 19 March 2007; Published online 1 August 2007


## Summary

*Background.* The ventro-lateral thalamus is the stereotactic target of choice for severe intention tremor. Nevertheless, the optimal target area has remained controversial, and targeting of the subthalamic area has been suggested to be superior.

*Patients and methods.* Eleven patients with disabling intention tremor of different etiology (essential tremor ($n = 8$), multiple sclerosis ($n = 2$) and one with, spinocerebellar ataxia) were implanted bilaterally with DBS electrodes targeted to the ventro-lateral thalamus using micro-recording and micro-stimulation. Among five tracks explored in parallel optimal tracks were chosen for permanent electrode implantation. Postoperative tremor suppression elicited by individual electrode contacts was quantified using a lateralised tremor rating scale at least 3 months (in most patients >1 year) after implantation. The position of electrode contacts was determined retrospectively from stereotactic X-ray exams and by correlation of pre- and postoperative MRI.

*Results.* In all patients, DBS suppressed intention tremor markedly. On average, tremor on the left and right side of the body was improved by 68% (±19; standard deviation) and 73% (±21), respectively. In most patients, distal electrode contacts located in the subthalamic area proved to be more effective than proximal contacts in the ventro-lateral thalamus. In stereotactic coordinates, the optimal site was located 12.7 mm (±1.4; mean ± standard deviation) lateral, 7.0 (±1.6) mm posterior, and 1.5 (±2.0) mm ventral to the mid-commissural point. In general, the best contacts could be selected for permanent stimulation. Nevertheless, in some instances, more proximal contacts had to be chosen because of adverse effects (paraesthesiae, dysarthria, gait ataxia) which were more pronounced with bilateral stimulation resulting in slightly less tremor suppression on the left and right side of body (63 ± 18 and 68 ± 19%, respectively).

*Conclusion.* Direct comparison of different stimulation sites in individual patients revealed that DBS in the subthalamic area is more effective in suppressing pharmacoresistant intention tremor than the ventro-lateral thalamus proper. Anatomical structures possibly involved in tremor suppression include cerebello-thalamic projections, the prelemniscal radiation, and the zona incerta.

*Keywords:* Deep brain stimulation; tremor; thalamus; subthalamic area; zona incerta

Correspondence: Dr. Wolfgang Hamel, Neurochirurgische Klinik, Universitätsklinikum-Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany. e-mail: w.hamel@uke.uni-hamburg.de

## Introduction

Deep brain stimulation (DBS) within the ventro-lateral thalamus is an effective treatment for tremor, the most common movement disorder, irrespective of aetiology [2, 4, 7, 9, 10, 23, 37, 43, 55, 56, 60, 65]. The ventro-lateral thalamus has been introduced by Hassler [26, 27] and later adopted by numerous stereotactic centers for the treatment of tremor and other hyperkinetic disorders [1, 8, 13, 22, 32, 34, 49–51, 60, 68]. According to intraoperative electrophysiological mapping the nucleus ventralis intermedius has been suggested as the principle target area within the ventro-lateral thalamus for tremor control [1, 32, 49, 51]. The ventralis intermedius nucleus (Hassler's nomenclature) is part of the ventro-lateral motor thalamus and equivalent to Hiarai and Jones posterior ventro-lateral nucleus (VLp) [31, 39, 44]. This represents the thalamic subnucleus receiving cerebellar afferents and projecting to the primary motor cortex (Brodman's area 4).

However, detailed post-mortem studies performed by Hassler revealed that lesions associated with the best effect on Parkinsonian tremor could not be found within the nucleus ventralis intermedius but rather at the base of the ventro-lateral thalamus, and especially in the area where cerebello-thalamic projections (in particular dentato-thalamic fibers) entered the thalamus [25]. Similar observations have been made in post-mortem studies performed after ventralis intermedius stimulation [12, 18].

In fact, direct targeting of different anatomical structures located within the subthalamic area has been suggested to result in superior tremor suppression, in particular for severe intention tremor. These favourable effects have been ascribed to the zona incerta, prelemniscal radiation (RAPRL), fields of Forel, but also the subthalamic nucleus [3, 5, 10, 28, 30, 33, 38, 40, 46, 47, 57, 58, 61, 62]. Thus, clearly distinct stereotactic targets located several millimeters apart have been suggested to result in best tremor suppression. This is illustrated in Laitinen's survey among neurosurgeons requested to indicate their preferred target for the treatment of Parkinsonian tremor [41]. Unfortunately, modern imaging modalities were not available at the time most operations were performed, thus, the exact site of lesioning performed in thousands of patients has to remain obscure. Nowadays, DBS has taken the place of lesioning [7, 55, 56, 59, 60] making bilateral operations feasible, and the selection of active contacts allows for spatial adjustments after the operation. In this study the actual position of implanted electrodes was determined retrospectively by stereotactic means and correlated with clinical efficacy in patients suffering from disabling bilateral intention tremor.

## Patients and methods

### *Patients*

Eleven patients (6 females and 5 males; mean and median age 61 and 66 yrs, respectively), with a long history (mean and median duration 28 and 25 years, respectively) of severe, disabling kinetic tremor (essential tremor (ET; $n=8$), multiple sclerosis (MS; $n=2$) and one with spinocerebellar ataxia) diagnosed according to the criteria of the Movement Disorder Society [14] were analysed retrospectively. Tremor involved postural, intention and usually head and other axial tremor, which were refractory to betablockers, primidone, anticholinergics, and clozapine. All patients operated at our institution for bilateral intention tremor for which lateralised tremor scores and the stereotactic position of electrode contacts could be obtained were included in this study.

### *Operative targeting and electrode implantation procedure*

The ventro-lateral thalamus was targeted 13–15 mm lateral and 6–7 mm anterior to the posterior commissure at the intercommisural level depending on the width of the third ventricle and the inter-commissural length, respectively. In all patients, symmetric targets were chosen on the right and left side. 3D-planning of safe trajectories using a Windows NT-based StereoplanPlus 2.3 software (Stryker Leibinger, Freiburg, Germany) involved the avoidance of blood vessels, lateral ventricles, and sulci as depicted in Gadolinium-enhanced, volumetric T1-weighted MRI (1.0 mm slice thickness) acquired parallel to the inter-commissural plane with a Siemens Magnetom Vision 1.5-tesla MRI scanner (Siemens, Erlangen, Germany) in general anesthesia [20]. The T1-weighted-MRI is devoid of image distortion and, in all patients, the coordinates determined for the anterior and posterior commissure (anterior and posterior commissure, respectively) from T1WI-MRI were cross-checked with anterior and posterior commissure coordinates defined from stereotactic CT scans [19, 20].

DBS-electrodes were implanted in local anesthesia following mapping of the target by micro-recording and micro-stimulation using 5 microelectrodes (10 MΩ; FHC, Bowdoinham, USA) advanced in parallel using a multi-electrode guiding system (MEAS, Stryker Leibinger, Freiburg, Germany). Recordings were started 8–10 mm above and terminated 3–5 mm below the inter-commissural level. Intraoperative on-line assessment of activity displayed by oscilloscopes and the Axoscope software (Axon Instruments, Union City, USA) as well as audio-equalizer monitoring was performed [19]. Tremor-synchronous neuronal activity and bursting cells were not only recorded in the ventro-lateral thalamus but also within the subthalamic area as described previously [1, 32, 49, 51, 61]. Thus, it is difficult to define precisely the base of the thalamus by neurophysiological means. Nonetheless, overall activity was reduced in the subthalamic area usually beginning within 1 mm from the inter-commissural level.

Micro-recording was followed by micro-stimulation at 130 Hz with 0.1–10 mA (Accupulser A310 and Stimulus Isolator A365, World Precision Instruments, Sarasota, FL) with evaluation of tremor and side effects. Micro-stimulation was usually performed 2–5 mm below the inter-commissural plane, at the level of the inter-commissural plane, and 2–4 mm above this level. Since the subthalamic region was not targeted intentionally this area was not evaluated systematically. The results of micro-recording and micro-stimulation were reassessed before one of the five trajectories was selected for permanent electrode implantation (model 3387; Medtronic, Minneapolis, MN) under fluoroscopic control. The frequency with which the different trajectories were chosen were as follows: central trajectory ($n = 10$ electrodes), medial ($n = 5$), posterior ($n = 2$), anterior ($n = 2$), lateral ($n = 2$), and posteromedial placement as shown in Fig. 3A ($n = 1$, left electrode). The depth of implantation was adjusted according to the area of best tremor suppression which was generally observed at the base of the ventro-lateral thalamus and in the subthalamic area, similar to Alusi *et al.* [3]. However, in most instances this area was only covered by the distal two contacts of the permanent electrode in order to miminize the risk of side effects which are more frequently observed with more ventral stimulation and to retain additional contacts within the ventro-lateral thalamus proper. Tremor control and potential side effects were re-evaluated intraoperatively by macro-stimulation with the screening device.

### *Tremor rating and postoperative stimulation*

Tremor severity was rated according to the Fahn-Tolosa-Marin tremor rating scale [17] before operation and at least 3 months (in most patients >1 year) after electrode implantation. At the time the tremor was rated a postoperative thalamotomy-like effect ('Setzeffekt') which could be observed in almost all patients had resolved. The efficacy of individual electrode contacts was assessed by determining a lateralised tremor score for the contralateral limb including items 5, 6, 8, 9, 11–14 of the Fahn-Tolosa-Marin tremor rating scale [17]. Postoperative improvements (as percentages) were calculated based on baseline values obtained preoperatively. All patients were right-handed, and test stimulation usually started with the left electrode. To allow for comparison, all contacts of an individual electrode were stimulated with the same parameters, i.e. the parameters resulting in most effective tremor suppression, and the optimal contacts were also chosen for all the other contacts. Stimulation was performed with 2.0–3.6 V, 60 µsec, and 130–145 Hz. Permanent stimulation was performed with electrode contacts regarded optimal for bilateral stimulation, i.e. effective tremor suppression achieved with the least side effects [63]. The clinical effects remained stable with the contacts chosen for permanent stimulation.

### *Stereotactic position of electrode contacts*

Stereotactic coordinates for individual electrode contacts were determined retrospectively by different approaches, i.e. correlation of pre- and postoperative T1WI-MRI (0.98 mm voxel size) and postoperative stereotactic skull X-ray [20]. It has been demonstrated that with both approaches comparable stereotactic coordinates will be obtained [20]. Nevertheless, the X-ray-based approach may be regarded as being more straightforward and is beyond the suspicion of geometric inaccuracy [20]. Thus, the X-ray-based coordinates were used for further calculations and illustrations. However, in one patient, only MRI coordinates were available because a postoperative X-ray could not be obtained. Fusion of a postoperative MRI with a digitized Schaltenbrand and Wahren-atlas integrated into the Neuro Navigation System (Stryker Leibinger, Freiburg, Germany) was done by referencing different landmarks including AC, PC, and a mid-sagittal point allowing for linear adjustment and rotational correction of the atlas to adapt to the patient's MRI.

## Results

In all patients tremor was improved substantially with DBS (cf. Table 1) and, to the extent assessed, this was associated with a marked gain in tremor-relevant activities of daily living (pre- and postoperative ADL scores 35/75 and 5/75, respectively, with data from five patients with essential tremor). Tremor suppression

Table 1. *Tremor improvement with the best vs. permanent contact*

| | Electrode | *x* | *y* | *z* | % Tremor improvement | |
|---|---|---|---|---|---|---|
| | | | | | Mean | SD |
| Best | right | 12.8 | −7.1 | −1.5 | 67.6 | 18.6 |
| Permanent | right | 13.3 | −6.5 | −0.4 | 63.4 | 18.3 |
| Best | left | −12.5 | −6.9 | −1.5 | 72.6 | 21.3 |
| Permanent | left | −12.8 | −6.6 | −1.0 | 68.4 | 18.8 |

Postoperative improvement in unilateral Fahn-Tolosa-Marin tremor scores achieved with the most effective contacts ('best') and contacts selected for chronic stimulation ('permanent'). The average position of respective electrode contacts is given in stereotactic coordinates indicating the distance (in mm) from the mid-commissural point (cf. Table 2). The results obtained with left and right electrodes are listed separately. Preoperatively, both sides were similarly affected (lateralised Fahn-Tolosa-Marin tremor rating score: *left* 22.5 ± 5.6; *right* 20.5 ± 6.5). *SD* standard deviation

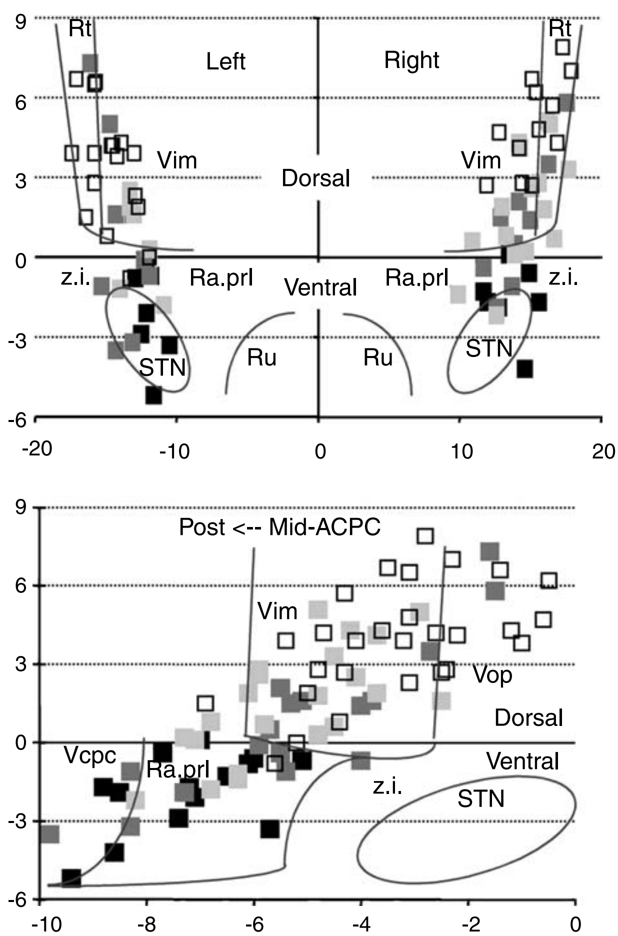


Fig. 1. Effect of electrode location on tremor suppression. The stereotactic position of electrode contacts was plotted in commissure-based coordinate systems (mid-commissural point: $x = 0$, $y = 0$, and $z = 0$) representing a coronal (*left plot*) and sagittal (*right plot*) view. The efficacy of individual contacts is indicated as follows: *white* 0–25% tremor suppression; *light gray* 25–50%; *dark grey* 50–75%; *black* 75–100%. To aid interpretation the borders of relevant basal ganglia structures are outlined in red as interpolated from adjacent Schaltenbrand and Wahren atlas planes

remained stable during follow-up visits after at least one to several years after the operation. The extent of tremor suppression elicited by individual electrode contacts was grouped in four categories (Fig. 1). To compare clinical effects with electrode location the stereotactic position of each contact was plotted into a commissure-based coordinate system (Fig. 1). In general, distal electrode contacts were more effective than proximal contacts. Most effective tremor suppression (>75% postoperative improvement) was achieved at or below the inter-commissural plane (Fig. 1). This is supported by comparison of contacts located dorsal and ventral to the inter-commissural plane. Tremor suppression was significantly better when stimulation was performed ventral (and

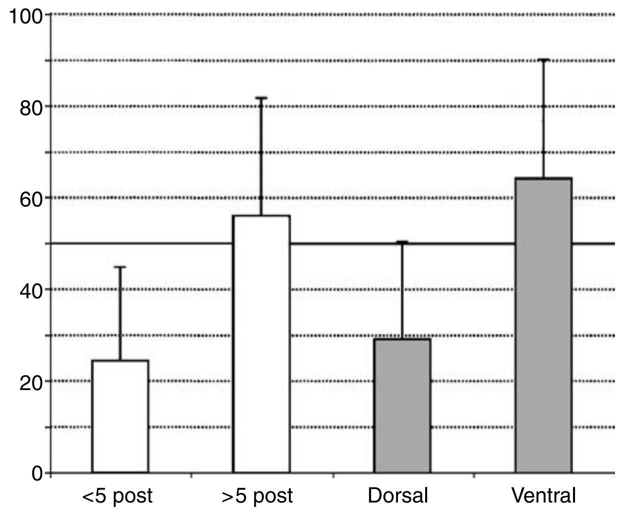


Fig. 2. Postoperative tremor improvements (in %) in unilateral Fahn-Tolosa-Marin tremor rating scores is dependent on the site of stimulation. Electrode contacts located more than 5 mm posterior and ventral to the inter-commissural point resulted in more effective tremor suppression (white and grey bars, respectively). Bars indicate standard deviations. Differences between '<5 mm post' vs. '>5 mm post' and 'dorsal' vs. 'ventral' were statistically significant (ANOVA ($p < 0.001$) followed by Student Newman–Keuls test ($p < 0.05$) for between group analysis)

Table 2. *Coordinates of most effective contacts and contacts chosen for permanent stimulation*

| | Most effective | | | Permanent | | |
|---|---|---|---|---|---|---|
| | *x* | *y* | *z* | *x* | *y* | *z* |
| Mean | 12.7 | −7.0 | −1.5 | 13.1 | −6.5 | −0.7 |
| Median | 12.6 | −7.1 | −1.6 | 13.0 | −6.7 | −1.1 |
| SD | 1.4 | 1.6 | 2.0 | 1.6 | 1.6 | 2.1 |
| 95%-CI | 0.6 | 0.7 | 0.8 | 0.7 | 0.7 | 0.9 |
| Min | 9.9 | −9.8 | −5.2 | 9.9 | −9.8 | −3.5 |
| Max | 14.9 | −2.9 | 5.0 | 15.6 | −2.9 | 5.0 |

Stereotactic coordinates (in mm relative to the mid-commissural point) of the 'most effective' electrode contacts and contacts chosen for 'permanent' stimulation (all shown in Fig. 5)

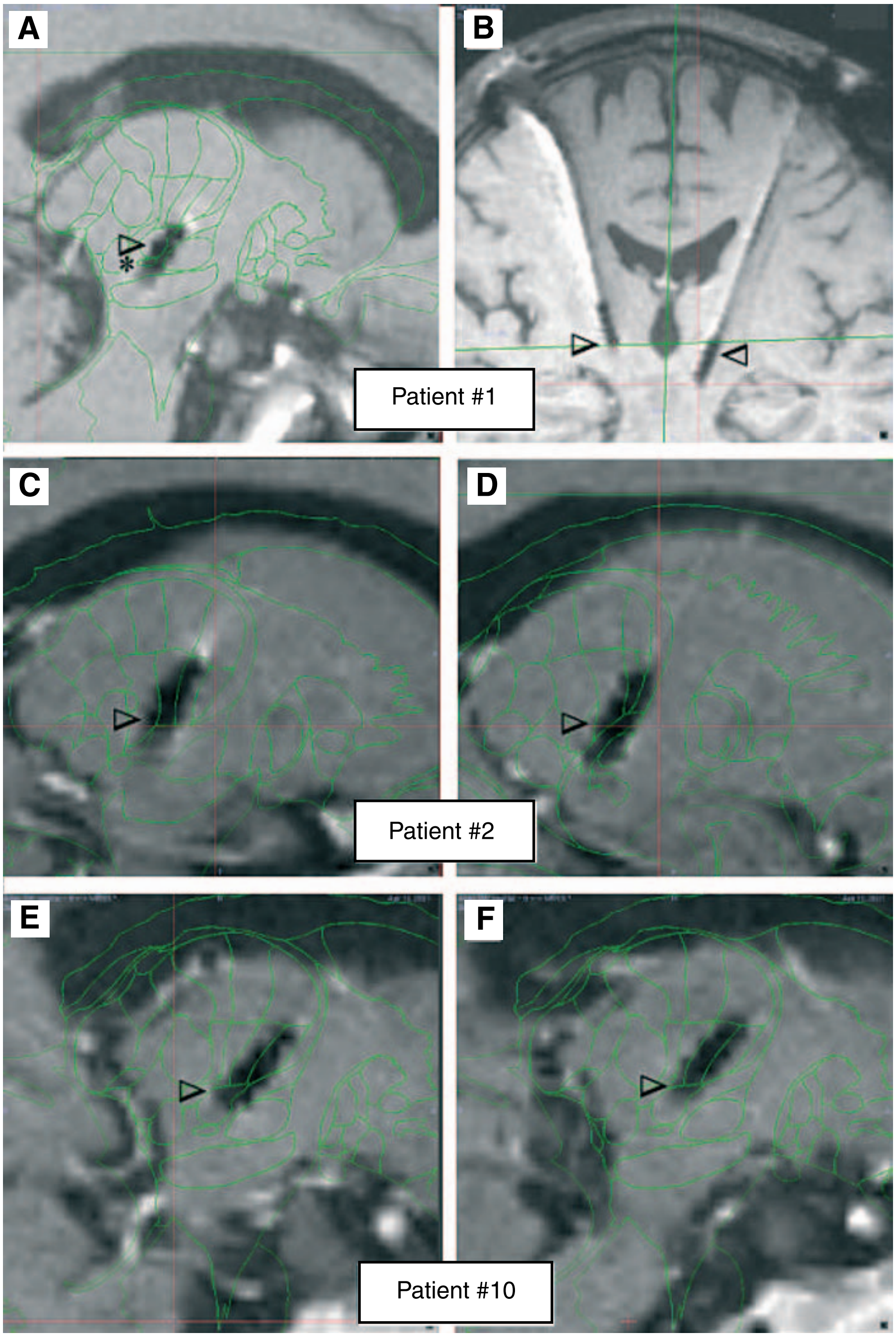


Fig. 3. Assessment of DBS electrodes in postoperative MRI. (A) A sagittal reconstruction of the postoperative T1WI-MRI correlated with the Schaltenbrand and Wahren atlas (12 mm lateral) as described in Patients and methods. The artifacts of all four contacts of the left electrode can be distinguished. The active contact (arrowhead) resulting in best suppression of head and contralateral intention tremor projects into the subthalamic area in close vicinity to the zona incerta, the subthalamic nucleus, and the prelemniscal radiation (stereotactic coordinates relative to the mid-commissural point: $x = -12.5$; $y = -7.4$; $z = -2.9$). The contact below (*) was slightly more effective but associated with side effects. (B) An oblique coronal reconstruction along both electrodes of the same patient (number 1) is shown. All contacts of the asymmetrically placed electrodes can be distinguished. The left electrode was positioned more ventrally and medially. The green lines indicate the midsagittal and the horizontal planes crossing at the inter-commissural line. The tilt in the horizontal line is due to reconstruction of the image in order to depict both electrodes. Stimulation on the right side proved best with the lowest contact which is located at the base of ventralis intermedius (stereotactic coordinates relative to the mid-commissural point: $x = 14.7$; $y = -7.3$; $z = 0.2$). (C–F) The active contacts (arrowheads) of the left (C) and right (D) electrode of another patient (number 2) project onto the base of nucleus ventralis intermedius and base of nucleus ventralis intermedius/subthalamic area, respectively. The stereotactic coordinates relative to the mid-commissural point are: *left* $x = -14.2$, $y = -7.0$, $z = 0.1$; *right* $x = 15.6$, $y = -7.2$, $z = -1.7$. The same analysis in another patient (number 10; cf. Fig. 1) revealed both active contacts (E, left; F, right electrode) within the subthalamic area touching the base of nucleus ventralis intermedius. The stereotactic coordinates relative to the mid-commissural point are: *left* $x = -10.9$, $y = -6.8$, $z = -1.8$; *right* $x = 9.9$, $y = -6.3$, $z = -1.4$

more than 5 mm posterior) to the mid-commissural point (Fig. 2). Approximation of all contacts to the Schaltenbrand and Wahren atlas suggests several subthalamic structures to be possibly involved in effective tremor suppression, in particular the prelemniscal radiation, the zona incerta, and cerebello-thalamic projections at the base of the ventro-lateral thalamus (Fig. 1). Contacts projecting into the nucleus ventralis intermedius proper resulted in strikingly less tremor suppression (Fig. 1). However, superiority of the two distal contacts was not observed in two patients. In the patient suffering from spinocerebellar ataxia the two proximal contacts of the left electrode resulted in better tremor suppression (50–75%) than the distal contacts (<50%). In one patient with essential tremor all contacts of the left electrode were similarly effective (only <50% tremor suppression).

In general, the best contacts (Fig. 1) could be selected for permanent stimulation. In some instances, however, bilateral stimulation gave rise to adverse effects (paraesthesiae, dysarthria, and gait ataxia), while more proximal contacts had to be chosen for chronic stimulation. The mean and median z-values (dorsal-ventral axis) of the most effective vs. permanent stimulation site differed by 0.8 and 0.5 mm, respectively (stereotactic coordinates for both stimulation sites are summarised in Table 2). As summarised in Table 1, overall tremor improvement was affected only little by using 'permanent' instead of 'best' contacts. With permanent DBS intention tremor on the left and right body side was improved by 63 and 68%, respectively (Table 1). The average stereotactic position of the most effective contacts was comparable on the right and left side (Table 1).

In contrast to the subthalamic nucleus or globus pallidus internus, different ventro-lateral thalamic subnuclei and the subthalamic area cannot be delineated by MR imaging. Thus, the anatomical position of DBS electrodes cannot be determined directly from these images. However, the anatomical position of electrode contacts may be estimated from a digitized Schaltenbrand and Wahren atlas provided that an appropriate correlation of the postoperative MRI with the atlas can be achieved. In Fig. 3, MR-images indicating the DBS electrodes of three patients are presented. Sagittal reconstructions of the postoperative T1WI-MRI were correlated with the Schaltenbrand and Wahren atlas (12 mm lateral) as described in Patients and methods. The artifacts generated by individual electrode contacts can be distinguished.

In patient number 1 (Fig. 3A and B), the left active contact (Fig. 3A, indicated by an arrowhead) resulting in best suppression of head and contralateral intention tremor projects into the subthalamic area. The contact below (Fig. 3A, indicated by a star) was slightly more effective but also elicited side effects. Stimulation on the right side proved best with the lowest contact which is located at the base of ventralis intermedius. During the operation implantation of the right electrode was followed by an immediate thalamotomy-like effect with a decrease in contralateral intention tremor which was improved with macro-stimulation. On the left side, symmetric targeting resulted in side effects including dysarthria and vertigo without tremor reduction during micro-stimulation. The target was moved 2 mm medial and 4 mm posterior where macro-stimulation induced right-sided paraesthesiae, and, with higher amplitudes, tremor reduction, but also mild dysarthria, sweating, tonic extension of the hallux, and ocular deviation to the right. Renewed insertion of the electrode 4 mm medial and 2 mm posterior to the original track resulted in good control of head and contralateral limb tremor after the electrode had been advanced below the thalamus.

In patient number 2, the active contacts of the left and right electrode (Fig. 3C and D, respectively) project onto the base of ventralis intermedius and base of ventralis intermedius/subthalamic area, respectively. In patient number 10, the active contacts of the left and right electrode (Fig. 3E and F, respectively) project into the subthalamic area touching the base of nucleus ventralis intermedius.

## Discussion

In this study the position of DBS electrode contacts was analysed systematically with respect to their efficacy on severe intention tremor as rated by a lateralised Fahn-Tolosa-Marin tremor score. The actual site of stimulation was determined by stereotactic means since mere assumptions about the (intended) position of electrode contacts, as frequently presented, have to be regarded as highly imprecise. Our data suggest that distal electrode contacts located below the inter-commissural plane, i.e. in the subthalamic area, were most effective in suppressing intention tremor. Proximal electrode contacts had little if any effect on tremor, although, most of these contacts projected into the ventro-lateral thalamic nuclei proper, in particular the nucleus ventralis intermedius. Notably, in most patients a clear pattern was observed with tremor improvement gradually increasing from dorsal to ventral placement. Thus, our data corroborate the concept that the subthalamic area is superior to the ventralis intermedius nucleus in suppressing severe intention tremor. This has been proposed almost since ablative procedures in the ventro-lateral thalamus had become an established treatment, and this is supported by the fact that the electrical energy required to excite myelinated fibre tracts is lower than that required for somata [3, 5, 10, 30, 46, 47, 57, 58, 61, 62].

Since the distal contacts often proved most effective it remains unclear whether deeper electrode insertion could have resulted in even superior tremor suppression in some patients. In fact, the subthalamic area was not targeted deliberately and the four contacts of the permanent electrode were not centered in the area of best tremor suppression as identified by intraoperative micro-stimulation which, in most instances, was below the inter-commissural plane. However, deeper electrode insertion and even more ventral (postero-medial) stimulation are more likely to be limited by adverse events. In contrast to the ventro-lateral thalamus, targeting of the subthalamic area bears a higher risk of dysarthria, paraesthesiae, and gait ataxia which is pronounced with bilateral stimulation (possibly mimicking a bilateral subthalamotomy) [56, 68]. In some instances, side effects required permanent stimulation with a contact proximal to the optimal contact which, however, had only a slight effect on postoperative tremor improvement.

In a recent study, the optimal target for essential tremor was located 6.3 mm anterior to the posterior commissure and 12.3 mm lateral to the midline which is similar to our data [52]. The most effective electrode contacts clustered at and below the inter-commissural plane. Although, the location of effective contacts varied in the dorso-ventral direction at least as much as in both other directions, this important axis had not been addressed and different electrode contacts of the same electrode have not been compared. Nonetheless, most effective contacts were located close to and below the inter-commissural plane, and this appears similar to the position of nucleus ventralis intermedius electrodes in tremor patients reported by Benabid *et al.* [8]. It has to be taken into account, however, that the latter study (as many others) also included Parkinsonian tremor. This tremor entity is much more amenable to surgical interventions than severe and proximal intention tremor.

In fact, several facts indicate that a proper target for (distal) resting and postural (Parkinsonian) tremor may not suffice for severe (proximal) intention tremor [3, 8, 28]. Correct targeting of the ventro-lateral thalamus has been reported to result in insufficient intraoperative tremor control [6, 29, 36, 37, 64], and superior effects on severe intention tremor in ET and MS have been ascribed to DBS in the posterior subthalamic white matter [3, 36, 45, 48, 53]. In one of our patients we did not achieve sufficient tremor control until the left electrode which had been inserted properly into the ventro-lateral thalamus was repositioned to be finally placed into the subthalamic area [21]. Kitagawa *et al.* reported about a patient in whom DBS in the subthalamic area could suppress intention tremor which was controlled insufficiently following a previous thalamotomy [36]. Furthermore, intraoperative test stimulation performed by Alusi *et al.* revealed that suppression of intention tremor (in MS patients) was achieved at lower voltages when performed ventromedial to and up to 13 mm apart from the intended target in the ventro-lateral thalamus [3]. Whittle *et al.* described in 12 tremor patients suffering from MS an optimal target in the subthalamic area (2.5 mm ventral to the inter-commissural plane) which was located slightly more lateral (13.5 mm) than our mean target [66]. This may be related to the increased width of the third ventricle in this disease. Interestingly, the target was located only 2 mm posterior to the mid-commissural point. Thus, this target is located more anterior than our target, and projects clearly into the zona incerta and the area of cerebello-thalamic projections.

The perception of distinct target areas for tremor suppression also gain support from observations in patients with severe post-traumatic intention tremor. Thermocoagulations in the subthalamic area (zona incerta) combined with lesions in the ipsilateral ventro-lateral thalamus proved superior to single lesions and resulted in good long-term effects [40]. Furthermore, the comparison of thalamic targets between two different centers revealed that more ventro-postero-medial stimulation was more effective in suppressing choreic peak dose dyskinesias, and a role of the centre median and parafascicularis complex was suggested [11].

The exact pathophysiological mechanisms and anatomical structures driving different types of tremor remain a matter of debate [15]. Efficient suppression of intention tremor may be mediated by different structures contained in the subthalamic area, e.g. the zona incerta known to harbour tremor cells, the fields of Forel $H_2$, the prelemniscal radiation, and, possibly, dorsal parts of the subthalamic nucleus [5, 10, 30, 36, 38, 46, 47, 57, 58, 61, 62]. Notably, with DBS in the subthalamic area efferents from deep cerebellar nuclei will be modulated along their course through the prerubral field and along the zona incerta [24, 44, 54]. In addition, the prelemniscal radiation has been regarded to be part of an extralemniscal, reticulothalamic system mediating selective propriceptive attention and tremor, and this site has been propagated to be superior to ventralis intermedius lesioning for the treatment of (Parkinsonian) tremor [61, 62]. In addition, concomitant modulation of projections from/ to the reticular formation (e.g. to ventralis intermedius) and the red nucleus as well as proprioceptive muscle spindle afferents may occur [24, 54]. Superior suppression of intention tremor in the subthalamic region has been related to the fact that proximal muscle groups (paraspinal, limb girdle) used for locomotion, reaching, and axial movements are rather controlled by upper brain stem structures, whereas the predominant control of distal muscles is exerted by thalamocortical pathways [3, 24, 42, 54].

In one of our patients, best anti-tremor effects were observed with both proximal contacts of the left electrode, and, at least for the left electrode, stimulation was performed within the ventro-lateral thalamus, most likely ventralis intermedius. Although, postoperative tremor improvement did not exceed 75% this raises the possibility that in some instances more dorsal stimulation may be advantageous. Similarly, in few other studies contacts located within the thalamus were more effective in suppressing intention tremor [50, 67]. Recently, it has also been suggested that the optimal site for nucleus ventralis intermedius stimulation is located anterior and dorsal to the site where a thalamotomy had been performed [35]. Regarding tremor suppression by the ventro-lateral thalamus proper, one of several mechanisms hypothesized is based on inhibitory afferents (e.g. from the thalamic reticular nucleus) which are activated by DBS and possibly suppress thalamic neuronal activity by release of GABA [16].

Taken together, our data corroborate the concept that the subthalamic area is a superior target for the alleviation of severe intention tremor. Although, most centers target (the base) of the ventro-lateral thalamus (ventralis intermedius) we suppose that effective DBS for severe intention tremor in reality often involves unintentional targeting and stimulation of the subthalamic area.

## References

1. Albe-Fessard D, Arfel G, Guiot G, Hardy J, Vourch G, Hertzog E, Aleonard P, Derome P (1962) Dérivations d'activités spontanées et évoquées dans les structures cérébrales profondes de l'homme. Rev Neurol 106: 89–105
2. Alesch F, Pinter MM, Helscher RJ, Fertl L, Benabid AL, Koos WT (1995) Stimulation of the ventral intermediate thalamic nucleus in tremor dominated Parkinson's disease and essential tremor. Acta Neurochir 136: 75–81
3. Alusi SH, Aziz TZ, Glickman S, Jahanshahi M, Stein JF, Bain PG (2001) Stereotactic lesional surgery for the treatment of tremor in multiple sclerosis: a prospective case-controlled study. Brain 124: 1576–1589
4. Andy OJ (1983) Thalamic stimulation for control of movement disorders. Appl Neurophysiol 46: 107–111
5. Andy OJ, Jurko MF, Sias FR (1963) Subthalamotomy in treatment of Parkinsonian tremor. J Neurosurg 22: 860–870
6. Bakay RA (2004) Thalamic deep brain stimulation for essential tremor: relation of lead location to outcome. Neurosurgery 55: 266–267
7. Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 337: 403–406
8. Benabid AL, Pollak P, Seigneuret E, Hoffmann D, Gay E, Perret J (1993) Chronic ventralis intermedius thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir Suppl 58: 39–44
9. Blond S, Caparros-Lefebvre D, Parker F, Assaker R, Petit H, Guieu JD, Christiaens JL (1992) Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. J Neurosurg 77: 62–68
10. Brice J, McLellan L (1980) Suppression of intention tremor by contingent deep-brain stimulation. Lancet 1: 1221–1222
11. Caparros-Lefebvre D, Blond S, Feltin MP, Pollak P, Benabid AL (1999) Improvement of levodopa induced dyskinesias by thalamic deep brain stimulation is related to slight variation in electrode placement: possible involvement of the centre median and parafascicularis complex. J Neurol Neurosurg Psychiatry 67: 308–314
12. Caparros-Lefebvre D, Ruchoux MM, Blond S, Petit H, Percheron G (1994) Long-term thalamic stimulation in Parkinson's disease: postmortem anatomoclinical study. Neurology 44: 1856–1860
13. Cooper IS, Bravo GJ (1958) Chemopallidectomy and chemothalamectomy. J Neurosurg 15: 244–250
14. Deuschl G, Bain P, Brin M (1998) Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord 13: 2–23
15. Deuschl G, Wenzelburger R, Raethjen J (2000) Tremor. Curr Opin Neurol 13: 437–443
16. Dostrovsky JO, Lozano AM (2002) Mechanisms of deep brain stimulation. Mov Disord 17: S63–S68
17. Fahn S, Tolosa E, Marin C (1988) Clinical rating scale for tremor. In: Jankovic J, Tolosa E (eds) Parkinson's Disease and Movement Disorders. Urban & Schwarzenberg, Baltimore, Munich
18. Gross RE, Jones EG, Dostrovsky JO, Bergeron C, Lang AE, Lozano AM (2004) Histological analysis of the location of effective thalamic stimulation for tremor. Case report. J Neurosurg 100: 547–552
19. Hamel W, Fietzek U, Morsnowski A, Schrader B, Herzog J, Weinert D, Pfister G, Muller D, Volkmann J, Deuschl G, Mehdorn HM (2003) Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: evaluation of active electrode contacts. J Neurol Neurosurg Psychiatry 74: 1036–1046
20. Hamel W, Schrader B, Weinert D, Herzog J, Volkmann J, Deuschl G, Muller D, Mehdorn HM (2002) MRI- and skull X-ray-based approaches to evaluate the position of deep brain stimulation electrode contacts – a technical note. Zentralbl Neurochir 63: 65–69
21. Hamel W, Weinert D, Schrader B, Pöpping M, Müller D, Mehdorn HM, Deuschl G, Krack P (2000) High frequency stimulation of the subthalamic area: a new DBS target for intention tremor. Acta Neurochir 142: 1201 (Abstract)
22. Hanieh A, Maloney AF (1969) Localization of stereotaxic lesions in the treatment of Parkinsonism: a clinico-pathological comparison. J Neurosurg 31: 393–399

23. Hariz GM, Bergenheim AT, Hariz MI, Lindberg M (1998) Assessment of ability/disability in patients treated with chronic thalamic stimulation for tremor. Mov Disord 13: 78–83
24. Hassler R (1982) Architectonic organization of the thalamic nuclei. In: Schaltenbrand GaW W (ed) Stereotaxy of the human brain. Thieme, Stuttgart, pp 140–180
25. Hassler R, Mundinger F, Riechert T (1965) Correlations between clinical and autoptic findings in stereotaxic operations of parkinsonism. Confin Neurol 26: 282–290
26. Hassler R, Riechert T (1954) Indikationen und Lokalisationsmethode der Hirnoperationen. Nervenarzt 25: 441–447
27. Hassler R, Riechert T, Mundinger F *et al* (1960) Physiological observationsin stereotaxic operations in extrapyramidal motor disturbances. Brain 83: 337–351
28. Hirai T, Miyazaki M, Nakajima H, Shibazaki T, Ohye C (1983) The correlation between tremor characteristics and the predicted volume of effective lesions in stereotaxic nucleus ventralis intermedius thalamotomy. Brain 106: 1001–1018
29. Hooper J, Taylor R, Pentland B, Whittle IR (2002) A prospective study of thalamic deep brain stimulation for the treatment of movement disorders in multiple sclerosis. Br J Neurosurg 16: 102–109
30. Hullay J, Velok J, Gombi R, Boczan G (1970) Subthalamotomy in Parkinson's disease. Confin Neurol 32: 345–348
31. Ilinsky IA, Kultas-Ilinsky K (2002) Motor thalamic circuits in primates with emphasis on the area targeted in treatment of movement disorders. Mov Disord 17 Suppl 3: S9–S14
32. Jasper HH, Bertrand C (1964) Stereotaxic microelectrode studies of single thalamic cells and fibres in patients with dyskinesia. Trans amer neurol Acc 89: 79–82
33. Johansson G, Laitinen L (1965) Electrical stimulation of the thalamic and subthalamic area in Parkinson's disease. Confin Neurol 26: 445–450
34. Kelly PJ (1980) Microelectrode recording for the somatotopic placement of stereotactic thalamic lesions in the treatment of Parkinsonian and cerebellar intention tremor. Appl Neurophysiol 43: 262–266
35. Kiss ZH, Wilkinson M, Krcek J, Suchowersky O, Hu B, Murphy WF, Hobson D, Tasker RR (2003) Is the target for thalamic deep brain stimulation the same as for thalamotomy? Mov Disord 18: 1169–1175
36. Kitagawa M, Murata J, Kikuchi S, Sawamura Y, Saito H, Sasaki H, Tashiro K (2000) Deep brain stimulation of subthalamic area for severe proximal tremor. Neurology 55: 114–116
37. Koller W, Pahwa R, Busenbark K, Hubble J, Wilkinson S, Lang A, Tuite P, Sime E, Lazano A, Hauser R, Malapira T, Smith D, Tarsy D, Miyawaki E, Norregaard T, Kormos T, Olanow CW (1997) High-frequency unilateral thalamic stimulation in the treatment of essential and Parkinsonian tremor. Ann Neurol 42: 292–299
38. Krack P, Benazzouz A, Pollak P, Limousin P, Piallat B, Hoffmann D, Xie J, Benabid AL (1998) Treatment of tremor in Parkinson's disease by subthalamic nucleus stimulation. Mov Disord 13: 907–914
39. Krack P, Dostrovsky J, Ilinsky I, Kultas-Ilinsky K, Lenz F, Lozano A, Vitek J (2002) Surgery of the motor thalamus: problems with the present nomenclatures. Mov Disord 17 Suppl 3: S2–S8
40. Krauss JK, Mohadjer M, Nobbe F, Mundinger F (1994) The treatment of posttraumatic tremor by stereotactic surgery. Symptomatic and functional outcome in a series of 35 patients. J Neurosurg 80: 810–819
41. Laitinen L (1985) Brain targets in surgery for Parkinson's disease. Results of a survey of neurosurgeons. J Neurosurg 62: 349–351
42. Lawrence DG, Kuypers HG (1968) The functional organization of the motor system in the monkey. Brain 91: 15–36
43. Limousin P, Speelman JD, Gielen F, Janssens M (1999) Multicentre European study of thalamic stimulation in Parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 66: 289–296
44. Macchi G, Jones EG (1997) Toward an agreement on terminology of nuclear and subnuclear divisions of the motor thalamus. J Neurosurg 86: 670–685
45. Mobin F, De Salles AA, Behnke EJ, Frysinger R (1999) Correlation between MRI-based stereotactic thalamic deep brain stimulation electrode placement, macroelectrode stimulation and clinical response to tremor control. Stereotact Funct Neurosurg 72: 225–232
46. Mundinger F (1969) Results of 500 subthalamotomies in the region of the zona incerta. In: Third Symposium on Parkinson's Disease. E&S Livingstone, Edinburgh and London, pp 261–265
47. Mundinger F (1965) Stereotaxic interventions on the zona incerta area for treatment of extrapyramidal motor disturbances and their results. Confin Neurol 26: 222–230
48. Murata J, Kitagawa M, Uesugi H, Saito H, Iwasaki Y, Kikuchi S, Tashiro K, Sawamura Y (2003) Electrical stimulation of the posterior subthalamic area for the treatment of intractable proximal tremor. J Neurosurg 99: 708–715
49. Narabayashi H, Maeda T, Yokochi F (1987) Long-term follow-up study of nucleus ventralis intermedius and ventro-lateralis thalamotomy using a microelectrode technique in parkinsonism. Appl Neurophysiol 50: 330–337
50. Nguyen JP, Degos JD (1993) Thalamic stimulation and proximal tremor. A specific target in the nucleus ventrointermedius thalami. Arch Neurol 50: 498–500
51. Ohye C, Maeda T, Narabayashi H (1976) Physiologically defined ventralis intermedius nucleus. Its special reference to control of tremor. Appl Neurophysiol 39: 285–295
52. Papavassiliou E, Rau G, Heath S, Abosch A, Barbaro NM, Larson PS, Lamborn K, Starr PA (2004) Thalamic deep brain stimulation for essential tremor: relation of lead location to outcome. Neurosurgery 54: 1120–1129; discussion 1129–1130
53. Plaha P, Patel NK, Gill SS (2004) Stimulation of the subthalamic region for essential tremor. J Neurosurg 101: 48–54
54. Robertson LT, Dow RS (1982) Anatomy of the cerebellum. In: Schaltenbrand G, Walker AE (eds) Stereotaxy of the human brain. Georg Thieme Verlag, Stuttgart New York, pp 60–69
55. Schuurman PR, Bosch DA, Bossuyt PM, Bonsel GJ, van Someren EJ, de Bie RM, Merkus MP, Speelman JD (2000) A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 342: 461–468
56. Siegfried J, Lippitz B (1994) Chronic electrical stimulation of the VL-VPL complex and of the pallidum in the treatment of movement disorders: personal experience since 1982. Stereotact Funct Neurosurg 62: 71–75
57. Spiegel EA, Wycis HT, Szekely EG *et al* (1963) Campotomy in various extrapyramidal disorders. J Neurosurg 20: 871–884
58. Story JL, French LA, Chou SN, Meier MJ (1965) Experiences with subthalamic lesions in patients with movement disorders. Confin Neurol 26: 218–221
59. Sydow O, Thobois S, Alesch F, Speelman JD (2003) Multicentre European study of thalamic stimulation in essential tremor: a six year follow up. J Neurol Neurosurg Psychiatry 74: 1387–1391
60. Tasker RR, Munz M, Junn FS, Kiss ZH, Davis K, Dostrovsky JO, Lozano AM (1997) Deep brain stimulation and thalamotomy for tremor compared. Acta Neurochir Suppl 68: 49–53
61. Velasco F, Jimenez F, Perez ML, Carrillo-Ruiz JD, Velasco AL, Ceballos J, Velasco M (2001) Electrical stimulation of the prelemniscal radiation in the treatment of Parkinson's disease: an old target revised with new techniques. Neurosurgery 49: 293–306; discussion 306–298

62. Velasco F, Velasco M, Machado JP (1975) A statisticl outline of the subthalamic target for the arrest of tremor. Appl Neurophysiol 38: 38–46
63. Volkmann J, Herzog J, Kopper F, Deuschl G (2002) Introduction to the programming of deep brain stimulators. Mov Disord 17: S181–S187
64. Whittle IR, Haddow LJ (1995) CT guided thalamotomy for movement disorders in multiple sclerosis: problems and paradoxes. Acta Neurochir Suppl 64: 13–16
65. Whittle IR, Hooper J, Pentland B (1998) Thalamic deep-brain stimulation for movement disorders due to multiple sclerosis. Lancet 351: 109–110
66. Whittle IR, Yau YH, Hooper J (2004) Mesodiencephalic targeting of stimulating electrodes in patients with tremor caused by multiple sclerosis. J Neurol Neurosurg Psychiatry 75: 1210
67. Yamamoto T, Katayama Y, Kano T, Kobayashi K, Oshima H, Fukaya C (2004) Deep brain stimulation for the treatment of Parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity. J Neurosurg 101: 201–209
68. Yasui N, Narabayashi H, Kondo T, Ohye C (1976) Slight cerebellar signs in stereotactic thalamotomy and subthalamotomy for parkinsonism. Appl Neurophysiol 39: 315–320

## Comments

Even though pallidotomies and thalamotomies in the surgical treatment of movement disorders dominated during the lesional era, the posterior subthalamic area was also a frequently used target. This area has, however, received little attention as a target for DBS. Only recently have a few groups presented their experience of DBS in this area in the treatment of Parkinson's disease, essential tremor and tremor of other origin. Hamel *et al.* have in this interesting study demonstrated that even though they targeted the Vim, the effect of stimulation led them to advance the electrode more caudally into the underlying subthalamic area. Further, when they after surgery analyzed the effect of each individual contact on tremor, the contacts located in the subthalamic area were in most cases more efficient than those located in the Vim. I share the authors' belief, that many patients with a priori a Vim-DBS probably in reality are stimulated trough electrode contacts lying in the subthalamic area. Hopefully, the role of the posterior subthalamic area in the treatment of movement disorders will be further evaluated in future studies.

*Patric Blomstedt*

This paper addresses the target for optimal suppression of tremor in intention tremor. The literature review is extensive, and perhaps demonstrates that often many of our novel findings have been described by our neurosurgical forefathers! The techniques used by Hamel *et al.* are not dissimilar to those used by others who have also examined the electrode placements after successful resolution of movement disorders. The findings of this group add further weight to the subthalamic region being important in the genesis or connectivity that is required for tremor, and its abolition using DBS.

*Ian Whittle*
Edinburgh