Effects of Subthalamic Nucleus Stimulation and Levodopa Treatment on Gait Abnormalities in Parkinson Disease

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Background: Stimulation of the subthalamic nucleus is proposed for the treatment of patients presenting with severe Parkinson disease. The effect on gait is not clearly established.

Objectives: To evaluate objectively the influence of bilateral subthalamic nucleus stimulation on gait in Parkinson disease and to compare it with the effects of levodopa treatment.

Methods: Ten patients underwent bilateral subthalamic nucleus stimulation. The preoperative and postoperative (3 months after surgery) clinical gait disturbances, as well as spatial and temporal gait parameters, were analyzed in off and on-drug conditions. The gait analysis was performed using a video motion analysis system (optoelectronic VICON system; Oxford Metrics, Oxford, England).

Results: In the off condition, there was an improvement after surgery for the total motor score and the gait subscore. In the on-drug condition, there was an improvement in levodopa-induced dyskinesias and the motor score, whereas the gait subscore was unchanged. For the gait parameters measured by the video motion analysis system, there was also an improvement in the off condition and to a lesser extent in the on-drug condition.

Conclusions: Our method allowed exact quantification of the benefit of surgery on gait parameters. Compared with the levodopa treatment, the effect of stimulation on gait kinematic parameters seems to be qualitatively similar but quantitatively different with a lower benefit on gait velocity and stride length. Concerning the pathophysiology of gait troubles in Parkinson disease, the deficit in control of stride length would be the fundamental deficit. The study underlines the possible role of the subthalamic nucleus on the stride length regulation.

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METHODS

PATIENTS

Ten patients (3 females and 7 males) with severe PD (clinical criteria of Gibb and Lees13) were successively studied. The mean (SD) age was 57 (8) years, and the mean (SD) disease duration was 13 (5) years. All patients were graded on stage 3 to 5 of Hoehn and Yahr in the off condition. They presented with severe levodopa-related motor complications, mainly motor fluctuations, despite optimal medical treatment.

Motor disability (United Parkinson’s Disease Rating Scale Part III [UPDRS III]: optimal score, 0; worst score, 108), gait disorders (item 30 from the UPDRS III: optimal score, 0; worst score, 4), and dyskinesias (7 body parts: face, neck, trunk, right and left upper and lower limbs; each scored 0-4; optimal score, 0; worst score, 28) were assessed immediately before and 3 months after surgery, in the off condition (the patient had received no treatment for 12 hours or just the lowest dose of levodopa allowing him or her to walk for the gait analysis), and then in the on-drug condition (ie, after administration of 200 mg of levodopa). In the on-drug condition, the patients satisfied the definition of the best on state according to the Core Assessment Program for Intracerebral Transplantations committee.14 The mean results were then expressed for the 10 cases. The patients received antiparkinsonian medications (mean [SD] total levodopa equivalents dose, 1490 [420] mg/d) that were decreased by 32% three months after surgery.15,16

NEUROSURGICAL PROCEDURE

The overall method is similar to what has been previously described by Benabid et al.17 Our study was approved by the National Ethics Committee, Lille, France, and the patients gave their written informed consent.

GAIT ANALYSIS

The kinematic spatial and temporal gait measurements were automatically recorded using a video motion analysis system, with 5 infrared cameras with a sampling frequency of 50 Hz. Thirteen spherical retroreflective markers (2.5 cm in diameter) were used to define different segments of the pelvis and lower limbs. They were bilaterally placed on anatomically well-defined points of the lower limbs: anterior superior iliac spine, thighs, knees, heels, lateral malleoli, and toes, and on the sacrum. The markers were illuminated with infrared strobes. The 3-dimensional trajectories in the frontal, sagittal, and axial planes were recorded by the cameras, which were placed in defined positions in a room, delimiting a volume 2.5 × 1.2 × 1.4 m. The subjects walked at their own speed and passed through this area. Data acquisition began approximately 1 second before the subject entered this area and ended 1 second after the subject left this area. The video motion analysis system has been validated with a procedure close to ours by Ehara and Fujimoto.18 For each patient, 2 static trials were analyzed to calibrate certain internal axes of the limb segments: extra markers were placed on the heels of the subject, in addition to those worn during a walking trial, and the subject was asked to stand as still as possible. They were used to calculate ankle plantar flexion and foot rotation offset angles.

Usually, the patients who are supposed to undergo surgery are seen with severe PD, including gait disturbances. In the present study, our method required a 5-m walk. This is the reason why the patients who had severe gait disturbances, so that they were unable to walk in the off-drug condition, received the lowest dose of levodopa allowing them to walk. Otherwise, their gait cycles could not have been analyzed by the video motion analysis system. Thus, before surgery, 4 patients received a dose of levodopa (2 patients received 50 mg and 2 patients received 100 mg). So, we will call this condition the “off condition” rather than the off-drug condition. After acquisition of data in the off condition, these 4 patients had to return to their worst off state14 before receiving 200 mg of levodopa, to be in exactly the same condition as the 6 other patients. The clinical assessment was performed immediately before each recording session (off condition then on-drug condition). Then, 6 dynamic gait trials were successively analyzed in the off condition then in the on-drug condition, before and 3 months after surgery. Ten gait cycles could be analyzed for each condition described earlier, before and after surgery.

For each cycle, spatial kinematic gait parameters (stride and step lengths) and temporal gait kinematic parameters (cadence, velocity, stride and step times, single- and double-limb support times) were determined. Both single-limb and double-limb support time (respectively, time spent on one foot only and total time spent on both feet) corresponds to the stance phase. We also analyzed the single-limb support time/double-limb support time ratio, whose increase better reflects improvement of gait in PD. To compare the effect of levodopa treatment to that of STN stimulation on variability of stride length, all available gait cycles were used to calculate a coefficient of variation.19 Then, the preoperative temporal and spatial gait measurements were compared with the postoperative ones, in the off condition then in the on-drug condition. We also analyzed the effect of levodopa treatment on gait variables before stimulation. Finally, we compared the effect of stimulation in the off condition to that of levodopa treatment before surgery.

STATISTICAL ANALYSIS

A paired Wilcoxon rank sum test was performed to compare the clinical results in both drug conditions, before and after surgery (P<.05 was statistically significant). An analysis of variance (ANOVA) using a mixed linear model was performed to analyze each gait parameter. The fixed effects were drug condition (2 levels: on-drug/off) and stimulation status (2 levels: before stimulation/after stimulation). The subject effect was considered random. For each subject, the number of values in each of the 4 following conditions (off condition/before stimulation, off condition/after stimulation, on-drug condition/before stimulation, on-drug condition/after stimulation) was the same. Post hoc analysis of the interactions was studied by means of contrasts. P<.05 was statistically significant.

RESULTS

Concerning the clinical data (Table 1), in the off condition, there was a statistically significant improvement after surgery in the UPDRS III score (50%) (P=.05, paired Wilcoxon rank sum test) and gait (68%) (P=.05, paired Wilcoxon rank sum test). In the on-drug condition, in the postoperative state, there was a statistically significant improvement in the levodopa-induced dyskinesias (72%) (P=.05, paired Wilcoxon rank sum test) and the UPDRS III score (44%) (P=.05, paired Wilcoxon rank sum test), whereas the gait score was unchanged.

The ANOVA (Table 2 and Table 3) mainly showed a significant effect of surgery (whatever the drug condition) for all the spatial and temporal gait parameters. There was also a significant effect of levodopa treatment (whatever the surgery condition) for all parameters except the single-limb support time. Finally, there was an interac-
tion between surgery and levodopa treatment for all gait variables but not for the single-limb support time, so that the post hoc tests were performed for all the parameters except for the single-limb support time.

In the off condition, the post hoc tests (Table 2) showed statistically significant improvement of the following kinematic parameters after stimulation: velocity and stride and step lengths (which were increased by 90%, 54%, and 58%, respectively), and also stride, step, and double-limb support times (which were decreased by 25%, 24%, and 48%, respectively). The single-limb/double-limb support time ratio was increased by 61% (corresponding to an improvement). The cadence was also increased by 25%.

In the on-drug condition (Table 2), qualitatively levodopa treatment induced a statistically significant change for all the gait parameters with the same pattern as was observed with STN stimulation in the off condition. Quantitatively velocity and stride and step lengths were increased by 104%, 68%, and 71%, respectively, whereas stride, step, and double-limb support times were decreased by 26%, 26%, and 54%, respectively. The single-limb/double-limb support time ratio and the cadence were also increased by 73% and 24%, respectively. Finally, when the effect of levodopa treatment is compared in the preoperative state with the effect of STN stimulation alone (off condition), it is observed that levodopa increased velocity, stride and step length, and the single-limb/double-limb support time ratio, more than STN stimulation (Table 3). Cadence (and other parameters such as stride and step times) was not different in the 2 states.

In the off condition, variability was improved by 27% after STN stimulation: the coefficient of variation was 33.8 before surgery and 26.1 after surgery. In the on-drug condition, STN stimulation also induced an improvement of variability with a coefficient of 19.05 in the preoperative state and 12.04 in the postoperative state (−37%). Finally, before STN stimulation, levodopa treatment induced a marked improvement of variability with a coefficient of 35.8 in the off condition and 19.05 in the on-drug condition (−47%).

Our method allowed exact quantification of the influence of surgery on gait disorders and clearly quantifies the benefit of STN stimulation for spatial and temporal

### Table 1. Clinical Data

<table>
<thead>
<tr>
<th>Variable (Score Range)</th>
<th>Patients in the Off Condition</th>
<th>Patients in the On-Drug Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
</tr>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
</tr>
<tr>
<td>UPDRS III score (0-108)</td>
<td>52 (16)</td>
<td>26 (7)†</td>
</tr>
<tr>
<td>Gait (0-4)</td>
<td>2.2 (0.6)</td>
<td>0.8 (1)‡</td>
</tr>
<tr>
<td>Dyskinesias (0-28)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations: Off condition, the patient had received no treatment for 12 hours or merely the lowest dose of levodopa allowing him or her to walk for gait analysis; On-drug condition, after the administration of 200 mg of levodopa; UPDRS III, United Parkinson’s Disease Rating Scale Part III (motor function).

*Data are given as mean (SD). Ellipses indicate not applicable.

†Score ranges are given from the optimal to the worst.
‡P<.05, paired Wilcoxon rank sum test.
§P<.05, paired Wilcoxon rank sum test.

### Table 2. Temporal and Spatial Gait Parameters

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Preoperative Value</th>
<th>Postoperative Value</th>
<th>P Value</th>
<th>Preoperative Value</th>
<th>Postoperative Value</th>
<th>P Value</th>
<th>Preoperative Value</th>
<th>Postoperative Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadence, steps/min</td>
<td>93.00 (25.00)</td>
<td>116.00 (15.00)</td>
<td>&lt;.001</td>
<td>115.00 (11.00)</td>
<td>124.00 (8.00)</td>
<td>&lt;.001</td>
<td>93.00 (25.00)</td>
<td>115.00 (11.00)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Velocity, m/s</td>
<td>0.50 (0.26)</td>
<td>0.95 (0.26)</td>
<td>&lt;.001</td>
<td>1.02 (0.22)</td>
<td>1.25 (0.16)</td>
<td>&lt;.001</td>
<td>0.50 (0.26)</td>
<td>1.02 (0.22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stride time, s</td>
<td>1.41 (0.44)</td>
<td>1.06 (0.24)</td>
<td>&lt;.001</td>
<td>1.05 (0.1)</td>
<td>0.97 (0.06)</td>
<td>&lt;.01</td>
<td>1.41 (0.44)</td>
<td>1.05 (0.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Step time, s</td>
<td>0.70 (0.24)</td>
<td>0.53 (0.15)</td>
<td>&lt;.001</td>
<td>0.52 (0.05)</td>
<td>0.49 (0.04)</td>
<td>&lt;.05</td>
<td>0.70 (0.24)</td>
<td>0.52 (0.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Support time, s</td>
<td>0.40 (0.13)</td>
<td>0.37 (0.07)</td>
<td>...</td>
<td>0.39 (0.04)</td>
<td>0.37 (0.03)</td>
<td>...</td>
<td>0.40 (0.13)</td>
<td>0.39 (0.04)</td>
<td>...</td>
</tr>
<tr>
<td>Single limb</td>
<td>0.61 (0.34)</td>
<td>0.32 (0.18)</td>
<td>&lt;.001</td>
<td>0.28 (0.07)</td>
<td>0.23 (0.03)</td>
<td>&lt;.01</td>
<td>0.61 (0.34)</td>
<td>0.28 (0.07)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Double limb</td>
<td>0.83 (0.42)</td>
<td>1.34 (0.39)</td>
<td>&lt;.001</td>
<td>1.44 (0.32)</td>
<td>1.68 (0.29)</td>
<td>&lt;.001</td>
<td>0.83 (0.42)</td>
<td>1.44 (0.32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Single-limb/double-limb ratio</td>
<td>0.63 (0.23)</td>
<td>0.97 (0.25)</td>
<td>&lt;.001</td>
<td>1.06 (0.20)</td>
<td>1.21 (0.15)</td>
<td>&lt;.001</td>
<td>0.63 (0.23)</td>
<td>1.06 (0.20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Step length, m</td>
<td>0.31 (0.12)</td>
<td>0.49 (0.12)</td>
<td>&lt;.001</td>
<td>0.53 (0.11)</td>
<td>0.61 (0.08)</td>
<td>&lt;.001</td>
<td>0.31 (0.12)</td>
<td>0.53 (0.11)</td>
<td>&lt;.001</td>
</tr>
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Abbreviations: Off condition, the patient had received no treatment for 12 hours or merely the lowest dose of levodopa allowing him or her to walk for gait analysis; On-drug condition, after the administration of 200 mg of levodopa.

*All P values for interaction between surgery and levodopa treatment (analysis of variance), except for single-limb support time, were P<.001.
gait parameters, conversely to the clinical scales used in the other studies.\textsuperscript{5,10} In this study, we also observed that levodopa treatment was more efficient than STN stimulation on major gait parameters such as velocity, stride and step length, and the single-limb/double-limb support time ratio.

Other gait studies\textsuperscript{11,12} were only performed after surgery, comparing the off-stimulation state (the stimulator was turned off) to the on-stimulation state (the stimulator was turned on). However, in the off-stimulation state, a microsubthalamotomy effect can never be ruled out with certainty. So, we compared the 2 following states: before STN stimulation (gait analysis performed immediately before surgery) and 3 months after surgery. Indeed, we considered that during this short period, the neurodegenerative process was unlikely to significantly worsen.

After STN stimulation, in the off condition for clinical data, we observed outcomes comparable to the best results previously published for the gait subscore as well as for the UPDRS III score.\textsuperscript{5,6,8} In the on-drug condition, our results were more variable, as observed in the other studies.\textsuperscript{5-10}

Concerning gait analysis in the off condition (Table 2), the effects of surgery concerning velocity and stride length were consistent with what was described in other series.\textsuperscript{11,12} Moreover, both single-limb and mainly double-limb support time (the stance phase time) were decreased. This is correlated to an enhancement of the swing phase duration that is known to be decreased in PD.\textsuperscript{2} Indeed, in patients with PD, there is an increase of the time spent in double-limb support time to obtain a better stabilization of balance. In line with these data, it should be observed that after surgery, the single-limb/double-limb support time ratio was increased, which was due to a stronger decrease of the double-limb support time, suggesting an improvement of balance. Four patients received a very low dose of levodopa that allowed them to walk so that the improvement after surgery, in this condition, was probably underestimated.

In our study, for the kinematic parameters (especially velocity, stride length, and the single-limb/double-limb support time ratio), the benefit induced by STN stimulation was more obvious in the off condition than in the on-drug condition although the same improvement profile was found (Table 2). Moreover, the improvement observed in the on-drug condition is likely to be because of the improvement of hypokinesia rather than improvement of levodopa-induced dyskinesias. Indeed, these levodopa-induced dyskinesias were rather mild before surgery (score, 5.5 on item 28), suggesting they do not play an important part in gait disorders. This difference between the off condition and on-drug condition is in agreement with our clinical scores and with the findings of clinical studies previously described.\textsuperscript{5,10} Furthermore, the sensitivity of our method clearly showed that STN stimulation resulted in a benefit for gait in the on-drug condition (Table 2) while it was not underlined by the clinical gait subscore (Table 1).

Subthalamic nucleus stimulation induces an improvement of gait kinematic parameters (in the off condition), qualitatively similar to that observed with levodopa treatment (Table 2), as has already been reported in other studies evaluating the effect of levodopa treatment on gait disturbances.\textsuperscript{4,20} In gait disturbances, only the stride (and step) time is usually unchanged with levodopa treatment, while it was strongly decreased in our study, and maybe it could be correlated with the high level of levodopa responsiveness in our patients before surgery (>50% improvement on the UPDRS III score).

Furthermore, from a quantitative viewpoint, levodopa treatment was statistically more effective than STN stimulation (Table 3) as concerns major parameters such as velocity, stride and step length, and the single-limb/double-limb support time ratio. In line with what was observed with the kinematic parameters, STN stimulation induced an improvement of variability in the off condition by 27%, whereas levodopa treatment (before surgery) was more effective, with a classic 47% improvement.\textsuperscript{18} This could be explained by the influence of levodopa treatment on nondopaminergic systems, located outside the corticostriatopallidolothalamocortical loop, especially the noradrenergic system.\textsuperscript{21,22} In their study, Faist et al\textsuperscript{1} conclude that STN stimulation is as effective as levodopa treatment. However, the patients of their study were much younger than ours (Faist et al study: mean age, 48.1 years) and we suggest they presented with no or little nondopaminergic lesions.\textsuperscript{23} However, the findings from the study by Stolze et al,\textsuperscript{12} with patients as old as ours, demonstrate that levodopa treatment is more effective than STN stimulation. Thus, the effect of STN stimulation on gait does not seem to be equivalent to that of the levodopa treatment. However, the beneficial effect of levodopa treatment was potentiated by the addition of STN stimulation, suggesting a synergistic effect of the levodopa treatment and surgery.

We had also already analyzed the effect of globus pallidus (GPI) stimulation on gait in PD. Compared with GPI stimulation,\textsuperscript{24} STN stimulation seemed to be more effective, whereas the 2 groups of patients had similar UPDRS III scores, and were similarly levodopa responsive.

<table>
<thead>
<tr>
<th>Table 3. Surgery vs Levodopa Treatment*</th>
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<tbody>
<tr>
<td><strong>Temporal and Spatial Gait Parameters†</strong></td>
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<tr>
<td></td>
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<tr>
<td>Cadence, steps/min</td>
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<td>Stride length, m</td>
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Abbreviations: Off condition, the patient had received no treatment for 12 hours or merely the lowest dose of levodopa allowing him or her to walk for gait analysis; On-drug condition, after the administration of 200 mg of levodopa.

*Data are given as mean (SD). Ellipses indicate not applicable.
†All P values for interaction between surgery and levodopa treatment (analysis of variance), except for single-limb support time, were P=.001.
Another point of interest is the effect of stimulation and levodopa treatment on specific locomotor parameters and its implication in the pathophysiology of gait hypokinesia in PD. Morris et al. stated that in PD, a deficit in control of stride length, rather than a deficit in internal cueing that would affect cadence, constitutes the fundamental deficit. This hypothesis is only partially supported by data of the levodopa treatment, before stimulation: levodopa treatment resulted in an increase of gait velocity that was mainly related to an increase of stride length but also, to a lesser extent, to an increase of cadence. As has been previously emphasized, the effect of stimulation seems to be qualitatively similar to that of levodopa treatment. However, quantitatively levodopa treatment induces a greater increase of gait velocity and, what is more, a greater increase of stride length, whereas the cadence is increased in a surprisingly similar way (24% vs 25%). Thus, these data are fully in agreement with the hypothesis of Morris et al: the deficit in control of stride length is supposed to be the fundamental one.

Morris et al. suggested that cadence regulation could be influenced by locomotor regions at midbrain or spinal level and not by basal ganglia, whereas stride length control could be mediated by the basal ganglia. However, the results of other studies by ourselves concerning the effects of GPi stimulation on gait suggested only poor effects of GPi stimulation on the control of stride length. Thus, we had hypothesized that stride length control could be mediated by basal ganglia other than GPi. The results of the present study could point to the possible role of STN on that stride length regulation.

CONCLUSIONS

Our study showed that STN stimulation improved gait disturbances but the result is different from that obtained with levodopa treatment. However, it remains to be demonstrated whether the beneficial effect of STN stimulation on gait disturbances is lasting in the long term. Objective methods, as proposed in our study, and not only clinical scores must be used to assess the beneficial effect of deep brain stimulation.

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Author contributions: Study concept and design (Drs Krystkowiak, Blatt, Bourriez, Blond, Guieu, Destée, and Defebvre); acquisition of data (Drs Krystkowiak, Blatt, Perina, and Defebvre); analysis and interpretation of data (Drs Krystkowiak, Blatt, Bourriez, Duhamel, Blond, Guieu, Destée, and Defebvre); drafting of the manuscript (Drs Krystkowiak and Perina); critical revision of the manuscript for important intellectual content (Drs Krystkowiak, Blatt, Bourriez, Duhamel, Blond, Guieu, Destée, and Defebvre); statistical expertise (Dr Duhamel); obtained funding (Drs Blond and Destée); administrative, technical, and material support (Drs Blatt, Bourriez, Blond, and Destée);

study supervision (Drs Blatt, Blond, Guieu, Destée, and Defebvre).

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REFERENCES