Deep brain stimulation of the subthalamic nucleus in Parkinson’s disease: evaluation of active electrode contacts

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Background: The subthalamic nucleus is the preferred target for deep brain stimulation in patients with advanced Parkinson’s disease. The site of permanent stimulation is the subject of ongoing debate, as stimulation both within and adjacent to the subthalamic nucleus may be effective.

Objective: To assess the position of active electrode contacts in relation to the dorsal margin of the subthalamic nucleus as determined by intraoperative microrecordings and magnetic resonance imaging (MRI).

Methods: In 25 patients suffering from severe levodopa sensitive parkinsonism, deep brain stimulating electrodes (n = 49) were implanted following mapping of the subthalamic nucleus by microrecording and microstimulation along five parallel tracks. Postoperative stereotactic radiography and fusion of pre- and postoperative MRI studies were used to determine the stereotactic position relative to the midcommissural point of the most effective electrode contacts selected for permanent stimulation (n = 49). Intraoperative microrecordings were analysed retrospectively to define the dorsal margin of the subthalamic nucleus. In cases where the dorsal margin could be defined in at least three microrecording tracks (n = 37) it was correlated with the position of the active contact using an algorithm developed for direct three dimensional comparisons.

Results: Stimulation of the subthalamic nucleus resulted in marked improvement in levodopa sensitive parkinsonian symptoms and levodopa induced dyskinesias, with significant improvement in UPDRS III scores. In several instances, projection of the electrode artefacts onto the T2 weighted MRI visualised subthalamic nuclei of individual patients suggested that the electrodes had passed through the subthalamic nucleus. When the actual position of active electrode contacts (n = 35) was correlated with the dorsal margin of the subthalamic nucleus as defined neurophysiologically, most contacts were located either in proximity (±1.0 mm) to the dorsal border of the subthalamic nucleus (32.4%) or further dorsal within the subthalamic region (37.8%). The other active contacts (29.7%) were detected within the dorsal (sensorimotor) subthalamic nucleus. The average position of all active contacts (n = 49) was 12.8 mm (±1.0) lateral, 1.9 mm (±1.4) posterior, and 1.6 mm (±2.1) ventral to the midcommissural point.

Conclusions: Subthalamic nucleus stimulation appears to be most effective in the border area between the upper subthalamic nucleus (sensorimotor part) and the subthalamic area containing the zona incerta, fields of Forel, and subthalamic nucleus projections.

Abbreviations: MPTP, 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine; UPDRS, unified Parkinson’s disease rating scale
METHODS

Patients
We evaluated the position of the stimulating electrodes in 25 patients (12 male, 13 female; median age 61 years) with idiopathic levodopa sensitive Parkinson's disease who had undergone bilateral implantations into the subthalamic nucleus at the University of Kiel. Only patients meeting the inclusion criteria, and with none of the exclusion criteria, of the ongoing German multicentre study “Kompetenzzentrum Parkinson” had been considered for this procedure. All patients were operated on between May 1999 and March 2002. Patient selection for the present study was based on the availability of data regarding the stereotactic positioning of the electrode contacts, which was determined as described previously. Preoperative evaluation included repeated assessment of the levodopa response as rated by the unified Parkinson's disease rating scale (UPDRS III), magnetic resonance imaging (MRI), and additional neurological and neuropsychological examinations.

All patients provided written informed consent before surgical intervention, and the procedures were approved by the local ethics committee.

Forty nine electrodes were implanted in one unilateral operation. In one patient, unilateral electrode implantation into the ventrolateral thalamus had been done previously at another institution. Bilateral Itrel II or unilateral Kinetra neurostimulators (Medtronic, Minneapolis, Minnesota, USA) were implanted one to five days after electrode implantation. In another patient a unilateral thalamotomy had been done more than 10 years before as palliation for tremor dominant Parkinson's disease; in that patient continuous good relief of contralateral tremor was observed, but there had been progression of the disease and the development of levodopa induced side effects over recent years.

Surgical procedure
The surgical procedure has been described elsewhere in detail. In brief, a MRI compatible Zamorano-Dujovny frame (Stryker Leibinger, Freiburg, Germany) was positioned in an orbito-meatal direction. Planning of the tracks was undertaken with Windows NT based StereoplanPlus 2.3 software (Stryker Leibinger, Freiburg, Germany), using both gadolinium enhanced volumetric T1 weighted MRI (1.0 mm slice thickness) and T2 weighted spin echo MRI sequences (3.0 mm slice thickness) acquired with a Siemens Magnetom Vision 1.5 tesla MRI scanner (Siemens, Erlangen, Germany). Both sequences were acquired parallel to the intercommisural plane, which was defined in a midsagittal slice from a standard T1 weighted MRI planning sequence in a slice 3 mm ventral to the intercommissural line. The position of active electrode contacts relative to the dorso-lateral subthalamic nucleus was depicted in three dimensions (see Zhu et al.) the position of active electrode contacts relative to the dorso-lateral subthalamic nucleus was depicted in three dimensions (see Zhu et al.)

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the 12 months follow up for 48 patients with Parkinson’s disease (including all the patients evaluated in this study) were: 3.1 (0.6) V, 136 (14) Hz, and 62 (9) µA. Additional medical treatment resulted in further improvements, leading to UPDRS III scores that could not be achieved preoperatively (fig 1). The mean levodopa equivalent dose was reduced by more than 50% after electrode implantation. This was associated with a significant reduction in peak dose dyskinesias (> 50%), which was reflected in a marked improvement in the activities of daily living, rated according to UPDRS II (data not shown). These and subsequent clinical follow up examinations will be reported separately in greater detail.

Postoperative MRI based evaluation of deep brain stimulating electrodes

Correlations of preoperative and postoperative MRI can be used to delineate the deep brain stimulating electrodes with respect to the subthalamic nucleus, as depicted by T2 weighted spin echo imaging. This is best done with MRI of high resolution and devoid of artefacts, a situation achievable by the acquisition of the preoperative images under general anaesthesia. As demonstrated for a representative patient in fig 2, the subthalamic nucleus can be clearly delineated in preoperative axial spin echo images (panel A) as well as in coronal (panels G, H) and sagittal (panels L, M and N) reconstructions derived therefrom. The planning tracks are indicated by red lines (right) and blue lines (left). The implanted electrodes can be visualised relative to the subthalamic nucleus using different image fusion modes—that is, a detail of the postoperative image overlaid the preoperative image (panel D), or intermediate weighting of images reveals both the electrode and the subthalamic nucleus (panel F).

Sagittal (panel L) and coronal (panels G and H) T2 weighted MRI reconstructions correlated with postoperative T1 weighted MRI (panels M, J, and K), indicate placement of the left electrode along the planning track within the subthalamic nucleus, whereas the right electrode had been positioned along the anterior and ventral aspect of the subthalamic nucleus. By correlating the T2 weighted MRI with a patient-adapted Schaltenbrand and Wahren atlas, the MRI delineated subthalamic nucleus is congruent with the borders of the atlas-defined subthalamic nucleus in both sagittal and coronal reconstructions (panels N to Q). The patient matched atlas has then been used to evaluate the electrode artefact from postoperative T1 weighted MRI at different levels, also indicating positioning of the left electrode within the subthalamic nucleus (panels R to U).

MRI may also be valuable for the analysis of electrodes implanted in patients who previously had ablative procedures within the basal ganglia. In one patient a thalamo-subthalamicotomy had been placed within and towards the base of the Vop nucleus ventralis oralis posterior thalami according to the Schaltenbrand and Wahren atlas, which had been correlated with the T1 weighted MRI (fig 3). In this patient deep brain stimulation was done in the vicinity of, but in an area clearly distinct from, the site lesioned previously.
Coordinates of active electrode contacts

Retrospective analysis of the stereotactic position of the active electrode contacts was done in 25 patients for whom postoperative T1 weighted MRI of sufficient quality or stereotactic radiographic examinations were available. Such analyses could not be undertaken in other patients (n = 15) implanted with subthalamic nucleus electrodes during the same period because of motion artefacts in the postoperative MRI, missing postoperative T1 weighted MRI, or missing postoperative stereotactic x-rays. For the 25 patients evaluated, the mean and median coordinates (relative to the midcommissural point) of all active contacts are summarised in table 3. The mean (SD) laterality of all active electrode contacts (12.8 (1.0) mm; median 12.7 mm) correlated well with the laterality of the subthalamic nucleus, as determined 3 mm ventral to the intercommissural plane in T2 weighted MRI of 35 patients (12.7 (1.3) mm). However, in the dorso-ventral direction the mean (−1.6 mm) and median (−1.8 mm) z coordinate (table 3) of all active contacts do not project within the subthalamic nucleus proper, but suggest an area between the dorsal margin of the subthalamic nucleus and the subthalamic region according to different stereotactic brain atlases. Moreover, 12 of 49 active contacts (24.5%) were located within 0.5 mm of the intercommissural plane or further dorsal; they were thus most probably in the subthalamic area.

Correlation of active electrode contacts with microrecordings

To account for individual variability within the basal ganglia and the subthalamic area, the position of single (active) electrode contacts should preferentially be put in relation to the location of the structures of interest. For that purpose, we developed an algorithm for three dimensional plotting of the (active) electrode contact within the same stereotactic (commissure based) coordinate system, showing the microcording tracks explored intraoperatively (fig 4). The intercommissural plane is indicated (fig 4, grey square) for orientation purposes, while the three dimensional plots can be rotated to be viewed from different angles of interest. The area where subthalamic nucleus activity was first recorded (fig 4, green lines) and which corresponds to its dorsal margin was defined by retrospective off-line analysis of intraoperative microrecordings (Spike2 software; as described in Methods). Despite continuous on-line analysis during the operation, recordings of longer duration (one to two minutes) used for off-line reassessments had been made at intervals of 0.5 mm. This results in some uncertainty over the exact location of the border. Taking the length (1.5 mm) of single electrode contacts into account as well (the coordinates refer to the centre of the contact), contacts located within ±1.0 mm from the neurophysiologically mapped subthalamic nucleus margin (indicated by...
green lines in fig 4) were categorised as being located in the border area.

The findings in the representative patients show a heterogeneous pattern of localisation of active contacts (fig 4). Although fewer electrode contacts selected for permanent stimulation were located within the subthalamic nucleus (for example, patient 3, left electrode), most active contacts project onto the upper margin of the subthalamic nucleus or above the nucleus into the subthalamic area. Interestingly, such contacts were selected despite the fact that other electrode contacts were located within the subthalamic nucleus (fig 4). The position of active contacts relative to the border of the subthalamic nucleus was classified into three categories.

![Figure 3](image)

**Figure 3** In one patient in whom a thalamotomy had been undertaken previously the position of the hypointense electrode artefact is illustrated relative to the lesion (red arrow). The planning track for the DBS electrode (blue lines) is projected into a sagittal slice of the Schaltenbrand and Wahren atlas (upper left) and in a sagittal (upper right) and two coronal (lower panel; left image located dorsal to right image) T1 weighted MRI reconstructions. The position of the microelectrode tracks explored intraoperatively is also indicated (blue dots) in both coronal reconstructions (lower panel). The uppermost contact (No 3) was used for permanent stimulation. The pre-existing lesion had been placed within and towards the base of the Vop (nucleus ventralis oralis posterior thalami) according to the Schaltenbrand and Wahren atlas, which had been correlated with the T1 weighted MRI. Thus deep brain stimulation is done in the vicinity of, but in an area clearly distinct from, the site lesioned previously.

### Table 3

<table>
<thead>
<tr>
<th>x</th>
<th>y</th>
<th>z</th>
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<tr>
<td>12.8</td>
<td>-1.9</td>
<td>-1.6</td>
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Values [mm] of 49 electrodes implanted in 25 patients. CI, confidence interval.
Three dimensional plotting of (active) electrode contacts relative to the dorsal margin of the subthalamic nucleus, as defined by selected for permanent stimulation. In all patients, deep brain have evaluated the spatial position of electrode contacts the therapeutic effects of subthalamic nuclear stimulation, we To obtain information about the actual site of chronic stimu- part of the subthalamic nucleus. Most of these contacts appeared to be located in the upper, that is the sensorimotor, part of the subthalamic nucleus.

**DISCUSSION**

To obtain information about the actual site of chronic stimulation and the anatomical structures that might be involved in the therapeutic effects of subthalamic nuclear stimulation, we have evaluated the spatial position of electrode contacts selected for permanent stimulation. In all patients, deep brain stimulation resulted in marked improvements in UPDRS III scores, to an extent similar to that reported by others, and both levodopa induced dyskinesias and dopaminergic treatment could be reduced. We observed that UPDRS III scores at three and 12 months after surgery were improved without stimulation and medication when compared with the preoperative state. Possible explanations include the follow- ing: carryover effects of long acting dopamine agonist (caber- goline), despite the fact that the drug was discontinued approximately two days before evaluation; carryover effects after cessation of stimulation approximately one hour before clinical rating; and long lasting subthalamotomy-like effects still present three and 12 months after the operation, though this seems rather unlikely.

Projection of electrode artefacts from postoperative T1 weighted MRI onto the subthalamic nucleus, as visualised by preoperative T2 weighted MRI, provided direct evidence for electrode placement into the subthalamic nucleus. With this method, the position of the electrode can be assessed relative to the MRI defined anatomy of the subthalamic nucleus in individual patients. This approach has been useful for postop- erative routine evaluation preceding implantation of impulse generators to document the correct placement of electrodes. Such analysis, however, appears to be of limited value for assessments in the dorso-ventral axis and with respect to defining the dorsal border of the subthalamic nucleus— particularly as the axial T2 weighted MRI used had a slice thickness of 3 mm. This is in accordance with the perception that surgical targeting of the subthalamic nucleus based solely on its appearance in T2 weighted MRI is imprecise, and the relevance of intraoperative microrecordings for best target definition has always been stressed. Similarly, individual anatomy is defined more precisely by microrecordings than by correlation with different stereotactic brain atlases, although complex morphometric adjustments may improve upon correlation of atlas with patient data.

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In delineating the basal ganglia nuclei— that is, mapping the boundaries of the subthalamic nucleus on an individual basis—intraoperative neurophysiology has to be regarded as the most accurate procedure. For this purpose, we reviewed the results of elaborate microrecordings, including detailed off-line reassessment. As we routinely record from five tracks in parallel, an area of 4.6 × 4.6 mm was mapped systematically in intervals of 0.5 mm. To be suitable for three dimensional analysis, a minimum of at least three informative tracks was required, which exceeds the number of microelectrode tracks evaluated for similar purposes by another centre. This allowed the precise delineation of the dorsal border of the subthalamic nucleus in the vast majority of procedures (37 or 49 electrodes). As the average position of all active contacts suggested scattering in the upper subthalamic nucleus/ subthalamic area, we focused on the dorsal margin of the subthalamic nucleus instead of defining the whole nucleus or its ventral margin towards the substantia nigra.

The stereotactic position of single electrode contacts was determined from postoperative stereotactic x ray examinations and MRI done with high resolution (that is, 0.98 mm voxel size). These methods allow one to directly determine the definitive localisation of single electrode contacts, which otherwise may be done by intraoperative teleradiography when available. In general, methods based on postoperative imaging are preferable to procedures in which the position of electrode contacts is merely extrapolated from the position intended intraoperatively.

A novel algorithm was developed allowing for detailed patient by patient analysis in which the definitive position of the active electrode contact (n = 37 electrodes) could be com- pared with the dorsal margin of the subthalamic nucleus at a glance. Despite a considerable degree of variation with respect to active contact localisation, 70% of the active contacts were observed either at the margin of the subthalamic nucleus or clearly above the nucleus within the subthalamic region. Less than one third of the active contacts (29.7%) clearly projected within the subthalamic nucleus. Several of these contacts appeared to be located in the upper (sensorimotor) subthal- lamic nucleus.

This pattern of active contact localisation is reflected by the mean coordinates of the active contacts in all 25 patients which are summarised in table 4. To make this analysis most accurate, only procedures in which the dorsal border could be clearly determined from at least three microelectrode tracks were included (37 of 49 implanted electrodes; see table 4). As summarised in table 4, most active contacts were detected above (38%) or at the dorsal margin of the subthalamic nucleus (32%). Only 30% of the active contacts were located within the subthalamic nucleus. Most of these contacts appeared to be located in the upper, that is the sensorimotor, part of the subthalamic nucleus.

**Table 4**

<table>
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<tr>
<th>Procedures</th>
<th>&lt;3 Tracks</th>
<th>≥3 Tracks</th>
<th>Dorsal</th>
<th>Margin</th>
<th>Ventral</th>
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<td>49</td>
<td>12</td>
<td>37</td>
<td>14 (37.8%)</td>
<td>12 (32.4%)</td>
<td>11 (29.7%)</td>
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Microrecordings included five tracks per procedure which were explored in parallel (see Methods). With one unilateral procedure, 49 operations were done in 25 patients. To define the dorsal border of the subthalamic nucleus, at least three informative microrecording tracks were required. Classification into “dorsal,” “margin,” and “ventral” was done as described in Results.

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**Figure 4**

Three dimensional plotting of (active) electrode contacts relative to the dorsal margin of the subthalamic nucleus, as defined by intraoperative microrecording (see Methods). The results of five patients operated on bilaterally (left, right) are shown. Five microelectrode tracks separated by 2.3 mm were explored and analysed retrospectively with the Spike2 software (see Methods). Each track is indicated with a different colour: central in black, anterior in light blue, posterior in dark blue, medial (right side) in yellow, medial (left side) in red, lateral (right side) in red, and lateral (left side) in yellow. The positions of active (red dots) and non-active (black dots) electrode contacts relative to the dorsal margin of the subthalamic nucleus (thicker green lines) are illustrated in three different projections per implanted microelectrode: a slightly oblique sagittal view ("sagittal"), a slightly oblique coronal view ("coronal"), and an oblique view ("oblique"). In the latter view the image was rotated until the dorsal border of the subthalamic nucleus projected into a single plane. The intercommissural plane is outlined (grey lines), and circles indicate where microelectrodes penetrate the intercommissural plane. A perpendicular projection of the active contact onto the intercommisural plane is also shown (dotted red lines). As only the dorsal margin of the subthalamic nucleus had been of interest, and in order to keep the image easy to take in at a glance, the maximum microelectrode depth shown here corresponds to the defined surgical target (central track, 3 mm ventral to the intercommissural point). See previous page.
(n = 49 electrodes) which may serve as an approximation for a "best target at an average." This was located 12.8 mm lateral, 1.9 mm posterior, 1.2 mm ventral, and 1.6 mm medial (median 1.8 mm) to the midcomissural point. These coordinates compare well with recent studies in which the average position of the active contacts relative to the midcomissural point had been estimated at 12.3 mm lateral, 1.7 mm posterior, and 1.7 mm ventral,12 and 11.7 mm lateral, 1.6 mm posterior, and 2.5 mm ventral.13 However, Benabid reported somewhat different coordinates for more than 150 patients14: the average location of the contacts leading to the best clinical responses was more ventral to the intercommissural plane (3.16 mm) and slightly more medial (12.1 mm). A similar result (163 (25) Hz), and the variances of both parameters described recently by Starr et al15: that is, 11.8 mm lateral, 2.4 mm posterior, and 3.8 mm ventral to the midcomissural point.

According to different stereotactic atlases for basal ganglia anatomy,12-17 the average position of all active contacts in our patients coincides with the interface formed by the antero-dorso-lateral margin of the subthalamic nucleus, the zona incerta, and fields of Forel H. This is consistent with recent studies using MRI based techniques to determine the position of active contacts.13,14 Although the subthalamic zona incerta may have been described recently by Starr et al,15 that is, 11.8 mm lateral, 2.4 mm posterior, and 3.8 mm ventral to the midcomissural point. Without doubt, the exact mechanisms of deep brain stimulation will remain a matter of debate.18 Nevertheless, it is worthwhile considering the position of active contacts with respect to structures located at the interface between the subthalamic nucleus and the subthalamic area, as several of these may be involved in the therapeutic effects of subthalamic nucleus stimulation. High frequency stimulation within the subthalamic nucleus mimics the effect of a lesion, and inhibition of subthalamic nucleus neuronal activity may in fact be based on a rather direct effect on neuronal cell bodies (for example, modulation of membrane potential) within the sensorimotor region of the subthalamic nucleus.19 In these studies frequent stimulation at the dorsal margin of the subthalamic nucleus and within the subthalamic area has been observed.19-22 The volume of tissue stimulated with deep brain stimulating electrodes has been estimated to be in the range of 2 to 3 mm around the electrode contact.19 This is in agreement with estimations of Saint-Cyr et al,23 undertaking deep brain stimulation with amplitudes (2.8 V) similar to those used in our patients, although pulse width (89 (38) μs), frequency (163 (25) Hz), and the variances of both parameters were higher than in our patients.

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within the subthalamic nucleus (Herzog J et al, in preparation). Nevertheless, the border area may be regarded as superior because stimulation was more often given in this area than within the subthalamic nucleus, although more ventral contacts for stimulation within subthalamic nucleus were available.

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