Response to levodopa in parkinsonian patients with bilateral subthalamic nucleus stimulation

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Summary
The response to levodopa changes over time in Parkinson’s disease, probably due to alterations in the dopaminergic system, progression of the disease and pulsatile oral intake of the drug. Bilateral high-frequency stimulation of the subthalamic nucleus (STN) allows a large reduction or the complete cessation of levodopa intake in patients with advanced Parkinson’s disease. We studied variation in the motor short-duration response (SDR) during a levodopa challenge in bilaterally STN-stimulated patients. Twenty-eight consecutive patients with a mean duration of Parkinson’s disease of 16.6 ± 6.0 years at the time of surgery were enrolled. Fourteen patients were evaluated both before STN stimulation and 3 months after surgery (group 1) whereas the other 14 patients were assessed before implantation and after a mean of 3 years of STN stimulation (group 2). After drug withdrawal for one night, the hand-tapping test (TT) was carried out every 15 min, together with evaluation of dyskinesias using a modified Goetz scale. The Unified Parkinson’s Disease Rating Scale (UPDRS) motor score was assessed every 30 min. In operated patients, STN stimulation was stopped 15 min before starting the clinical evaluations. A suprathreshold oral levodopa dose was given after one motor evaluation and two TTs. The clinical evaluation was carried out until the TT score returned to the baseline. In group 1, six patients continued without levodopa after surgery and the other eight received a daily mean dose of 337 mg; in group 2, seven patients continued without levodopa and the other seven received a daily mean dose of 386 mg. The main change in the levodopa SDR was a significant reduction in levodopa-induced dyskinesias in both groups. In those patients of group 1 who did not receive levodopa after surgery, the motor UPDRS magnitude decreased and the ‘on’ UPDRS motor score worsened. In group 2, the results were similar, but in the patients who continued to receive levodopa after surgery the TT magnitude increased. On the whole, chronic bilateral STN stimulation tended to decrease the magnitude of the levodopa SDR without changing the duration and latency of the response. These results suggest that continuous STN stimulation induces long-term plastic changes of the dopaminergic system, with slow and partial desensitization. In addition, the persistence of levodopa intake after surgery might hinder this beneficial process.

Keywords: levodopa; subthalamic nucleus; deep-brain stimulation; Parkinson’s disease

Abbreviations: LEDD = levodopa equivalent daily dose; LDR = long-duration response; SDR = short-duration response; STN = subthalamic nucleus; TT = tapping test; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction
Levodopa remains the most effective treatment for Parkinson’s disease, but long-term levodopa therapy induces many motor complications (Fahn, 1974; Marsden and Parkes, 1976), principally dyskinesias and fluctuations in motor performance from one hour to the next, due to the appearance of the short-duration response (SDR) to levodopa. The therapeutic response to levodopa in Parkinson’s disease consists of a SDR and a long-duration response (LDR) (Muenter and Tyce, 1971; Nutt et al., 1992, 1995). The former is a clinical improvement that lasts some hours after a single levodopa dose while the latter is a sustained improvement in parkinsonian signs due to chronic levodopa therapy which lasts for some days after discontinuation of treatment. The clinical relevance of the LDR has not been widely
recognized, since in clinical practice levodopa is usually taken several times a day irrespective of the LDR \citep{Zappia1995}.

In patients with Parkinson’s disease, the response to levodopa changes over time. The durations of the SDR and LDR in groups of Parkinson’s disease patients with mild, moderate and severe disease are inversely proportional to disease severity \citep{Muenter1971,Contin1990,Nutt1993,Zappia1994}, despite the fact that the pharmacokinetics of the levodopa remains the same \citep{Fabbrini1988,Mouradian1988,Zappia1999}. As Parkinson’s disease progresses, the magnitude of the SDR increases, possibly in relation to the more severe baseline disability \citep{Zappia1997,Zappia1999}, while the dyskinesia threshold diminishes \citep{Mouradian1989}. The SDR could result partly from dopamine produced from levodopa in different sites of the brain, e.g. the glia \citep{Nutt1996}.

In contrast to the SDR, the magnitude of the levodopa LDR usually lessens with disease progression \citep{Muenter1971,Nutt1995,Nutt1996,Zappia1999}, as does the duration of the LDR, as observed in patients with motor fluctuations \citep{Ogasahara1984}. Since the LDR is thought to be due to the slow release of levodopa from the residual presynaptic neurones \citep{Quattrone1984}, the LDR would become less evident in comparison with the SDR in advanced Parkinson’s disease.

The pulsatile administration of levodopa has been suggested to be mainly responsible for the development of motor fluctuations \citep{Juncos1989} because of the induction of abnormal plasticity in the basal ganglia and, as a consequence, the induction of dyskinesias and reduction of the ‘on’ duration \citep{Mouradian1990}. For this reason, the concept of continuous dopaminergic stimulation is important in therapeutic strategies \citep{Obeso2000,Olanow2000,Olanow2001}. In advanced Parkinson’s disease, bilateral STN stimulation is a new surgical treatment which improves all the motor symptoms of the disease \citep{Limousin1995,Kumar1999,Houeto2000,Volkmann2001}. High-frequency STN stimulation is thought to continuously alter the activity of STN neurones in Parkinson’s disease \citep{Benabid2000,Beurrier2001}, whereas oral levodopa therapy has a pulsatile effect. Chronic bilateral STN stimulation allows the levodopa equivalent daily dose (LEDD) to be discontinued or greatly reduced \citep{Moro1999,Fraix2000,Molinuevo2000,Lopiano2001} with a consequent decline in levodopa-induced dyskinesias \citep{Krack1997,Krack1999,Bejjani2000}.

The LDR to chronic levodopa treatment can interfere with the evaluation of the SDR and prolonged washout is needed for SDR assessment. The combination of chronic STN stimulation and the decrease or halting of levodopa therapy offers the unique possibility of studying changes in the SDR to a levodopa challenge over time and of providing insights into the pharmacodynamics of levodopa. We studied the levodopa SDR before and after STN stimulation in patients with advanced Parkinson’s disease.

Table 1 Clinical characteristics of the two groups of STN-stimulated patients at the time of surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of Parkinson’s disease (years)</td>
<td>(38.8 \pm 7)</td>
<td>(39.9 \pm 7.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Men : women</td>
<td>11 : 3</td>
<td>10 : 4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of Parkinson’s disease (years)</td>
<td>(13.7 \pm 3.9)</td>
<td>(16.3 \pm 6.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean age at time of surgery (years)</td>
<td>(52.6 \pm 8)</td>
<td>(55.6 \pm 7.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>(3 \pm 0)</td>
<td>(36.6 \pm 7.2)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

n.s. = not significant; n.a. = not available.

Patients and methods

**Patients**

Twenty-eight patients with advanced Parkinson’s disease (21 men and seven women) were included in the study and were divided into two groups.

**Group 1** consisted of 14 consecutive patients who completed a prospective study of the levodopa SDR with evaluation before and 3 months after bilateral STN electrode implantation.

**Group 2** consisted of 14 patients who completed a prospective study of the levodopa SDR with evaluation before and \(\geq 2\) years (mean 36.6 \(\pm\) 7.2 months, range 24–72 months) after bilateral STN electrode implantation.

The clinical characteristics of the two groups of patients are detailed in Table 1. All the patients underwent the same neurosurgical procedure for bilateral electrode implantation in the STN \citep{Limousin1995}. In both groups, postoperative evaluation showed the same improvement in the UPDRS motor score of the Unified Parkinson’s Disease Rating Scale (UPDRS) \citep{Fahn1987}, calculated by comparing the off- and on-stimulation scores in an off-medication condition (60% improvement in group 1 and 58% in group 2).

**Methods**

All patients were assessed after one night of dopaminergic drug withdrawal and fasting (CAPIT (Core Assessment
Program for Intracerebral Transplantations) protocol] (Langston et al., 1992). STN stimulation was stopped 15 min before the postoperative levodopa challenge. The UPDRS motor score was assessed every 30 min, and every 15 min the tapping test (TT) was carried out together with evaluation of dyskinesias using a scale based on the studies of Goetz and colleagues and of Marconi and colleagues (Goetz et al., 1994; Marconi et al., 1994; Krack et al., 1999). The same raters evaluated individual patients before surgery and 3 months after surgery in group 1. However, in group 2, with assessment before surgery and 3 years after surgery, the raters were not always the same except for dyskinesias. Where the raters were different, the dyskinesia score was obtained by the same rater observing the videotapes recorded before surgery (all patients had the entire levodopa challenge videotaped). All motor assessments were unblinded. Biphasic dyskinesias were defined as abnormal movements of a rhythmic alternating type, generally disabling and affecting the lower limbs, occurring as the first sign of a levodopa effect (onset of dose) or heralding the recurrence of parkinsonism (end of dose). Peak-dose dyskinesias were defined as predominantly choreodystonic movements occurring at the same time as the greatest degree of clinical improvement. Patients were able to experience both types of dyskinesias (Marsden et al., 1982). A suprathreshold oral dose of levodopa was given after the first motor UPDRS test and two baseline TTs. The levodopa challenge dose was calculated as 120% of the usual first-morning levodopa dose plus 50% of the levodopa-equivalent dose of the first morning dose of dopamine agonists. The same dose of levodopa (Modopar Dispersible®) was administered before and after surgery. Domperidone 20 mg three times daily was administered for 2–3 days before the evaluation in the patients who continued without levodopa after surgery.

If the scores for the first 30 min of the test did not change by more than 15% from baseline, the 30-min score was included in the definition of the baseline score. The baseline TT score was consequently the mean of the first two or three assessments and the baseline motor score was the first or the mean of the first assessments. The baseline score was called ‘off 1’ while the score obtained within the 30 min after the decrease in the motor effect of levodopa was called ‘off 2’.

The magnitude of the SDR for the TT was calculated as the difference between the mean of the baseline TT and the mean of the three subsequent highest TTs (Nutt et al., 1997), while the magnitude of the SDR for the UPDRS was defined as the difference between the baseline UPDRS motor scores and the mean of the subsequent two best motor scores. The duration of the SDR was defined as the period during which the TT and motor UPDRS scores changed by 15% or more from baseline. The total motor UPDRS score and the following subscales were evaluated: tremor (items 20 and 21); rigidity (item 22); akinesia (items 23, 24, 25 and 26); and gait and postural stability (items 29 and 30).

Figure 1 shows the study protocol. Informed consent was obtained from the patients and the study was approved by the Grenoble University Hospital Ethics Committee.

**Statistical analysis**
Non-parametric tests were used to analyse and compare the data. Pairwise comparisons between the results of the mean of the preoperative and postoperative evaluations within each group were made with the Wilcoxon signed rank test. For comparison of the results between the two groups, the Mann–Whitney U test was used.

**Results**

**Global findings**
Before surgery, no significant differences were found between the two groups of patients except for the preoperative peak-dose dyskinesias, which were more severe in group 2 ($P = 0.019$), and the mean ‘on’ TT, which was better in group 1 ($P = 0.007$) (Tables 2 and 3).

**Group 1**
After surgery, the levodopa daily dose was significantly reduced, by 83%. Levodopa was stopped in six patients, while
eight patients received low doses of levodopa and dopamine agonists (Table 3). Table 2 reports the principal results of the pre- and post-surgery levodopa test. The mean ‘on’-drug UPDRS-III score worsened significantly after surgery (Fig. 2), although the worsening was significant only for akinesia ($P = 0.017$). After the operation, biphasic and peak-dose dyskinesias were significantly reduced, by 37 and 33%, respectively (Figs 3 and 4).

Before surgery, the ‘off 2’ score was significantly ($P = 0.0018$) worse than the ‘off 1’ score. Three months after surgery, there was no significant difference between the ‘off 1’ and ‘off 2’ scores. The other parameters did not change significantly.

**Group 2**

After surgery, the levodopa daily dose was significantly reduced, by 76%. Levodopa was stopped in seven of the 14 patients (Table 4). Compared with before surgery, the postoperative assessment showed that the mean on-drug UPDRS-III score was significantly worse (Fig. 2), whereas the on-drug TT score was significantly better. The deterioration of the UPDRS-III was caused mainly by worsening of the rigidity ($P < 0.045$) and akinesia ($P = 0.002$) scores. The UPDRS-III score was significantly reduced, whereas the TT magnitude was significantly increased. The ‘off’ TT score showed a significant difference ($P = 0.002$) between the most affected hand and the contralateral hand. Each hand showed a

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**Table 3**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Before surgery</th>
<th>3 months after surgery</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UHDRS-III score off medication</strong></td>
<td>46.6 ± 17.1</td>
<td>47.2 ± 14.9</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>UHDRS-III score on medication</strong></td>
<td>16.1 ± 11.6</td>
<td>20.8 ± 8.5</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Total LEDD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Levodopa intake (mg/day)</strong></td>
<td>360</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td><strong>Agonist Intake (LEDD)</strong></td>
<td>120</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td><strong>Total LEDD</strong></td>
<td>480</td>
<td>480</td>
<td></td>
</tr>
</tbody>
</table>

**Group 2**

<table>
<thead>
<tr>
<th>Before surgery</th>
<th>36 months after surgery</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UHDRS-III score off medication</strong></td>
<td>54.0 ± 11.8</td>
<td>55.3 ± 16.9</td>
</tr>
<tr>
<td><strong>UHDRS-III score on medication</strong></td>
<td>14.3 ± 8.7</td>
<td>25.0 ± 11.8</td>
</tr>
<tr>
<td><strong>Total LEDD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Levodopa intake (mg/day)</strong></td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td><strong>Agonist Intake (LEDD)</strong></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Total LEDD</strong></td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

The $P$ values refer to comparisons between preoperative and postoperative data. *Before surgery: 4 patients received ropinirole, 4 patients received bromocriptine, 3 patients received bromocriptine and apomorphine, 1 patient received ropinirole and apomorphine, 1 patient received pergolide and apomorphine, and 1 patient received pergolide and bromocriptine. **After surgery: 5 patients received ropinirole, 6 patients received bromocriptine, and 3 patients did not receive agonists.
significantly improved on-drug TT score ($P = 0.002$) compared with before surgery. Both biphasic and peak-dose dyskinesias decreased significantly (Table 2 and Figs 3 and 4). The 25% reduction in the time to reach the ‘on’ state was not significant. The duration of the levodopa SDR, retrospectively available in eight patients, did not decrease significantly ($-19.2\%$).

The off-drug UPDRS-III score, the off-drug TT score and off-drug dystonia remained unchanged.

**Patients with and without levodopa after surgery**

In order to verify if there was a difference in the SDR characteristics between patients with and without levodopa after surgery, we analysed the data of the following four subgroups. Group 1 was divided into group 1 LD−, comprising six patients without levodopa after surgery, and group 1 LD+, comprising eight patients with levodopa after surgery. Group 2 was divided into group 2 LD−, comprising seven patients who continued without levodopa after surgery, and group 2 LD+, comprising seven patients with levodopa after the operation. There was no difference in the STN stimulation efficacy in the off-medication UPDRS-III score between the groups with levodopa and the groups without levodopa.

In group 1 LD−, the on-drug UPDRS-III score worsened significantly ($P = 0.046$) (Fig. 2) and the UPDRS-III magnitude ($P = 0.0464$) and biphasic dyskinesias decreased significantly ($P = 0.027$) after surgery (Fig. 3), whereas in group 1 LD+ only biphasic dyskinesias were significantly ($P = 0.017$) reduced. The worsening of the UPDRS-III score was significant ($P = 0.02$) only for the akinesia score. After surgery, ‘off 2’ dystonia was significantly ($P = 0.04$) better than ‘off 1’ dystonia in group 1 LD−. In group 1 LD+, after surgery only the ‘off 2’ TT score was significantly worse ($P = 0.01$) compared with the ‘off 1’ TT score, whereas before surgery the ‘off 2’ UPDRS-III and TT scores were both significantly ($P = 0.02$) worse than the ‘off 1’ values.

In group 2 LD−, the peak-dose dyskinesias were significantly ($P = 0.02$) reduced (Fig. 4) and the on-TT score significantly improved ($P = 0.02$) after surgery, whereas in group 2 LD+ the on-drug UPDRS-III magnitude was significantly ($P = 0.018$) worse; the TT score increased significantly ($P = 0.018$) and ‘off 2’ dystonia was significantly ($P = 0.043$) worse compared with ‘off 1’ dystonia. In addition, for each hand of the group 2 LD− patients, the on-drug TT score was significantly better ($P = 0.04$ for the most affected hand and $P = 0.016$ for the contralateral hand).

There were no significant differences between group 2 LD− and 2 LD+ before surgery, but after surgery the ‘off 2’ was significantly ($P = 0.015$) worse in group 2 LD+.

**Discussion**

This study was designed to evaluate the changes in the levodopa SDR following a period of continuous STN stimulation for either 3 months (group 1) or a longer
mean period of 3 years (group 2). Since patients were not stimulated during the levodopa challenge, we were unable to assess the acute interaction between stimulation and levodopa.

Our results show that some characteristics of the levodopa SDR changed in patients with chronic bilateral STN stimulation. One of the main changes was the significant reduction in levodopa-induced dyskinesias in both groups (Figs 3 and 4). Since the presurgical dyskinesias in group 1 and group 2 were different, we were unable to assess the effect of the interval after surgery on the severity of dyskinesias. However, a previous study carried out on a cohort of a greater number of patients (24 patients) showed that levodopa test-induced biphasic and peak-dose dyskinesias were lower 12 months than 3 months after surgery (Fraix et al., 2000). In our group 2, the decrease in biphasic and peak-dose dyskinesias at 3 months (data not shown) was almost the same as that reported at 3 years of follow-up, with a trend towards a greater decrease for the peak-dose dyskinesias in the long term. These findings suggest that both the chronic decrease in the levodopa dose and the continuous STN stimulation can induce plastic neuronal changes that lead to improvement in levodopa-induced dyskinesias.

The reduction in the levodopa intake after surgery seems to play an important role in alleviating dyskinesias. The majority of the studies that give results following STN stimulation observed this reduction in dyskinesias and correlated it to the reduction in levodopa intake (Krack et al., 1999; Moro et al., 1999; Bejjani et al., 2000; Molinuevo et al., 2000). However, in our study, although the peak-dose dyskinesias decreased significantly only in patients who remained without levodopa 3 years after surgery, the difference in reduction in both types of dyskinesias was not significant between groups 2 LD-- and LD+. In addition, the fact that some dyskinesias can be

Table 4: Group 2: intake of antiparkinsonian drugs before and after surgery

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levodopa (mg/day)</td>
<td>Intake (no./day)</td>
</tr>
<tr>
<td>1</td>
<td>900</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>1150</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1150</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>1200</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>1900</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>1375</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>1062.5</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>350</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>2000</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>150</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>950</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>825</td>
<td>9</td>
</tr>
<tr>
<td>13</td>
<td>2075</td>
<td>22</td>
</tr>
<tr>
<td>14</td>
<td>900</td>
<td>7</td>
</tr>
</tbody>
</table>

The P values refer to comparisons between preoperative and postoperative data. *Before surgery: 3 patients received bromocriptine, 3 patients received apomorphine, 2 patients received lisuride, 1 patient received cabergoline, 2 patients received pergolide and bromocriptine, and 3 patients did not receive agonists. **After surgery: 3 patients received bromocriptine, 1 patient received ropinirole, 1 patient received pergolide, 1 patient received lisuride and 8 patients did not receive agonists.

![Fig. 4 Reduction in peak-dose dyskinesias in LD– and LD+ patients in groups 1 and 2 before and after surgery. Bars represent mean and standard deviation. *P < 0.05 for the comparison between preoperative and postoperative scores.](https://academic.oup.com/brain/article-abstract/125/11/2408/258653/125112008250635?download=1&date=07March2019)
induced by levodopa even after a 3-year cessation of levodopa suggests that the sensitization phenomenon is reversible only in part.

A direct role of STN stimulation in modifying dyskinesias has been advanced by some authors (Rodriguez et al., 1998b; Figueiras-Mendez et al., 1999). They observed a substantial reduction in dyskinesias in patients with STN stimulation who did not reduce the levodopa intake after implantation. Some neuronal structures or pathways mediating dyskinesias can be altered by lead implantation or stimulation. Chronic high-frequency stimulation of the STN may disrupt the transmission of neuronal misinformation caused by the disease, both by inhibiting neuronal output from the STN and by replacing the pattern of neuronal activity that constitutes the misinformation with a more effective pattern (Benabid et al., 2000; Montgomery and Baker, 2000). However, other authors have shown that STN stimulation may worsen dyskinesias, mainly in the postoperative period (Limousin et al., 1996; Krack et al., 1999).

Our study shows a significant reduction in the motor UPDRS magnitude and a significant worsening of the ‘on’ motor UPDRS score in group 1 LD– at 3 months of follow-up. Two reasons can be found to explain these findings. First, parkinsonian symptoms can be aggravated in both ‘on’ and ‘off’ periods by the loss of the levodopa LDR, which was evident only in patients who were able to stop levodopa after 3 months, after a washout period long enough to eliminate all the LDR ‘interference’ (Zappia et al., 1997). Secondly, the decrease in levodopa dose can lead to desensitization of the neuronal system involved in levodopa-induced motor complications (Bejjani et al., 2000).

According to some authors (Kempster et al., 1990; Nutt et al., 1992), the magnitude of the levodopa motor response may be related to the degree of postsynaptic dopaminergic receptor stimulation. In Parkinson’s disease, the hypersensitivity of the dopamine post-synaptic receptors has been suggested to be related to the intermittent oral chronic administration of levodopa, in conjunction with the loss of nigrostriatal neurones (Calne and Zigmund, 1991). This pulsatile dopaminergic activity is due to the absence of the usual buffering effect of presynaptic striatal dopaminergic terminals and results in a phasic release of dopamine at receptor sites which normally operate tonically (Lee et al., 1978). In fact, when levodopa is given intravenously, the stabilization of the plasma levodopa level decreases the motor fluctuations (Nutt and Holford, 1996). The pulsatile stimulation of dopamine receptors could induce persistent phenotypic changes in neurotransmitter and receptor expression, and functional alteration in signal transduction and synaptic plasticity (Canales and Graybiel, 2000; Calon et al., 2000). Consequently, in our study, the reduction or cessation of levodopa may have modified the receptor response, leading to a decreased UPDRS magnitude. Moreover, in addition to dopaminergic sensitization, other factors may be involved, such as alterations in the synaptic efficacy of striatal glutamate receptors (Chase and Oh, 2000).

As in group 1 LD–, the UPDRS magnitude decreased for all the patients of group 2, due to the significant worsening of the ‘on’ motor UPDRS score, with no change in the ‘off’ condition. A prolonged carry-over effect following the cessation of stimulation is unlikely because it would mainly improve the ‘off’ motor score (Nutt et al., 2001). The spontaneous evolution of Parkinson’s disease would have worsened the ‘off’ motor score and increased the magnitude of the levodopa response (Nutt et al., 1997; Zappia et al., 1997, 1999b). Therefore, the worsening of the ‘on’ motor score with no change in the ‘off’ motor score suggests a possible lack of progression of the disease over the 3-year follow-up or desensitization of the basal ganglia circuitry to levodopa. This observation suggests some neuroprotective effects produced by chronic STN stimulation, as some authors have hypothesized (Rodriguez et al., 1998a; Benabid et al., 2000). The STN hyperactivity could be toxic to the basal ganglia and the blockade of the glutamatergic release caused by the STN electrical stimulation (Beurrier et al., 2001) might be directly neuroprotective (Rodriguez et al., 1998a; Blandini et al., 2001).

When comparing patients who continued to receive levodopa with those who did not, there was a trend towards a better ‘off 1’ condition in group 2 LD+ and a worse ‘off 1’ in group 2 LD+. In addition, the worsening of the ‘off 2’ UPDRS and ‘off 2’ dystonia in group 2 LD+ may indicate that levodopa, even at low doses, may interfere with the benefit produced in the long term by chronic STN stimulation. Since all groups showed the same improvement produced by the STN stimulation, a possible variation in the stimulation effect cannot be responsible for this result. This may indicate a deleterious effect of levodopa in the process of basal ganglia desensitization produced by continuous STN stimulation. In group 1, the decision to continue small doses of antiparkinsonian drugs after surgery was taken in order to prevent or reduce the postsurgery apathy and depression observed in some operated patients when the large presurgery dose of dopamine medication was totally suspended in the immediate period after implantation (Krack et al., 1998; Volkmann et al., 2001). The maintenance of levodopa treatment in group 2, despite the STN stimulation having the same efficacy as in the other groups, can be explained by the spontaneous and more aggressive course of Parkinson’s disease. In fact, group 2 LD+, who still receive a mean daily dose of levodopa of 535 mg at 36 months of follow-up, show significant worsening in ‘off 2’ and UPDRS-III scores in the ‘on’ condition compared with groups 2 LD– and 1 LD+.

The increase in TT magnitude in group 2 is accounted for by the LD+ patient subgroup and can be explained partly by the postoperative reduction in disabling dyskinesias during the test, which leads to better motor performance. However, this increase in TT magnitude appears to be in contrast with the worsening in bradykinesia obtained in the ‘on’ UPDRS motor score. This discrepancy may result from the different nature of the assessed movement. Performance in the TT depends principally on a proximal movement of the upper
limbs and may be more influenced by technical and psychological factors, in the way that the use of a device may motivate the patient and make easier the execution of a task. Bradykinesia results are based on the subjective evaluation of three repetitive distal movements of the upper limbs and one of the lower limbs. This may indicate that chronic STN stimulation may change the motor pattern of movements, ameliorating the movements of the proximal upper limb more than those of the distal upper limb (Brown et al., 1999). This also suggests that it could be useful to assess both the TT and the motor UPDRS scores in the evaluation of the levodopa SDR. Nevertheless, in group 2 LD+, the improvement in the TT, reflecting an increase in the magnitude of the SDR, mitigates the results concerning the UPDRS bradykinesia scores, which indicate a reduction in magnitude of the SDR. Consequently, this result weakens the hypothesis of desensitization of the basal ganglia loop induced by STN stimulation, possibly hindered by the continuation of levodopa intake.

The absence of baseline worsening after prolonged levodopa withdrawal and the absence of ‘off’ worsening at 3 months in group 1 suggest that chronic STN deep-brain stimulation acts like the levodopa LDR, operationally defined as the gradual recurrence of parkinsonian disability over time following levodopa withdrawal, even if the acute benefit produced by stimulation is suddenly lost (after a few minutes for bradykinesia, tremor and rigidity) when the stimulation is switched off. This is indeed what occurred after STN deep-brain stimulation in a group of patients with advanced Parkinson’s disease, in whom the levodopa LDR is expected to be greatly reduced.

These findings, together with the important reduction in levodopa-induced dyskinesias, strongly support the view that chronic STN stimulation can modify the therapeutic window for levodopa (Mouradian et al., 1990; Pollak, 1998). In fact, high-frequency stimulation of the STN seems to widen the threshold for dyskinesias and stabilize the baseline, allowing a sort of beneficial regression towards earlier stages of Parkinson’s disease. This is reminiscent of the clinical improvement obtained by chronic infusion of levodopa (Nilsson et al., 2001) or apomorphine (Manson et al., 2001).

In conclusion, our results show that chronic bilateral STN stimulation tends to decrease the magnitude of the levodopa SDR without changing the duration and latency of the response. Levodopa-induced dyskinesias also decrease but are still present. All these findings suggest that continuous STN stimulation induces a long-term plastic change in the dopaminergic system, but this desensitization phenomenon is slow and reversible only in part. In addition, the persistence of pulsatile oral intake of levodopa after implantation might interfere with the beneficial effects of continuous STN stimulation.

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References


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