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Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease

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Summary

The aim of this study was to compare, retrospectively, the value of chronic bilateral stimulation of the internal globus pallidus (GPi) and the subthalamic nucleus (STN) in patients with young onset Parkinson's disease. We selected 13 consecutive patients with similar characteristics at the time of surgery: age at onset <40 years, disabling motor fluctuations (Hoehn and Yahr stage 4 or 5 in off-drug phases) and levodopa-induced dyskinesias (LID). Eight patients were operated on in the STN and five in the GPi. The Unified Parkinson's Disease Rating Scale (UPDRS), timed motor tests and a LID scale were compared in on- and off-drug conditions before surgery and 6 months after surgery on stimulation using the chronic electrical parameters found to improve best the motor state of the individual patient, without adverse effects. In off-drug phases, the motor score of the UPDRS was improved by 71% with STN stimulation and by 39% with GPi stimulation on average. This difference was statistically significant ($P < 0.05$*). Whereas rigidity and tremor showed good improvement in both groups, the decrease in the akinesia score was more pronounced in the STN group. In the STN group, the improvement of all motor symptoms was very close, or equal, to the best levodopa response. Thus the levodopa test was predictive of outcome. The improvement in off-drug period motor handicap allowed a decrease in the levodopa-equivalent dose only in the STN group (–56%). The voltage, frequency and pulse width used for chronic stimulation were lower in the STN group. In the on-drug phases there was a marked improvement in LID in the GPi group, as measured by the dyskinesias score during an acute levodopa test, whereas there was only a small decrease in the STN group (*$P < 0.05$*). However, in the long term, the reduction of levodopa dosage in the STN group led to an indirect reduction of LID similar to that in the GPi group during activities of everyday life. In conclusion, the overall results favour the neurosurgical treatment of Parkinson's disease by stimulating the STN rather than the GPi.*

Keywords: Parkinson's disease; stereotaxy; subthalamic nucleus; globus pallidus internus; stimulation

Abbreviations: GPi = internal globus pallidus; LID = levodopa-induced dyskinesia; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Pallidotomy for Parkinson's disease, a common therapy in the 1960s before the introduction of levodopa (Svennilson *et al*., 1960), has regained interest in recent years (Laitinen *et al*., 1992). Recent publications have confirmed that pallidotomy improves tremor, rigidity, akinesia, gait and levodopa-induced dyskinesias (LID) (Lozano *et al*., 1995; Baron *et al*., 1996). High frequency stimulation is an alternative to ablative surgery as it leads to less permanent morbidity, at least in bilaterally operated patients (Benabid *et al*., 1991). Pallidal stimulation has been shown to reproduce the effects of pallidal lesioning in small series of patients (Siegfried and Lippitz, 1994; Krack *et al*., 1997*a*; Pahwa *et al*., 1997). Because of the potential side effects of brain surgery, stereotaxic therapy is generally restricted to patients with long-term motor complications of levodopa therapy, i.e. on–off fluctuations, off-drug dystonia and LID. The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model has led to new insights into the pathophysiology of Parkinson's disease (DeLong *et al*., 1985), and it has been shown that the subthalamic nucleus (STN) plays a major role. Lesions of the STN in MPTP monkeys induced a dramatic improvement in the parkinsonian triad (Bergman *et al*., 1990). This could be replicated by the stimulation technique in monkeys (Benazzouz *et al*., 1993) and in patients with Parkinson's disease (Pollak *et al*., 1993; Limousin *et al*., 1995). As two different targets are now available, we analysed

Table 1 *Patient characteristics in the STN and GPi stimulation groups*

	STN group	GPi group
Sex (male, female)	5 M, 3 F	4 M, 1 F
Age at surgery (years)	51 ± 10	51 ± 4
Disease duration (years)	16 ± 5	16 ± 4
Hoehn and Yahr score in 'off' condition	4–5	4–5
Hoehn and Yahr score in 'on' condition	2–3	2–3
UPDRS III in 'off' condition	57.5 ± 14.5	53.6 ± 10.4
UPDRS III in 'on' condition	18.2 ± 10.6	23.2 ± 4.0
Dyskinesia (summed scores/24)	11.4 ± 6.6	15.5 ± 4.2
Levodopa equivalent (mg/day)	1560 ± 930	870 ± 370

the effects of stimulating STN or internal globus pallidus (GPi) on the different symptoms in on- and off-drug period motor states. The dopaminergic inhibition of the neuronal activity of both the STN and GPi is reflected by overactivity in MPTP monkeys (a model of pure dopaminergic nigrostriatal lesion), so young onset parkinsonian patients seem to be the best candidates for surgery, because all of their symptoms are highly levodopa-responsive (Quinn *et al*., 1987).

Patients and methods

Thirteen consecutive patients with onset of Parkinson's disease before the age of 40 years were bilaterally operated for placement of stimulating electrodes, eight in the STN and five in the GPi. The study received the approval of the Grenoble University Hospital ethical committee and all patients gave their informed consent. Table 1 shows the general characteristics of the patients in the two groups, which were virtually identical except for non-significant differences in LID and levodopa-equivalent dosages, LID being slightly more severe, and levodopa dosage being lower, in the GPi group. The levodopa-equivalent dose was calculated on the basis of the following correspondences, adapted from Lozano *et al*. (1995): 1 mg pergolide = 1 mg lisuride = 10 mg bromocriptine = 10 mg apomorphine = 100 mg levodopa with a dopa-decarboxylase inhibitor. We tried to keep the antiparkinsonian drug dosage constant, but changes were allowed depending on the long-term motor effects induced by the stimulation. The postoperative evaluation was carried out 6 months after surgery.

The same neurosurgical procedure and neurological evaluation were used for both groups (Limousin *et al*., 1995; Pollak, 1997). The electrodes were implanted in a single operative session according to preoperative MRI as well as intraoperative microrecordings and stimulations. A brain MRI was performed a few days after electrode implantation to check the location of the electrodes and possible surgical complications. The implanted quadripolar electrodes were positioned as close as possible to the locations of lowest threshold for motor benefit and highest for adverse effects, with continuous monopolar (cathodal) stimulation; the case

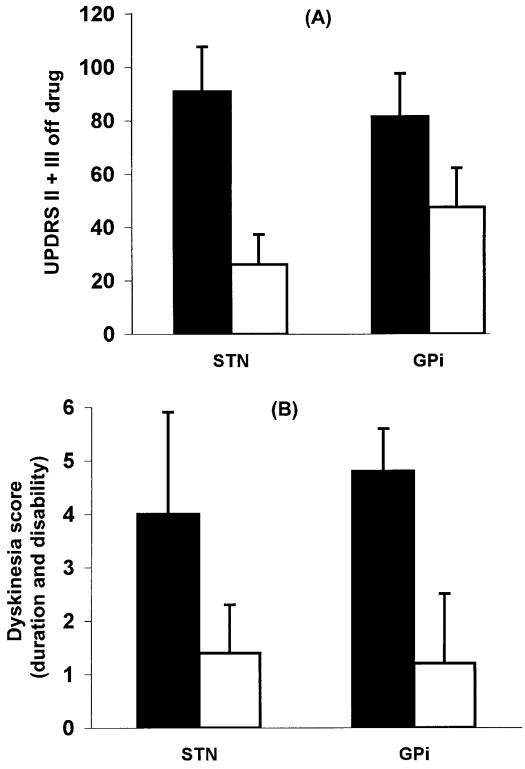

Fig. 1 (**A**) Improvement in activities of daily living and parkinsonism (i.e. reductions in UPDRS parts II and III scores) in off-drug condition and (**B**) reduction in duration and disability scores of LID during activities of daily living (UPDRS part IV, items 32 and 33) induced by STN and GPi stimulation at 6 months follow-up (open bars) compared with preoperative evaluation (closed bars). The improvement in parkinsonism and activities of daily living in off-drug condition was significantly better in the STN group in comparison with the GPi group ($P < 0.001$), whereas there was no significant difference in the LID reduction during activities of daily living between the two groups.

was used as the anode. Electrical parameters (pulse width, frequency and voltage) were progressively adjusted by telemetry, using a console programmer, until an optimal effect was reached, both in on- and off-drug conditions (Limousin *et al*., 1995; Pollak, 1997). The Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987), a hand tapping test (number of taps with the forefinger on two counters 20 cm apart for 30 s, addition of scores of two tests), and an abnormal involuntary movement scale (Limousin *et al*., 1995) in on- and off-drug conditions before surgery were compared with those 6 months after surgery in the on-stimulation condition using the chronic stimulation parameters. Stimulation parameters were repeatedly adapted during the first 2 weeks after surgery in both on- and off-drug conditions. At 3- and 6-month follow-up, the stimulation parameters were again adjusted for possible further optimization of the motor state. The off-drug condition corresponded to the definition given in the CAPIT (core assessment program for intracerebral transplantation) recommendations (Langston *et al*., 1992). The on-drug

Table 2 *Comparison of preoperative scores in 'off' (drug) condition and postoperative scores in 'off' (drug) and 'on' stimulation condition, in patients with bilateral STN/GPi stimulation*

Off levodopa	Bilateral STN stimulation (n = 8)			Bilateral GPi stimulation (n = 5)			P-value*
	Preoperative	Postoperative	Difference	Preoperative	Postoperative	Difference	
UPDRS II	33.3 ± 5.4	9.1 ± 3.9	–24.1 ± 6.3	27.8 ± 8.2	15.0 ± 6.4	–12.8 ± 3.8	<0.05
UPDRS III	57.5 ± 14.5	17.1 ± 8.2	–40.5 ± 15.4	53.6 ± 10.4	32.5 ± 12.4	–21.1 ±13.5	<0.05
Tremor score	4.0 ± 4.3	0.5 ± 0.8	–3.5 ± 4.6	4.0 ± 3.1	1.6 ± 1.5	–2.4 ± 2.5	n.s.
Rigidity score	13.8 ± 2.8	4.5 ± 2.7	–9.3 ± 2.2	13.9 ± 2.0	6.8 ± 4.8	–7.1 ± 3.6	n.s.
Akinesia score	19.9 ± 6.0	5.7 ± 4.6	–14.3 ± 6.1	19.7 ± 6.0	13.7 ± 6.2	–6.0 ± 6.4	<0.05
Taps per minute	66 ± 25	138 ± 39	+72 ± 36	74 ± 20	112 ± 38	+38 ± 28	<0.05
Gait score	14.1 ± 4.4	3.0 ± 1.7	–11.1 ± 5.2	13.5 ± 3.9	8.0 ± 4.2	–5.5 ± 2.3	<0.05

STN = subthalamic nucleus, GPi = internal globus pallidus; n.s. = not significant. *Pre- and postoperative score differences are compared across the two groups.

Table 3 *Comparison of preoperative scores in 'on' (drug) condition and postoperative scores in 'on' (drug) and 'on' stimulation condition, in patients with bilateral STN/GPi stimulation*

Off levodopa	Bilateral STN stimulation (n = 8)			Bilateral GPi stimulation (n = 5)			P-value*
	Preoperative	Postoperative	Difference	Preoperative	Postoperative	Difference	
UPDRS II	7.9 ± 4.8	4.6 ± 4.1	–3.3 ± 6.2	13.6 ± 4.9	10.6 ± 6.8	–3.0 ± 7.0	n.s.
UPDRS III	18.2 ± 10.6	14.7 ± 9.1	–3.5 ± 8	23.2 ± 4.0	26.5 ± 6.5	+3.3 ± 10.1	n.s.
Tremor score	0.7 ± 0.9	0.3 ± 0.5	–0.4 ± 0.7	0.6 ± 1.1	0.6 ± 0.9	0 ± 0.4	n.s.
Rigidity score	4.2 ± 3.6	2.9 ± 3.1	–1.3 ± 2.9	7.7 ± 3.4	5.5 ± 4.0	–2.2 ± 1.6	n.s.
Akinesia score	5.9 ± 5.1	5.6 ± 5.4	–0.3 ± 3.3	7.4 ± 4.7	11.1 ± 5.5	+3.7 ± 7.3	n.s.
Dyskinesia							
levodopa	11.4 ± 6.6	6.8 ± 4.3	–4.7 ± 5.6	15.5 ± 4.2	2.8 ± 3.8	–12.7 ± 4.6	<0.05
duration	1.6 ± 0.7	1.0 ± 0.5	–0.6 ± 1.1	1.8 ± 0.8	0.8 ± 0.8	–1.0 ±1.0	n.s.
disability	2.4 ± 1.5	0.4 ± 0.5	–2.0 ± 1.6	3.0 ± 0.0	0.4 ± 0.5	–2.6 ± 0.5	n.s.

STN = subthalamic nucleus, GPi = internal globus pallidus; n.s. = not significant; dyskinesia levodopa = dyskinesia score with a supra-threshold levodopa dose; dyskinesia duration/disability = duration/disabling effects of dyskinesia during activities of daily living with the current drug and electrical treatment. *Pre- and postoperative score differences are compared across the two groups.

condition was defined as the best motor state following a suprathreshold dose of levodopa, i.e. 50 mg higher than the usual effective dose taken in the morning, or 100 mg higher if the patient was on ⩾15 mg/day of bromocriptine or an equivalent dose of dopamine agonist drugs. The same dose was used pre- and postoperatively. Subscales of the UPDRS were analysed as follows (Lozano *et al*., 1995): tremor = rest and action tremor (items 20 and 21); rigidity = rigidity of the neck and the four limbs (item 22); akinesia = finger taps, hand movements, rapid alternating movements of the hands and leg movements (items 23, 24, 25 and 26); gait = walking, freezing and falling from the UPDRS II, and gait and postural stability from the UPDRS III (items 13, 14, 15, 29 and 30). Dyskinesias were evaluated separately for the face, the trunk and the four limbs during a levodopa test with a suprathreshold dose of levodopa (maximal score 24). Both biphasic and peak-dose dyskinesias were evaluated, and the most severe dyskinesias were taken into consideration. To obtain a measure of the handicap related to dyskinesias in everyday life, we used the combined scores obtained for the duration and disability of dyskinesias (items 32 and 33 of the UPDRS part IV). Off-drug dystonia was present in six out of the eight patients in the STN group and in four out of the five patients in the GPi group.

The Mann–Whitney U test was used for statistical comparison of the preoperative dyskinesia scores between the two groups and of pre- versus postoperative differences in the UPDRS scores between the groups. The difference in preoperative drug dosage between the two groups and the pre- versus post-differences in tapping test, drug doses and stimulation parameters were compared between the groups using Student's t test. Pre-surgical evaluations were performed twice and averaged. Scores of the left and right hand tapping tests were averaged. The relationship between preoperative levodopa-induced improvement in akinesia and postoperative stimulation-induced improvement in akinesia was analysed using the one-tailed Pearson's coefficient.

Results

Pre- and postoperative scores in the off-drug phase are given in Table 2. The motor score (UPDRS III) and activities of daily living (UPDRS II) were improved by stimulation of both targets, but the improvement was greater in the STN group ($P < 0.01$ for UPDRS III, $P < 0.05$ for UPDRS II) (Fig. 1A). Whereas there was no significant difference between the two groups for tremor and rigidity, the effect of STN stimulation was greater on akinesia ($P < 0.05$), gait

Table 4 *Comparison of medical and electrical treatment in the STN and GPi groups*

Therapy	Bilateral STN stimulation ($n = 8$)			Bilateral GPi stimulation ($n = 5$)			*P*-value*
	Preoperative	Postoperative	Difference	Preoperative	Postoperative	Difference	
Levodopa equivalent (mg/day)	1556 ± 928	681 ± 419	–875 ± 102	865 ± 366	1110 ± 444	+245 ± 464	< 0.05
Voltage (V)		2.8 ± 0.6			3.5 ± 0.2		<0.05
Frequency (Hz)		140 ± 20			145 ± 30		<0.01
Pulse width (ms)		60 ± 0.0			100 ± 15		<0.001

STN = subthalamic nucleus; GPi = internal globus pallidus. Differences between pre- and postoperative levodopa-equivalent dosage are compared between the two groups. Postoperative electrical stimulus parameters are also compared.

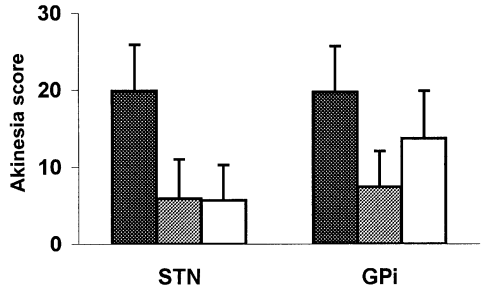

Fig. 2 Improvement in akinesia (dark grey bars, presurgery off drug) with the preoperative levodopa test (light grey bars) and with bilateral STN or GPi stimulation (off the drug, open bars). Whereas bilateral STN stimulation replicates the levodopa effect, the improvement in akinesia with bilateral GPi stimulation is smaller than with levodopa.

score ($P < 0.05$) and hand-tapping score ($P < 0.01$). Akinesia was decreased to the same extent by levodopa (–70%) and bilateral STN stimulation (–71%), whereas in the other group of patients the levodopa effect (–62%) was not reached with bilateral GPi stimulation (–30%) (Fig. 2). The stimulation-induced improvement in akinesia correlated with the preoperative levodopa-induced improvement in akinesia ($r = 0.68$, $P = 0.033$).

On-drug preoperative results and those 6 months after surgery on stimulation are shown in Table 3. There was a trend towards a mild aggravation of akinesia in the GPi group. This was a major problem for one patient, but on average this trend did not reach statistical significance with the electrical parameters chosen for chronic stimulation. LID during the acute levodopa challenge, using the same dose as before surgery, was markedly decreased (–82%) in the GPi group and moderately decreased (–41%) in the STN group. The decrease in the GPi group was significantly greater than that in the STN group ($P < 0.05$). The duration and disability scores of the dyskinesias decreased to the same extent in both groups (Fig. 1B). Off-period dystonia disappeared in both groups, immediately after switching on the stimulation, in all of the 10 patients affected by this symptom.

Table 4 shows drug and electrical treatment in the STN and GPi groups. In the STN group it was possible to reduce the levodopa-equivalent dose by 56%, whereas in the GPi group the levodopa-equivalent dose was slightly increased (29%). All the stimulation parameters were significantly lower in the STN group.

In the STN group, one patient had a grand mal seizure after ventriculography, three patients were confused for a few days after electrode implantation, and one patient developed confusion and bradyphrenia for 1 month. In this patient a postoperative brain MRI showed a hyperintense signal in the T_2-weighted sequence in the region of the left head of the caudate nucleus and anterior arm of the internal capsule, along the electrode trajectory. In the GPi group, four patients were confused for a few days after electrode implantation. None of the patients experienced permanent adverse effects related to the surgical procedure. In particular, there was no permanent change detected in the neuropsychological follow-up examinations (data not shown). There was a transitory aggravation of dyskinesias in all STN-stimulated patients during the first postoperative weeks, mostly in those suffering from the most severe LID. These dyskinesias were effectively managed by a decrease in levodopa dosage and a progressive increase in voltage over a period of days to months. Two patients in the STN group complained of a lack of energy and initiative during off-drug phases and of other non-motor off-drug symptoms such as anxiety following a major decrease in levodopa dosage, while the objective motor examination was similar to their best on-drug periods. One patient in the GPi group showed a reduction of time spent in on-drug phases, loss of his sleep benefit and worsening of on-drug phase akinesia. Two other patients in the GPi group complained of a worsening of hypophonia. On examination, a slight worsening of on-drug period hypophonia and freezing was found in three GPi-stimulated patients, and another patient experienced a mild unilateral hand tremor, not present during pre-surgical on-drug periods. One patient in the GPi group developed stimulation-induced mild dystonic posturing of the hand, and another had a so-called ‘apraxia’ of lid opening.

Discussion

In a group of young onset Parkinson’s disease patients, chronic bilateral electrical stimulation of STN or GPi was effective in reducing parkinsonian symptoms, off-drug period

dystonia and LID. The degree of improvement was the same for tremor, rigidity and LID in both groups. STN stimulation was more effective than GPi stimulation on akinesia. The effect of STN stimulation was approximately double that of GPi stimulation in the akinesia score of the UPDRS and in the hand-tapping test. In the STN-stimulated group, the average preoperative levodopa-induced improvement in akinesia was the same as the average stimulation-induced improvement of akinesia; the preoperative levodopa-induced improvement was also predictive in this group; i.e. it was correlated with the individual's stimulation-induced improvement.

There are some reasons why this study was not randomized. We tried GPi stimulation in 1992 in one patient, but the absence of a clear beneficial effect in this patient and the favourable results of STN lesioning (Bergman *et al*., 1990) and STN stimulation (Benazzouz *et al*., 1993) in MPTP monkeys led us (Benazzouz *et al*., 1993) to propose STN stimulation in patients suffering from severe disabling akinesia during their off-drug periods. As we were afraid of inducing ballism in this target (Aziz *et al*., 1992; Guridi *et al*., 1996), we initially selected patients with mild LID. Given the favourable results of posteroventral pallidotomy, including dramatic reduction of LID (Laitinen *et al*., 1992), and the publication of the results of GPi stimulation by Siegfried and Lippitz (1994), we again took up GPi stimulation in patients suffering from severe LID in 1995. As the initial results of STN stimulation were very satisfactory (Limousin *et al*., 1995), both for the antiparkinsonian effect and the lack of uncontrollable worsening of LID, we progressively extended the indication of STN stimulation to patients with more severe LID. The choice between STN and GPi targets became difficult. In order to compare the preliminary results of STN and GPi stimulation in a homogenous group of patients, we selected all consecutive patients with Parkinson's disease onset before the age of 40 years, because these patients generally suffer from the most severe motor complications of levodopa, i.e. dyskinesias and motor fluctuations. Furthermore, there is little comorbidity in young patients, which could represent a reason for bias. In this consecutive, but non-randomized, series, the patients operated in the STN and GPi were in fact relatively similar, which alleviates the bias of non-randomization. In fact, six patients of the STN group suffered from severe LID, and the other two patients experienced only mild LID, which explains the (non-significant) differences between the groups in the mean dyskinesias score and the levodopa dosage.

Although LID was reduceded by chronic STN or GPi stimulation to a similar degree, the mechanisms of this effect seem to be quite different in the two situations. In GPi stimulation, the decrease or arrest of LID is synchronous with the stimulation. High frequency stimulation is supposed to induce an inhibitory effect on GPi neurons as lesioning results are reproduced by stimulation of the GPi, STN and Vim targets (Benazzouz *et al*., 1995). The pathophysiology of this dramatic effect on GPi neurons, very similar to that induced by pallidotomy (Lozano *et al*., 1995; Baron *et al*., 1996), is difficult to explain. According to the current model of basal ganglia circuitry (Alexander and Crutcher, 1990), inhibiting or lesioning GPi would favour dyskinesias. We can hypothetize that LIDs are related to an imbalance in GPi neuronal activities which is disrupted by GPi surgery. STN stimulation can initially worsen pre-existing LID or induce new dyskinesias (Limousin *et al*., 1996). These dyskinesias can be controlled by adjusting the stimulation voltage and/or by lowering the levodopa dosage. The threshold for STN stimulation-induced dyskinesias tends to increase over time. This is reminiscent of the reduction in drug-induced dyskinesias, when the pulsatile administration of levodopa is replaced by a more continuous dopaminergic activation, using levodopa infusions (Mouradian *et al*., 1990; Obeso *et al*., 1994), or dopaminergic agonist drugs (Montastruc *et al*., 1994; Mouradian and Chase, 1994). Furthermore, the reduction of levodopa dosage is responsible for a decrease in LID to the same extent as for the GPi group. The initial increase in dyskinesias was expected, since STN lesions both in humans and animals are well known to induce chorea/ballism. However, chorea or ballism tend to decrease over time (Shannon, 1990). In the same way chronic stimulation was less prone to trigger dyskinesias and adjustment of the stimulation parameters avoided disabling dyskinesias. Acute lesions of the STN (Obeso *et al*., 1997) appear to be risky in Parkinson's disease patients because of the possible occurrence of severe abnormal movements, difficult to manage. As opposed to on-drug period dyskinesias, off-drug period dystonia was directly and synchronously improved by STN stimulation, which suggests a different pathophysiology.

The main difference between the two groups of patients was the better anti-akinetic effect of STN stimulation in comparison with GPi stimulation. These two groups of patients had very similar disabilities during the off-drug periods and their levodopa response was comparable. The better effect of STN stimulation on akinesia could be explained by the following hypotheses. First, STN is a very small structure, the major part of which could be influenced by low voltage stimulation, whereas the larger size of GPi could lead to an inter-individual variation of the electrode localization inside Gpi, and this could result in variable clinical effects. Accordingly all electrical parameters used in the GPi group were higher than in the STN group. Secondly, stimulating different parts of the GPi can induce different clinical effects (Krack *et al*., 1997*a*, *b*). For example, stimulation of the more ventral part of GPi, which is very effective on LID, inhibits the anti-akinetic effect of levodopa, whereas an antiparkinsonian effect is obtained more dorsally. Thirdly, the two main basal ganglia output structures are the GPi and the substantia nigra pars reticularis. Whereas GPi stimulation influences only the GPi output pathways, the stimulation of STN, which projects excitatory pathways to GPi and substantia nigra pars reticularis, theoretically influences both output pathways. Comparing the antiparkinsonian effects of STN and GPi stimulation with

the best levodopa-induced effects is interesting. The beneficial effects of STN stimulation on the parkinsonian symptoms were close to or identical with, but never significantly greater than, the levodopa effects. Moreover, switching on the stimulation in the on-drug condition did not lead to further improvement. This emphasizes the importance of using a suprathreshold levodopa dose in order to ascertain the best motor state. The levodopa test has not only a diagnostic value; it is also predictive of the improvements following bilateral STN stimulation, and it can be considered as a major selection criterion for this type of surgery. This means that overactivity of STN plays a key role in the pathophysiology of Parkinson's disease and represents the principal change induced by dopamine deficiency. In GPi stimulation, the average improvements in rigidity and tremor could also be predicted by the levodopa effect, but akinesia improvement reached only 50% of that induced by levodopa. Although the antiparkinsonian effect induced by STN stimulation was satisfactory, some patients complained of fatigue and lack of initiative and motivation after reduction of their levodopa dosage. Thus, STN stimulation seems to be unable to completely replace the action of levodopa, which influences all dopaminergic systems of the brain, including not only the direct striato-GPi pathway but also non-motor structures. Alternatively, these complaints could perhaps be explained by an addiction to levodopa due to overstimulation of the nucleus accumbens or the prefrontal cortex (Nutt, 1996), but these symptoms did not improve with time even after 12 months of follow-up.

In conclusion, this preliminary comparison of the effects of GPi and STN stimulation greatly favours the STN target in young onset Parkinson's disease with severe levodopa-induced motor complications. Larger and randomized studies are needed to evaluate the new surgical procedures available for the treatment of Parkinson's disease.

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