

Bilateral high frequency subthalamic stimulation in Parkinson's disease: long-term neurological follow-up

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Aim. High frequency stimulation of the subthalamic nucleus (STN) is gaining recognition as a new symptomatic treatment for Parkinson's disease (PD). The first available long-term observations show the stability of the efficacy of this procedure in time.

Methods. Quadripolar leads were implanted bilaterally under stereotactic conditions in the STN of patients with advanced PD. High frequency stimulation was applied for 24 hours a day. Following implant, antiparkinsonian medication was reduced as much as possible and stimulation was gradually increased. The patients were evaluated in the practically defined "off" condition and in the "on" condition using the unified PD rating scale (UPDRS) and the Schwab & England scale. Neuropsychological testing was performed before and after the implant. Thirty-three patients were followed up for at least 3 months and 13 among them until 36 months.

Results. The patients had a mean age of 56.8 ± 7.1 years and a mean disease duration of 13.8 ± 5.5 years; they were followed-up for an average of 25.7 ± 13.5 months. At the time of the last available visit, the stimulation amplitude was 2.47 ± 0.40 V (the total energy delivered averaged 1.57 ± 0.8 μ W). The levodopa-equivalent daily dose was reduced by 56.2% ($p < 0.001$). Parkinsonian features were improved in all patients, the greatest changes were seen for tremor, gait, bradykinesia and postural stability, then rigidity and limb akinesia. Compared with the pre-implant conditions, the UPDRS motor score in the "off" condition was improved by 51.6% at the time of the last visit ($p < 0.001$), the UPDRS activities of daily living score was improved by 68.5% ($p < 0.001$), the Schwab & England scale was improved by 196.8% ($p < 0.001$). The neuro-

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psychological data did not show significant changes. Night sleep improved in all patients, due to increased mobility at night. In almost all patients insomnia was resolved. All patients gained weight after surgery with an increase of 11.1% ($p < 0.001$) compared to their pre-implant weight.

The most common permanent side effects consisted in hypophonia and dysarthria, transient side effects were increased sexuality and mania, the most common side effects related to stimulation were ballistic or choreic dyskinesias. The most common adverse event related to the surgical procedure was transient psychosis; unexplained switching-off of the stimulator was the most common device-related effect.

Conclusion. This study extends our recently published 3-years FU series. It confirms again that symptomatic efficacy of STN stimulation is retained during the 2nd and 3rd years following the implant, without any obvious decay of efficacy or need for increase of energy delivered. Improvement of dyskinesias also persists and the procedure is well tolerated. Side effects and adverse events are sometimes severe, but can be managed in most cases. The improvement of daily living activities outweighs by far the motor benefit, indicating that the use of this procedure significantly improves the patients' lifestyle.

KEY WORDS: Electric stimulation therapy - Parkinson disease - Surgery - Subthalamic nucleus - Brain.

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Parkinson's disease (PD) is a progressive disorder affecting the motor system. Pharmacological treatments have been attempted since the last century¹. Surgical procedures were first introduced in the '40s^{2, 3} and later almost abandoned in the '60s after the introduction of levodopa⁴. Current drug treatment is based on the use of multiple agents, such as levodopa, dopamine agonists, COMT and MAO inhibitors, often in combination. Although providing optimal symptomatic benefit, drug treatment for PD has some important limitations, especially in the long term. Most patients chronically treated with levodopa or other antiparkinsonian drugs present with motor fluctuations or dyskinesias. Two main approaches are used to reduce motor fluctuations, one being the use of surgical procedures (*e.g.* pallidotomy)⁵ or anti-dyskinetic drugs to directly attenuate on-state dyskinesias and the other the continuous, rather than pulse, administration of dopaminergic drugs⁶.

High frequency stimulation (HFS) of the subthalamic nucleus (STN) has been effectively used to treat PD patients allowing to reduce medication requirements⁷ and providing a better control of motor fluctuations and the reduction of dyskinesias⁸. The STN is hyperactive in parkinsonian states⁹ and a direct lesion or the functional inactivation of STN relieve parkinsonian features in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-poisoned monkeys¹⁰. In man, STN lesions also relieve parkinsonian symptoms¹¹, suggesting that STN inactivation may provide a basis for the treatment of off-related signs of PD. Stereotactic neurostimulation provides a suitable tool for functionally inactivating the STN in parkinsonian patients without producing a permanent lesion. STN HFS has been firstly introduced in Europe, and recently approved in the United States. The clinical course of patients is well established for the 1st year following the implant^{7, 8, 12-14}. The first available long-term observations show the stability of the efficacy of this procedure beyond the 1st year¹⁵⁻¹⁶.

Materials and methods

Clinical features

Parkinsonian patients were selected on the basis of the following criteria: a) diagnosis of PD according to the UK Parkinson's Disease Brain Bank criteria¹⁷; b) disabling motor fluctuations with prolonged and at

least occasionally unpredictable "off" periods (patients spent 25% or more of the waking day in the "off" state) and on-state dyskinesias; c) unsatisfactory management of fluctuations with medication; d) Hoehn and Yahr stage equal to, or greater than, III in the practically defined "off" condition¹⁸. Patients with the following features were excluded: a) pace-maker bearer; b) mild parkinsonian features or unstable drug regimen; c) severe cognitive impairment or dementia, as defined by DSM¹⁹; d) ongoing psychiatric problems (*e.g.* persistent hallucinations, psychosis, or sustained depression); e) prior brain surgery; f) unsatisfactory general condition, or g) inability to comply with the study protocol. Each patient received a brain MRI and was assessed using a standard protocol.

Antiparkinsonian medication was unchanged for at least 1 month before the implant. The levodopa-equivalent daily dose (LEDD) was computed for each antiparkinsonian medication by multiplying the total daily dosage of each drug by its potency relative to a standard levodopa preparation assigned the value of 1. The following conversion factors were used: levodopa controlled release preparations=0.77, bromocriptine=10, apomorphine=15, ropinirole=20, pramipexole=60, and pergolide=100. The total LEDD was then calculated.

Evaluations were performed in the morning, in the practically defined "off" condition¹⁸ and in the best "on" condition under the patient's current drug regimen. The study was approved by the ethical committee of Gemelli hospital, and the patients gave their written informed consent. Only the patients with at least a follow-up of 1 year were evaluated.

Surgery

All patients received a bilateral simultaneous STN implant in the Gemelli hospital. Unilateral STN implants were performed when necessary for lead re-implantation. Stereotactic surgery was performed in the practically defined "off" condition. Under local anesthesia, a stereotactic frame modified for a polar approach²⁰ was applied. A precoronal burr hole was drilled, followed by ventriculography, which made it possible to delimit the mid-line of the 3rd ventricle, and the anterior (AC) and posterior (PC) commissure. The target was found using coordinates according to a proportional geometrical scheme based on the AC-PC line.²¹ The initial subthalamic theoretical coordinates were the middle of the AC-PC line, 4 mm below, and

12 mm lateral to, the AC-PC line (calculated on the basis of ²²). The track for the stimulation lead was prepared by inserting a probe (1.1 mm outer diameter) 10 mm from the target. A Medtronic 3389 quadripolar lead was then implanted in the stereotactic target.

In order to identify the functional target, peroperative stimulation (pulses of 60 μ s at a frequency of 130 Hz) was performed in a double-blind fashion. Current amplitude was increased or decreased in a random order until clinical efficacy or side effects were observed by the examining neurologist or the patient, who were blind to the stimulation setting. A target was accepted when a current of less than 3 V reversed parkinsonian signs on the side contralateral to the implanted hemisphere. Changes in rigidity was assessed by evaluating changes in passive resistance to active displacement of the wrist, elbow or knee, either at rest or while performing voluntary contralateral movements. Bradykinesia/akinesia was estimated by measuring amplitude and speed variations while performing repetitive movements (*e.g.* finger or foot tapping, or repetitive sequences with the fingers). Tremor was evaluated before and after activation by stress, both at rest and while maintaining a posture. All patients were assessed double blind while awake by 2 neurologists. When transient STN inactivation did not allow clinical efficacy to be evaluated during peroperative testing, elicitation of side effects helped to identify the structures stimulated. Side effects were observed when peroperative stimulation was gradually increased and usually consisted of facial hemispasm, paresthesias, tachycardia, hyperpnea, diplopia or tonic eye deviation.

Following identification of the functional target, the electrode was secured to the skull bone. The lead position was checked throughout the procedure by teleradiography. After surgery, the patients were kept on low doses of antiparkinsonian medication, sufficient to provide an intermediate motor condition, but not a complete "on" motor state. Chronic stimulation by means of an external device was started on the day following the implant. A 130 Hz (60 μ s) current was applied to the lead contact previously identified during peroperative stimulation. The voltage was gradually increased and other lead contacts stimulated when necessary. The frequency or pulse width was adjusted in order to keep the voltage as low as possible. The following clinical features were evaluated in order to set the stimulation settings: tremor (when present), rigidity, bradykinesia, and gait. An MRI scan was always performed before implanting a

Medtronic Itrel or Kinetra pulse generator in the subclavicular region approximately 1 week after the stereotactic placement.

Clinical evaluation

STN stimulation was continuous for 24 hours a day. The patients were scheduled for evaluation 1, 3, 6, 12, 18, 24 months after the implant and once a year thereafter. The clinical conditions of the patients were not considered stable before 3 months; therefore 1-month evaluations were only established for the purpose of computing variations of the drug regimen and of the stimulation settings. Each postoperative assessment was performed in the morning, 12 hours after withdrawal of antiparkinsonian medication and after having turned off the IPG. Four consecutive UPDRS evaluations were performed: (a) without drugs and stimulation; (b) without drugs, 30 minutes after switching stimulation on; (c) with drugs (according to the daily schedule) at least 60 minutes after switching stimulation off; (d) on drugs, 30 minutes after resuming stimulation. The patient, but not the examiner, did not know whether his stimulator was on or off. At the time of each follow-up visit, daily living activities and quality of life were evaluated by means of the unified PD rating scale (UPDRS) activities of daily life (ADL) score and the Schwab & England scale, respectively, under conditions (b) and (d). After clinical assessment, medication was reduced as much as possible and the stimulation settings readjusted, according to the criteria outlined above.

Changes in scores for daily living activities and motor performances were compared, at each visit, with the LEDD and the energy delivered by the pulse generators.

A battery of neuropsychological tests was administered before the implant and at each scheduled follow-up visit, to evaluate mental status (Mini Mental State Examination, MMSE), verbal episodic memory (Rey's Auditory Verbal Learning Test, RAVLT), visuo-spatial memory (Corsi's Span;), abstract reasoning (Raven's Progressive Matrices '47) and visuo-spatial ability (Trail Making Test parts A and B; Symbol-Digit Modalities Test). Tests were also administered to evaluate executive functions (Modified Wisconsin Card Sorting Test; Stroop Color-Word Test; Phonemic Verbal Fluency letters A-F-S). The neuropsychological evaluations at 3 and 18 months were performed with stimulation turned off, while the other assessments were per-

TABLE I.—*Variation of UPDRS activities of daily living and motor scores, of disease staging, of levodopa equivalents administered*

	Before	3 months	Before	6 months	Before	12 months
UDPRS-III						
Off	61.6±11.6	31.5±13.3	60.2±11.3	29.7±12.6	59.6±8.9	29.9±13.4
On	26.4±14.1	27.4±11.6	24.3±14.3	21.0±12.7	24.2±8.6	22.1±10.7
Variation off		-48.9%*		-50.7%*		-49.9%*
Variation on		3.8%		-13.4%*		-8.7%
LEDD, mean	1 349.3±692.9	626.5±380.3	1 321.3±686.8	616.7±333.0	1 389.6±733.5	471.4±281.4
Variation		-53.6%*		-53.3%*		-66.1%*
UPDRS-II						
Off	32.2±5.8	10.6±6.6	29.9±7.9	9.0±5.8	29.2±8.3	9.8±6.2
On	11.3±9.6	8.2±5.9	10.3±9.1	6.9±5.1	10.3±7.7	7.1±5.0
Variation off		-67.1%*		-69.9%*		-66.3%*
Variation on		-27.7%		-32.9%*		-31.4%*
S&E**						
Off	23.2±14.1	80.0±11.5	27.3±19.5	84.0±12.2	29.6±20.5	84.0±12.6
On	74.8±16.1	88.8±7.3	77.7±16.5	90.5±10.4	75.6±17.3	92.2±7.1
Variation off		244.8%*		207.3%*		183.8%*
Variation on		18.7%		17.8%		22.0%
H&Y						
Off	4.3±0.8	2.4±0.9	4.2±0.9	2.0±0.9	4.0±1.0	2.0±1.1
On	2.5±0.7	1.9±0.9	2.2±1.1	1.6±1.0	2.4±0.9	1.5±1.0
Patients	33		33		25	

*) Statistically significant variances. **) At variance with UPDRS scores, improvement of Schwab & England scores is indicated by increasing values.

formed with stimulation turned on, in order to evaluate the possible direct influence of the STN stimulation on cognitive performance. Finally, the following items were anecdotally collected from the patients: quality of sleep and extent of caregiver involvement.

The energy delivered by the stimulating electrodes (expressed in Watts) was calculated considering the total surface area under the stimulation pulses, times the number of pulses per second, using the formula $E = (\text{amplitude} \cdot \text{pulse width} \cdot \text{frequency rate})^2 / \text{impedance}$. For each patient, the total energy delivered on the 2 sides was calculated.

Statistical analysis was carried out using Wilcoxon's matched pairs test for nonparametric variables; the limit for statistical significance was $p < 0.05$.

Results

Thirty-three patients (19 men and 14 women) had a follow-up of at least 3 months. The patient with the

longest postimplant observation period reached 54 months. At the time of implant, these patients were aged 56.8 ± 7.1 (mean $\pm$ SD) years and had a mean disease duration of 13.8 ± 5.5 years. In August 2002 their follow-up averaged 25.7 ± 13.5 months.

Transient intraoperative STN inactivation associated with a marked clinical improvement occurred unilaterally in 7 patients and bilaterally in 5, lasting for a maximum of 3 weeks.

The drugs being taken by the patients at the time of implant were levodopa (33 patients), pergolide (18 patients), bromocriptine (1 patient), apomorphine (subcutaneous infusion in 3 patients), ropinirole (5 patients) and amantadine (6 patients). The LEDD was progressively reduced throughout the observational period. Compared to pre-implant values, LEDD reduction was 66.1% ($p < 0.001$) at 12 months, 64.4% ($p < 0.001$) at 24 months, 51.6% ($p < 0.001$) at 36 months and 56.2% ($p < 0.001$) at the available visit (Table I). The energy delivered was gradually increased during the 1st quarter after the implant and remained stable thereafter (Figure 1); an average of $1.18 \pm 0.79 \mu\text{W}$ was delivered 3 months after the implant and $1.57 \pm 0.84 \mu\text{W}$ were delivered at the last available visit. Stimulation

daily and of energy delivered. Values with stimulation are compared to baseline values.

Before	18 months	Before	24 months	Before	36 months	Before	Last FU
61.7±8.0	29.6±15.1	63.9±6.2	32.0±12.7	62.2±8.3	31.8±12.5	59.8±10.9	28.9±12.0
23.7±8.9	22.7±11.3	28.7±6.4	21.9±12.1	27.2±8.0	23.5±9.7	24.5±13.7	21.2±10.2
	-52.0%*		-49.9%*		-48.8%*		-51.6%*
	-4.0%		-23.7%		-13.6%		-13.3%
1 257.9±630.7	460.5±304.4	1 311.7±676.6	467.2±317.4	1 298.1±678.5	627.8±448.1	1 296.8±690.5	567.5±428.7
	-63.4%*		-64.4%*		-51.6%*		-56.2%*
29.3±8.2	9.0±5.8	33.1±5.8	10.5±6.7	34.0±6.2	11.8±6.2	29.3±8.2	9.2±5.6
10.5±8.9	6.9±5.7	12.7±8.6	8.1±6.8	12.5±9.3	9.8±7.1	10.5±8.9	7.4±5.7
	-69.3%*		-68.3%*		-65.4%*		-68.5%
	-34.2%*		-36.6%*		-21.0%		-29.0%
28.2±18.8	82.5±17.7	24.7±15.1	79.3±16.7	20.0±11.8	77.7±16.4	28.2±18.8	83.6±13.2
77.6±16.2	91.6±10.9	75.3±17.3	88.3±12.2	73.6±20.6	84.6±12.0	77.6±16.2	90.5±10.8
	192.7%*		221.6%*		288.5%*		196.8%*
	18.0%		17.3%		15.0%		16.6%
4.0±0.9	1.8±1.0	4.4±0.9	2.3±0.8	4.5±0.8	2.2±0.8	4.2±0.9	1.8±0.7
2.5±0.8	1.6±0.9	2.7±0.8	1.5±1.1	2.7±0.9	1.8±0.9	2.2±1.1	1.6±0.7
15		15		13		33	

amplitude was on average 2.47 ± 0.40 at 3 months and 2.94 ± 0.34 V at the last available visit. Stimulation settings and the choice of stimulating leads were seldom changed after the first 6 months.

When the patients were evaluated without drugs and with stimulation turned on, the UPDRS motor score improved by 51.6%, at the last available visit compared to pre-implant values ($p < 0.001$). In the same condition, the UPDRS ADL score improved by 68.5% ($p < 0.001$), and the Schwab & England scale by 196.8% ($p < 0.001$; Table I).

The following items improved remarkably: rigidity, akinesia/bradykinesia, gait and postural impairment (Table II). Rest tremor disappeared in 20 patients, who were severely tremulous before the implant, and improved significantly in 5. In most patients, turning the stimulation off at the time of clinical assessment caused a rebound of tremor to pre-implant level within the next few minutes. In 3 patients, when stimulation was turned off, rest tremor recurred but was on average 79.3% milder than baseline tremor. Overall, rest tremor was reduced by 86% ($p < 0.001$) compared to pre-implant values.

Motor fluctuations and dyskinesias improved in all

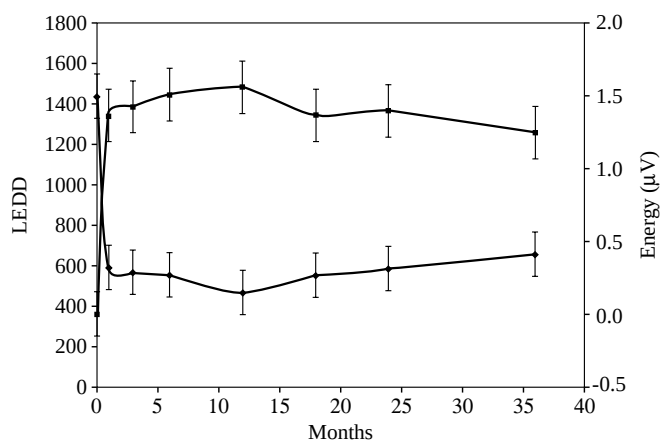


Fig. 1.—Average levodopa equivalent daily dose and average energy delivered at programmed follow-up evaluations.

patients (Table III). Off-state dystonia disappeared in all patients from the 3-month visit and did not recur. Freezing and on-state dyskinesias disappeared in 31 patients, whose clinical condition after surgery was a permanent on motor state. In the remaining 2 patients, freezing and on-state dyskinesias did not disappear,

TABLE II.—*Variation of individual motor signs at the last available visit compared to baseline evaluation. The data are calculated on the total of 33 patients, with the exception of rest tremor (25 patients).*

Signs	Baseline	Last visit	p
<i>Speech</i>			
Off	2.2±0.7	1.7±0.9	
On	1.4±0.7	1.8±1.0	
Variation off		-24.3%	NS
Variation on		28.9%	NS
<i>Rest tremor</i>			
Off	9.7±4.3	1.4±1.8	
On	1.5±2.9	0.3±0.8	
Variation off		-86.0%	<0.001
Variation on		-78.4%	NS
<i>Postural and kinetic tremor</i>			
Off	4.5±2.0	1.8±1.6	
On	1.7±1.8	0.9±1.4	
Variation off		-59.3%	<0.001
Variation on		-45.6%	NS
<i>Rigidity</i>			
Off	11.0±3.7	5.8±3.6	
On	5.4±3.8	3.9±2.9	
Variation off		-47.7%	<0.001
Variation on		-27.4%	NS
<i>Akinesia</i>			
Off	19.5±5.4	12.1±6.5	
On	9.3±6.1	8.9±6.4	
Variation off		-38.1%	<0.001
Variation on		-4.6%	NS
<i>Postural stability</i>			
Off	1.8±1.1	0.9±0.8	
On	1.3±2.0	0.7±0.8	
Variation off		-49.2%	<0.001
Variation on		-44.2%	NS
<i>Gait</i>			
Off	2.3±1.0	0.9±0.9	
On	0.8±1.0	0.6±0.7	
Variation off		-60.0%	<0.011
Variation on		-25.9%	NS
<i>Body bradykinesia</i>			
Off	3.1±0.9	1.3±0.7	
On	1.1±1.1	0.8±0.7	
Variation off		-59.5%	<0.001
Variation on		-25.1%	NS

but were significantly improved providing satisfactory control.

Cognitive assessment showed a postoperative decline of literal verbal fluency only at 3 months, but not at 18 months, with stimulators off. Six months after surgery, with stimulators on, there was a significant improvement on the Mini-Mental State

TABLE III.—*Variation of dyskinesia and fluctuation scores at the last available visit compared to baseline evaluation.*

Signs	Baseline	Last visit	p
<i>Dyskinesia duration</i>			
On	2.0±1.0	0.4±0.6	
Variation on		-80.3%	<0.001
<i>Dyskinesia severity</i>			
On	2.1±1.1	0.3±0.6	
Variation on		-87.0%	<0.001
<i>Early morning dystonia</i>			
On	0.7±0.5	0.0±0.0	
Variation on		-100%	<0.001
<i>Off-period duration</i>			
On	2.1±0.8	0.1±0.3	
Variation on		-94.2%	<0.001

Examination and a trend towards an improved performance on a task of executive function (Modified Wisconsin Card Sorting Test). No other changes were observed.

Night sleep and nocturnal akinesia were reportedly improved in all patients; insomnia was resolved in all but 2. All patients gained weight after surgery. The patients' weight averaged 56.6±15.0 kg before surgery and increased by 11.1% to 73.9±15.9 kg at the time of last available visit (p<0.001). Weight gain was remarked as unexpected by 5 patients and reported as troublesome by 2.

Adverse events are listed in Table IV. Four patients presented a transient increase of sexuality, that lasted for some months and was accompanied in 2 of them by manic psychosis. The most common event, that did not improve when stimulation was turned off and persisted, was a worsening of parkinsonian hypophonia affecting 12 patients. In 5 of them, a progressive hypokinetic dysarthria was also observed. The most common stimulation-dependent side effects were paresthesias and dyskinesias. Adverse events, related to the surgical procedure or the device, are listed in Table IV. The most common adverse event was a transient psychosis (with hallucinations and delusions), which started during the surgical procedure and resolved spontaneously in less than 1 hour. Unexplained switch-off occurred in 3 patients using Itrel II stimulators. Sudden end of battery life also occurred in 3 patients bearing Itrel II stimulators and in 1 bearing Kinetra stimulator. In 2 cases this required the emergency managing of patients residing far from our center.

TABLE IV.—*Adverse events observed in 33 patients.*

Events	Patients
<i>Transient</i>	
Increased sexuality	4
Manic psychosis	2
Seizure	1
<i>Long-lasting (unresponsive to stimulation withdrawal for few hours)</i>	
Hypophonia	12
Hypophonia and dysarthria	5
Eyelid opening apraxia	4
Worsening of depression	3
Psychic akinesia	2
Limb dystonia	1
Bilateral buccinator spasm	1
<i>Stimulation dependent (responsive to stimulation withdrawal for few hours)</i>	
Paresthesias	10
Ballic-choreic dyskinesias	3
Blepharospasm	2
Diplopia	2
Monolateral buccinator spasm	1
<i>Events occurring during surgical procedure</i>	
Transient intraoperative psychosis	7
Lead migration	2
Subarachnoid hemorrhage	1
<i>Device failure</i>	
Unexplained switching-off	3
Sudden end of battery life	4

Discussion and conclusions

The present series extends and completes our previous observations on the efficacy of STN HFS in PD^{7, 16}. Compared to the previous long-term analysis, which included only 22 of the patients described here, it is observed that the improvement of motor signs persists during the 25.7 ± 13.5 months of average evaluation of this larger cohort and in particular in the subgroup of 13 patients with a 36 months FU. The present data are also consistent with other published reports on the efficacy of STN HFS (Table V)^{7, 8, 12-14, 23-31}, only 5 of which deals with such long-term observational time. In a series of 24 patients implanted bilaterally in the STN, a 60% improvement of the UPDRS motor score and a 50% reduction of the LEDD were reported 1 year after the implant¹². No detailed information is provided for the 10 patients who were followed-up for more than a year. Three reports evaluated patients exactly 1 year after STN implant^{8, 12, 28}. They deal in total with 64 patients, who had an average UPDRS motor improvement of 62.2% and an average LEDD reduction of 65.3%. The present observation on patients evaluated for a period of 1 to 3 years after STN implant (with an average follow-up of about 2 years) show comparable results. This means that there is no evidence for decay of efficacy of STN HFS

TABLE V.—*Summary of available data on implants for bilateral STN HFS in PD.*

Patients	Follow-up (mo)	UPDRS-III (%)	LEDD (%)	Dyskinesia duration (%)	Dyskinesia disability (%)	Time spent off daily (%)	Reference
33	25.7±13.5	-51.6	-56.2	-80.3	-87.0	-94.2	Present report
24	12	-60	-50	-55	-64	-72.2	Ref. ¹²
10	6-18	-54	-40	Not available	Not available	Not available	Ref. ¹³
7	16±8	-42	-65	-66.7	-85.7	-83.3	Ref. ⁷
8	6	-74	-47	-52	-68	Not available	Ref. ²³
8	6	-50	-56.7	-78.4*			Ref. ²⁴
41	6	-64	-61	-70.1*			
23	6	-67	-61	-77**		-77***	Ref. ²⁵
10	3-6	-66	Not available	Not available	Not available	Not available	Ref. ²⁶
24	12	-66.5	-80.6	-77.7	-92.6	Not available	Ref. ⁸
10	6	-62	-62	-80**		-90***	Ref. ²⁷
10	6-18	-53.8	Not available	Not available		Not available	Ref. ¹⁴
16	12	-60.2	-65.3	-83.3****		No off periods	Ref. ²⁸
91	6	-51.3	-37.3	-57.9*		Not available	Ref. ²⁹
22	23.1±12.2	-50.2	-67.5	-82.1	-91.3	-97.9	Ref. ¹⁶
17	14	-62.1	-65.5	-91.3*	Not available	Not available	Ref. ³⁰
22	12-24	-63.2	-32	Not available	Not available	Not available	Ref. ³¹

*) Value refers to the total UPDRS-IV score; **) value refers to items 32, 33, 34 and 35 of the UPDRS-IV score; ***) value refers to items 36, 37, 38 and 39 of the UPDRS-IV score; ****) value refers to items 32, 33, 34 and 35 of the UPDRS-IV score.

during the first 3 years after implant. In keeping with this, no significant variations of the energy delivered, of the UPDRS motor score or of the LEDD were observed (Table I).

In the present series, chronic bilateral STN HFS was effective in reducing parkinsonian signs, off state related phenomena and motor fluctuations. Analysis of individual items showed that motor improvement was more pronounced on some signs and symptoms than on others. Tremor, gait, body bradykinesia, postural stability and rigidity improved more than akinesia. This is in keeping with our previous short-term and long-term observation^{7, 16}, and at odds with other series reporting a marked improvement of akinesia^{12, 14, 28, 32}. Drug reduction is particularly pronounced in the present report compared to other published series, thought less than our previous long-term observation¹⁶. This may have influenced the improvement of akinesia, as the clinical effects of long-duration responses of drugs are less evident when patients, who are evaluated in the practically defined off condition (*i.e.*, after overnight withdrawal), receive less dopaminergic medication. In the only one report accounting for a more pronounced LEDD reduction than the present series⁸, the total UPDRS motor score improved by 66.5% 1 year after implant and the LEDD was reduced by 80.6%. However, no information on the akinesia subscore is provided. Computation of the LEDD is an artificial, although useful, tool to summarize the total daily medication given to a patient. The formulas for computing LEDD vary slightly in different reports and flexibility must be used when making comparisons.

The daily time spent off was abolished; off state dystonia disappeared in all patients (Table III). No motor fluctuations were observed from the 3-month visit on. This is in keeping with other published observations on shorter-term follow-up^{7, 8, 23}.

Activities of daily living and quality of life indexes improved more markedly than motor scores, indicating that functional changes in daily life were not completely assessed by neurological evaluation of motor condition. Particularly women showed a striking benefit in coping with domestic chores and social life. Some patients even resumed working after years of unemployment. In all, the regaining of self-care greatly reduced the need for helpers. In general, younger patients improved more than the elder ones. Marked changes were reported in the patients' everyday life, and the Schwab & England scale improved more

markedly than the UPDRS motor score. This indicates that some features, not considered in the motor score (*e.g.* improvement of sleep and raising of the mood or smoothing of motor fluctuations), but affecting daily living activities, had also improved.

HFS was applied continuously for 24 hours a day. Changes of non-motor symptoms are in part the aftermath of around-the-clock motor improvement. The efficacy of the continuous treatment was particularly evident at night, when drugs are usually not very effective, because of their short half-lives. Nocturnal akinesia and rigidity were greatly reduced, thus improving the quality of sleep. This is in keeping with a previous observation showing that insomnia in PD patients may predominantly result from nighttime motor disability²⁶. Complete resolution of early-morning dystonia was reported in all patients of the present series.

The present study also shows that on-state dyskinesias are greatly reduced following STN HFS. This is considered an indirect effect of the efficacy of such procedure brought about by a reduction of antiparkinsonian medication^{8, 33}. An increase of stimulation settings beyond an individual threshold elicited choreic or ballistic dyskinesias in the neck or the contralateral limbs in a stimulation-dependent fashion, but did not mimic the complex phenomenology of drug-related on-state dyskinesias³⁴. Choreic and ballistic dyskinesias elicited in these patients by supra-threshold stimulation corresponded to the dyskinesias elicited by lesions of the subthalamic region in man³⁵ or monkey³⁶.

Neuropsychological tests showed that bilateral STN HFS is a safe procedure, as regards the cognitive and behavioral morbidity, although some individual variability in postoperative cognitive and behavioral outcome invites caution. These observations confirm and expand previous reports that no cognitive effect of HFS is detected up to 1 year after surgery^{24, 37, 38}.

In the present series, stimulation settings were increased over time in order to provide the best possible clinical condition. The most relevant reduction of drugs and increase of stimulation occurred during the 1st month after implant. Minor variations of drug regimen and of stimulation settings were performed throughout the follow-up time. Dopaminergic drugs, particularly levodopa, could not be stopped completely in all patients, although they were reduced to a minimum.

The side effects and adverse events reported in the present series are comparable to those observed in

other studies. In a recent series it has been reported that more adverse events occurred following implant in the STN than in the globus pallidum internum²⁸. The adverse event profile following STN implant is similar to that reported here. A remarkable list of adverse events following implant of HFS leads in different brain regions has been recently reported³⁹. Long-term observation of patients receiving STN implants provides now a better view of the safety profile of this procedure. The impressive benefit retained by the patients is well evaluated when adverse events (such as unexplained switching off or sudden end of battery life) allow for the sudden withdrawal of stimulation. In some cases, these events are true medical emergencies.

The mechanism of action of HFS is not completely understood⁴⁰⁻⁴². First, the effects of HFS may vary from one site to another in the nervous system. Second, it is currently believed that cell bodies located in the stimulated area are functionally impaired by the current delivered, while myelinated fibers may be excited^{42, 43}. A recent *in vitro* study has shown that high-frequency tetanus can induce a strong depression of intrinsic voltage-gated current, which is essential for the expression of the tonic and burst-firing modes of STN neurons, thus provoking the interruption of their spontaneous activities⁴⁴. The functional impairment induced by STN HFS may be considered in part equivalent to the ablation of the stimulated region. Time is required before data on longer-term follow-ups (of at least 10 years) of patients bearing STN stimulators will become available. In the meantime, the efficacy and safety profile of this technique support its use in selected PD patients.

References

- Charcot JM. Leçons sur les maladies du système nerveux. Paris: A. Delahaye; 1872.
- Bucy PC, Case JT. Tremor: physiologic mechanism and abolition by surgical means. Arch Neurol Psychiatr 1939;41:721-46.
- Klemme RM. Surgical treatment of dystonia, paralysis agitans and athetosis. Arch Neurol Psychiatr 1940;44:926.
- Cotzias GC, van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. N Engl J Med 1967;276:374-9.
- Lang AE, Lozano AM, Montgomery E, Duff J, Tasker R, Hutchinson W. Posteroventral medial pallidotomy in advanced Parkinson's disease. N Engl J Med 1997;337:1036-42.
- Mouradian MM, Chase TN. Improved dopaminergic therapy of Parkinson's disease. In: Marsden CD, Fahn S, editors. Movement disorders 3. London: Butterworth-Heinemann; 1994.p.180-99.
- Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A. Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology 1999;53:85-90.
- Fraix V, Pollak P, Van Blercom N, Xie J, Krack P, Koudsie A *et al*. Effect of subthalamic nucleus stimulation on levodopa-induced dyskinesia in Parkinson's disease. Neurology 2000;55:1921-3.
- Albin RL, Young AB, Penney JB. The functional anatomy of disorders of the basal ganglia. Trends Neurosci 1995;18:63-4.
- Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 1990;249:1436-8.
- Sellal F, Hirsch E, Lisovsky F, Mutschler V, Collard M, Marescaux C. Contralateral disappearance of parkinsonian signs after subthalamic hematoma. Neurology 1992;42:255-6.
- Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D *et al*. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998;339:1105-11.
- Kumar R, Lozano AM, Kim YJ, Hutchison WD, Sime E, Hallett E *et al*. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology 1998;51:850-5.
- Kumar R, Lozano AM, Sime E, Hallett E, Lang AE. Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. Neurology 1999;53:561-6.
- Vingerhoets FJ, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J. Subthalamic DBS replaces levodopa in Parkinson's disease: 2-year follow-up. Neurology 2002;58:396-401.
- Romito LM, Scerrati M, Contarino MF, Bentivoglio AR, Tonali P, Albanese A. Long-term follow up of subthalamic nucleus stimulation in Parkinson's disease. Neurology 2002;58:1546-50.
- Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease? A clinicopathologic study. Neurology 1992;42:1142-6.
- Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T *et al*. Core assessment program for intracerebral transplantations (CAPIT). Mov Disord 1992;7:2-13.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington: American Psychiatric Association; 1994.
- Scerrati M, Fiorentino A, Fiorentino M, Pola P. Stereotaxic device for polar approaches in orthogonal systems. Technical note. J Neurosurg 1984;61:1146-7.
- Guiot G, Arfel G, Derome P. La chirurgie stéréotaxique des tremblements de repos et d'attitude. Gaz Méd Fr 1968;75:4029-56.
- Schaltembrand G, Wahren W. Atlas for stereotaxy of the human brain. Stuttgart: Georg Thieme Publishers, 1977;
- Krack P, Pollak P, Limousin P, Benazzouz A, Deuschl G, Benabid AL. From off-period dystonia to peak-dose chorea. The clinical spectrum of varying subthalamic nucleus activity. Brain 1999;122:1133-46.
- Ardouin C, Pilon B, Peiffer E, Bejjani P, Limousin P, Damier P *et al*. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol 1999;46:217-23.
- Houeto JL, Damier P, Bejjani PB, Stedler C, Bonnet AM, Arnulf I *et al*. Subthalamic stimulation in Parkinson disease: a multidisciplinary approach. Arch Neurol 2000;57:461-5.
- Arnulf I, Bejjani BP, Garna L, Bonnet AM, Houeto JL, Damier P *et al*. Improvement of sleep architecture in PD with subthalamic nucleus stimulation. Neurology 2000;55:1732-4.
- Bejjani BP, Gervais D, Arnulf I, Papadopoulos S, Demeret S, Bonnet AM *et al*. Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation. J Neurol Neurosurg Psychiatry 2000;68:595-600.
- Volkman J, Allert N, Voges J, Weiss PH, Freund HJ, Sturm V. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 2001;56:548-51.
- [No authors listed]. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001;345:956-63.
- Thobois S, Mertens P, Guenet M, Hermier M, Mollien H, Bouvard M *et al*. Subthalamic nucleus stimulation in Parkinson's disease: clinical evaluation of 18 patients. J Neurol 2002;249:529-34.

31. Figueiras-Mendez R, Regidor I, Riva-Meana C, Magarinos-Ascone CM. Further supporting evidence of beneficial subthalamic stimulation in Parkinson's patients. *Neurology* 2002;58:469-70.
32. Krack P, Benazzouz A, Pollak P, Limousin P, Piallat B, Hoffmann D *et al*. Treatment of tremor in Parkinson's disease by subthalamic nucleus stimulation. *Mov Disord* 1998;13:907-14.
33. Krack P, Limousin P, Benabid AL, Pollak P. Chronic stimulation of subthalamic nucleus improves levodopa-induced dyskinesias in Parkinson's disease. *Lancet* 1997;350:1676.
34. Quinn NP. Classification of fluctuations in patients with Parkinson's disease. *Neurology* 1998;51 Suppl 2:S25-9.
35. Martin JP. Hemichorea resulting from a focal lesion of the brain (syndrome of the body of Luys). *Brain* 1927;50:637-51.
36. Benazzouz A, Gross C, Féger J, Boraud T, Bioulac B. Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. *Eur J Neurosci* 1993;5:382-9.
37. Jahanshahi M, Ardouin CM, Brown RG, Rothwell JC, Obeso J, Albanese A *et al*. The impact of deep brain stimulation on executive function in Parkinson's disease. *Brain* 2000;123:1142-54.
38. Pillon B, Ardouin C, Damier P, Krack P, Houeto JL, Klinger H *et al*. Neuropsychological changes between "off" and "on" STN or GPi stimulation in Parkinson's disease. *Neurology* 2000;55:411-8.
39. Lyons KE, Koller WC, Wilkinson SB, Pahwa R. Surgical and device-related events with deep brain stimulation [abstract]. *Neurology* 2001; 56 Suppl 3:A147.
40. Benazzouz A, Hallett M. Mechanism of action of deep brain stimulation. *Neurology* 2000;55 Suppl 6:S13-6.
41. Hallett M, Litvan I. Evaluation of surgery for Parkinson's disease: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The Task Force on Surgery for Parkinson's Disease. *Neurology* 1999;53:1910-21.
42. Nowak LG, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements. *Exp Brain Res* 1998;118:477-88.
43. Ashby P, Kim YJ, Kumar R, Lang AE, Lozano AM. Neurophysiological effects of stimulation through electrodes in the human subthalamic nucleus. *Brain* 1999;122:1919-31.
44. Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. *J Neurophysiol* 2001;85:1351-6.