Clinical and economic results of bilateral subthalamic nucleus stimulation in Parkinson’s disease


Background: High frequency stimulation of the subthalamic nucleus (STN) is an alternative but expensive neurosurgical treatment for parkinsonian patients with levodopa induced motor complications.

Objective: To assess the safety, clinical effects, quality of life, and economic cost of STN stimulation.

Methods: We conducted a prospective multicentre study in 95 consecutive Parkinson’s disease (PD) patients receiving bilateral STN stimulation and assessed its effects over 12 months. A double blind randomised motor evaluation was carried out at 3 month follow up, and quality of life, self care ability, and predictive factors of outcome following surgery were assessed. The cost of PD was estimated over 6 months before and after surgery.

Results: The Unified Parkinson’s Disease Rating Scale (UPDRS) motor score improved by 57% (p < 0.0001) and activities of daily living improved by 48% (p < 0.0001) at 12 month follow up. Double blind motor scoring improved by 51% at 3 month follow up (p < 0.0001). The total PD Quality of Life Questionnaire (PDQL-37) score improved by 28% (p < 0.001). The better the preoperative motor score after a levodopa challenge, the better the outcome after STN stimulation. Five patients developed an intracerebral haematoma during electrode implantation with permanent after effects in two. The 6 month costs of PD decreased from €10 087 before surgery to €1 673 after surgery (p < 0.0001) mainly because of the decrease in medication. These savings allowed a return on the procedure investment, estimated at €36 904 over 2.2 years.

Conclusions: STN stimulation has good outcomes with relatively low risk and little cost burden in PD patients with levodopa induced motor complications.

Abbreviations: PD, Parkinson’s disease; PDQL-37, Parkinson’s Disease Quality of Life Questionnaire; STN, subthalamic nucleus; UPDRS, Unified Parkinson’s Disease Rating Scale.
Life Questionnaire (PDQL-37) validated for use in French patients.\

**Surgical technique**
Implantation of the electrodes was performed bilaterally in one session under local anaesthesia, according to the practice of each centre. In all centres, the STN was identified with intraoperative stimulations, using one to five microelectrodes; microrecordings were also used in all but one centre. A chronic electrode with four contacts 1.5 mm long and 0.5 mm apart (contact 0 distal to contact 3 proximal; DBS-3389, Medtronic, Minneapolis, MN, USA) was implanted and secondarily connected to a neurostimulator (two single channel Itrel II in n = 39 patients or one dual channel Kinetra in n = 56 patients; Medtronic). The placement of the electrodes was checked by T2 weighted MRI performed before implantation of the neurostimulator and also by stereotactic x rays in two centres.

**Electrical settings**
Chronic parameters of STN stimulation and daily doses of antiparkinsonian drugs were progressively and concomitantly adjusted according to guidelines.

**Economic evaluation**
During both 6 month periods of observation, resources use data related to the patients’ care and including hospitalisations, outpatient visits, auxiliary care, and antiparkinsonian medication, were collected monthly from individual questionnaires. Healthcare expenditures which occurred within the first 6 postoperative months were included in the cost of the procedure as the patient’s global state was not yet stable. Medical consultations and auxiliary care related to PD were valued at their national costs. Hospitalisation costs were estimated from the national Diagnosis Related Group database. Medication costs were determined from the national formulary list. The cost of the procedure included

![Study design diagram](image-url)

Figure 1  Study design.

![Motor examination score (UPDRS part III, mean ± SD) in the off-medication and on-medication conditions before (n = 97) and 3 (double blind evaluation) and 12 months after surgery (n = 95). White bars: off medication and off stimulation; black bars: on medication and off stimulation; light grey bars: off medication and on stimulation; dark grey bars: on medication and on stimulation. *p < 0.0001 for the comparison with the off medication and off stimulation condition at the same time of follow up; †p < 0.0001 for the comparison with the preoperative off-medication score.](image-url)

Figure 2  Motor examination score (UPDRS part III, mean ± SD) in the off-medication and on-medication conditions before (n = 97) and 3 (double blind evaluation) and 12 months after surgery (n = 95). White bars: off medication and off stimulation; black bars: on medication and off stimulation; light grey bars: off medication and on stimulation; dark grey bars: on medication and on stimulation. *p < 0.0001 for the comparison with the off medication and off stimulation condition at the same time of follow up; †p < 0.0001 for the comparison with the preoperative off-medication score.
a 4–5 day stay in hospital for confirmation of surgical indication, surgery, material, check ups, and all inpatient or outpatient visits related to stimulator parameter adjustment required over a 1 year period. The perspective was that of health insurance. Currencies were converted at the rates on 1 January 2000 (€1 = US$1.0053).

### Statistical analysis

The primary outcome measures were the scores on part III (motor examination) of the UPDRS in the off-medication and on-stimulation conditions at 12 month follow up, motor evaluation at 3 month follow up, the health related costs of the procedure, and the scores of the PDQL-37. The secondary measures were the other subscores of the UPDRS, including parts I (mentation and behaviour) and II (activities of daily living), items 32 and 33 of part IV (dyskinesias, maximal daily dose), and the scores of the Global Frontal Score (maximal score 50) and the Mattis Dementia Rating Scale (maximal score 144).

Examiners made errors in eight patients. All patients and examiners were available for 72 patients. On the first day of randomisation, 44 patients guessed incorrectly (10 thought they were off although they were on, and four thought the opposite). At the 3 month follow up, the double blind off-medication motor score was 44 ± 16 without stimulation and 21.7 ± 11.3 with stimulation (fig 2). Self evaluation of the stimulation condition was 16 without stimulation and 21.7 ± 11.3 with stimulation (fig 2). Self evaluation of the stimulation condition was 16 without stimulation and 21.7 ± 11.3 with stimulation (fig 2).

### RESULTS

The study was conducted between November 1998 and March 2002. Of 110 selected PD patients, 97 were included in the clinical study and 95 were chronically stimulated (fig 1).

### Clinical results

The clinical characteristics of the patients at baseline are reported in table 1. In the off-medication condition, the mean UPDRS motor score was 49.2 ± 16.4 before surgery, but significantly decreased to 19.4 ± 11.5 at the 12 month follow up in the on-stimulation condition (fig 2). At the 3 month follow up, the double blind off-medication motor score was 44 ± 16 without stimulation and 21.7 ± 11.3 with stimulation (fig 2). Self evaluation of the stimulation condition was 16 without stimulation and 21.7 ± 11.3 with stimulation (fig 2).

### Table 1 Characteristics of patients before surgery (n = 97)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery (mean ± SD, years)</td>
<td>57 ± 8</td>
</tr>
<tr>
<td>Age at onset of PD (mean ± SD, years)</td>
<td>43 ± 9</td>
</tr>
<tr>
<td>Duration of PD (mean ± SD, years)</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>Duration of levodopa therapy (mean ± SD, years)</td>
<td>13 ± 4</td>
</tr>
<tr>
<td>Duration of levodopa induced dyskinesias (mean ± SD, years)</td>
<td>6 ± 4</td>
</tr>
</tbody>
</table>

### Table 2 Results of neuropsychological tests before and after surgery

<table>
<thead>
<tr>
<th>Test</th>
<th>Score (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before surgery</td>
</tr>
<tr>
<td>Mattis Dementia Rating Scale (maximal score 144)</td>
<td>136.3 ± 5.8</td>
</tr>
<tr>
<td>Grober and Buschke Verbal Learning Test</td>
<td>Free recall (maximal score 48)</td>
</tr>
<tr>
<td></td>
<td>Total recall (maximal score 48)</td>
</tr>
<tr>
<td></td>
<td>Delayed recall (maximal score 16)</td>
</tr>
<tr>
<td></td>
<td>Total recall (maximal score 16)</td>
</tr>
<tr>
<td></td>
<td>Wisconsin Card Sorting Test (maximal score 20)</td>
</tr>
<tr>
<td></td>
<td>Beck Depression Inventory (maximal score 59)</td>
</tr>
<tr>
<td></td>
<td>Lexical Fluency (maximal score 10)</td>
</tr>
<tr>
<td></td>
<td>Graphic Series (maximal score 10)</td>
</tr>
<tr>
<td></td>
<td>Motor Series (maximal score 10)</td>
</tr>
<tr>
<td></td>
<td>Global Frontal Score (maximal score 50)</td>
</tr>
</tbody>
</table>

* p<0.002 compared with the preoperative score; ** p<0.0001 compared with the preoperative score.

Figure 3 Subscores of the Parkinson’s Disease Quality of Life Questionnaire (PDQL-37) before and 12 months after surgery. Black bars: before surgery; white bars: 12 months after surgery. * p<0.001 for the comparison with the preoperative score. The total score ranged from 0 (worst) to 185 (best), encompassing four subscores (parkinsonian symptoms: 70; systemic symptoms: 35; emotional symptoms: 45; social symptoms: 35).
The duration of the on-period without dyskinesias increased from $5.5 \pm 3.4$ h daily before surgery to $10.6 \pm 5.0$ h daily 12 months after surgery ($p<0.0001$). The dyskinesia score decreased from $4.07 \pm 1.83$ to $1.03 \pm 1.35$ at the 12 month follow up ($p<0.0001$).

### Disability and activities of daily living
The mean score of the Schwab and England scale in the off-medication condition was $42.1 \pm 19.3$ before surgery and improved to $74.8 \pm 18.8$ at the 12 month follow up ($p<0.0001$). Before surgery, 85 of the 97 patients were dependent on a caregiver for some activities of daily living in the off-medication condition, whereas only 30 were similarly dependent at the 12 month follow up. In off-medication condition, the UPDRS part II score decreased from $26.8 \pm 6.9$ before surgery to $13.8 \pm 7.3$ at the 12 month follow up ($p<0.0001$). No change in this score was noted in the on-medication condition. According to the home diaries, sleep duration significantly increased from $7.8 \pm 1.7$ h before surgery to $8.6 \pm 1.8$ h 12 months after electrode implantation ($p<0.0001$).

### Quality of life
The mean total score of the PDQL-37 scale improved from $95.1 \pm 17.2$ to $120.9 \pm 23.8$ ($p<0.0001$). All subscores significantly increased (Fig 3).

### Behaviour and cognitive functions
The total UPDRS part I score increased from $1.7 \pm 1.5$ before surgery to $2.4 \pm 1.9$ at the 12 month follow up ($p<0.0001$). This increase was mainly related to worsening in the motivation score (item 4) from $0.3 \pm 0.5$ before surgery to $0.8 \pm 0.9$ at the 12 month follow up ($p<0.0001$). A motivation subscore higher than 2/4 was found in one patient before surgery and in 22 patients at the 12 month follow up. Changes in cognition and mood after surgery were generally minor (Table 2). At the 3 month follow up, the Mattis Dementia Rating Scale score declined in seven patients by more than 1.5 SD from the whole group baseline value. Four of these patients were older than 65 and had a preoperative Mattis Dementia Rating Scale score less than the mean score of all participating patients. None of these four patients had a worsening in quality of life according to their scoring in the PDQL-37.

### Predictive factors
After discarding factors with low predictive power, we found that the best predictive factor for surgery induced benefit was a low preoperative on-medication motor score. This means that the better the 12 month postoperative on-stimulation off-medication motor score, the better the preoperative motor score under levodopa (one centre had a different formula from the others). We could not find any predictive factor for speech and postural stability subscores.

### Table 3: Electrical parameters of bilateral STN stimulation

<table>
<thead>
<tr>
<th>Type of stimulation (n = number of electrodes)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monopolar 1 contact</td>
<td>155</td>
</tr>
<tr>
<td>Monopolar 2 contacts</td>
<td>29</td>
</tr>
<tr>
<td>Bipolar 1 contact</td>
<td>3</td>
</tr>
<tr>
<td>Bipolar 2 contacts</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 4: Antiparkinsonian drugs before and after surgery

<table>
<thead>
<tr>
<th>Medication</th>
<th>Before surgery</th>
<th>12 months after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa (n = number of patients)</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Dopamine agonist (n = number of patients) (sc apomorphine)</td>
<td>2 [1]</td>
<td>23 [0]</td>
</tr>
<tr>
<td>Levodopa-dopamine agonist (n = number of patients) (sc apomorphine)</td>
<td>89 [26]</td>
<td>41 [0]</td>
</tr>
<tr>
<td>Apomorphine repeated injections (n = number of patients)</td>
<td>23</td>
<td>–</td>
</tr>
<tr>
<td>Unitary dose (mg) (mean ± SD) (number of injections/day)</td>
<td>11 ± 4 [1–7]</td>
<td>–</td>
</tr>
<tr>
<td>Apomorphine continuous infusion (n = number of patients)</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Flow rate/h (mg) (mean ± SD) (number of hours/day)</td>
<td>5 ± 2 [12–24]</td>
<td>–</td>
</tr>
<tr>
<td>No drug (n = number of patients)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total (n = number of patients)</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>Levodopa equivalent daily dose (mg) (mean ± SD)</td>
<td>1240 ± 586</td>
<td>506 ± 429**</td>
</tr>
</tbody>
</table>

**p<0.0001 for the comparison with the preoperative dose**
Additional visits and adverse events

We recorded 520 visits in addition to the planned 3 and 12 month follow-up visits, including 121 hospitalisations for 57 patients and 399 outpatient visits for 80 patients, mainly within the first 6 months of follow up (fig 4). Seventy nine per cent of all additional visits were related to worsening of parkinsonism or stimulation induced dysequilibria and concerned 82 patients. These symptoms always improved after the electrical stimulation parameters were adjusted.

Five patients developed an intracerebral haematoma during electrode implantation. This was responsible for permanent left hemiparesis in one patient, in whom a chronic electrode was not implanted, and permanent frontal lobe dysfunction and worsening in the Mattis Dementia Rating Scale score in a second patient. The three other patients developed hemiparesis or confusion with complete remission within 1 week. Two patients became confused during electrode implantation but were back to normal within the following postoperative days. In one patient the electrode migrated 3 months after the operation and was reimplanted. Infestation of one extension lead occurred in one patient, necessitating the removal of all implanted material and general antibiotherapy. The patient was operated on again 9 months later without sequelae. Two patients caught pneumonia in the immediate postoperative period. Cognitive and behavioural adverse events that led to an additional visit involved depression in nine patients, psychosis in two patients, hypomania in five patients, and apathy in two patients. At the end of the study, the two patients with sequelae following intracerebral haematoma had adverse events with ongoing consequences for daily living.

Economic evaluation

Complete data for the economic study were available for 88 of the 96 patients selected for surgery. Eight patients refused to fill in charts of health related costs. One of these patients was the 96 patients selected for surgery. Eight patients refused to complete data for the economic study were available for 88 of the 95 stimulated patients still required at least some help for activities of daily living according to the Schwab and England scale. At the 3 month follow up, the blinded off-medication UPDRS motor score was improved by 51% and the non-blinded evaluation at the 12 month follow up was improved by 57%. The magnitude of motor changes induced by STN stimulation makes a double blind condition difficult to apply, as motor improvement is the only effect that allows a patient guess at the stimulation condition. This might explain why almost all patients correctly guessed the stimulation condition. Three other double blind studies of STN stimulation reported almost similar improvement in motor function.5–8

The patients operated upon had a highly levodopa responsive PD which has been shown to be the main inclusion criterion for positive outcome after surgery.12 29 30 We found that the best predictive factor for surgery induced benefit was a low preoperative on-period motor score, whatever its severity during off periods. Therefore, the most suitable candidates for STN stimulation should exhibit an excellent on-period motor function, even if off-period motor disability or levodopa induced dyskinesias are severe. In one centre the postoperative on-stimulation motor score was worse than in the others. We were unable to determine the reasons for this difference since the patients’ characteristics were similar in all centres and postoperative imaging showed that, in all cases, the active contact corresponded to the theoretical area of the STN.20 31 The degree of motor benefit could be related to this homogeneous targeting checked by imaging in all patients.

Consistent with previously published data, no cognitive impairment was reported in most patients after surgery, except deterioration in verbal fluency.32–34 The seven patients whose cognitive functions deteriorated were older than...
average or had lower preoperative cognitive performance, in keeping with other reports. Two of these patients developed cognitive impairment due to intracerebral complications related to electrode implantation, with ongoing consequences in daily living. A worsening in motivation was observed in some patients and might be responsible for an apathetic state; however, only two patients required an additional visit due to this adverse effect. Since apathy can be improved by an increase in dopaminergic treatment, it might be the consequence of too great a decrease in postoperative dopaminergic medication. The proportion of severe complications after STN stimulation is in keeping with previous studies and inherent to any stereotactic neurosurgical procedure and implantation of material. The benefit of STN stimulation on motor function allowed a major improvement in all aspects of quality of life, especially the social functioning subscale, as already reported with this procedure.

The global cost of STN stimulation in patients with PD, including material, personnel, hospital stays, and all follow-up visits, amounted to €36 904. This total is higher than that previously reported in another prospective study of the effects of STN stimulation on health status and healthcare resources conducted in 16 PD patients. The cost of equipment, medication at baseline, and the mean duration of stay in hospital were similar in both reports. In our study, after discharge from hospital, additional visits were required to adjust electrical settings. The distance the participating patients lived from the four centres may explain why most needed to stay a few days in hospital for these adjustments. These visits may partly account for the higher cost of the procedure obtained in our study, but the hospital cost is also higher than that of the German study. This cost is determined by the national Diagnosis Related Group database and may differ from that in other countries and thus influence interpretation of the results. The improvement in motor function after STN stimulation was similar in both studies with considerable impact on self care ability and quality of life, but the decrease in dopaminergic medication costs after surgery was greater in our study. This difference might be explained by the high number of patients receiving subcutaneous apomorphine in our study, all of whom discontinued this treatment after STN implantation, whereas no patient with apomorphine participated in the other study. Given the savings in healthcare expenditure obtained in a 6 month period, the cost of the procedure would allow a return on investment over 2.2 years. Thus, we may consider that STN stimulation is cost effective, confirming previously published theoretical models estimating the costs of this technique.

However, some limitations of our study have to be addressed. Estimation of the cost of the procedure and savings after STN implantation did not consider the additional costs from neurosurgical complications in one patient for whom no economic data were available. The assumed increase in healthcare expenditure for this single case would have had a minor impact on the savings for the total group of patients. Calculation of the costs of the procedure were only based on direct medical costs and did not include indirect costs such as loss of productivity due to early retirement or care provided by families, which have been proved to have a heavy impact on health resources. We did not take into account the cost of the replacement of the neurostimulator, estimated at €15 000 every 5 years. Our study was conducted over a 1 year period in relatively young patients and we did not consider the possible long term occurrence of disabling symptoms such as dementia, postural instability, speech deficit, and dysautonomia. These symptoms may be responsible for an increase in scores of the UPDRS activities of daily living scale while on stimulation and a higher risk of institutionalisation, substantially contributing to health expenditure. However, it has been demonstrated that nursing home admissions were less frequent in patients who have had STN implantation compared to medically treated patients. Since the major benefit on motor function is largely maintained over 5 years, the results of this study are valuable at least for this period of time; further long term studies are warranted.

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CONTRIBUTORS

Doctor Pollak had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Valérie Fraix participated in the recruitment, clinical evaluation, and follow up of the participants in the study, in data interpretation, and in the writing of the paper. Jean-Luc Houeto contributed to the clinical evaluation and follow up of the patients and to the writing of the paper. Christelle Lagrange was responsible for the on-site management of the study and data collection, and participated in data statistical analysis and interpretation and in the writing of the paper. Pierre Krystkowiak contributed to the recruitment and follow up of the patients in the study and to the writing of the paper. Dominique Guehl, Marie-Laure Welter, Luc Defebvre, and Valérie Mesnage participated in the study as clinical investigators. Claire Ardouin contributed to the neuropsychological evaluation of the patients. Alain Rougier, Serge Blond, Alim-Louis Benabid, and Philippe Cornu performed the electrode implantation in the patients. Pierre Burbaud, Bernard Bioulac, and Alain Destexhe participated in the recruitment of the patients. Claude Le Peñ designed and implemented the economic study. Frédérique Maurel supervised economic data management and participated in the interpretation of the data and in the writing of the paper. Marie Liguère carried out the statistical analysis of the economic data. Pierre-Paul Pollak was the main investigator, designed the study, participated in the recruitment, clinical evaluation and follow up of the participants, and in the interpretation of the results and the writing of the paper.

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