Evidence of functional somatotopy in GPi from results of pallidotomy

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Summary

The objective of this study was to explore the functional anatomy of the globus pallidus internus (GPi) by studying the effects of unilateral pallidotomy on parkinsonian ‘off’ signs and levodopa-induced dyskinesias (LID). We found significant positive correlations between the preoperative levodopa responsiveness of motor signs and the levodopa responsiveness of scores in timed tests (Core Assessment Program for Intracerebral Transplantations) in the contralateral limbs and the improvement in these scores after surgery, whereas there was no correlation with the improvement in LID. We also found a highly significant correlation ($P < 0.0001$, $r = 0.8$) between the volume of the ventral lesion in the GPi and the improvement in LID in the contralateral limbs, whereas there was no correlation between the ventral volume and the improvement in parkinsonian ‘off’ signs. The volumes of the total lesion cylinder and the dorsal lesion did not correlate with the outcome of either dyskinesias or parkinsonian ‘off’ signs. The differential predictive value of levodopa responsiveness for the outcome of parkinsonian ‘off’ signs and LID and the different correlations of ventral lesion volume with dyskinesias and parkinsonian ‘off’ signs indicate that different anatomical or pathophysiological substrates may be responsible for the generation of parkinsonian ‘off’ signs and dyskinesias. Whereas cells in a wider area of the GPi may be implicated in parkinsonism, the ventral GPi seems to be crucial for the manifestation of LID. We suggest that our observations are additional proof of the functional somatotopy of the systems within the GPi that mediate parkinsonism and dyskinesias, especially along the dorsoventral trajectory used in pallidotomy. The outcome of pallidotomy in which the lesion involves the ventral and dorsal GPi could be the net effect of alteration in the activity of pathways which mediate different symptoms, and hence could be variable.

Keywords: Parkinson’s disease; pallidotomy; MRI; somatotopy; globus pallidus internus

Abbreviations: CAPIT = Core Assessment Program for Intracerebral Transplantations; GPe = globus pallidus, pars externa; GPi = globus pallidus, pars interna; LID = levodopa-induced dyskinesias; SPS = surgical planning system; STN = subthalamic nucleus; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction

Surgical treatment of Parkinson’s disease by unilateral radiofrequency lesioning of the globus pallidus internus (GPI) has been shown to be effective and safe in several recent, carefully conducted clinical studies (Laitinen et al., 1992; Dogali et al., 1995; Lozano et al., 1995; Baron et al., 1996; Kishore et al., 1997; Samuel et al., 1998). The most dramatic benefit of unilateral pallidotomy reported by these studies is the alleviation of levodopa-induced dyskinesias (LID) on the contralateral side. Quantitatively, the improvement in parkinsonian ‘off’ signs varies in these reports, whereas the striking improvement in LID is consistent. The variation in the outcomes of pallidotomy reported by different centres can be attributed to many factors, such as differences in the selection of surgical candidates, evaluation methods, surgical techniques, methods of radiological targeting (such as MRI, CT and ventriculography), the use of intraoperative electrophysiological mapping, the size and location of the radio-frequency lesion and the experience of the surgical team. However, the common pattern of different degrees of improvement in parkinsonian ‘off’ signs and LID suggests that the mechanisms mediating these two sets of symptoms are altered differently by pallidotomy, irrespective of the technique used.

On the initial reports of unilateral pallidotomy, we have suggested that the paradoxical improvement in dyskinesias along with parkinsonian ‘off’ signs might occur because the
neurones or pathways mediating dyskinesias are situated at
the posteroventral pallidum or because there is a convergence
of inputs generating parkinsonism and dyskinesias at the
posteroventral pallidum, which is lesioned in pallidotomy
(Kishore et al., 1997).

Few studies have looked at the predictive value of the
levodopa responsiveness of parkinsonian signs with respect
to the outcome of pallidotomy, though it is generally agreed
that good levodopa responsiveness is a selection criterion for
pallidotomy. Kazumata and colleagues showed that
preoperative levodopa responsiveness, measured as changes
in the results of the timed tests of the Core Assessment
Program for Intracerebral Transplantations (CAPIT)
performed on the upper limb, could be a useful indicator
of improvement in parkinsonian signs after pallidotomy
(Kazumata et al., 1997). The optimal site and size of the
pallidal target and how far it should extend along the pallidal
axis are also unclear. Some authors have reported a lack of
significant correlation between the clinical outcome and the
postoperative MRI measurements of lesion volume and lesion
location (Hariz et al., 1990; Krauss et al., 1997). The
influence of lesion volume on the differential improvement
in parkinsonian ‘off’ signs and LID has not been examined
carefully. There are no studies of the influence of the volumes
of the ventral and dorsal segments of the lesion cylinder on
these signs.

In this study, we explored the functional anatomy of the
GPi by assessing the correlation between preoperative
levodopa responsiveness and the outcome of unilateral
pallidotomy, and by examining the influence of lesion volume
on parkinsonian ‘off’ signs and LID. Total lesion cylinder
volume and the volume of the lesion in the ventral and dorsal
portions of GPi were compared separately in relation to the
outcome of pallidotomy.

**Material and methods**

Twenty-nine patients with clinically definite, levodopa-
responsive Parkinson’s disease underwent pallidotomy for
severe motor fluctuations (n = 29) and LID (n = 25) that
had not improved with optimal medical adjustments. The
patients comprised 17 men and 12 women, whose mean age
at surgery was 51.5 years (SD 9.2 years) and whose mean
duration of disease was 11.4 years (SD 5.5 years). The
selection criteria employed have been reported earlier
(Kishore et al., 1997). All cases were assessed according to
the CAPIT protocol in the ‘practically defined off’ period
(12 h off medication) and in the ‘best on’ period after a
therapeutic dose of levodopa/carbidopa. The Unified
Parkinson’s Disease Rating Scale (UPDRS version 3, subsets
I–IV) (Fahn et al., 1987), timed tests of the CAPIT protocol
(pronation–supination, hand–arm movements between two
points and finger dexterity) (Langston et al., 1992) and the
Goetz rating scale for dyskinesias (Goetz et al., 1994) were
used for clinical assessment. Dyskinesias were also scored
separately for the limbs and axial structures (Kishore et al.,
1997). In UPDRS subset III, scores for rest tremor (item 20),
rigidity (item 22) and bradykinesia (items 23–26) were
measured separately for the limbs contralateral and ipsilateral
to the side of surgery. All subjects gave informed consent
to participation in the study, which was approved by the Ethics
Committee of Sree Chitra Tirunal Institute for Medical
Sciences and Technology, Kerala.

The preoperative levodopa responsiveness of individual
parkinsonian signs and scores for CAPIT timed tests was
calculated as (‘off’ score – ‘on’ score)/‘off’ score × 100.
Levodopa responsiveness was measured for the total motor
score (UPDRS subset III), gait (item 29), postural stability
(item 30) and for individual subscores of rest tremor, rigidity
and bradykinesia for the contralateral limbs. Postoperative
assessments were made by the same examiner at 48 h,
1 month, 3 months and 6 months, using the same protocol.
The outcome of surgery was measured for ‘off’ scores, ‘on’
scores and dyskinesias using the formula:
outcome of surgery = (preoperative score – postoperative
score)/preoperative score × 100

**MRI**

All patients had preoperative and 27 patients had
postoperative MRI scans within 2–4 h after surgery, on a 1.5
tesla MR unit (Signa; General Electric, Milwaukee, Wis.,
USA) with the Leksell stereotactic frame. Fast multiplanar
inversion recovery sequences (echo time = 34, repetition
time = 4000, inversion time = 200, field of view = 27 × 27,
Nex = 4, matrix = 256 × 256, scan time = 14.08 min,
slice thickness = 3 mm without interslice gap) in the axial
and coronal planes were transferred to the surgical planning
system (SPS; Elekta Instrument, Sweden) for preoperative
surgical planning of the radiographic target on the
posteroventral pallidum. The standard surgical coordinates
of Laitinen and colleagues (Laitinen et al., 1992) were
applied initially (2 mm anterior to the midpoint of the
intercommissural line, 5–6 mm below the intercommissural
plane and 21–23 mm lateral to the intercommissural line).
The coordinates were modified on the SPS in the axial and
coronal images so as to target the posteroventral pallidum
1–2 mm above the optic tract, based on individual anatomy
in MRI.

**Postoperative MRI**

Postoperative MRI was done within 2–4 h in 27 cases (two
patients could not afford a second MRI). The sequences used
were similar to those employed preoperatively, and the images
were transferred to the SPS for analysis. The total lesion
volume was computed from the cross-sectional area and the
length of the lesion cylinder in the postoperative MRI, using
the SPS software. In the axial images, the lesion was seen
in three or four MRI slices. It was circular and consisted of
an inner hypointense core of haemorrhagic necrosis
surrounded by a hyperintense ring of oedema (Fig. 1). The
Fig. 1 Postoperative MRI showing a case of ventrodorsal extent of lesion. (A) and (B) were used for measuring ventral volume and (C) and (D) for dorsal volume.

The volume of the hypointense core of the lesion cylinder was taken as the total lesion volume. We did not use the volume of the zone of oedema. The volume of the ventral lesion was calculated separately as the volume of lesion from the most ventral location of the lesion to the MRI slice 3 mm above it. The entire GPi has a dorsoventral extent of ~8 mm but can be narrower depending on the laterality (Talairach and Tournoux, 1988). We chose the lower 3 mm arbitrarily as the ventral extent of the GPi (Fig. 1A and B). The difference between total and ventral volume was taken as the dorsal lesion volume (Fig. 1C and D).

**Surgery**

Before surgery, all antiparkinsonian medications were withheld overnight. An MR-compatible Leksell G stereotaxic frame (Elekta Instrument, Sweden) was applied under local anaesthesia and MRI images were acquired. A monopolar electrode with an exposed tip of $1 \times 4$ mm was introduced through a frontal, precoronal burr hole under local anaesthesia. Macrostimulation was used for electrophysiological targeting. Stimulation was carried out at 200 Hz with a constant-current lesion generator (LNG 30–1; Elekta Instrument, Sweden) with currents ranging from 0.5 to 5 mA at a pulse width of 200 ms at 6, 4 and 2 mm above target, at target and 1–2 mm ventral to target. Intraoperative assessment was made by the movement disorder specialist in order to assess (i) the response of parkinsonian signs to macrostimulation and (ii) side-effects, such as contralateral muscle-twitching in orofacial structures and the limbs and phosphenes in the contralateral visual field. If there were no untoward effects, an initial lesion was made at 45°C, and if no ill effects occurred, the temperature was raised to 60°C and later to 70°C, 75°C or 80°C, based on the threshold assessed by
Table 1 Mean contralateral scores before and after pallidotomy

<table>
<thead>
<tr>
<th></th>
<th>Before operation (n = 29)</th>
<th>After operation (n = 29)</th>
<th>After operation (n = 29)</th>
<th>After operation (n = 29)</th>
<th>After operation (n = 29)</th>
<th>Overall P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>48 h</td>
<td>1 month</td>
<td>3 months</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>‘Off’ scores</td>
<td></td>
<td>(n = 29)</td>
<td>(n = 29)</td>
<td>(n = 27)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rest tremor</td>
<td>3.3 (2.3)</td>
<td>1.4 (1.6)</td>
<td>1.4 (1.6)</td>
<td>0.9 (1)</td>
<td>0.9 (1)</td>
<td></td>
</tr>
<tr>
<td>Rigidity</td>
<td>4.9 (1.2)</td>
<td>1.7 (1.3)</td>
<td>1.7 (1.3)</td>
<td>1.7 (1.5)</td>
<td>2.3 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>10.6 (3)</td>
<td>4.1 (2.8)</td>
<td>4.8 (3.1)</td>
<td>5.3 (3.5)</td>
<td>5.9 (3.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pronation–supination test</td>
<td>43.1 (28.9)</td>
<td>24.1 (22.4)</td>
<td>23.6 (21.8)</td>
<td>23.2 (21.8)</td>
<td>21.2 (9.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hand–arm movement</td>
<td>34.8 (26.3)</td>
<td>17 (5.12)</td>
<td>21.1 (23.1)</td>
<td>22.5 (21.1)</td>
<td>18.2 (11)</td>
<td>0.009</td>
</tr>
<tr>
<td>Finger dexterity</td>
<td>41.1 (27.7)</td>
<td>23.4 (13.7)</td>
<td>24.2 (19.2)</td>
<td>28.5 (18.5)</td>
<td>29.5 (18.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>‘On’ scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>3.6 (2.2)</td>
<td>0.7 (0.8)</td>
<td>0.3 (0.9)</td>
<td>0.5 (0.9)</td>
<td>0.5 (1)</td>
<td></td>
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</tbody>
</table>

Data are mean (SD).

Table 2 Total and midline scores before and after surgery

<table>
<thead>
<tr>
<th></th>
<th>Before operation (n = 29)</th>
<th>After operation (n = 29)</th>
<th>After operation (n = 29)</th>
<th>After operation (n = 29)</th>
<th>After operation (n = 29)</th>
<th>Overall P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>48 h</td>
<td>1 month</td>
<td>3 months</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 29)</td>
<td>(n = 29)</td>
<td>(n = 27)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Total dyskinesias</td>
<td>9.2 (5.1)</td>
<td>3.7 (2.9)</td>
<td>3.6 (2.7)</td>
<td>3.8 (2.6)</td>
<td>4 (2.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>UPDRS III, ‘off’</td>
<td>58.2 (16.2)</td>
<td>36.4 (13.2)</td>
<td>38.1 (16.1)</td>
<td>38.5 (17.7)</td>
<td>35.2 (13.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gait, ‘off’</td>
<td>2.4 (0.9)</td>
<td>1.4 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.5 (0.9)</td>
<td>1.5 (0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Postural stability, ‘off’</td>
<td>2.6 (1.1)</td>
<td>1.6 (1)</td>
<td>1.3 (1.2)</td>
<td>1.5 (1.2)</td>
<td>1.5 (1)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are mean (SD).

Results

All 29 patients completed the 48 h and 1 month follow-up. Twenty-seven patients completed the 3 month and 20 patients the 6 month follow-up. There was a significant improvement in ‘off’ motor subscores and in the scores for the CAPIT timed tests on the contralateral side (Tables 1 and 2). There were also significant improvements in the scores for total dyskinesias and contralateral dyskinesias in the ‘on’ state (Table 2). The improvements were statistically significant at all follow-up times and were stable over time. Medication was kept constant in all patients except two, for whom minor dose adjustments were made.

There was a significant positive correlation between the preoperative levodopa responsiveness of the scores for rest tremor, rigidity and bradykinesia in the contralateral limbs and the corresponding outcomes of surgery at all follow-up times (Table 3). There was also a significant positive correlation between the levodopa responsiveness of the scores for timed tests and the improvement of these scores after surgery (Table 3). There was no correlation between the levodopa responsiveness of gait, balance or total UPDRS subset III motor scores and their postoperative improvement (Table 3). We did not find any significant correlation between the levodopa responsiveness of contralateral bradykinesia (P = 0.7), tremor (P = 0.5) or rigidity (P = 0.6) and the outcome of surgery with respect to contralateral dyskinesias.

In the 27 postoperative MRIs, it was possible to distinguish between the GPi and the GPe in most of the axial images. Well-placed lesions were found in all patients in the GPi. In two patients, a major portion of the lesion involved the GPe in the dorsal part of the lesion cylinder. The periphery of the circular zone of oedema impinged on the internal capsule in five patients, and in 12 patients the periphery of the ring of oedema encroached on the GPe in the dorsal segments of macrostimulation. The first lesion was made at the most ventral point that was safe and subsequent lesions were made 2, 4 and 6 mm above the deepest lesion as a cylindrical column along a single trajectory.

Statistical analysis

The paired t-test was used to compare the preoperative score with each of the postoperative clinical scores at 48 h, 1 month, 3 months and 6 months after operation. Repeated measures analysis of variance was performed on the differences between baseline scores and each of the follow-up scores. Clinical scores and scores in timed tests which showed statistically significant improvement after surgery were chosen for correlation analysis. Pearson’s correlation coefficient was used to measure the correlation of the variables. P values <0.05 were considered statistically significant.
The lesion cylinder. In six patients, the oedema and lesion were seen exclusively in the GPi.

Lesion volume could be measured in 20 patients. In seven patients, the postoperative images were lost from the MRI workstation before transfer to the SPS for the measurement of volumes. In all these cases, postoperative MRI films were available for the confirmation of lesion location. The mean volume of the total lesion cylinder was 106.2 mm$^3$ (SD 36.5, range 30–60, median 45). The mean dorsal lesion volume was 57.35 mm$^3$ (SD 26, range 27–109, median 56). The first lesion (most ventral) was created at a temperature of 60°C in the first seven consecutive patients because of concern for visual side-effects, even though macrostimulation showed safe thresholds. In two consecutive patients, mechanical trouble with the lesion generator prevented raising the temperature above 75°C. This problem was subsequently identified and corrected. The temperatures used in all patients are shown in Table 4, the duration being 60 s in all patients.

There was no significant correlation between the improvement in any of the ‘off’ scores of the contralateral limbs and the total lesion volume, ventral lesion volume or dorsal lesion volume (Tables 5–7). There was also no correlation between the improvement in contralateral dyskinesias and the total volume or dorsal lesion volume. However, there was a significant positive correlation between the volume of the ventral lesion and improvement in dyskinesias on the contralateral limbs ($P < 0.0001$, $r = 0.8$)

(Fig. 2 and Table 7). The significant positive correlation was seen consistently until the 6 month follow-up.

Intraoperatively, dyskinesia were seen during macrostimulation or lesioning in 10 patients. However, there was no significant difference ($P = 0.3$) in the outcome with respect to dyskinesia or parkinsonian ‘off’ signs between the groups of patients who had and those who did not have intraoperative dyskinesia.

There was only one single permanent postoperative complication, a scotoma (detected by field charting). Transient dysarthria was seen in four patients (the postoperative scan
Table 7  Correlation between ventral lesion volume and improvement in contralateral clinical signs

<table>
<thead>
<tr>
<th>Ventral lesion volume</th>
<th>48 h</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest tremor</td>
<td>$P = 0.6$</td>
<td>$P = 0.6$</td>
<td>$P = 0.5$</td>
<td>$P = 0.7$</td>
</tr>
<tr>
<td>r = 0.1</td>
<td>r = 0.1</td>
<td>r = 0.1</td>
<td>r = 0.1</td>
<td>r = 0.1</td>
</tr>
<tr>
<td>Rigidity</td>
<td>$P = 0.3$</td>
<td>$P = 0.5$</td>
<td>$P = 0.8$</td>
<td>$P = 0.6$</td>
</tr>
<tr>
<td>r = 0.2</td>
<td>r = 0.2</td>
<td>r = 0.1</td>
<td>r = 0.1</td>
<td>r = 0.1</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>$P = 0.2$</td>
<td>$P = 0.5$</td>
<td>$P = 0.6$</td>
<td>$P = 0.3$</td>
</tr>
<tr>
<td>r = 0.2</td>
<td>r = 0.2</td>
<td>r = 0.1</td>
<td>r = 0.3</td>
<td>r = 0.3</td>
</tr>
<tr>
<td>Contralateral</td>
<td>$P &lt; 0.0001^*$</td>
<td>$P &lt; 0.0001^*$</td>
<td>$P &lt; 0.0001^*$</td>
<td>$P &lt; 0.0001^*$</td>
</tr>
<tr>
<td>dyskinesias</td>
<td>$r = 0.7$</td>
<td>$r = 0.7$</td>
<td>$r = 0.6$</td>
<td>$r = 0.8$</td>
</tr>
</tbody>
</table>

*Statistically significant P values.

Fig. 2  Relationship between ventral lesion volume and percentage improvement in contralateral dyskinesias.

showed oedema extending to the internal capsule in two of them). Transient mild facial weakness was seen in two patients (one had oedema extending to the internal capsule). All these patients had recovered completely when seen 1 month after surgery. One patient had a generalized seizure during the macrostimulation phase. Surgery had to be abandoned, but was carried out uneventfully after 1 month.

Discussion
In keeping with previous studies, we found that the most dramatic response to pallidotomy was the relief of LID in the contralateral limbs. The degree of improvement in individual parkinsonian ‘off’ signs was less striking but clinically relevant, as in earlier reports. We found a significant correlation between the levodopa responsiveness and surgical outcome with respect to rest tremor, rigidity and bradykinesia of the contralateral limbs. On the contrary, we found that the levodopa responsiveness of bradykinesia, rigidity and tremor scores could not predict the improvement in contralateral dyskinesias. In addition, we found that the volume of the ventral lesion in the Gpi correlated with the improvement in dyskinesias, while no such correlation was found for parkinsonian signs. These dissociations suggest that different neuronal populations or pathways in the Gpi mediate dyskinesias and parkinsonian ‘off’ signs.

The pathophysiological basis of parkinsonian signs is considered to be the increased inhibitory output from the Gpi/substantia nigra reticulata to the thalamus, blocking the thalamocortical relay to the supplementary motor area and motor cortex (Albin et al., 1989; DeLong, 1990). According to current models of the basal ganglia (Alexander and Crutcher, 1990; DeLong, 1990), the reduction in the output of the Gpi after pallidotomy would be expected to worsen dyskinesias. The effect of apomorphine during microelectrode recording for pallidotomy was studied by Hutchison and colleagues, who found decreased firing rates of Gpi neurones after apomorphine treatment (Hutchison et al., 1997), indicating that dopamine agonists do reduce Gpi activity in man. It is therefore likely that levodopa and pallidotomy relieve parkinsonian ‘off’ signs by the common mechanism of reducing the inhibitory output from the Gpi. However, it is not known whether the effects of surgery or dopamine agonists are mediated through neurones within the medial Gpi, which gives rise to the lenticular fasciculus, or through neurones within the lateral Gpi, from which the ansa lenticularis originates, or through both groups of neurones. The preoperative levodopa responsiveness of parkinsonian signs appears to be a good indicator of the contribution of the abnormal cellular activity of Gpi neurones to the development of the major parkinsonian signs in individual patients.

The mechanism by which pallidotomy reduces levodopa-induced dyskinesias rather than worsening them is not known. The subthalamic nucleus (STN) receives dopaminergic innervation from the substantia nigra compacta and has both dopamine D1 and D2 receptors (Johnson et al., 1994; Kreiss et al., 1996), and activation of these receptors could also contribute to the effects of levodopa on parkinsonian signs and the development of dyskinesias. Levodopa may also reduce the heightened excitatory output from the STN to the Gpi, the substantia nigra reticulata and the pedunculopontine nucleus, and produce a more diffuse effect. Such a diffuse effect of levodopa may induce dyskinesias that are not induced by focal destruction of the Gpi. Alternatively, the
neurones or neural pathways mediating dyskinesias may be located in the ventral pallidum and destroyed by lesioning (Kishore et al., 1997).

The relationship of improvement in dyskinesias measured using standardized rating scales with lesion volume measured at a uniform interval after surgery has not been reported earlier. In our study, we used only the volume of the necrotic lesion and excluded the zone of oedema around the lesion in calculating correlations with outcome at follow-up intervals at which oedema would have resolved. This might be one of the reasons for our smaller total lesion volume. Even though our total lesion volume was much less than in other series, we observed good clinical improvement, indicating that a strategic location in the ventral pallidum is important in the genesis of dyskinesias, and that the ablation of a critical volume ensures the resolution of dyskinesias. A further increase in the volume of the ventral lesion may not provide additional benefits with respect to dyskinesias, and may produce side-effects. This might also explain the more or less uniform effects of pallidotomy on dyskinesias that have been reported by different centres irrespective of the differences in the radiological and electrophysiological techniques used to target the posteroventral pallidum.

The volumes of the ventral lesion, dorsal lesion and total lesion cylinder did not correlate with the improvement in any of the parkinsonian ‘off’ signs. The degree of improvement in parkinsonian signs was similar to those in previous reports on pallidotomy with intraoperative microelectrode recording, a technique which helps to create a map of the sensory motor neurones in the GPI and to define the borders of the posteroventral pallidum. Even though the lesion volume created along a single tract with three or four lesions, as in our study, was less than the reported volume of lesions made using microelectrode recording and lesions along multiple tracks (Baron et al., 1996; Lozano et al., 1996), the clinical results are similar. This indicates that there is probably no critical lesion volume which determines the improvement in parkinsonian ‘off’ signs. Rather, the benefits may be related to the inclusion of the relevant neurones or efferents in the lesion, irrespective of the total volume of the lesion created with or without microelectrode guidance. An alternative explanation for the lack of correlation of improvement in parkinsonian ‘off’ signs with lesion volume is that it is not the volume of neurones destroyed but the postlesional reorganization of neural circuits or the normalization of the firing patterns of the surviving neurones that is responsible for the benefits of pallidotomy. The benefits of pallidotomy with respect to parkinsonian signs are seen during macrostimulation and also immediately after lesioning, and hence they are unlikely to be due to the reorganization of neural circuits. A third explanation is that, if the effects of lesioning different regions of GPI have opposing effects, the net result may not correlate with lesion volume.

Lehmann and colleagues suggested that lesion volume is a factor that affects clinical outcome, according to MRI studies done within 1 week and 4–6 weeks after surgery in six patients, but they provided no data supporting such an effect (Lehmann et al., 1994). Hariz reported a lack of correlation of mean volume of lesion measured from CT scans with the clinical outcome in five patients who were scanned 3–12 months after operation (Hariz, 1990). Krauss and colleagues reported a lack of correlation between the clinical outcome measures and the volumes of lesion and oedema in early-phase MRI and lesion volume in the late phase (Krauss et al., 1997). They also mentioned that there was no statistically significant association between the indices for UPDRS outcome measures (data not shown) and lesion volume. Nevertheless, they found that contralateral dyskinesias tended to be abolished when the distance from the lesion to the optic tract was less than 2 mm, which supports the role of the ventral segment of the lesion in the relief of dyskinesias.

The sensorimotor region in the GPI is arranged somatotopically in a complex pattern (Sterio et al., 1994; Vitek et al., 1997). Electrophysiological studies have justified the choice of the posterolateral GPI as the appropriate target, as this part contains neurones whose discharge is modulated by joint movements and is involved in the basal ganglia–thalamocortical circuit (DeLong, 1971). Destruction of these neurones would influence the output through both the ansa lenticularis and the fasciculus lenticularis (Carpenter, 1976). We found that a fourth lesion (~6 mm above our most ventral target) dorsally was necessary to reduce parkinsonian signs in the legs in many patients. We found slightly greater improvement in bradykinesia scores than in earlier studies with (Lozano et al., 1995; Baron et al., 1996) and without microelectrode recording (Kishore et al., 1997). This better result may have been related to the presence of a fourth lesion dorsally in the GPI in the majority of our patients. Dorsal stimulation in the GPI has been shown to produce good relief of bradykinesia during deep brain stimulation (Krack et al., 1998). This effect of deep brain stimulation could be because of the stimulation of the dorsal GPI or GPi. However, only two of our patients had significant dorsal lesions in the GPi and the parkinsonian signs in both of them showed only a partial response, especially in the lower limbs. It has also been suggested that large lesions that involve all the outflow of the GPI may not be beneficial for akinesia (Krack et al., 1998). Large lesions are more likely to be created when multiple lesions are made in different tracks (Vitek et al., 1998) or higher temperatures are used for a longer time when lesions are being made (Lozano et al., 1996). Large lesions may also exceed the boundaries of the microelectrode-mapped target. Gross and colleagues showed that there was a trend for larger lesions to be associated with worse postoperative outcome scores in the ‘off’ period but better scores in the ‘on’ period (Gross et al., 1999). These authors also examined the relationship between the clinical outcome and the lesion centre in the anteromedial and posterolateral planes within the posteroventral pallidum. They showed that the location of the centre of the lesion which was associated with greater improvement in akinesia was not...
the same as the location that produced maximum relief of contralateral dyskinesias. Gross and colleagues chose the location of the lesion centre in the mediolateral plane, whereas we analysed the entire lesion volume in the dorsoventral plane in order to examine its relationship with the outcome of surgery. It is possible that the site of the anteromedial lesion that resulted in greater improvement in dyskinesias in their study is the origin of the fibres that were included in the ventral lesion volume which we examined.

Recent experience with deep brain stimulation has shown that ventral stimulation of GPi in the ‘on’ state results in improvement in dyskinesias and rigidity and worsening of akinesia, whereas dorsal stimulation in the ‘off’ state leads to relief of akinesia and the induction of dyskinesia, which suggests functional somatotopy in the GPi (Bejjani et al., 1997; Krack et al., 1998). Bejjani and colleagues and Krack and colleagues suggested that the pathophysiology of rigidity and akinesia were different and involved different pallidal outflows. Krack and colleagues contended that dorsal stimulation could have affected the dorsal lenticular fasciculus arising from the inner segment of the GPi and the GPe–STN pathway, whereas ventral stimulation could have influenced the ansa lenticularis arising from the outer segment of the GPi, and they offered this anatomical segregation of fibres as an explanation of the paradox of pallidal surgery.

Our study suggests that, for the relief of LID, a well-placed, adequately sized lesion in the most ventral segment of posterior GPi is sufficient. The anti-dyskinetic effect is probably mediated by destruction of the neurones in the most ventral part of the GPi—its afferents or its efferents, which form the ansa lenticularis. Whether such a lesion in pallidotomy would worsen bradykinesia, as seen in deep brain stimulation, if more dorsal pathways were not destroyed is worth considering. The degree of relief of parkinsonian ‘off’ signs may be improved by the destruction of a more diffusely located neuronal population in the GPi, including its dorsal segments, by strategically placed, perhaps smaller lesions. The dorsal lesion is likely to include the efferents from the medial pallidal segment that form the lenticular fasciculus and also afferents to the pallidum from the STN. Destruction of the dorsally located subthalamic pallidal fibres alone, or together with the dorsal efferents arising from the medial GPi in pallidotomy, may be responsible for the relief of parkinsonian signs, especially bradykinesia, and may generate dyskinesias (depending on the stimulation parameters used for deep brain stimulation or thermolesioning).

The intraoperative dyskinesias seen during pallidotomy may represent this phenomenon. A good correlation has been shown between the occurrence of intraoperative dyskinesias and the motor outcome of pallidotomy (Merello et al., 1997). However, dyskinesias may not be manifested intraoperatively in all cases or postoperatively, as the ventral pallidal neurones which generate dyskinesias or their efferents crucial for transmitting the signals to targets beyond the GPi are destroyed. The measured improvements in bradykinesia and other parkinsonian ‘off’ signs after pallidotomy may be the net effect of improvement resulting from the dorsal lesion and worsening resulting from the ventral lesion. The STN would therefore be a better target for reducing parkinsonian ‘off’ signs. A lesion or deep brain stimulation in the STN would (i) cause direct reduction of activity in the efferents from the STN to the pallidum at their origin, where it is more compact than in the pallidum, and (ii) spare the lateral GPi and their efferents, which if destroyed could worsen bradykinesia and relieve dyskinesias. The results of deep brain stimulation in the STN (Kumar et al., 1998; Limousin et al., 1998; Hoveto et al., 2000) support this argument.

Whether these dorsal and ventral locations in the GPi are the site of termination of the indirect and direct pathways, respectively, is an interesting question. According to the current basal ganglia model (DeLong, 1990), in Parkinson’s disease selective reduction of activity in the indirect pathway (STN–pallidum) could result in improvement of parkinsonism, and could also generate dyskinesias if the direct pathway is intact; these effects are similar to the results of selective dorsal deep brain stimulation. On the contrary, selective reduction of activity in the direct pathway could worsen parkinsonism by reducing the inhibition of inhibitory pallidal outflow. In addition, if an intact direct pathway were also necessary for the manifestation of dyskinesias, then dyskinesias would not be seen after its destruction when levodopa is administered postoperatively. If so, lesioning of the direct pathway, like selective ventral deep brain stimulation, could relieve dyskinesias and worsen parkinsonism. If both pathways were destroyed in pallidotomy, there might be different degrees of improvement in parkinsonism and dyskinesias. In experimental studies, abnormal hyperkinetic movements occurred after partial lesions of the GPi (Hore and Villis, 1980; Horak and Anderson, 1984; Mink and Thach, 1991; Inase et al., 1996), whereas experimental lesioning of the entire GPi did not produce hyperkinesias (DeLong MR and Coyle, 1979).

We conclude that the preoperative responsiveness to levodopa of the major parkinsonian signs and timed tests of the CAPIT protocol in the contralateral limbs correlates well with the improvement of these signs after unilateral pallidotomy, but not with that of dyskinesias. In addition, we also found different relationships between ventral lesion volume and the improvement in contralateral dyskinesias and parkinsonian ‘off’ signs. We suggest that our observations are additional proof of the functional somatotopy of the systems within the GPi that mediate parkinsonism and dyskinesias, especially along the dorsoventral trajectory used in pallidotomy. The outcome of pallidotomy in which the lesion involves the ventral and dorsal GPi would be the net effect of alteration in the activity of pathways that mediate different symptoms, and hence could be variable. This needs to be examined in further anatomical and physiological studies.

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