Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease

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Article abstract—*Objective:* To reduce antiparkinsonian medication in parkinsonian patients with bilateral high frequency subthalamic nucleus (STN) stimulation. *Background:* Parkinsonian syndromes are characterized by hyperactivity of the STN. Preliminary data indicate that functional inactivation of the STN may reduce the requirement for dopaminergic therapy in PD. *Methods:* Bilateral quadripolar leads were implanted stereotactically in the STN of seven patients with advanced PD (mean age, 57.4 years; mean disease duration, 15.4 years). High-frequency stimulation was applied for 24 hours a day. Following implantation, antiparkinsonian medication was reduced to the minimum possible and stimulation was gradually increased. The patients were evaluated in the practically defined "off" and "on" conditions using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Schwab & England scale. The average follow-up was 16.3 ± 7.6 months. A battery of neuropsychological tests was applied before and 9 months after the implant. *Results:* Parkinsonian features improved in all patients—the greatest change seen in rigidity, then tremor, followed by bradykinesia. Compared with the presurgical condition, off-drug UPDRS motor scores improved by 41.9% on the last visit ($p = 0.0002$), UPDRS activities of daily living (ADL) scores improved by 52.2% ($p = 0.0002$), and the Schwab & England scale score improved by 213% ($p = 0.0002$). The levodopa-equivalent daily dose was reduced by 65%. Night sleep improved in all patients due to increased mobility at night, and in five patients insomnia was resolved. All patients gained weight after surgery and their appetite increased. The mean weight gain at the last follow-up was 13% compared with before surgery. During the last visit, the stimulation amplitude was 2.9 ± 0.5 V and the total energy delivered per patient averaged 2.7 ± 1.4 $W \times 10^{-6}$. The results of patient self-assessment scales indicated a marked improvement in five patients and a moderate improvement in the other two. The neuropsychological data showed no changes. Side effects were mild and tolerable. In all cases, a tradeoff between the optimal voltage and the severity of side effects made it possible to control parkinsonian signs effectively. The most marked side effects directly related to STN stimulation consisted of ballistic or choreic dyskinesias of the neck and the limbs elicited by contralateral STN stimulation above a given threshold voltage, which varied depending on the individual. *Conclusions:* Parkinsonian signs can be controlled by bilateral high-frequency STN stimulation. The procedure is well tolerated. On-state dyskinesias were greatly reduced, probably due to the reduction of total antiparkinsonian medication. Bilateral high-frequency STN stimulation compensated for drug reduction and elicited dyskinesias, which differ from those observed following dopaminergic medication. ADL improved significantly, suggesting that some motor tasks performed during everyday chores, and that are not taken into account in the UPDRS motor score, also improved.

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PD is a progressive disorder affecting the motor system. Pharmacologic treatments have been attempted since the last century.[1] Surgical procedures first proved efficacious in the 1950s,[2] but their use was short-lived due to the introduction of levodopa.[3] Current drug treatment, based on the use of multiple agents, is very helpful, but has limitations. Most patients treated chronically with levodopa or other antiparkinsonian drugs present with motor fluctuations or psychiatric side effects. Two main approaches are used to reduce motor fluctuations, one being the use of surgical procedures (e.g., pallidotomy)[4] or antidyskinetic drugs to attenuate on-state dyskinesias directly, and the other is the continuous, rather than the pulse, administration of dopaminergic drugs.[5] It has been shown that the subthalamic nucleus (STN) is hyperactive in parkinsonian states[6] and that a direct lesion or functional inactivation of the STN relieves parkinsonian features in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–poisoned monkeys.[7] In humans, STN lesions also relieve parkinsonian symptoms,[8] suggesting that STN inactivation may provide a basis for the treatment of off-related signs of PD. It is well established that anatomic lesions of the STN expose the patient to the risk of hemiballism,[9] therefore stereotactic neurostimulation may provide a suitable tool for functionally inactivating the STN in parkinsonian patients without producing a permanent lesion.

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We implanted a chronic, high-frequency stimulator bilaterally in the STN of parkinsonian patients and tried to reduce their medication to the minimum.

Methods. *Clinical features.* Seven parkinsonian patients (six women and one man) were selected on the basis of the following criteria: 1) diagnosis of PD according to the UK Parkinson's Disease Brain Bank criteria,[10] 2) 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, 3) unsatisfactory management of fluctuations with medication, and 4) Hoehn & Yahr stage ≥ III in the practically defined "off" condition.[11] Patients with the following features were excluded: those with a heart pacemaker; mild parkinsonian features or unstable drug regimen; severe cognitive impairment or dementia, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition[12]; ongoing psychiatric problems (e.g., persistent hallucinations, psychosis, and sustained depression); prior brain surgery; an unsatisfactory general condition; or an inability to comply with the study protocol. Each patient underwent brain MRI and was assessed using a standard protocol. Antiparkinsonian medication was unchanged for at least 1 month before implantation. The drugs being taken by the patients at the time of implantation were levodopa (n = 7), pergolide (n = 7), bromocriptine (n = 1), apomorphine (n = 2, subcutaneous infusion), and amantadine (n = 1). The study was approved by the ethical committee of Gemelli Hospital, and the patients gave their written informed consent.

Evaluations were performed twice in the morning in the practically defined "off" condition and twice in the best "on" condition under the patient's current drug regimen. The baseline "off" and the best "on" scores were obtained by averaging the two evaluations. 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 one. The following conversion factors were used: levodopa controlled release preparations, 0.77; bromocriptine, 10; apomorphine, 50; and pergolide, 100. The total LEDD was then calculated.

Surgery. With the exception of one implant performed in two sessions, all patients received a bilateral simultaneous STN implant. Stereotactic surgery was performed in the practically defined "off" condition. With the patient under local anesthesia, a stereotactic frame modified for a polar approach[13] was applied. A precoronal burr hole was drilled, followed by ventriculography, which made it possible to delimit the midline of the third ventricle, the anterior commissure (AC), and the posterior commissure (PC). The target was found using coordinates according to a proportional geometric scheme based on the AC/PC line.[14] 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 the atlas of Schaltembrand and Wahren[15]). The track for the stimulation lead was prepared by inserting a probe (1.1-mm outer diameter) 10 mm from the target. A 3389 quadripolar lead (Medtronic Inc., Minneapolis, MN) was then implanted in the stereotactic target.

To identify the functional target, perioperative stimulation (pulses of 60 μsec at a frequency of 185 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 parkinsonian signs were reversed by a current of less than 3 V on the side contralateral to the implanted hemisphere. Changes in rigidity were 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 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 stress activation, both at rest and while maintaining a posture. All patients were assessed in a double-blind fashion while awake by two neurologists.

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 implantation. A 130-Hz (60-μsec) current was applied to the lead contact identified previously during perioperative stimulation. The voltage was increased gradually and other lead contacts stimulated when necessary. The frequency or pulse width was adjusted to keep the voltage as low as possible. The clinical features evaluated to set the stimulation settings were tremor (when present), rigidity, bradykinesia, and gait. MRI was always performed before implanting a Medtronic 7424 pulse generator in the subclavicular region approximately 1 week after stereotactic placement.

Clinical evaluation. STN stimulation was continuous for 24 hours a day. The patients were scheduled for evaluation 1, 3, 6, and 12 months after the implant, and once a year thereafter. Each assessment was performed in the morning, 12 hours after withdrawal of antiparkinsonian medication and after having turned off the internal pulse generator (IPG). Four consecutive Unified Parkinson's Disease Rating Scale (UPDRS) evaluations were performed: 1) off drugs and without stimulation; 2) off drugs, 30 minutes after turning on the stimulation; 3) on drugs (according to the daily schedule) at least 60 minutes after turning off the stimulation; 4) on drugs, 30 minutes after having resumed 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, activities of daily living (ADL) were evaluated by means of the UPDRS ADL score, and quality of life was evaluated using the Schwab & England scale under conditions 2 and 4. A global patient self-assessment scale (considering gross degrees of improvement or worsening on a scale of 0 to 100%) was also administered to each patient. After clinical assessment, medication was reduced and the stimulation settings readjusted, according to the criteria outlined earlier. Brain CT was performed 6 months after implantation.

The following neuropsychological tests were performed before and 9 months after implantation: Mini-Mental State Examination (MMSE), tests of verbal memory (Rey's Audi-

Table 1 *Motor and ADL scores before surgery and at regular follow-up visits for patients with stimulation*

Variable	Baseline	1 Month	3 Months	6 Months	12 Months	Last visit
UPDRS ADL score						
Off drug, mean score ± SD	36.1 ± 5.3	19.4 ± 9.1	18.6 ± 8.9	18.2 ± 8.5	18.8 ± 8.6	17.3 ± 7.9
On drug, mean score ± SD	15.3 ± 8.7	13.4 ± 7.6	14.3 ± 10.6	13.5 ± 9	15.8 ± 8.6	14.3 ± 7.7
Percent change off drug	—	−46.2	−48.6	−49.7	−48	−52.2
Percent change on drug	—	−12.1	−6.5	−11.7	3.4	−6.5
UPDRS motor score						
Off drug, mean score ± SD	67.6 ± 9.9	45.3 ± 15.6	44.6 ± 13	43.5 ± 11.5	39.8 ± 10.9	39.3 ± 12.0
On drug, mean score ± SD	29.3 ± 9.4	32.9 ± 15	34.7 ± 14.1	31.7 ± 12.2	32.4 ± 11.5	30.7 ± 13.1
Maximal on/off fluctuation,* %	56.7	27.4	22.2	27.1	18.6	21.9
Percent change off drug†	—	−33.0	−34.0	−35.6	−41.1	−41.9
Percent change on drug†	—	12.2	18.5	8.1	10.6	4.9
Schwab & England Scale‡						
Off drug, mean score ± SD	21.4 ± 12.1	54.3 ± 23	67.1 ± 18.0	68.3 ± 20.4	62.0 ± 21.7	67.1 ± 19.8
On drug, mean score ± SD	70.0 ± 14.1	77.1 ± 18.0	78.6 ± 14.6	80.0 ± 15.5	78.0 ± 16.4	80.0 ± 14.1
Percent change off drug†	—	153.3	213.3	218.9	189.3	213.3
Percent change on drug†	—	10.2	12.2	14.3	11.4	14.3
LEDD, mean ± SD	1507.3 ± 821.5	600.4 ± 137.4	558.7 ± 124.9	526.7 ± 106.8	535.8 ± 87.9	521.3 ± 90.4
Percent change LEDD†	—	−60.2	−62.9	−65.1	−64.5	−65.4
Energy delivered per patient ($W \times 10^{-6}$ ± SD)	—	2.0 ± 1.0	1.9 ± 0.9	2.3 ± 0.6	2.9 ± 1.5	2.7 ± 1.4
Patients, n	7	7	7	6	5	7

* Percent variation in the UPDRS motor score in best "on" compared with worst "off."
† Compared with baseline.
‡ In contrast to the UPDRS, an increase in the score indicates an improvement.

UPDRS = Unified Parkinson's Disease Rating Scale; ADL = activities of daily living; LEDD = levodopa-equivalent daily dose.

tory Verbal Learning Test), and verbal fluency and intelligence (Raven's progressive matrices '47).

The energy delivered by the stimulating electrodes (expressed in watts) was calculated considering the total surface area under the stimulation pulses multiplied by the number of pulses per second, using the formula

$$E = (\text{amplitude} \times \text{pulse width} \times \text{frequency rate})^2/\text{impedance}$$

For each patient, the total energy delivered by the two IPGs was calculated.

Statistical analysis was carried out using Student's *t*-test for independent variables or Wilcoxon's rank sum test for the neuropsychological evaluations.

Results. At the time of implantation, the patients were age 57.4 ± 5.5 years (mean ± SD) and had a mean disease duration of 15.4 ± 7.6 years. The average follow-up until July 1998 was 16.3 ± 7.6 months.

During perioperative stimulation, different degrees of improvement were observed in all patients during high-frequency stimulation. Clinical amelioration occurred—the greatest change being seen in rigidity, then tremor, followed by bradykinesia. Rigidity generally improved a few minutes after starting continuous stimulation, whereas the time required for suppression of tremor varied from 0.5 to 4 minutes. Bradykinesia was difficult to estimate clinically due to the large variability in patient cooperation. When observed, improvement in bradykinesia occurred after approximately 1 minute of continuous stimulation. The highest amplitude setting for perioperative stimulation was 10 V (frequency, 185 Hz; pulse width, 60 μs) in bipolar combinations. The average number of tracks performed before a functional target was identified was 1.68 (range, 1 to 5).

In three patients, unilateral transient STN inactivation associated with a marked contralateral clinical improvement occurred immediately after electrode placement. This was interpreted as the aftermath of local edema, which did not allow clinical efficacy to be evaluated during perioperative testing. Elicitation of side effects helped to identify the structures stimulated, and was particularly helpful in these cases. Side effects were observed when perioperative stimulation was increased gradually and consisted of facial hemispasm, paresthesias, tachycardia, and abnormal eye movements. In two patients, transient STN inactivation occurred following surgery, lasting for a few days in one patient and 2 weeks in the other.

Changes in scores for ADL and motor performances were compared, at each visit, with the LEDD and the energy delivered by the two IPGs. The LEDD was reduced progressively by an average of 65.1% within the first 6 months and then remained essentially stable, whereas the stimulation energy was gradually increased (table 1).

At the time of programmed evaluations, when in the defined "off" condition, all the patients turned "on" within 30 minutes of continuous stimulation and turned "off" when stimulation was stopped. The first change was the

Table 2 *Parkinsonian features measured in the off-drug condition, with or without stimulation*

Item	Before surgery*	Last visit*	Percent change	*p* Value
Speech	3.0 ± 0.8	2.0 ± 0.8	−33.3	0.040
Tremor				
At rest	8.6 ± 5.9	0.6 ± 1.1	−93.3	0.0040
Postural	4.3 ± 2.1	1.3 ± 1.1	−70.0	0.0064
Total	12.9 ± 3.0	1.9 ± 0.5	−85.6	0.0039
Rigidity	12.6 ± 3.5	4.7 ± 3.1	−62.5	0.00075
Akinesia/bradykinesia				
Finger tapping	5.9 ± 1.7	5.4 ± 2.0	−7.3	0.55
Hand grip	5.6 ± 1.7	4.7 ± 1.4	−15.4	0.32
Hand pronate/supinate	5.7 ± 2.2	4.7 ± 1.4	−17.5	0.33
Leg agility	6.4 ± 1.3	5.7 ± 1.7	−11.1	0.39
Total	23.6 ± 17.7	20.6 ± 15.1	−12.7	0.34
Gait	3.0 ± 1.2	1.7 ± 0.8	−42.9	0.030
Postural stability	2.4 ± 1.1	1.6 ± 1.4	−35.3	0.23

*Values are mean ± SD.

disappearance and reappearance of tremor, followed by changes in rigidity and akinesia/bradykinesia. Tremor reappeared less than 1 minute after turning off stimulation: In three patients, the tremor amplitude was less than the off-state tremor before surgery, whereas in two patients the magnitude was comparable with tremor before surgery. A rebound increase in tremor, compared with the presurgical state, was seen in one patient. Reappearance of rigidity and bradykinesia occurred between 5 and 10 minutes after discontinuation of stimulation. In order of decreasing effect, tremor, rigidity, gait, postural stability, speech, and akinesia/bradykinesia improved when the off-drugs presurgical evaluation was compared with that for the last visit (table 2). With the exception of postural stability and akinesia/bradykinesia, these changes were significant. Stimulation stopped tremor completely in four severely tremulous patients and produced a marked improvement in two.

Motor fluctuations improved in all patients. Table 1 shows that the maximal average differential on/off fluctuation (defined as the percent variation of the UPDRS motor score in best "on" compared with worst "off") was reduced from 56.7% before surgery to 18.6% 1 year after implantation. Freezing and on-state dyskinesias disappeared in four of seven operated patients. Their clinical condition after surgery was a permanent "on" motor state. In the remaining three patients, freezing and on-state dyskinesias were significantly improved, providing satisfactory control.

The off-drug UPDRS motor score without stimulation did not change relative to the presurgical condition: baseline value, 67.6 ± 9.9; score on the last visit, 66.7 ± 13.7. The off-drug UPDRS motor score with stimulation improved by 41.9% at the time of the last visit ($p = 0.0002$), the UPDRS ADL score improved by 52.2% ($p = 0.0002$), and the Schwab & England Scale score improved by 213.3% ($p = 0.0002$). The total LEDD was reduced by 65.4% compared with presurgical doses (see table 1). Night sleep improved in all patients due to increased mobility at night. In five patients, insomnia was resolved. All patients gained weight after surgery and their appetite increased. Body weight, which averaged 56.1 ± 5.8 kg before surgery, increased by an average of 12.8% to 64 ± 6 kg at the time of the last visit. This weight gain was undesirable in three patients and especially troublesome for one.

At the time of the last visit, the mean average stimulation amplitude was 2.9 ± 0.5 V and the total energy delivered per patient averaged 2.7 ± 1.4 W × 10^{-6} (see table 1) Patient self-assessment scales indicated a marked improvement in five patients and a moderate improvement in two at the time of the last visit, compared with the presurgical state.

Neuropsychological data showed nonsignificant improvements in the MMSE score (mean, +24.4%) and Raven's matrices (mean, +16.1%; $p = 0.068$ in both cases). A trend toward an improved performance ($p = 0.109$) was seen for Rey's delayed recall (mean, +34.6%; $p = 0.091$), whereas a trend toward a worse performance was observed for verbal fluency (mean, −17.3%; $p = 0.109$).

Side effects were mild and tolerable. They consisted of slight transient paresthesias when switching on the IPG in four patients, unilateral anisocoria in one patient (which resolved spontaneously 3 months after implantation), and hemiballism following an increase of the stimulation amplitude in two patients (described later). In all patients a tradeoff between the optimum voltage increase and severity of side effects proved effective in controlling parkinsonian signs. Speech impairment occurred in one patient, who presented marked hypophonia during stimulation (either unilateral or bilateral) that resolved completely after about 1 year. One patient manifested depression and abulia, with loss of interest and motivation, during the month following implantation, which resolved completely.

A marked side effect related directly to STN stimulation consisted of ballistic or choreic dyskinesias of the neck or limbs, elicited by contralateral STN stimulation above a given threshold voltage, which varied with the individual. This was observed in two patients, in whom it was clearly dependent on voltage and lead contact. In one patient, satisfactory control was obtained by a careful choice of the contacts for stimulation, whereas in the other patient it was necessary to decrease the voltage at the expense of ideal symptom control.

Discussion. In a group of seven PD patients, chronic, bilateral high-frequency stimulation of the STN was effective in reducing parkinsonian signs and off-drug-related phenomena. The analysis of individual signs showed that tremor and rigidity improved more than akinesia or bradykinesia. ADL and quality of life indexes also improved, indicating a remarkable functional change in daily life. Women, who represented most of the patients in the current series, reported a striking improvement in coping with domestic chores and social life. Five housewives regained the ability to cook, wash, iron, and take care of the family. In all patients the improvement in self-care reduced the need for helpers.

The data available for high-frequency STN stimulation are limited. A study with a short follow-up of 6 months after implantation reported a 57.9% improvement in the UPDRS motor score, and the total

Table 3 *Baseline and last-visit dyskinesia and off-state condition*

Variable	Before surgery	Last visit	Percent change	*p* Value
Dyskinesia duration, UPDRS item 32 score ± SD	1.7 ± 1.0	0.6 ± 0.5	−66.7	0.017
Dyskinesia disability, UPDRS item 33 score ± SD	3.0 ± 0.8	0.4 ± 0.8	−85.7	0.0006
Off-time duration, UPDRS item 39 score ± SD	2.6 ± 1.0	0.4 ± 0.5	−83.3	0.0003

UPDRS = Unified Parkinson's Disease Rating Scale.

LEDD was reduced by 40%.[16] A study with a longer follow-up reported a 50% reduction in total LEDD, a 60% improvement in off-state motor scores, and a significant improvement in ADL.[17] Compared with the previous observations, the improvement in motor and ADL scores seen in the current study is less, but is associated with a greater reduction of medication. The most relevant difference between this study and the two just mentioned is in akinesia, which improved by 55.9% after 1 year in the study of Limousin et al.[17] compared with only 12.7% in the current series. Improvement of rigidity, tremor, and gait, as seen in the current series, is in keeping with these and other reports.[18,19] There are four possible explanations for the discrepancy in the improvement in akinesia: namely, 1) differences in lead placement, 2) differences in the total reduction of medication (greater in the current series), 3) differences in medication given after overnight withdrawal (for the evaluations on drugs with stimulation), and 4) differences in short-duration responses, related to stimulation or to drug challenge, when the evaluation with stimulation preceded that without stimulation due to randomization.[16,17] Future studies will attempt to measure the duration of the washout period for the effects of high-frequency STN stimulation and the duration of short- and long-term responses related to this procedure.

The current study showed that on-state dyskinesias were greatly reduced following STN high-frequency stimulation (table 3). This was considered to be an indirect effect of the procedure, brought about by a reduction in antiparkinsonian medication.[20] 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 dyskinesias.[21] The choreic and ballistic dyskinesias elicited in these patients by suprathreshold stimulation corresponded to the dyskinesias elicited by lesions of the subthalamic region in humans[22] or monkeys.[9]

The mechanism of action of high-frequency stimulation is not completely understood. Clinical experimentation started before basic research could provide an answer to the fundamental issues related to this procedure. It is currently believed that cell bodies located in the stimulated area are functionally impaired by the current delivered, whereas myelinated fibers may be excited.[23] This functional impairment could be considered equivalent in part to an ablation of the stimulated region. The current observation indicates that high-frequency stimulation of the STN acts synergistically with dopaminergic drugs to correct parkinsonian signs, but does not produce on-state dyskinesias comparable with those seen following administration of levodopa or dopamine agonists. This discrepancy raises some interesting pathophysiologic questions related to the model of basal ganglial functioning.[24]

In the current series, the stimulation settings were increased over time to provide the best available clinical condition. Changes in the stimulation settings and the drug regimen were performed gradually over the first 6 months (see table 1). Dopaminergic drugs were usually not stopped completely, but were reduced to a minimum, at the request of the patients, who typically demanded at least a minimal dose of medication (particularly of levodopa) to retain a subjective sense of well-being. Little is known about the behavioral implications of dopamine withdrawal, and this request was interpreted as meaning that drug reduction depressed the patient's mood or did not provide the expected periodic mood increase to which some patients were accustomed. The total energy delivered by stimulation was increased over time (see table 1). This may reflect a loss of efficacy of stimulation or a progressive increase in tolerability for higher stimulation settings at the expense of medication. Based on the current study, in which clinical evaluations were aimed at reducing the total drug charge to the minimum, these two alternatives remain open questions. A partial answer may come from data on the long-term effects of high-frequency stimulation of brain sites other than the STN.[25]

High-frequency stimulation was applied continuously for 24 hours a day. The efficacy of this continuous treatment was particularly evident at night, when drugs are usually not very effective because of their short half-lives. Stimulation at night was probably responsible not only for the improved nocturnal mobility and sleep, but also for the disappearance of early-morning dystonia. Off-state dystonia also disappeared in all patients, indicating that in all patients, STN stimulation guaranteed a minimum threshold of motor condition. Marked changes were seen in the patients' everyday life, and Schwab & England Scale scores also improved markedly. This may indicate that some features, not considered in the motor score (e.g., improvement of sleep and rais-

ing of the mood or smoothing of motor fluctuations), but ADL, had also improved.

STN stimulation did not appear to cause any significant changes in cognition, as measured by the current battery of tests, suggesting that patients with good cognitive performance should be selected for this procedure.

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References

1. Charcot JM. Leçons sur les maladies du système nerveux. Paris: A. Delahaye, 1872.
2. Guiot G. Le traitement des syndromes parkinsoniens par la destruction du pallidum interne. Neurochirurgia 1958;1:94–98.
3. Cotzias GC, van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. N Engl J Med 1967; 276:374–379.
4. 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;337:1036–1042.
5. Mouradian MM, Chase TN. Improved dopaminergic therapy of Parkinson's disease. In: Marsden CD, Fahn S, eds. Movement disorders 3. London: Butterworth-Heinemann, 1994: 180–199.
6. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366–375.
7. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 1990;249:1436–1438.
8. Sellal F, Hirsch E, Lisovoski F, Mutschler V, Collard M, Marescaux C. Contralateral disappearance of parkinsonian signs after subthalamic hematoma. Neurology 1992;42:255–256.
9. Carpenter MB, Whittier JR, Mettler FA. Analysis of choreoid hyperkinesia in the rhesus monkey. Surgical and pharmacological analysis of hyperkinesia resulting from lesions in the subthalamic nucleus of Luys. J Comp Neurol 1950;92: 293–331.
10. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
11. Langston JW, Widner H, Goetz CG, et al. Core Assessment Program for Intracerebral Transplantations (CAPIT). Mov Disord 1992;7:2–13.
12. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.
13. Scerrati M, Fiorentino A, Fiorentino M, Pola P. Stereotaxic device for polar approaches in orthogonal systems. Technical note. J Neurosurg 1984;61:1146–1147.
14. Guiot G, Arfel G, Derome P. La chirurgie stéréotaxique des tremblements de repos et d'attitude. Gazette Médicale de France 1968;75:4029–4056.
15. Schaltembrand G, Wahren W. Atlas for stereotaxy of the human brain. Stuttgard: Georg Thieme Publishers, 1977.
16. Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology 1998;51:850–855.
17. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998;339:1105–1111.
18. Krack P, Pollak P, Limousin P, Benazzouz A, Benabid AL. Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease. Lancet 1997;350:1675.
19. Moro E, Scerrati M, Roselli R, Tonali P, Albanese A. Deep brain stimulation for parkinsonian tremor. Neurology 1999 (in press).
20. 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.
21. Quinn NP. Classification of fluctuations in patients with Parkinson's disease. Neurology 1998;51:S25–S29.
22. Martin JP. Hemichorea resulting from a focal lesion of the brain (syndrome of the body of Luys). Brain 1927;50:637–651.
23. Nowak LG, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. II. Evidence from selective inactivation of cell bodies and axon initial segments. Exp Brain Res 1998;118:489–500.
24. Albanese A. The current model of basal ganglia organization: a clinician's view. Mov Disord 1998;13:980–981.
25. Benabid AL, Pollak P, Gao D, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 1996;84: 203–214.