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

Dominique Caparros-Lefebvre, Serge Blond, Marie-Pierre Feltin, Pierre Pollak, Alim Louis Benabd

Abstract
Objective—To define the reason why two teams using the same procedure and the same target for deep brain stimulation (DBS) obtained different results on levodopa induced dyskinesias, whereas in both, parkinsonian tremor was improved or totally suppressed.

Methods—Deep brain stimulation can replace lesions in the surgical treatment of abnormal movements. After 10 years of experience with DBS in Parkinson’s disease, a comparison of results between the teams of Lille (A) and Grenoble (B) was carried out, for as long as they used intraoperative ventriculography. Both teams aimed at the same target, the ventralis intermedius nucleus of the thalamus (VIM), but team A found a clear improvement of choreic peak dose dyskinesias, whereas team B did not consistently. Therefore all teleradioanatomical data of both teams were re-examined and compared with the therapeutic effects. Location of 99 monopolar electrodes of thalamic stimulation applied to treat parkinsonian tremor has been retrospectively measured (team A included 21 patients, 22 electrodes; team B included 52 patients, 74 electrodes). Peak dose levodopa dyskinesias were suppressed by DBS in all nine patients of team A, four of which were severely disabling. Only eight out of 32 patients from team B experienced a moderate (four) or clear (four) improvement of dyskinesias, whereas in the remaining 24 patients, dyskinesias were unchanged with stimulation.

Results—The mean centre of team A’s electrodes was on average 2.9 mm deeper, more posterior and medial than team B’s (t=8.05; p<0.0001). This does not correspond to the coordinates of the VIM, but seems to be closer to those of the centre median and parafascicularis complex (CM-Pf), according to stereotaxic atlases. Considering only the dyskinetic patients, significant differences were found in the electrode position according to the therapeutic effects on levodopa dyskinesias, but they were not related to the team membership. Improvement in levodopa dyskinesias was significantly associated with deeper and more medial placement of electrodes.

Conclusion—The retrospective analysis of patients treated with DBS using comparable methodologies provides important information concerning electrode position and therapeutic outcome. The position of the electrode is related to the therapeutic effects of DBS. The results support the hypothesis that patients experiencing an improvement of dyskinesias under DBS are actually stimulated in a structure which is more posterior, more internal, and deeper than the VIM, very close to the CM-Pf. These results are consistent with neuroanatomical and neurophysiological data showing that the CM-Pf is included in the motor circuits of the basal ganglia system and receives an important input from the internal pallidum. This suggests that the CM-Pf could be involved specifically in the pathophysiology of levodopa peak dose dyskinesias.

Keywords: deep brain stimulation; nucleus centromedianus and parafascicularis; Parkinson’s disease; levodopa induced dyskinesias

Deep brain stimulation (DBS) has become a widely accepted method for the treatment of Parkinson’s disease symptoms and concerns three major targets—namely, the nucleus ventralis intermedius (VIM), the internal part of the globus pallidus (GPi), and the subthalamic nucleus (STN). Since 1987, clinical evaluation of the effects of DBS has identified the VIM as an effective DBS target for tremor alleviation. Deep brain stimulation of the VIM is as effective as thalamotomy, but produces fewer adverse effects. The only postmortem case of long lasting DBS of the VIM failed to show neuronal lesions and suggested that the electrode was in fact in the lowest and most internal part of the VIM, very close to the centre median and parafascicularis complex (CM-Pf). Based on this, various targets could be considered, as the basal ganglia constitute a complex neuronal network the disruption of which at several sites could be effective in different movement disorders. However, this complex network involved in the pathophysiol-
Improvement of levodopa induced dyskinesias by thalamic stimulation

remain to be related to subtle effects on tremor, but other therapeutic effects of thalamic DBS reported previously, still remain to be related to subtle differences in electrode placement. Indeed team A (Lille group) has obtained an additional significant effect on peak dose levodopa induced dyskinesias, whereas team B (Grenoble group) has obtained an additional significant effect on peak dose levodopa induced dyskinesias in this subgroup: the choice of stimulation parameters was not significantly different between both teams: intensity 1.5 to 3.75 V, pulse width 60 to 210 µs, frequency 130 Hz.

Electrode position measurements

Electrode position measurements were made by the same investigator (ALB) on the final radiographs, using the ventriculographic data. He was blinded as to the dyskinesia improvement with DBS. The electrode position was determined by the coordinates (in mm) of its lower and upper tips and its centre (the length of the active tip was 3.5 mm, the outer diameter 1.3 mm), versus the PC (anteroposterior coordinates expressed as 12ths of the AC-PC line for normalisation against individual variability of the AC-PC line length), the height above the AC-PC line (expressed in 1/8 of the height of the thalamus) and laterality from the midline of the third ventricle (expressed in mm without normalisation against an individual anatomical landmark).

Patients and methods

SURGICAL PROCEDURE

Both teams, trained in the same Talairach's methodology, used ventriculographic determination of the target, which was further validated by electrophysiological methods, such as stimulation and additional microrecordings (the microrecordings were performed by team B only). Patients were held in a Talairach frame, positioned at the focus of a biorthogonal tele x ray apparatus (in teams A and B, respectively 5 m and 3.5 m from the x ray source to the centre of the patient's head, resulting in a magnification coefficient of 1.03 and 1.05). Ventriculographic landmarks (antero (AC) and posterior (PC) commissures, top of the thalamus shown as the floor of the lateral ventricle, and midline of the third ventricle) were determined after injection of 6.5 ml Iopamiron (Schering). The target coordinates were determined following the Guiot scheme. The VIM target is 1 mm above the level of the PC, the laterality is 1.25 mm plus half of the third ventricle width at the level of implantation. Both teams implanted their electrodes along the axis of the VIM nucleus with an angle in the sagittal plane which, from the Guiot’s scheme, can be calculated as α = Arctg(4ht/ap) where ht represents the height of the thalamus and ap the intercommissural distance. The height of the thalamus was the distance from the the AC-PC line to the lower limit of the lateral ventricle. However, in the frontal plane, team A used a trajectory at 5° to 10° from the midsagittal plane, to avoid the lateral ventricle, whereas team B went through this ventricle, in a plane parallel to the midsagittal plane. Then the differences of procedure between each team consisted only in electrode approach, introduced with double frontal and sagittal obliquity in team A and in simple sagittal obliquity in team B. Recording of cells bursting synchronously to tremor and observation of tremor suppression at a 130 Hz stimulation allowed optimal positioning of the electrode (Medtronic Inc, Minneapolis, MN, USA) which was then secured to the skull by dental cement (team B) or by a Straumann-Avery screw (team A). Final radiographs taken at the end of the procedure allowed precise measurement of the electrode position versus the ventriculographic Guiot’s landmarks. After a postoperative evaluation of efficacy using an external stimulator, a programmable pulse generator was implanted and connected to the electrode (ITREL I or II, Medtronic). The parameters of stimulation were not significantly different between both teams: intensity 1 to 3.75 V, pulse width 60 to 210 µs, frequency 130 Hz.

DYSKINESIA ASSESSMENT

Dyskinesias were scored before and after surgery, every 6 months, during standardised acute
Table 1 Mean values of the coordinates of the centre, upper, and lower tips of the electrodes in the two series. Statistical differences are calculated using the Student’s t test (AP = anterior-posterior)

<table>
<thead>
<tr>
<th></th>
<th>Laterality</th>
<th>AP position</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grenoble</td>
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<td>Grenoble</td>
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<tr>
<td>Centre of electrodes</td>
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<td>74</td>
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<tr>
<td>t Value</td>
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</tr>
<tr>
<td>p Value</td>
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<td>&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
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<td></td>
<td></td>
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<tr>
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<td>SD</td>
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<td>t Value</td>
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<tr>
<td>p Value</td>
<td>NS</td>
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<tr>
<td>Inferior tip:</td>
<td></td>
<td></td>
<td></td>
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<td>Lille</td>
<td>Grenoble</td>
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<tr>
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<td>2.6</td>
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<tr>
<td>SD</td>
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</tr>
<tr>
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<td>0.98</td>
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</tr>
<tr>
<td>p Value</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
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levodopa tests, with repeated measurements of the motor part of the unified Parkinson’s disease rating scale (UPDRS). The rating scale used for dyskinesias was semiquantitative: 0=no dyskinesias; 1=mild and transient dyskinesias involving the distal part of one or two limbs; 2=moderate dyskinesias with social disability during more than 1 hour; 3=marked dyskinesias involving more than two limbs producing motor disability; 4=severe disabling dyskinesias, more than 8 hours a day.

DATA PROCESSING
The electrode position (lower tip, upper tip, centre) was compared in both groups, using the mean and SD and was graphically displayed showing the projection on the midplane and coronal plane perpendicular to the AC-PC line.

STATISTICAL METHOD
Student’s t test was used to check the significance of differences between coordinates of the upper and lower electrode tips, and the centre of the electrodes.

Results
ASSESSMENT OF THE EFFECT OF DBS ON DYSKINESIAS
Choreic peak dose dyskinesias were prominent in all dyskinetic patients, and dystonic dyskinesias were found in four of team A. In the same group, during the levodopa test, the mean score of dyskinesias was 2.7 (SD 1) (range 1–4), whereas peak dose dyskinesias were suppressed by stimulation in all patients, with a posteffect lasting from 1 to several hours. The four patients of team A with onset and end of dose dystonic dyskinesias improved transiently but dyskinesias recurred after 3 to 6 months. The mean score of dyskinesias was 0.5 when DBS was applied, due to the persistence of moderate dystonic dyskinesias in three patients. Off period dystonia, seen in one patient before surgery, was not improved and even worsened after 2 years of stimulation. In team B, mild dyskinesias were found before surgery in a few patients (mean score<1), but as the disease progressed, 32 patients out of 52 experienced levodopa induced dyskinesias, which improved in only 19 under stimulation. This improvement was important in four, and moderate in four others. Eleven patients exhibited a mild improvement and 13 had no effect of DBS on their abnormal involuntary movements. Fourteen patients had off period dystonia which never improved with stimulation. In one patient of team B, a GPi stimulation was performed to treat disabling biphasic onset and end of dose dyskinesias, in addition to previous bilateral DBS of the VIM, which was still controlling totally the tremor on both sides.

ANATOMICAL LANDMARKS
Both series (Grenoble and Lille) were comparable on the basis of the anatomical structures (mean width of the third ventricle respectively 6.48 (SD 2) mm and 6.34 (SD 1.9) mm; mean AC-PC length respectively 26.8 (SD 2) mm and 26.3 (SD 2.5) mm), except for the height of the thalamus (respectively 17.84 (SD 1.36) mm and 16.71 (SD 1.8) mm, t=2.86, p<0.01), which had no strong influence on the definition of the target at the level of the AC-PC line. The ratio “height of thalamus to length of the AC-PC” mainly determines the obliqueness of the VIM nucleus, but the usual placement of the electrodes was very close to the level of the AC-PC line. However, it might change the angle of the electrode approach during implantation and could account for differences when the active electrode tip goes below the intercommissural level. The height of the thalamus in the team A series could account for a more posterior position of the electrodes below the intercommissural line, and this was actually the case.

POSIIONS OF ALL THE ELECTRODES IN THE TWO GROUPS
For the centre of the electrode as well as for its upper and lower tips, the position of the electrodes was significantly different between teams A and B (table 1). The average coordinates of the centre of the electrodes were different in the three spatial directions between
**Table 2  Mean values of the coordinates of the lower (inferior) tips of the electrodes in the dyskinetic subgroups from teams A and B segregated according to the improvement or absence of improvement**

<table>
<thead>
<tr>
<th>Subgroups with good effect on dyskinesias: centre of electrodes</th>
<th>Laterality</th>
<th>AP position</th>
<th>Height</th>
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<td>Lille</td>
<td>Grenoble</td>
</tr>
<tr>
<td>Mean value</td>
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<td>2.56</td>
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<tr>
<td>SD</td>
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<td>p Value (18 degrees of freedom)</td>
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<td>NS</td>
<td>NS</td>
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<tr>
<td>Lille subgroup with AIMs</td>
<td>Laterality</td>
<td>AP position</td>
<td>Height</td>
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<tr>
<td>Mean value</td>
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<td>13.21</td>
<td>2.60</td>
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<tr>
<td>SD</td>
<td>1.2</td>
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<td>0.5</td>
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<tr>
<td>t Value</td>
<td>2.81</td>
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<td>p Value (33 degrees of freedom)</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.001</td>
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<td>Grenoble subgroups with AIMs</td>
<td>Laterality</td>
<td>AP position</td>
<td>Height</td>
</tr>
<tr>
<td>Mean value</td>
<td>14.32</td>
<td>14.60</td>
<td>2.77</td>
</tr>
<tr>
<td>SD</td>
<td>1.62</td>
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<td>t Value</td>
<td>0.58</td>
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<td>3.78</td>
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<tr>
<td>p Value (39 degrees of freedom)</td>
<td>NS</td>
<td>&lt;0.001</td>
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</table>

Figure 2  Graphs of average position (with SD represented by rectangles) of the centre of electrodes in the dyskinetic patients improved by stimulation (same conventions as in fig 1).

the two groups: the electrodes of team A were more medial, more posterior, and lower than those of team B (table 1). The average centre to centre distance between the two groups was 2.91 mm. The mean values of the coordinates of the upper and lower tips of these electrodes were still significantly different. Because team A had used a trajectory at 5°C to 10° from the midsagittal plane in the frontal plane, their active tips were closer to the midsagittal plane as they went deeper, and in every case, their lower tips were even more medial (3.06 mm distance from team B mean centre of electrodes) than their upper tip (2.86 mm distance from team B mean centre of electrodes). The difference in laterality already seen between the centre of the electrodes was even greater when the lower tip was considered, whereas it was not significantly different for the upper tips. Upper and lower tip coordinates were significantly different in height above (team B) or below (team A) the intercommissural plane, whereas the anteroposterior coordinates were significantly different for the upper tips but not for the lower. This can be seen on the graphs showing the average centre of the electrodes with SD (fig 1).

**Figure 2**  Graphs of average position (with SD represented by rectangles) of the centre of electrodes in the dyskinetic patients improved by stimulation (same conventions as in fig 1).

POSITIONS OF THE ELECTRODES OF THE DYSKINETIC PATIENTS IN THE TWO GROUPS

Although the number of patients in each subgroup of dyskinetic patients was small, the position of the electrodes differed significantly between the subgroups from team A or B with dyskinesia improvement and the subgroup of team B without improvement (table 2). The mean coordinates of upper and lower tips, and the centre of the electrodes, were not different in subgroups separated according to the occurrence (or not) of dyskinesias. All comparisons were then made on the lower tip position, to focus on the most active and most representative tips. Indeed, in team A, the mean coordinates were not different in the subgroup with dyskinesias in comparison with the whole team (respectively 13.2 and 13.3 mm apart from the midline, 2.85 and 2.65 12ths of the AC-PC line in the anterior-posterior plane, −0.7 and −1.37 8ths of the thalamus height with regard to the AC-PC line). The negative sign in height coordinates means that the electrode lower tips were below the AC-PC line. In team B, the mean coordinates were also identical between the subgroup with dyskinesias in comparison with the whole team. The comparison of subgroups confirmed that the improvement of dyskinesias depended on the electrode position. The subgroup with clear improvement in team B (n=8) did not differ from the same subgroup in team A (n=9). In team B's patients experiencing a mild improvement (n=11), the laterality did not differ significantly, but the electrode was significantly higher than team A's electrodes (height A=0.77, height B=− 0.7; p<0.001). In team B's patients with no improvement of dyskinesias (n=13), both the laterality and height were significantly different from team A's patients (table 2). For team B, the electrode location in patients with a good improvement of dyskinesias (n=8) differed significantly in height from the subgroups with mild improvement (n=11) (respectively, the height was 0.07 and 0.77; p<0.01) or no improvement (n=13) (respectively, the height was 0.07 and 0.61; p<0.001). We also found a tendency suggesting that electrodes located at more than 14.5 mm apart from the midline had no effects on dyskinesias.
As 0.7 8ths of the thalamus height represents about 1.5 mm, this distance could account for obvious therapeutic differences. The electrodes of team A were probably closer to the CM-Pf than those of team B, which were mainly centred on the the VIM nucleus. This is shown in figs 2 and 3. The electrode position of an extremely disabled patient from team A who had his AIMS suppressed by DBS was drawn on a diagram where the outlines of the the CM-Pf nucleus were added, according to Talairach and Andrew coordinates of the CM-Pf.\(^23\),\(^24\)

**Figure 3** Schematic drawing of the the VIM (light shaded) and the CM-Pf (dark shaded and open rectangle), with special reference to the limits of the CM-Pf according to stereotactic data issued from Talairach and Andrew atlases.\(^23\),\(^24\) The figure also represents the targets and one oblique electrode from team A and two vertical electrodes from team B. This shows that two tracks aiming at the same area might end in different places: the vertical track loses its stimulation effects when leaving the VIM to enter the internal capsule (IC) whereas the oblique track may then enter the lower part of the the CM-Pf complex or its afferents from the spinal cord.

The questions raised by our results are: (1) where are the electrodes improving both tremor and levodopa dyskinesias, and do they really stimulate the CM-Pf whereas those of patients with no improvement of dyskinesias could be more centred on the VIM nucleus? (2) would it make sense according to the pathophysiology of movement disorders?

(1) Cytoarchitectonic data obtained from the unique postmortem case, operated on by team A, had confirmed that the active tip was in the deepest and most internal part of the VIM, very close to the CM-Pf.\(^4\) The mean coordinates of electrodes improving dyskinesias (at least at the upper tips) are also consistent with those of most schematic representations of the CM-Pf. The CM-Pf outlines have been determined either stereotactically or on cytoarchitectonic delineations by Talairach,\(^23\) Andrew and Watkins,\(^24\) Van Buren and Burke\(^25\) and May et al.\(^26\) The last authors showed that the CM-Pf terminates 2 mm below the AC-PC line at the anteroposterior level of the electrodes (2 or 3 12ths of the AC-PC line). The posterior, medial, and deep location of team A’s electrodes was obviously far away from the coordinates of the more anterior thalamic nucleus receiving pallidal afferents (ventral oralis nucleus (VO)). Lesioning simultaneously both the VIM and the VO had been performed previously by Narabayashi et al and seemed to be necessary to improve all types of dyskinesias,\(^16\) as did pallidotomy. Based on this experience, we could have expected that the electrodes improving dyskinesias would be located more anteriorly than those failing to improve dyskinesias. Actually, we found the opposite. Because the CM-Pf and VO receive common projections from the GPi, the CM-Pf seems a good candidate target according to morphological and anatomical data.\(^27\) It is inconceivable to suggest that the more posterior, deep, and internal electrodes could control dyskinesias by VO inhibition, when electrodes nearer to the VO did not.

(2) Our hypothesis of CM-Pf involvement would make sense with regard to the pathophysiology of levodopa induced dyskinesias. Various hypotheses have tried to explain the consecutive occurrence of dystonic dyskinesias followed by choreic dyskinesias during levodopa test, without any certainty.\(^21\) Increased sensitivity of dopaminergic receptors, due to striatal denervation, could modify the neuronal activity at the efferent site, along the basal ganglia network. Both types of dyskinesias probably result from abnormal activity of different loops.\(^21\) The Nauta-Mehler circuit is in size the second efferent/afferent pathway connecting the CM-Pf and the GPi.\(^10\) The GPi is known to be involved in levodopa dyskinesias as its suppression of function (by destruction or inhibition) suppresses levodopa induced abnormal
movements. The efficacy of pallidotomies or pallidal stimulation or the Vim plus VO lesions has been clearly shown on both types of levodopa induced dyskinesias whereas CM-Pf stimulation seems to have improved only choreic dyskinesias in our study. Moreover, off period dystonia was not improved by thalamic stimulation. This differential effect is a strong argument for the segregation of pallidal pathways involved in either choreic or dystonic dyskinesias inside the thalamus.

The second key result of this study was to show the possible effects of DBS on the CM-Pf (or related afferents) on parkinsonian tremor, which has been suggested previously by Andén. This result also raises the following question: does it act by CM-Pf inhibition itself, or is it due to a spreading of current to the Vim? The pathogenesis of tremor is poorly understood, despite several electrophysiological studies in both animals and humans. Albe-Fessard et al, Lenz et al, Lamrè et al, Ohye et al, and many others have identified rhythmic activities, synchronous with tremor, and produced by thalamic neurons, particularly in the Vim. Their origin is unknown and abnormal bursts synchronous with tremor are recorded in most nuclei of the basal ganglia. Tremor suppression, either due to Vim thalamic stimulation or to levodopa treatment induces a reduction of regional cerebral blood flow, not only in the premotor and motor cortex but also in the striatum and in cerebellar deep nuclei. By another route, the effect of anticholinergic drugs on tremor has been shown to be related to an inhibition of small cholinergic neurons connecting striatal neurons, but their functional role, though shown in rats, has not been assessed in humans as they are morphologically different and represent only 1% of striatal neurons. More recently, another cholinergic pathway involved in motor processes has been described emerging from the pedunculopontine nucleus and projecting to the parafascicular part of the CM-Pf. Anticholinergic drugs could then act as this level rather than at the intrastriatal site. Moreover, it has been shown that the CM-Pf exerts a potent control on the subthalamic nucleus through its glutamatergic excitatory projections to both the STN and the GPI. The CM-Pf also projects to the striatum and the cerebral cortex. Therefore, the CM-Pf probably has a crucial role in the regulation of basal ganglia activity via the subthalamic nucleus. Since it is a smaller target than the GPI, stimulation could be easier, with less heterogeneity or risk of missing the functional area. Different studies suggested that the CM-Pf and the VO are involved in common motor functions, as several pallidal axons ending in the ventrolateral region make a collateral branch projecting to the CM-Pf.

In conclusion, this report emphasizes the necessity of ventriculography as the ultimate reference for the definition of target coordinates in collaborative studies. The position of the electrode is strongly related to the therapeutic effects (and vice versa). This shows that there is a strong spatial-functional relation within brain structures, particularly within the basal ganglia and thalamus. Patients experiencing an improvement of both tremor and levodopa induced dyskinesias are supposed to be stimulated, whereas CM-Pf (or at least CM-Pf afferents and the Vim afferents simultaneously). As a result, a potential new target for DBS has emerged which is based on clinical experience and observation.

We thank G Percheron for valuable help in the discussion, and Todd Langevin for proof reading the manuscript.

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