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# Bilateral subthalamotomy in Parkinson's disease: initial and long-term response

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## Summary

**We conducted an open label pilot study of the effect of bilateral subthalamotomy in 18 patients with advanced Parkinson's disease. In seven patients, the first subthalamotomy pre-dated the second by 12–24 months ('staged surgery'). Subsequently, a second group of 11 patients received bilateral subthalamotomy on the same day ('simultaneous surgery'). Patients were assessed according to the CAPIT (Core Assessment Program for Intracerebral Transplantation) protocol, a battery of timed motor tests and neuropsychological tests. Evaluations were performed in the 'off' and 'on' drug states before surgery and at 1 and 6 months and every year thereafter for a minimum of 3 years after bilateral subthalamotomy. Compared with baseline, bilateral subthalamotomy induced a significant ($P < 0.001$) reduction in the 'off' (49.5%) and 'on' (35.5%) Unified Parkinson's Disease Rating Scale (UPDRS) motor scores at the last assessment. A blind rating of videotape motor exams in the 'off' and 'on' medication states preoperatively and at 2 years postoperatively also revealed a significant improvement. All of the cardinal features of Parkinson's disease as well as activities of daily living (ADL) scores significantly improved ($P < 0.01$). Levodopa-induced dyskinesias were reduced by 50% ($P < 0.01$), and the mean daily levodopa dose was reduced by 47% at the time of the last evaluation compared with baseline ($P < 0.0001$). Dyskinesias occurred intraoperatively or in the immediate postoperative hours in 13 patients, but were generally mild and short lasting. Three patients developed severe generalized chorea that gradually resolved within the next 3–6 months. Three patients experienced severe and persistent postoperative dysarthria. In two, this coincided with the patients exhibiting large bilateral lesions also suffering from severe dyskinesias. No patient exhibited permanent cognitive impairment. The motor benefit has persisted for a follow-up of 3–6 years. This study indicates that bilateral subthalamotomy may induce a significant and long-lasting improvement of advanced Parkinson's disease, but the clinical outcome was variable. This variability may depend in large part on the precise location and volume of the lesions. Further refinement of the surgical procedure is mandatory.**

**Keywords**: subthalamic nucleus; Parkinson's disease; motor complications; surgery; subthalamotomy

**Abbreviations**: ADL = activities of daily living; CAPIT = Core Assessment Program for Intracerebral Transplantation; DBS = deep brain stimulation; FAB = Frontal Assessment Battery; GPi = globus pallidum pars interna; LID = levodopa-induced dyskinesia; MMSE = Mini-Mental Status Examination; MDRS = Mattis Dementia Rating Scale; NPI = neuropsychiatric inventory; STN = subthalamic nucleus UPDRS = Unified Parkinson's Disease Rating Scale; WAIS = Wechsler Adult Intelligence; WCST = Wisconsin Card Sorting Test

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## Introduction

Surgery for Parkinson's disease has been revitalized in recent years. The globus pallidus pars interna (GPi) and the subthalamic nucleus (STN) are currently considered the targets of choice. Pallidotomy induces significant improvement of bradykinesia, rigidity and tremor, and has a striking effect against levodopa-induced dyskinesias (LIDs) in advanced Parkinson's disease patients (Baron *et al*., 1996; Lang *et al*., 1997; Lang and Lozano, 1998; Vitek *et al*., 2003). The motor benefits of unilateral pallidotomy are mainly contralateral to the lesion, with axial motor features such as gait and balance abnormalities being less affected (for reviews see Bronstein *et al*., 1999; Fine *et al*., 2000; Hallett and Litvan, 2000). Bilateral pallidotomy may convey a greater benefit (Parkin *et al*., 2002; Scott *et al*., 2002), but often has been associated with a high incidence of severe complications such as cognitive impairment, dysarthria and swallowing defects (Favre *et al*., 2000: Merello *et al*., 2001). This may be related to the lesion volume and other technical factors (Scott *et al*., 1998, 2002), but nevertheless bilateral pallidotomy is seldom recommended (Lang and Lozano, 1998; Bronstein *et al*., 1999). Deep brain stimulation (DBS) of the STN or GPi can be safely performed bilaterally and is associated with motor improvement that is significantly more than that obtained with unilateral lesions (Benabid *et al*., 1994). Thus, bilateral DBS has rapidly become the preferred surgical approach for the management of motor complications in advanced Parkinson's disease patients. However, DBS is expensive in terms of equipment and labour (McIntosh *et al*., 2003), and requires the dedication of specialized personnel. Thus, DBS has been limited to countries with access to this technology. Subthalamotomy was proposed as a feasible approach for Parkinson's disease (Guridi *et al*., 1993) on the basis of positive results in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) monkey model of Parkinson's disease (Bergman *et al*., 1990; Brotchie *et al*., 1991; Guridi *et al*., 1996), but the fear of inducing hemiballism halted its clinical application until recently. Two initial independent pilot studies in a few patients indicated that unilateral subthalamotomy could be performed without noticeable adverse events (Gill and Heywood, 1997; Obeso *et al*., 1997). Subsequently, we reported in more detail the results of unilateral subthalamotomy in 11 patients with Parkinson's disease that resulted in significant benefit without dyskinetic complications in all but one patient (Alvarez *et al*., 2001). In this study (Obeso *et al*., 1997; Alvarez *et al*., 2001), we maintained the levodopa daily dose constant during the first year, without encountering problems in terms of enhanced dyskinesias in the operated side. Positive results following unilateral STN lesions have been reported more recently by others (Su *et al*., 2002; Vilela and da Silva, 2002; Patel *et al*., 2003). No relevant clinical complication in terms of cognitive deficit, dysequilibrium or dysphagia has been described (McCarter *et al*., 2000; Alvarez *et al*., 2001. These positive clinical results and the lack of severe side effects with unilateral lesions encouraged us to proceed with a study of bilateral lesions of the STN in patients with advanced Parkinson's disease. A preliminary report of this initial experience suggested that the procedure was safe and effective (Alvarez *et al*., 2000). In addition, Su *et al*. (2002) reported that bilateral staged STN lesions in four patients led to favourable outcomes. We now report the results in patients with bilateral staged subthalamotomy and bilateral simultaneous subthalamotomy with a follow up of 3–6 years.

## Patients and methods

All patients were recruited and operated on in the Centro Internacional de Restauracion Neurologica (CIREN), La Habana (Cuba). The general characteristics of the 18 patients included in this study are summarized in Table 1. Patients fulfilled the diagnostic criteria of the UK Parkinson's disease Brain Bank (Hughes *et al*., 1992) and had developed motor complications such as motor fluctuations, and dyskinesias which could not be adequately controlled pharmacologically (i.e. adjusting dose and schedule of levodopa–benserazide or carbidopa administration, adding a dopamine agonist such as bromocriptine or pergolide, and amantadine, trihexyphenydil, etc.). The study was divided into two parts according to the sequence when the lesions were made. Seven patients underwent unilateral subthalamotomy between October 1995 and July 1997 (staged group, Table 1). In those patients, the contralateral STN was lesioned 12–24 months following the first operation. The second lesion was not associated with any noticeable cognitive defect or worsening of speech except for one patient who developed clinical and MRI features compatible with multiple system atrophy and was dropped from the study 6 months after the second surgery.

In view of the lack of major complications associated with staged bilateral surgery, a protocol aimed to undertake bilateral subthalamotomy in the same surgical session (simultaneous group, Table 1) was started in January 1998 and completed in March 2000.

**Table 1** *General clinical characteristics* of patients submitted to bilateral subthalamotomy in two separate operations (staged) and in one (simultaneous) surgical procedure*

| | Staged surgery | Simultaneous surgery |
|---|---|---|
| Age (years) | 59.6 (53–69) | 54.8 (44–63) |
| Male/female | 6/1 | 9/2 |
| Disease duration (years) | 11.8 (7–18) | 11.3 (7–17) |
| Years of treatment | 10.1 (8–16) | 9.6 (7–17) |
| Levodopa daily dose(mg)$^{+}$ | 783 (250–1000) | 843 (200–1600) |
| No. of doses/day | 5.6 (5–6) | 4 (4–8) |
| Hoehn and Yahr$^{\dagger}$ | Stage III $n = 2$<br>Stage IV $n = 5$ | Stage III $n = 2$<br>Stage IV $n = 9$ |
| UPDRS-part III in 'off' state | 61.6 (53–73) | 57 (37–74) |
| UPDRS-part III in 'on' state | 23 (16–28) | 15 (12–24) |
| Levodopa-induced dyskinesias | $n = 7$ | $n = 8$ |
| 'Off' period dystonia $n = 4$ | $n = 6$ | |

*Data correspond to baseline preoperative evaluation.
$^{+}$Levodopa equivalents calculated as 10 mg of bromocriptine = 1 mg of pergolide = 100 mg of levodopa.
$^{\dagger}$Hoehn and Yahr scale in the 'off' medication state.
Data are presented as mean and range.

Eleven patients were included. Levodopa therapy was temporarily discontinued following the second surgery and reintroduced as needed as judged by the patients' disability.

These series represent the initial experience with bilateral subthalamotomy by the study group. The study protocol was approved by the institutional scientific committee and the Cuban National Ethical Committee and was undertaken according to the Declaration of Helsinki. All patients gave informed consent to participate in the study.

## *Surgical technique*

Details of the procedure have been reported elsewhere (Macias *et al*., 1997; Lopez-Flores *et al*., 2003). Surgery was undertaken under local anaesthesia. The Estereoflex stereotactic frame was used to obtain a series of axial parallel slices by CT of the brain to identify the anterior and posterior commissures. The length of the intercommissural line was measured and the mid-commissural point (MCP) defined for each surgery. Coordinates for targeting the STN were 13 mm lateral and 4 mm below the intercommissural plane and 2 mm behind the MCP. The trajectory to the target was defined by a software program for surgical planning system (STASSIS). Semi-microrecording of multiunit action potentials (Ohye *et al*., 1989) and on-line integration of the amplitude and number of spikes at the recording sites were used to localize the STN (Macias *et al*., 1997). This method provides a measurement of the level of neuronal activity throughout the trajectory of the recording track. The beginning of the STN was defined by an abrupt and large increment in the integrated electrical activity. The modification of neuronal activity in response to passive limb displacement and movements of the limbs, face, neck and trunk and recording of 'tremor cells' served to localize the sensorimotor region of the STN in its dorsolateral portion (Rodriguez-Oroz *et al*., 2001; Theodosopoulos *et al*., 2003). A mean of 7.2 (range 4–14) recording tracks per patient were performed in the overall patient population. Stimulation (60–180 Hz, 0.1–5 mA, 0.3 ms pulse width) through the recording electrode was used to look for therapeutic effects, possible induction of dyskinesias and sensory or motor responses.

Both the recording and stimulation data were used to define the boundaries of the STN and for planning the topography and coordinates of the lesions (Lopez-Flores *et al*., 2003).

A thermolytic lesion was applied with a radiofrequency lesioning probe of 1.1 mm diameter and a 2 or 4 mm exposed tip (Elekta Instruments AB, Sweden). The region to be lesioned was first warmed to 42, 50 and 60°C during periods of 10 s separated by 1–2 min intervals. Subsequently, a lesion was made with a power of 8 W at 70°C for 60 s. The strategy of performing the lesion changed slightly during the study. Patients in the staged group had the first lesion made in a single track with a 4 mm exposed tip electrode. This produced a lesion with an estimated volume of ~30–50 $mm^3$ (Fig. 1). In two patients from this group, the second subthalamotomy was also made with the same 4 mm tip electrode. All other subthalamotomies (five unilateral lesions in the staged group and all 22 lesions in the simultaneous group) were made with a 2 mm exposed tip electrode through two different tracks separated by <3 mm in the rostrocaudal and mediolateral planes. Lesions made with this strategy had an approximate volume of 50–70 $mm^3$. In most instances, the lesion extended upward into the zona incerta (Fig. 1).

Patients remained under intensive surveillance at the neurosurgical unit for 24 h and in the hospital for a total of 7–12 days. A routine CT brain scan was made 24–48 h postoperatively. MRI (1.5 T) of the brain was obtained in all patients, but in many this was carried out some 12–24 months after surgery. As a result, the lesion boundaries could not be measured adequately or even seen in some instances, which prevented us from performing an accurate estimation of the volume of the lesions in each patient.

## *Assessments*

Patients were assessed 1–4 weeks before surgery and at 1 and 6 months during the first year postoperatively and annually thereafter by the study group. The last patient assessment took place in March 2003.

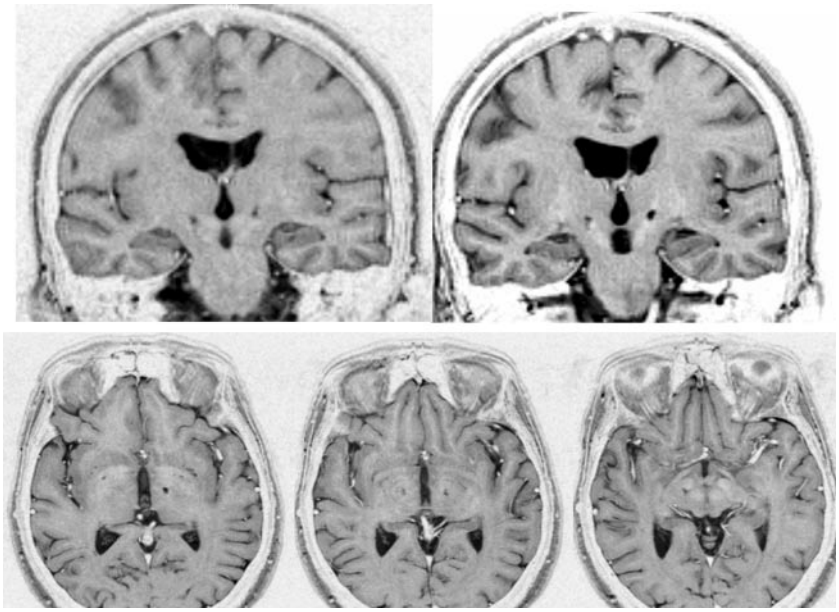

**Fig. 1** MRI of a bilateral subthalamic lesion in one representative patient. Top left and right show consecutive coronal views (T1-weighted sequence) with typical lesions in terms of location and size. Bottom left, centre and right show axial views (T1-weighted sequences) of the dorso-ventral extension of the lesions.

For the purpose of the analysis, the postsurgical evaluations of the staged group were considered as those undertaken after the second subthalamotomy. The guidelines of CAPIT were followed for clinical assessment (Langston *et al*., 1992). The Unified Parkinson's Disease Rating Scale (UPDRS) part II (Activities of Daily Living) and part III (Motor Part) and a revised version of the CAPIT dyskinesias scale were used for evaluations (Goetz *et al*., 1994). The latter scale rates the intensity and duration of LIDs from 0 (absent) to 4 (very severe, continuous and generalized) and scores separately 'off' period dystonia, diphasic and 'on' dyskinesias.

Three timed tests were used to evaluate motor performance further: (i) the number of times the patient is able to pronate–supinate the hands in 30 s; (ii) the time (seconds) required to complete in bed a full body rotation to the left and right; and (iii) the time required (seconds) to rise from a chair, walk 3.5 m and return to the sitting position (the 'stand and walk' test). These evaluations were undertaken preoperatively and at 1 and 2 years postoperatively.

In each evaluation, patients were scored in the 'off' state after a minimum of 12 h overnight without medication. The assessment was repeated in the 'on' state following 200/50 mg of levodopa/benserazide or 250/25 mg of levodopa/carbidopa at 9 a.m. in the fasting state. Patients were videotaped according to a pre-established protocol (Lang *et al*., 1997) to show the main motor features of Parkinson's disease in the 'on' and 'off' medication state. Two neurologists (M.C.R.-O. and E.T.S.) evaluated these videotapes under blinded and randomly ordered conditions. The videotapes were obtained preoperatively, and 1 and 2 years postoperatively The UPDRS-part III score, maximum 84 (excluding rigidity and speech), was used for video rating. A battery of neuropsychological tests was administered to assess the cognitive status of 10 patients and eight age-, gender- and education-matched Parkinson's disease controls at baseline, 1, 6, 12 and 24 months. Here we report the results of both groups at baseline, 12 and 24 months. The Mini-Mental Status Examination (MMSE) (Folstein *et al*., 1975), the Wechsler Adult Intelligence Scale (WAIS) and the Mattis Dementia Rating Scale (MDRS) (Mattis, 1976) were performed to evaluate the overall level of cognition. Executive function was evaluated using specific subtests of the MDRS subtests (Initiation and Perseveration, Attention and Conceptualization), the Frontal Assessment Battery (FAB) (Dubois *et al*., 2000), Wisconsin Card Sorting Test (WCST) and a test of verbal fluency which comprises a phonological (i.e. say as many words as possible starting with the letter S over a 1 min period) and a semantic (i.e. nominate objects found in a supermarket in 1 min). The former test scores from 0 (<3 words) to 3 (⩾9 words) and the latter gives 1 point (from 0 to 20) per word; the normal performance is established for a score of 13 or above in the MDRS (Mattis, 1976). Memory was tested using the Weschler Memory Scale and construction praxis with the Rey Figure Test (Lezak, 1995). Neuropsychiatric behaviours were evaluated with the neuropsychiatric inventory (NPI) (Cummings *et al*., 1994; Lezak, 1995) and the Hamilton Depression Scale. All evaluations were performed by the same investigator. Statistical tests included: analysis of variance with repeated measures and Spearman rank correlation tests. Detailed report of these evaluations will be provided in a separate article.

At the last visit, after a minimum follow-up of 3 years, patients and relatives as well as the attending neurologists (L.A., E.A. and C.M.) were asked to provide a global assessment of the degree of clinical benefit derived from surgery. This was evaluated as 0, no improvement or worsening; 1 = less than 25% improvement; 2 = 25 to <50% improvement; 3 = 50 to <75% improvement; and 4 = >75% benefit.

### *Statistical analysis*

The primary outcome measurement was the change induced by bilateral subthalamotomy in the UPDRS-part III (motor) in the 'off' state at the time of last evaluation (i.e >3 years) compared with the presurgery score. Secondary end-points included the effect of bilateral subthalamotomy in the following items: (i) UPDRS subscores for bradykinesia, rigidity, tremor, gait and postural instability in the 'off' medication state; (ii) UPDRS-part II ADL in the 'off' and 'on' medication states; (iii) UPDRS-part III motor score in the 'on' medication state; and (iv) levodopa daily dose equivalents. Additional secondary end-points were differences in the UPDRS-part III in the 'off' medication state at 1 year and at the time of the last assessment (i.e. >3 years); the change in the videotaped UPDRS-part III (modified) and timed test at 2 years postoperatively; and modifications in the battery of neuropsychological tests at 1 year after surgery.

The Friedman test was applied for repeated measurements of the effect of subthalamotomy on the various outcome variables and the Bonferroni's correction applied for pair-wise comparisons. The Wilcoxon test was used for paired evaluations. Significance level was $P < 0.05$.

## Results

### *Staged subthalamotomy*

These patients have been followed for a minimum of 4 years following the second subthalamotomy. Specific follow-up times since the second subthalamotomy are 6 years ($n = 3$), 5 years ($n = 2$) and 4 years ($n = 1$).

#### *Motor scores*

At the last evaluation, there was a significant reduction of 50% (62 preoperatively versus 31 postoperatively, $P < 0.01$) in the 'off' UPDRS-part III score with respect to the preoperative assessment (Fig. 2A). The motor score in the 'on' state was also significantly reduced by 38% (24 preoperatively versus 15 postoperatively, $P < 0.01$). The UPDRS subscores for bradykinesia, rigidity, tremor, gait and postural instability as well as the UPDRS-part II score for ADL were all significantly improved in the 'off' medication state (Table 2A). The UPDRS-part II in the 'on' state was significantly improved up to the last evaluation (Table 3A). Comparison of the 'off' UPDRS III scores at the first year postsurgery and the last observation revealed no significant difference ($P > 0.1$) (Fig. 2A), suggesting that the antiparkinsonian effect was maintained for 4–6 years.

At the last assessment, the daily dose of levodopa was reduced by 40% ($P < 0.01$) compared with the preoperative dose (Table 2). After surgery, two patients stopped taking levodopa and dopamine agonists for up to 2 years with maintained clinical benefit under treatment with amantadine (300 mg daily) and trihexyphenydil (2 mg daily).

#### *Timed tests*

There was a significant postoperative improvement in all three timed tests that was maintained at 2 years postoperatively (Table 3A).

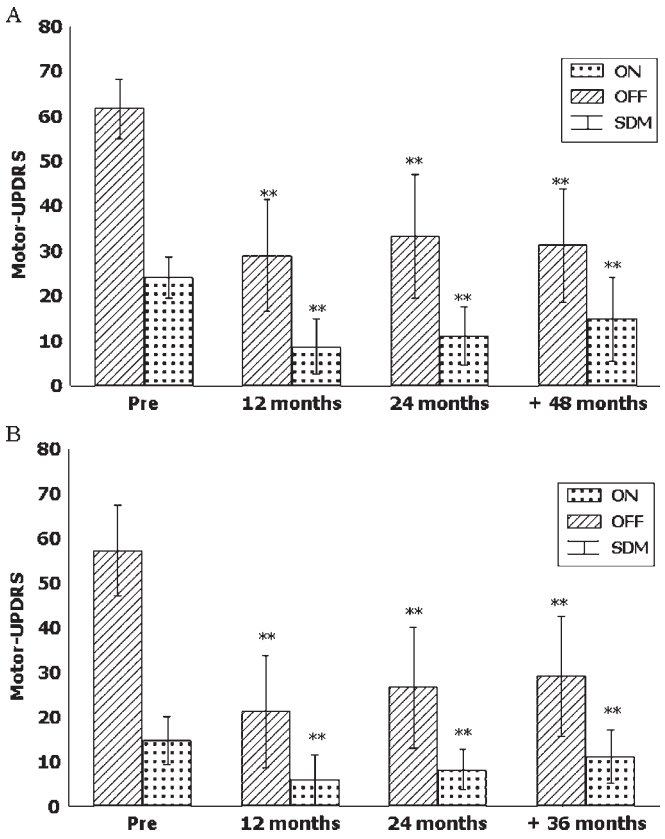


**Fig. 2** Long-term effect of bilateral subthalamotomy on the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS) in the 'off' and 'on' medication state. (**A**) Patients ($n$ = 6) submitted to staged surgery and followed for a minimum of 4 years. (**B**) Patients ($n$ = 11) treated with simultaneous surgery and followed for a minimum of 3 years. A marked and significant reduction in both the 'off' and 'on' UPDRS scores was obtained and maintained throughout the evaluation period. The asterisk indicates a $P < 0.001$ difference between baseline and follow-up evaluations.

## *Dyskinesias*

Postoperative dyskinesias appeared within the initial 24–48 h in six of the seven operated patients on the side contralateral to the lesion. Dyskinesias in the side contralateral to the lesion previously undertaken were seen in the lower limb of one patient for <24 h after surgery. Dyskinesias induced by subthalamotomy were scored as 3 (moderately to severe) in two patients and as 2 (mild, discontinuous and restricted to one body segment) in the other four. The intensity of dyskinesias decreased gradually over the next 1–3 months. At postoperative year 1, dyskinesias had disappeared in five patients and persisted with mild intensity (score 1) in one. Regarding LIDs in this group, 'on' dyskinesias, diphasic dyskinesias and 'off' period dystonia were all significantly ($P < 0.01$) reduced throughout the postoperative period (Fig. 3A). At the last assessment, there was a further and significant reduction in 'peak dose' and diphasic dyskinesias (Fig. 3A) probably related to the reduction in daily levodopa intake that occurred after the second year of follow-up.

## ***Simultaneous surgery***

In this group, the most recent evaluations were conducted on postoperative year 5 in three patients, year 4 in five patients and year 3 in three patients.

## *Motor scores*

Subthalamotomy produced a significant ($P < 0.003$) reduction (49.1%) in the 'off' UPDRS-part III score at the last assessment compared with the preoperative baseline score (57 preoperatively versus 29 postoperatively) (Fig. 2B). The motor score in the 'on' state was also significantly ($P < 0.003$) reduced by 33% (Fig. 2B). The UPDRS subscores for bradykinesia, rigidity, tremor, gait and postural instability, and the UPDRS-part II score for ADL significantly decreased in the 'off' medication state (Table 2B) at the last visit compared with baseline values. The UPDRS-part II in the 'on' state was significantly improved up to the last evaluation (Table 3B). Comparison of the 'off' UPDRS III scores at the first year postsurgery and the last observation (3–5 years) revealed no significant difference ($P > 0.1$) (Fig. 2B). The mean daily levodopa dose decreased by 53% (Table 2B) compared with baseline ($P < 0.001$). Four patients stopped levodopa and remained on amantadine 200 mg/day and trihexyphenedil 3 mg/day for 1 year. After 2 years, two of them required the addition of levodopa (200 mg/day). The other two maintained excellent motor control up to 3 and 4 years without dopaminergic agents.

## *Timed tests*

Significant improvement in all three timed tests was maintained during the first and second postsurgical years (Table 3B).

## *Dyskinesias*

Ten patients developed intraoperative or immediate (24–48 h) postoperative dyskinesias. These 'off' dyskinesias were very severe, affected the four limbs, neck and trunk continuously and interfered with normal motor control (score 4) in three patients (see below under Complications); dyskinesias were severe (score 3) in three other patients, moderate (score 2) in three and very mild (score 1) in one. Dyskinesias disappeared within the next 1–3 months in seven patients and were occasionally present with mild intensity and focal distribution (score 1) over the follow-up period in three patients. The latter patients correspond to the ones who had initially experienced very severe dyskinesias (see below). In contrast, the scores for 'on' dyskinesias, diphasic dyskinesias and 'off' period dystonia were significantly ($P < 0.01$) reduced throughout the evaluations (Fig. 3B). However, one patient who did not exhibit a good antiparkinsonian response to subthalamotomy also continued to show diphasic dyskinesias that had increased in severity at the last evaluation.

## *Videotape assessment*

All patients ($n$ = 17) were pooled together for this analysis and the results are therefore presented jointly. Blind analysis of

**Table 2** *Effect of bilateral subthalamotomy on activities of daily living (UPDRS-part II) and cardinal features of Parkinson's disease*

A. Bilateral staged subthalamotomy ($n$ = 6)

| | Pre surgery mean ± SD ($n$ = 6) | 12 months mean ± SD ($n$ = 6) | 24 months mean ± SD ($n$ = 6) | >48 months mean ± SD ($n$ = 5) |
|---|---|---|---|---|
| UPDRS II 'on' | 12.67 ± 4.37 | 5.17 ± 1.72* | 5.00 ± 1.67* | 7.20 ± 4.26 |
| UPDRS II 'off' | 28.83 ± 4.45 | 14.17 ± 8.33* | 12.83 ± 7.44* | 16.00 ± 2.54* |
| Axial 'on' | 2.67 ± 0.82 | 1.50 ± 1.52 | 0.67 ± 0.82* | 1.80 ± 2.38 |
| Axial 'off' | 7.33 ± 1.75 | 3.67 ± 2.88* | 3.33 ± 3.01* | 3.80 ± 2.58* |
| Tremor 'on' | 3.83 ± 3.97 | 0.50 ± 0.84 | 0.50 ± 0.84 | 1.40 ± 1.94 |
| Tremor 'off' | 11.17 ± 5.38 | 3.67 ± 2.07 | 3.33 ± 2.94* | 3.00 ± 3.08 |
| Rigidity 'on' | 4.17 ± 0.98 | 0.83 ± 1.17* | 0.50 ± 0.55* | 2.20 ± 2.68 |
| Rigidity 'off' | 11.83 ± 1.72 | 5.17 ± 3.19* | 5.17 ± 2.14* | 6.00 ± 2.00* |
| Bradykinesia 'on' | 10.33 ± 2.88 | 4.83 ± 3.87* | 3.83 ± 3.06* | 6.60 ± 4.15 |
| Bradykinesia 'off' | 27.17 ± 4.54 | 13.67 ± 5.01* | 12.67 ± 5.65* | 14.80 ± 6.61* |
| Levodopa daily dose | 783.33 ± 301.10 | 225.00 ± 206.76* | 241.66 ± 217.75* | 530.00 ± 216.79 |

B. Bilateral simultaneous subthalamotomy ($n$ = 11)

| | Pre surgery mean ± SD | 12 months mean ± SD | 24 months mean ± SD | >36 months mean ± SD |
|---|---|---|---|---|
| UPDRS II 'on' | 10.54 ± 3.55 | 3.90 ± 2.50* | 5.63 ± 3.13* | 6.45 ± 3.80 |
| UPDRS II 'off' | 28.45 ± 7.69 | 11.09 ± 4.96* | 14.81 ± 6.86* | 15.36 ± 7.85* |
| Axial 'on' | 2.18 ± 0.87 | 1.27 ± 0.90* | 1.36 ± 0.92* | 1.81 ± 1.53 |
| Axial 'off' | 8.09 ± 2.07 | 2.90 ± 2.07* | 3.90 ± 2.70* | 3.81 ± 2.63* |
| Tremor 'on' | 0.54 ± 1.03 | 0.09 ± 0.30 | 0.36 ± 0.67 | 0.45 ± 0.68 |
| Tremor 'off' | 7.00 ± 4.66 | 2.63 ± 3.38* | 3.18 ± 3.70* | 3.27 ± 3.63* |
| Rigidity 'on' | 3.00 ± 2.00 | 0.81 ± 1.83* | 1.18 ± 1.53* | 1.81 ± 1.53 |
| Rigidity 'off' | 12.9 ± 2.30 | 3.72 ± 3.49* | 5.27 ± 3.63* | 5.63 ± 3.85* |
| Bradykinesia 'on' | 6.72 ± 2.86 | 2.09 ± 3.26* | 3.36 ± 3.26* | 5.36 ± 2.80 |
| Bradykinesia 'off' | 24.72 ± 5.31 | 3.72 ± 3.49* | 10.63 ± 6.68* | 12.54 ± 5.85* |
| Levodopa daily dose | 843.18 ± 36.41 | 245.45 ± 228.53* | 263.63 ± 240.92* | 397.72 ± 295.47** |

*$P \leqslant 0.05$; **$P \leqslant 0.001$.

videotaped UPDRS-part III (modified) revealed a significant ($P < 0.01$) reduction from a mean of 48 ± 19 preoperatively to 21 ± 14 in the 'off' state. In the 'on' state, there was also a significant ($P < 0.05$) change from a mean of 13 ± 8 preoperatively to 7 ± 4 postoperatively. Variability in scoring between the two observers was not significant ($P > 0.05$).

## *Cognitive function*

Following surgery, the MDRS scores significantly ($P < 0.002$) improved from a mean of 133.7 ± 8.9 preoperatively to 140.7 ± 7.6 at 1 year and 138.6 ± 10 at 2 years. Improvements in the MDRS scores were mostly due to a better performance in the MDRS initiation and perseveration (31.6, 36 and 35.6 at baseline, 1 and 2 years, respectively, $P < 0.0001$) and attention subtests (34.9, 35.9 and 35.8; $P = 0.037$). Evaluation of the individual MDRS scores reveals that these scores improved in all the Parkinson's disease patients undergoing bilateral subthalamotomy, including three patients in whom anticholinergic medication was discontinued or reduced after surgery. There were also significant improvements in the WCST test (decreased total errors, $P < 0.048$) and in the semantic fluency test ($P < 0.028$), but the remaining cognitive tests remained stable or the improvement did not achieve significance (i.e. FAB).

Significant improvements were also observed in the Hamilton Depression Scale score (26, 14.3 and 18.6, at baseline, 1 and 2 years, $P < 0.016$) and NPI scores. Improvements in the NPI scores were mostly due to an improvement in the depression ($P < 0.003$) and apathy subscores ($P < 0.0004$). Significant correlations were found between the Hamilton Depression Scores and the total MDRS scores ($r = -0.4$, $P < 0.039$, Spearman rank correlation); total errors in the WCST ($r = 0.4$, $P < 0.04$); semantic fluency ($r = -0.53$, $P < 0.0064$); MDRS Initiation and Perseveration subtest score ($r = -0.38$, $P < 0.05$); and FAB ($r = -0.57$, $P < 0.0035$). The significant inverse correlations found between the depression scores and the total cognitive scores indicate that improvement in depression (lower scores) correlated with better cognition (higher scores). Similarly, improvement in depression (lower scores) correlated with improvement in frontal scores (higher scores in the WCST, semantic fluency, MDRS Initiation and Perseveration subtest scores and FAB scores). In addition, hyperactive behaviours (i.e. disinhibition,

**Table 3** *Effect of bilateral subthalamotomy on timed tests*

| A. Bilateral staged subthalamotomy ($n$ = 6) | | | |
|---|---|---|---|
| | Baseline (mean ± SD) | 1 year (mean ± SD) | 2 years (mean ± SD) |
| Bed turning (s) | | | |
| Left side | 16.83 ± 9.08 | 5.00 ± 1.04* | 6.16 ± 4.57* |
| Right side | 19.16 ± 11.40 | 5.50 ± 1.03* | 6.33 ± 5.27* |
| Sit and walk (s) | 42.00 ± 32.01 | 19.66 ± 8.09 | 23.16 ± 20.22 |
| Prono/supination/30 s | | | |
| Left hand | 40.16 ± 12.20 | 16.33 ± 3.44* | 18.00 ± 4.60* |
| Right hand | 32.33 ± 6.43 | 15.33 ± 2.42* | 15.16 ± 2.31* |
| B. Bilateral simultaneous subthalamotomy ($n$ = 11) | | | |
| | Baseline (mean ± SD) | 1 year (mean ± SD) | 2 years (mean ± SD) |
| Bed turning (s) | | | |
| Left side | 21.27 ± 14.01 | 6.54 ± 3.85** | 3.81 ± 1.47** |
| Right side | 22.54 ± 12.01 | 6.45 ± 4.20** | 4.36 ± 3.04** |
| Sit and walk (s) | 66.81 ± 38.80 | 28.27 ± 14.73* | 20.72 ± 11.44* |
| Prono/supination/30 s | | | |
| Left hand | 38.27 ± 23.77 | 16.00 ± 5.03** | 14.18 ± 3.28** |
| Right hand | 24.90 ± 7.94 | 14.81 ± 1.88** | 14.09 ± 1.37** |

*$P \leq 0.05$; **$P \leq 0.005$.

hypomania, excessive cheerfulness, talkativeness, etc.) were present in five patients, including the three who also suffered from severe dyskinesias. The hyperactivity peaked in severity 1 month after surgery but gradually settled after 1 year post-surgery. Slight improvements in the NPI anxiety and agitation scores did not achieve statistical significance.

The longitudinal evaluation of a control group of eight Parkinson's disease patients of similar age (54.5 ± 11, NS) and education as those undergoing surgery showed no significant changes in the MDRS (135.5, 133.9 and 132.8, at baseline, 1 and 2 years), and Hamilton Depression Inventory.

### *Global assessment (17 patients)*

The global clinical response to subthalamotomy was not homogenous. There was a complete agreement in the assessment made by patients or relatives and the attending physicians. Six patients were given a score of 3 or 4 indicating marked improvement in ADL in the 'off' medication state; seven patients scored 2 (limited but capable of undertaking most ADL when 'off' medication) and four were given a 0 score, indicating minimal or no improvement. Indeed, the subjective classification was correlated with the motor UPDRS score in all but one patient. Thus, seven patients exhibited at least a 60% improvement in the 'off' UPDRS motor score, six had a 30–60% improvement and four showed <30% benefit. The latter four patients corresponded to the same ones given a 0 score in the global assessment. Notably, the three patients who suffered the most severe dyskinesias after the lesions fell into the subgroup with the largest

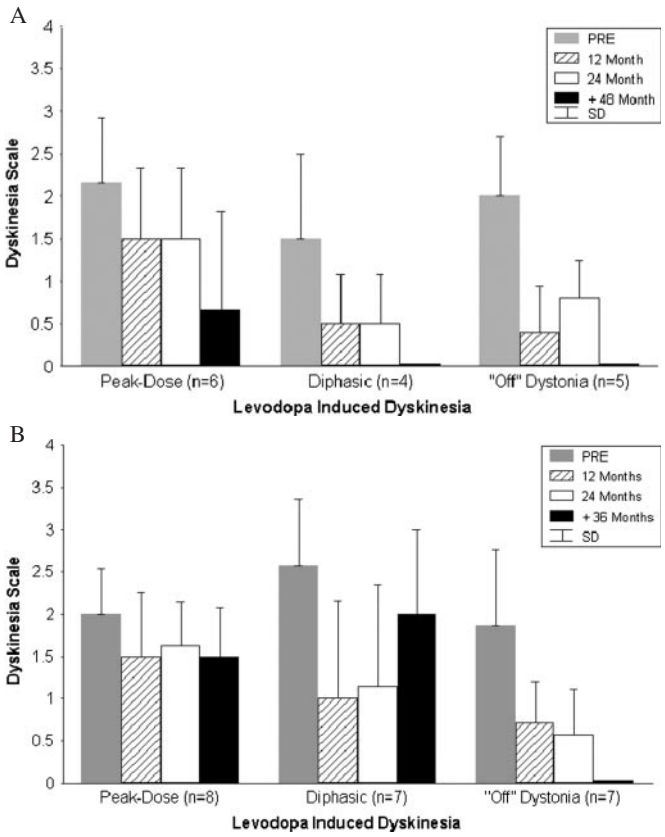


**Fig. 3** Effect of bilateral subthalomotomy on levodopa-induced dyskinesias in the staged (**A**, top) and simultaneous (**B**, bottom) surgery groups. There is a significant ($P < 0.01$) reduction in all three presentation patterns in both groups of patients with respect to baseline. No statistical difference was found for any one type when comparing the scores at 1 year and the last assessment postoperatively.

reduction in the 'off' UPDRS-part III and the best global clinical improvement.

## *Complications*

Side effects are presented together for the overall patient population regardless of whether surgery was performed simultaneously or staged.

### *General complications*

There were no intraoperative complications. One patient fell at home and developed a subdural haematoma which was surgically treated without any further complication. Infection of the scalp occurred in one patient and was treated with antibiotics and local drainage. One patient who had a generalized seizure 1 month after surgery was treated with phenytoin (300 mg daily) without recurrence 2 years after stopping the antiepileptic treatment.

### *Dyskinesias*

Three patients (from the simultaneous surgery group) developed severe and bilateral dyskinesias immediately after

surgery. The movements were choreo-ballistic in nature and generalized, reaching a maximum score of 4 in the dyskinesias scale. In those patients, all antiparkinsonian drugs were stopped but severe dyskinesias continued over the next 2–4 weeks. The evolution and circumstances of these three patients deserve some additional explanation. The bilateral lesions in the first patient (a 61-year-old female with a 13 year history of Parkinson's disease) were normal in size and location. She suffered severe LIDs prior to surgery. Severe bilateral dyskinesias appeared before the end of surgery and continued over several weeks without any dopaminergic treatment. The intensity of the hemichorea-ballism waned spontaneously and gradually over the next 4–6 weeks until near to complete resolution some 3 months later. The antiparkinsonian benefit has been maintained, without levodopa treatment, for the next 4 years. Dyskinesias were longer lasting in the other two patients that are described conjunctly. These were 58- and 54-year-old men with a 10 and 8 year history, respectively, of Parkinson's disease and severe 'off' episodes (UPDRS scores of 56 and 64, respectively) but only mild dyskinesias in the 'on' state. Severe and generalized dyskinesias began within the next few hours after surgery. All antiparkinsonian drugs were halted and unsuccessful attempts were made to control them with tetrabenazine (100 mg/daily) and sulpiride (200 mg/daily). This led to no improvement in dyskinesias and a worsening of parkinsonism, speech, swallowing and equilibrium requiring their discontinuation after 3 weeks. Over the next several months, the dyskinesias gradually decreased in both patients until resolution without additional treatment. An MRI done some 3 weeks after surgery revealed large lesions spreading beyond the STN dorsally as well as caudally and medially (Fig. 4). Revision of the surgical procedure showed that a defect in the isolation of the lesion probe had occurred during surgery of the first patient. In the other case, the initial lesions were not associated with the expected and usual motor improvement intraoperatively. This led to increasing the temperature of the radiolesion probe up to 80°C, which resulted in a much larger lesion than intended. These lesions were estimated to be some 30–40% bigger than the average for the whole group. However, this is a tentative evaluation as no prospective and blind assessment of the images was undertaken At the 2 years follow-up exam, dyskinesias were not present in either of these two patients and the extent of the lesion has decreased to what is typically seen in most patients (Fig. 1).

## *Ataxia*

Three patients developed severe ataxia mainly involving the trunk and gait immediately after surgery. Clinically, this consisted of gait instability with widening of the base, marked alteration of the 'pull test' and positive Romberg test on standing. In bed, there was dysynergia of the trunk when trying to incorporate and dysmetria in the heel to knee test in both legs. Muscle tone was reduced to palpation at rest and to passive displacement in the four limbs, but did not dramatically interfere with voluntary movement. There was no nystagmus nor dysmetria in the upper limbs. The ataxia improved substantially over the next year postoperatively in two patients who are the same ones that suffered severe dyskinesias as described above. The third patient developed ataxia and marked disequilibrium (without dyskinesias) that continue to improve but remained the only source of disability in this patient. The lesion was also larger than expected in this patient and appeared similar to that of the other two patients. He in fact had been operated on just before the first patient described above with severe dyskinesias postsurgery and, therefore, the large lesions were attributed to the same defect in the isolation of the thermo needle.

## *Speech*

Fifteen patients exhibited clinically relevant speech difficulties before surgery in the 'off' medication state. This consisted of hypophonia and articulation deficit (i.e. dysarthria), with moderate impairment of speech fluency and word finding, particularly during automatic speech. For the overall patients population, statistical analysis of item 18 (speech) of the motor UPDRS-part III showed no change pre- and postoperatively in the 'off' ($2.23 \pm 0.60$ and $2.37 \pm 0.95$, respectively) or in the 'on' ($1.76 \pm 0.9$ and $1.81 \pm 1.1$, respectively) medication states. During the first year after surgery, speech was noticed to deteriorate in seven patients in both the 'off' and 'on' medication states. Speech became low in volume,

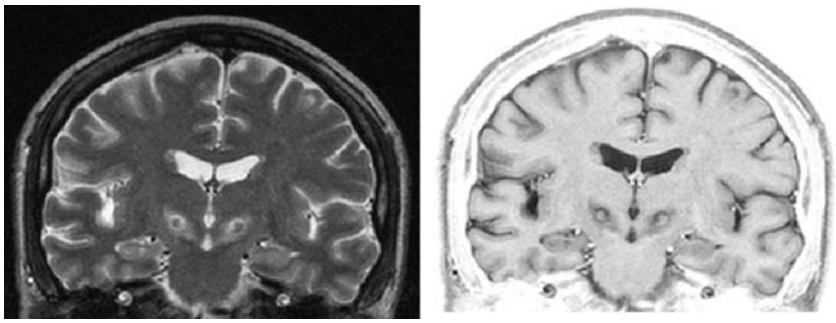

**Fig. 4** Coronal view (T2-weighted on the left and T1-weighted on the right) of a large bilateral lesion corresponding to one of the patients who developed severe dyskinesias, ataxia and dysarthric speech. The MRI study was undertaken 3 weeks after surgery.

words were not properly pronounced and terminated, giving rise often to a concatenation of sounds that were difficult to understand. This type of dysarthria is quite typical of advanced Parkinson's disease and shared no feature of pseudo-bulbar speech. This problem was particularly relevant and disabling in three patients. Two of these patients were the ones described above with severe postoperative dyskinesias and ataxia who exhibited larger than average bilateral lesions.

## Discussion

### *Antiparkinsonian effect of bilateral subthalamotomy*

The results of the present series indicate that bilateral subthalamotomy can lead to a significant and maintained improvement of the cardinal features of Parkinson's disease. Surgery was generally well tolerated, with no severe complications. Interpretation of these results has the limitations inherent with open label studies examining new therapeutic techniques. For one, we cannot rule out a placebo effect. Up to 50% improvement in the motor UPDRS has been associated with a placebo response (Goetz *et al*., 2002) in Parkinson's disease patients. However, such an effect was observed in patients with milder disease studied for relatively short periods (26 weeks) compared with this series. In two recent double-blind studies comparing the effect of striatal fetal cell grafting or sham surgery in advanced Parkinson's disease patients, the placebo effect was negligible (Freed *et al*., 2001; Olanow *et al*., 2003). The demographics of our patients (i.e. disease severity and duration, motor complications, etc.) were very similar to those in these two placebo-controlled studies. In addition, the prolonged and sustained motor benefit on tremor and axial signs, features previously poorly controlled pharmacologically, and the reduction in levodopa dose requirements argue against a placebo effect being the main explanation for our results. On the other hand, there might have been a bias in the observers, more sensitive to score for improvement after surgery, and a high expectative among both patients and investigators, leading to an overall overestimation of the improvement. The placebo effect for the cardinal features of Parkinson's disease was, in part, addressed by the blind video evaluation that revealed the same degree of improvement in the UPDRS-part III as the unblinded assessments. Admittedly, patients received greater medical supervision and enjoyed the special attention of the auxiliary personal more than typically occurs when a new therapy is began, which may have had a greater impact on evaluations such as global assessment and cognition (see below).

Altogether, the present results and data from the literature (Su *et al*., 2002; Vilela and da Silva, 2002; Patel *et al*., 2003) indicate that subthalamotomy may be a useful technique with a favourable therapeutic profile for the surgical treatment of Parkinson's disease. Interpretation of these results must consider the inevitable effect of the learning curve accompanying any newer technique or novel surgical approach. This is associated with small changes and refinements that probably account for some of the variability in the results. In this respect, the methodological evolution and clinical outcome for bilateral subthalamotomy should be expected to improve as has occurred for DBS (Eskandar *et al*., 2003; Terao *et al*., 2003). It remains to be formally assessed whether or not simultaneous subthalamotomy may be established as a routine approach. For the time being, it appears safer to conduct staged lesions when considering bilateral subthalamotomy as the best treatment alternative.

Bilateral subthalamotomy provided marked amelioration of all the cardinal features of Parkinson's disease in the 'off' motor state and also improved the 'on' state. The reduction in the 'off' UPDRS score induced by subthalamotomy was of such a magnitude that roughly matched the best ('on') response obtained with levodopa before surgery (see Fig. 2). This resulted in a practical abolition of 'off' periods in the majority of patients. Thus, even when we were not able to assess 'on–off' hours in this study, it is more than likely that motor fluctuations were drastically diminished in the overall group or even eliminated in some patients (i.e. those who drastically reduced or stopped levodopa after surgery). Indeed, the magnitude of improvement in the 'off' state is very similar to that for DBS of the STN, that is known to be associated with a marked reduction in motor fluctuations (Molinuevo *et al*., 2000; Obeso *et al*., 2001*a*; Krack *et al*., 2003). In addition, subthalamotomy (similar to DBS of the STN) (Molinuevo *et al*., 2000; Obeso *et al*, 2001*a*) also improved the 'on' state. We analysed this aspect before (Alvarez *et al*., 2001) and concluded that the improvement in the 'on' state was probably related to the fact that tremor and axial signs were not completely controlled by levodopa but had improved after subthalamotomy. In this larger experience, however, the effect in the 'on' state was also present against rigidity and bradykinesia (Table 2). Thus, the 'on' state in our patients might have not been their actual best motor response to levodopa. In order to address this point, a formal dose–response curve should be performed. In principle, the experience reported here ascribes to the principle that the motor benefit derived from subthalamotomy is by and large limited to those signs that respond to levodopa. The benefit in the 'on' state occurred with a drastic reduction in the severity of LIDs (Fig. 3). The latter may only be partially related to the reduction in levodopa daily dose since we maintained the preoperative dose for the first year after the initial subthalamotomy for patients in the staged group.

The benefit obtained in this pilot study remained significant after a minimum follow-up period of 3 years. This was also the case in the four patients reported by Su *et al*. (2002) with 18 months of postoperative follow-up. In fact, for the staged surgery patients, the antiparkinsonian effects associated with the first operated side encompass some 6–8 years of follow-up and most of those patients remained in a better motor state than preoperatively. This sustained benefit is all the more remarkable considering our patients had reached a relatively advanced stage of disease at baseline and in light of the anticipated progression of symptoms (8–10 points in the

UPDRS-part III scale/year) during the study (Olanow *et al*., 2003). The possibility of recurrent signs that had initially responded well to subthalamotomy has been mentioned in some reports (Su *et al*., 2002; Patel *et al*., 2003), particularly as regards tremor. In our experience, the cardinal features remained well controlled in the majority of our patients, who exhibited a good initial response, although tremor did recur in some patients. We believe such cases will prove to have poorly placed lesions or a suboptimal volume of the lesion, as has been documented for thalamotomy (Tasker *et al*., 1983).

## *Mechanism of action*

The marked antiparkinsonian effect of subthamotomy is in keeping with previous data indicating a paramount role for increased and abnormally patterned STN neuronal activity in the parkinsonian state (Crossman, 1987; Wichmann and DeLong, 1996; Terman *et al*., 2002). In the rat with a 6-hydroxydopamine lesion of the nigrostriatal dopaminergic bundle, and in primates with MPTP intoxication, lesion of the STN reduces neuronal hyperactivity in the GPi and substantia nigra reticulata (Wichmann *et al*., 1994; Delfs *et al*., 1995; Guridi *et al*., 1996). This is also supported by findings with [$^{18}$F]fluorodeoxyglucose ([$^{18}$F]FDG) uptake measured by PET in humans. [$^{18}$F]FDG uptake is a well established index of regional metabolic neuronal activity and is characteristically increased in the GPi and motor thalamus but reduced in the premotor area, supplementary motor area, dorsolateral prefrontral cortex and the parieto-occipital region of patients with Parkinson's disease (Carbon and Eidelberg, 2002). Subthalamotomy induced a significant reduction in [$^{18}$F]FDG uptake in both pallidal segments (GPi and GPe) and substantia nigra reticulata, as well as the thalamus and pons (Su *et al*., 2001; Trost *et al*., 2003), in keeping with experimental results. The impact of unilateral subthalamotomy on the abnormal metabolic pattern associated with the parkinsonian state is greater than those produced by an infusion of levodopa, unilateral pallidotomy or pallidal DBS (Carbon and Eidelberg, 2002). Conceivably, bilateral subthalamotomy reduces to a large extent the excessive neuronal inhibitory activity from the output of the basal ganglia in the parkinsonian state (Crosmann, 1987; DeLong, 1990) and normalizes the internal circuits of the basal ganglia (Obeso *et al*., 2000; Trost *et al*., 2003). This in turn may result in a marked attenuation of the abnormalities present in the thalamo-cortical motor and brainstem motor systems (Pahapill and Lozano, 2000; Nandi *et al*., 2002; Trost *et al*., 2003), in terms not only of neuronal firing frequency but also of abnormal rhythms and patterns. Such a widespread functional impact of subthalamoty may be the explanation for its clinical effect on the cardinal features of Parkinson's disease.

MRI findings obtained in this study did not conform to a uniform protocol due to logistical limitations. This has made it difficult to pool our radiographic data or to provide rigorous reconstruction of the lesions, and thus valid clinico-anatomic correlations were not possible. Recently, discussion has arisen regarding the possibility that the antiparkinsonian benefit associated with DBS is conveyed by electrode contacts placed dorsal to the STN, in the region of the zona incerta and lenticular fasciculus (Alterman *et al*., 1999; Saint-Cyr *et al*., 2002). To what extent this plays a role in the antiparkinsonian effect we have observed cannot be ascertained precisely in this series. However, the STN lesions made in MPTP monkeys were performed mainly with excitotoxins (ibotenic and kainic acid) (Bergman *et al*., 1990; Guridi *et al*., 1996) that spare fibres, and the outcome was similar to that obtained in the same model with a thermolytic lesion (Brotchie *et al*., 1991). We therefore would provisionally conclude that lesion or blockade of the motor region of the STN is a key component of the antiparkinsonian effect conveyed by subthalamotomy.

## *Hemichorea-ballism and other complications*

In normal individuals, lesions confined to the STN are expected to provoke hemichorea-ballism in most but not all cases (Dierssen and Gioino, 1961). This variable response is thought to depend on the size and location of the lesion (Peterson *et al*., 1949; Whittier and Mettler, 1949). The natural history of hemichorea-ballism is one of gradual spontaneous resolution (Postuma and Lang, 2003). This gradual resolution has been attributed to autoregulatory mechanisms in the output circuits of the basal ganglia (Obeso *et al*., 2000; Bevan *et al*., 2002). In patients with Parkinson's disease undergoing thalamotomy, unintended unilateral lesions of the subthalamic region were only rarely associated with severe and persistent hemichorea-ballism (Guridi and Obeso, 2001). We have argued that the threshold to develop hemichorea-ballism following subthalamotomy is higher in the parkinsonian state due to functional changes in the striatopallidal circuits induced by the dopamine depletion (Guridi and Obeso, 2001). Thus, it was predicted (Guridi *et al*., 1993; Guridi and Obeso, 1997) that hemichorea-ballism was not likely to be a major complication of subthalamotomy in Parkinson's disease. Certainly, hemichorea-ballism is common after subthalamotomy, but in most cases the dyskinesias wane spontaneously and resolve in days to months. Admittedly, three of our patients did suffer severe and persistent hemichorea-ballism, associated with ataxia and dysarthria in two, that represented a clinical management problem. A few other cases of severe hemiballism after subthalamotomy have been described recently (Chen *et al*., 2002; Doshi and Bhatt, 2002; Tseng *et al*., 2003). Previously we also reported a patient with unilateral subthalamotomy who developed severe and persistent hemiballism associated with a secondary stroke in the subthalamic–thalamic region, a few days after surgery (Alvarez *et al*., 2001).

The main variables determining the onset of severe dyskinesias after subthalamotomy are not clearly known in humans. In normal monkeys, Whittier and Mettler (1949) established that the lesion to induce hemiballism should abate a minimum of 20% of the STN volume with integrity

of the fibres adjacent to the STN, particularly the thalamic fasciculus carrying the pallido-thalamic projection. Accordingly, the low incidence of severe and permanent hemiballism after subthalamotomy has been explained as a pallidotomy-like effect due to interruption of the pallido-thalamic projection by lesions extending dorsally (Lozano, 2001; Su *et al*., 2001; Tseng *et al*., 2003). However, our experience suggests that severe hemichorea-ballism is mainly associated with large lesions. Thus, the severe and long-lasting hemichorea-ballism induced in our three patients was related to larger than anticipated bilateral lesions (Fig. 4). Moreover, the only patient in our series of unilateral subthalamotomy with severe hemiballism suffered a large infarction of the region (Obeso *et al*., 2001*b*); no other patient with unilateral subthalamotomy had a lesion as large as the ones associated with hemiballism in the group with bilateral subthalamotomy. Interestingly, lesions clearly spreading dorsally and reaching the thalamus have been encountered in parkinsonian patients who developed severe hemiballism (Dierssen *et al*., 1961; Obeso *et al*., 2001*b*; Tseng *et al*., 2003). It appears, therefore, that the larger the lesion the greater the volume of the STN affected. but also the probability of destroying the pallido-thalamic fibres running dorsally (Baron *et al*., 2001; Hamani *et al*., 2003). Thus, we find it difficult to reconcile our observations with the view that subthalamotomy has a pallidotomy-like effect due to dorsal extension of the lesion to interrupt the thalamic fasciculus (Lozano, 2001; Su *et al*., 2001; Tseng *et al*., 2003). It may be that large lesions affect other subcortical regions that are also relevant for the induction of dyskinesias. For example, blockade of the zona incerta with bicuculline in the rat has been shown to induce involuntary movements similar to those provoked by STN inhibition (Perier *et al*., 2002). The effect of simultaneous bilateral lesion of the STN may be another concurrent variable. The data reported here may be taken to suggest that bilateral lesions performed simultaneously are associated with a higher incidence of severe dyskinesias. However, both patients populations (i.e. staged versus simultaneous surgery) were not really identical in terms of the severity of dyskinesias preoperatively and overall exposure to levodopa. Thus, surgery in the initial patients included in this study was staged and we purposely chose subjects who had not developed severe LIDs. Overall, the experience is limited and the number of intervening variables (i.e. patients' preoperative state, dose of levodopa prior to surgery, topography and size of the lesion, etc.) too large to allow an accurate assessment of the effect of bilateral and simultaneous lesion and dyskinesias. Meanwhile, a cautious approach would be to defer subthalamotomy in patients with severe LIDs and consider pallidotomy instead (Scott *et al*., 2002). However, it is necessary to balance the risk of dyskinesias by subthalamotomy with the severe complications frequently encountered with bilateral pallidotomy (Merello *et al*., 2001).

Three patients developed clinically disabling ataxia which evolved towards partial resolution. This might have been associated with a caudo-medial extension of the lesion to damage crossing fibres from the superior cerebellar peduncle and brainstem included in the H-1 field of Forel (Parent *et al*., 2000; Hamani *et al*., 2003). Aggravation of dysarthria was the other relevant complication encountered in this series. This could be related to a rostro-lateral extension of the lesion to interrupt cortical projections to the lower brainstem motor nuclei but, on the other hand, DBS of the STN in Parkinson's disease is also frequently associated with speech deterioration (Krack *et al*., 2003; Whelan *et al*., 2003; Rodriguez-Oroz *et al*., 2004). We found dysarthria to be specifically associated with automatic, spontaneous speech and less affected when patients were asked to repeat single words, possibly explaining the insensitivity of the UPDRS item 18 to assess this defect in our patients. It may be that unlike the relative paucity of deficits associated with basal ganglia lesions (DeLong and Georgopoulos, 1981; Marsden and Obeso, 1994), the highly automatic movements of speech are particularly sensitive to bilateral disruption of the basal ganglia as previously described for bilateral pallidotomy (Merello *et al.*, 2001).

## *Cognitive functions*

We observed no cognitive impairment as a result of the bilateral lesions in this selected patient population. On the contrary, there was an unexpected improvement in a number of neuropsychological tests. The latter is a surprising, albeit favourable, outcome that requires specific discussion and recognition of uncontrolled variables probably affecting the results. First of all, our data clearly indicate that depression was much improved after surgery and the degree of improvement in most neuropsychological tests correlated with the benefit observed in the Hamilton scale. Three of the 10 patients included in this evaluation stopped taking an anticholinergic drug after surgery, which may have also contributed to better performance. However, the results were quite homogenous and not due to improvement in those three patients only. It should be stressed here that patients included in this study were submitted to a degree of attention and care that surpasses the standard and probably led to a better emotional state and williness to cooperate in the evaluations, particularly after surgery when most of them were improved. Finally, one may consider the possibility that interruption of the STN connections with the associative and limbic system could portray a beneficial effect on executive and other cognitive tasks. Certainly, the dorsolateral–prefrontal cortex is hypoactive in the parkinsonian state, and pallidotomy (Samuel *et al*., 1997) and DBS of the STN enhances its activity (Hilker *et al*., 2004). Subthalamotomy could result in similar changes. In conclusion, our results may be taken to support the relative safety of subthalamotomy regarding cognitive impairment; the circumstances surrounding this type of pilot trials and the lack of prospective neuroimaging studies make it impossible to reach a definitive interpretation of the precise effects and mechanisms involved in the changes we described. Interestingly, we encountered in a few patients

transient but intense behavioural manifestations, including disinhibition, hypomania and silly attitudes. In the rat, Baunez *et al*. (2002) have described that unilateral lesion of the STN is associated with behavioural abnormalities such as premature responses to an external stimulus and abnormal feeding. Thus, subthalamotomy in humans should not be considered completely immune to cognitive or behavioural disturbances. Clearly, further studies on this issue are warranted.

### *Therapeutic profile*

Currently, DBS of the STN is the most widely used surgical approach for Parkinson's disease. The technical approach for subthalamotomy is similar, but there is general agreement in that placement of the electrodes for stimulation is easier and safer than making a lesion. In addition, the idea that stimulation is adjustable and reversible is particularly attractive nowadays when emphasis is put on restorative neuroscience (Lindvall and McKay, 2003). It is, therefore, quite conceivable that subthalamotomy will never replace DBS as the preferred surgical option. Equally, it is difficult to conceive that a prospective and randomized study will ever be conducted to compare both procedures. Subthalamotomy may be considered as a potential option for some patients under special clinical circumstances. This may apply to the occasional patient who lives in a remote place where DBS management is impractical, patients treated with a cardiac pacemaker, people who are not willing to accept the limitations associated with the chronic use of an implanted device and patients who have suffered infection of the device (Oh *et al*., 2001). All of these circumstances account for a minority of surgical candidates only. However, a large population of patients needing surgical treatment cannot gain access to DBS due to economic reasons. In such instances, subthalamotomy becomes an excellent option. Further refinements to the subthalamotomy procedure in order to provide better targeting, more consistent control over lesion volume, and thus more predictable outcomes will improve the benefit to risk ratio. The initial results presented here are encouraging as, apart from speech deterioration and truncal ataxia in a small proportion of patients, there was no permanent motor deficit associated with the lesion. The results presented here may be taken to indiacte that simultaneous subthalamotomy is associated with a higher risk of complications than staged surgery. This is not supported by our ongoing experience that continues to indicate that severe side effects are particularly related to large lesions. However, it may be reasonable for the time being to consider staged over simultaneous surgery whenever possible. We may conclude that bilateral subthalamotomy induces a sustained benefit in patients with Parkinson's disease who required surgical treatment. The risk of persistent and severe hemiballism appears to be relatively small. The antiparkinsonian effect of bilateral subthalamotomy appears to be similar to the 3–5 year benefit following DBS of the STN (Krack *et al*., 2003; Kleiner-Fisman *et al*., 2003; Rodriguez-Oroz *et al*., 2004). The latter technique is associated with a relatively large number of hazards on long-term follow-up that should also be taken into account for a balanced analysis (Oh *et al*., 2002). Ultimately, the application of either option has to be judged according to the specific circumstances of patients, teams and those paying for the treatment.

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