Transient effects of 80 Hz stimulation on gait in STN DBS treated PD patients: a 15 months follow-up study.

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Background

Subthalamic nucleus deep brain stimulation (STN DBS) is an effective therapeutic option for advanced Parkinson's disease (PD). Nevertheless, some patients develop gait disturbances despite a persistent improvement of PD segmental symptoms. Recent studies reported that stimulation of STN with low frequencies produced a positive effect on gait disorders and freezing episodes.

Objective

To evaluate the effects of 80 Hz stimulation frequency on gait in PD patients undergoing STN DBS and to determine whether such effects are maintained over time.

Methods

We evaluated 11 STN DBS treated PD patients who had developed gait impairment several years after surgery. Gait was assessed by means of the Stand-Walk-Sit (SWS) test. Motor symptoms and activities of daily living were evaluated through the Unified PD Rating Scale (UPDRS). The stimulation frequency was switched from 130 Hz to 80 Hz, adapting the voltage to maintain the same total delivered energy. Patients were assessed at baseline and 3 hours after switching the stimulation frequency to 80 Hz. Follow-up evaluations were carried out after 1, 5, and 15 months. The clinical global improvement scale was rated at every follow-up visit.

Results

A significant improvement of gait (SWS test) was evident immediately after switching the stimulation frequency to 80 Hz, with no deterioration of PD segmental symptoms. However, gait improvement was no longer detectable by the SWS test at follow-up evaluations 1, 5, and 15 months later. Three patients were switched back to 130 Hz because of unsatisfactory control of motor symptoms. Of the eight patients maintained at 80 Hz up to 15 months, five showed a global improvement and three showed no change.

Conclusions

Stimulation frequency at 80 Hz has an immediate positive effect on gait in STN DBS treated patients; however, the objective gait improvement is not maintained over time, limiting the use of this frequency modulation strategy in the clinical setting.

Keywords: subthalamic nucleus; deep brain stimulation; Parkinson's disease; gait

Subthalamic nucleus (STN) deep brain stimulation (DBS) is generally recognized as an established therapeutic option for selected patients with advanced Parkinson's disease (PD).[1] Prospective studies have shown that bilateral high-frequency stimulation of STN improves cardinal symptoms of PD[2]; however, the effectiveness on appendicular PD symptoms (tremor, rigidity, and bradykinesia) is maintained over time,

whereas improvement of axial symptoms (gait, postural stability, and speech) deteriorates after 5 years of follow-up.[3-9] In particular, some patients show a worsening of gait even though the general motor outcome is still significantly improved.[10] Gait disorders and freezing of gait become partially resistant to L-dopa and STN stimulation at the usual high frequencies (i.e., 130-180 Hz). Recent findings[11,12] suggest that modulation of the activity of the pedunculopontine nucleus (PPN) with low-frequency stimulation (15-25 Hz) might be useful in the treatment of these symptoms, even though the benefit of this approach is still a matter of debate. The consideration of frequency modulation as a possible therapeutic strategy in STN DBS treated PD patients who develop severe gait disorders has been raised by Moreau et al.[13] who reported an improvement of gait disturbances and a reduction of freezing episodes by lowering the frequency of STN stimulation from the usual 130 Hz to 60 Hz. However, it has also been reported that STN 60 Hz stimulation had a positive effect on gait and speech but was unable to adequately improve cardinal PD symptoms.[14] The aim of this study was primarily to test the hypothesis that an intermediate stimulation frequency of 80 Hz could improve gait disturbances in STN DBS treated PD patients without loosing effectiveness on cardinal symptoms, and secondarily to determine whether such improvement was maintained over time.

Methods

Patients

We enrolled 11 consecutive PD patients (three females, eight males) submitted to STN DBS who developed gait impairment with frequent falls and/or freezing of gait within the first 5 years from surgery. A written informed consent was obtained from every patient to participate in the study.

Patients were 62.9 ± 4.3 (mean ± SD) years old at surgery and the mean age at PD onset was 46.8 ± 4.1 years. Outcome of surgery was good for all patients; at the first postoperative evaluation 1 year after surgery, the Unified Parkinson's Disease Rating Scale (UPDRS) motor score improved 43% (P = 0.003) with STN stimulation and 52% (P = 0.003) after administration of a suprathreshold dose of L-dopa (1.5 times the usual morning dose). There were no significant L-dopa-resistant axial symptoms.

At the beginning of the study, the mean time interval since STN DBS initiation was 4.5 ± 1.4 years. The UPDRS motor score improved 35% (P = 0.003) with STN stimulation and 48% (P = 0.003) after administration of a suprathreshold dose of L-dopa.

All patients were stimulated with cathodic unipolar stimulation, at a frequency of 130 Hz, a pulse width of 60 microseconds and a mean voltage of 3.3 V (range 3.2-3.4 V) for the left STN and 3.4 V (range 3.2-3.4 V) for the right STN; dorsal contacts (2 and 3 for the left STN and 6 and 7 for the right STN) were used in all but one patient for whom contacts 1 and 5 were used. Dopaminergic therapy, expressed in L-dopa equivalent daily dose (LEDD) according to standard conversions[15] was 757 ± 262 mg/d.

Study protocol

The study protocol was divided in two phases: phase-1, to test the acute effect of switching the stimulation frequency from 130 Hz to 80 Hz and phase-2, to determine whether this effect was maintained over time.

Phase-1

Patients were evaluated at baseline with the usual stimulation frequency of 130 Hz during "ON-drug" conditions after the usual morning dose of L-dopa. The stimulation frequency was then switched to 80 Hz and the voltage adjusted to maintain constant the total energy delivered (TEED) according to the equation: TEED (1s) = voltage2 × frequency × amplitude/impedance. After 3 hours of stimulation at 80 Hz the evaluation was repeated.

Phase-2

Follow-up evaluations were carried out after 1, 5, and 15 months of chronic 80 Hz stimulation under the same "ON-drug" conditions after the first morning dose of L-dopa.

The evaluation included the UPDRS part II (Activities of Daily Living) and part III (Motor Examination); subscores for falling (item 13), freezing of gait (item 14), walking (item 15), resting tremor (item 20), rigidity (item 22), bradykinesia (items 23-26), and axial symptoms (items 18, 27-30) were analyzed.

A video recording of the standardized timed Stand-Walk-Sit (SWS) test over a distance of 7 meters was used for gait evaluation.[16] One blinded investigator assessed by video the SWS test completion time, the number of steps and the number of freezing episodes, while the second unblinded investigator scored UPDRS part II and III and modified stimulation parameters. If required on clinical basis, the unblinded investigator could adjust dopaminergic therapy and stimulation settings in order to optimize PD symptoms improvement. Stimulation amplitude was adjusted by 0.2 V steps maintained for at least 1 hour. The investigator's clinical global impression of patient improvement (CGI-I) was rated at every follow-up visit on a five-point scale: (1) great improvement, (2) moderate improvement, (3) slight improvement, (4) no change, (5) worsening.[17]

Adjustments of stimulation amplitude and dopaminergic therapy were allowed to optimize PD symptoms improvement.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL). As normality could not be assumed in this small group of patients, the nonparametric Friedman test for repeated measures followed by a Wilcoxon test was used to compare UPDRS scores and SWS test results in different conditions and at different time points; a probability (P) values < 0.05 was considered statistically significant.

Results

Acute effects

The time and the number of steps needed to complete the SWS test were significantly reduced in the 80 Hz stimulation condition compared with the baseline 130 Hz stimulation condition, whereas there were no freezing episodes elicited during the test in neither of the stimulation conditions (Table 1).

Table 1 Stand-Walk-Sit Test: results are expressed as median (first quartile-third quartile)

SWST	Baseline 130 Hz	3 h 80 Hz	1 mon 80 Hz	5 mon 80 Hz	15 mon 80 Hz
Completion time	24 (18.5-29)	19 (16-23.5)[a,b]	22 (22-26)	25 (22-30)	23 (22-31.5)
Number of steps	24 (20.5-29.5)	21 (18-23.6)[a,b]	23 (20-29)	26 (20.5-31.5)	29 (24-38)[a,c]
FOG episodes	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1.5)	0 (0-1.5)

SWST = Stand-Walk-Sit Test; FOG = freezing of gait.

[a] Friedman test; $P < 0.05$.

[b] Wilcoxon test; $P < 0.05$ baseline 130 Hz $\neq$ 3 h 80 Hz.

[c] Wilcoxon test; $P < 0.05$ baseline 130 Hz $\neq$ 15 mon 80 Hz.

Follow-up evaluations

Eight of the 11 patients completed the study and were followed up to 15 months with chronic 80 Hz stimulation. Three patients were switched back to 130 Hz frequency stimulation after the first month

evaluation because of increased tremor (two patients) or worsening of gait and rigidity (one patient). Comparing the 80 Hz stimulation condition at 1, 5, and 15 months, to the 130 Hz stimulation condition at baseline, the time needed to complete the test was not significantly different at all follow-up evaluations, whereas the number of steps was not significantly different from baseline at 1 and 5 months, but it was significantly increased at 15 months. The number of freezing episodes did not vary significantly at any time point (Table 1). Compared to the 130 Hz baseline condition, there was a significant reduction of the UPDRS total motor score at 1 month that was no longer evident at 5 and 15 months. Analyzing UPDRS motor subscores, only akinesia showed a transient improvement after 1 month that was no longer evident at 5 and 15 months; no significant differences were found for tremor, rigidity, and axial score (Table 2).

Table 2 UPDRS II and III motor scores, LEDD, and stimulation settings: results are expressed as median (first quartile-third quartile)

	Baseline 130 Hz	1 mon 80 Hz	5 mon 80 Hz	15 mon 80 Hz
UPDRS II: Activities of daily living				
UPDRS II total score (/52)	18.25 (15.25-22.75)	15 (11.12-17.87)	18 (10.5-21.5)	18.25 (16.25-22.12)
Falling (/4)	1 (0-2.75)	0.5 (0-1)	0.5 (0-1.75)	1 (0-2)
Freezing of gait (/4)	2.5 (2-3)	1 (0-2)[a,b]	2.5 (1-3)	2 (1-2.75)
Walking (/4)	1.5 (1-2)	1 (1-1.9)	1.5 (1-2)	2 (1-2)
UPDRS III: Motor examination				
UPDRS III total score (/108)	19.5 (12.87-29.25)	14 (10.25-19.12)[a,b]	20 (13.12-26.62)	21.5 (13.12-27)
Rest tremor (/20)	0.25 (0-0.5)	0 (0-0.5)	0 (0-0.37)	0 (0-0)
Rigidity (/20)	3.75 (2.75-5.25)	3.25 (1.75-3.87)	3 (2.12-4)	2.75 (1.37-4.25)
Akinesia (/32)	4.25 (1.62-8.87)	1.75 (0.62-3.12)[a,b]	5.75 (1.75-9.62)	5.25 (1-8.75)
Axial score (/16)	7.25 (4.12-8.37)	5 (3.75-7.25)	6 (4.62-8.25)	7.25 (4.87-7.87)
LEDD	740 (520-1037)	740 (520-1050)	815 (520-1050)	650 (505-1037)
Voltage right STN	3.4 (3.2-3.4)	4.5 (3.9-4.5)	4.5 (4.3-4.9)	4.8 (4.5-5.0)
Voltage left STN	3.4 (3.0-3.5)	4.5 (4.0-4.5)	4.5 (4.2-4.9)	4.7 (4.5-5.0)

UPDRS = Unified Parkinson's Disease Rating Scale; LEDD = L-dopa equivalent daily dose; STN = subthalamic nucleus.
[a] Friedman test; $P < 0.05$.
[b] Wilcoxon test; $P < 0.05$ baseline 130 Hz $\neq$ 1 mon 80 Hz.

The UPDRS part II subscore for freezing of gait transiently improved after 1 month of 80 Hz stimulation, but returned to values comparable to baseline at the 5 and 15 months evaluations. No significant variations were detected in the UPDRS part II total score and in subscores for falling and walking.

The stimulation voltage (3.4 [3.2-3.4] V) in use with 130 Hz frequency at baseline was increased when switching the stimulation frequency to 80 Hz (4.5 [3.9-4.5] V) to maintain equivalent delivered energy levels. The voltage remained unchanged at 1 and 5 months and it was increased slightly at 15 months (4.7 [4.5-5.0] V). No significant modifications of dopaminergic therapy were made at 1 and 5 months; at 15 months, there was a slight reduction of median LEDD (90 mg/d) that did not reach significance.

At the first month evaluation, according to the CGI-I scale (Table 3), five patients showed great improvement, three moderate improvement, and three a worsening. The three patients who worsened were switched back to 130 Hz stimulation and dropped out of the study. At 5 months, two patients showed great improvement, one moderate improvement, two slight improvement, and three no change. At 15 months, two patients still showed great improvement, two moderate improvement, one slight improvement, and three no change.

Table 3 CGI-I: investigator's clinical global impression of patient improvement ratings at each follow-up evaluation

CGI-I (no. of patients)	1 mon (n = 11)	5 mon (n = 8)	15 mon (n = 8)
Great improvement	5	2	2
Moderate improvement	3	1	2
Slight improvement	0	2	1
No change	0	3	3
Worsening	3	–	–

CGI-I = Clinical Global Impression-Improvement scale.

Discussion

The results of the current study show that there is an immediate positive effect on gait by reducing the stimulation frequency from 130 Hz to 80 Hz at equivalent delivered energy levels. This improvement of gait is, however, not maintained over time. The slight reduction in the number of steps and completion time quantified on the SWS test was present only straightaway after the frequency change, but it was no longer evident after 1 month of continuous 80 Hz stimulation. Conversely, only three of the 11 patients had to be switched back to 130 Hz for incomplete control of motor symptoms, whereas in the remaining eight patients, there was no significant modification of the UPDRS motor score up to 15 months from the frequency change. Freezing of gait was reduced according to the UPDRS II subscore at the first month evaluation, but this improvement, as well was short lasting, was no longer evident at 5 and 15 months. Still after 15 months, patients were able to walk better on the 80 Hz stimulation, even though this subjective benefit in gait performances could not be objectively quantified on the SWS test nor in the ratings of UPDRS subscores.

In the seminal study by Moreau et al.,[13] follow-up data at 8 months indicate that the clinical gait benefit with 60 Hz stimulation was still satisfactory in 85% of patients, although it was necessary to slightly increase the daily L-dopa dose to achieve the same clinical benefit. Our findings show that eight of 11 patients (72%) could be maintained with 80 Hz stimulation up to 15 months, and five of these patients (45%) displayed a clinical global improvement, whereas three patients (27%) showed no change.

An interesting similarity between the two studies is the slight improvement of akinesia with stimulation at low frequencies that may have contributed to the reduction of freezing of gait.[13] In our study, the number of freezing of gait episodes elicited during the SWS test was very low even if patients reported freezing in everyday life conditions. It is possible that a more complex and naturalistic walking task and the use of a specific questionnaire could have better measured this intrinsically variable phenomenon.[18]

One open question is whether different disease phenotypes of PD are better candidates to frequency modulation than others. In our group of patients, the nontremor dominant phenotype was apparently favored for lower frequency stimulation, because two of three patients who did not tolerate the stimulation at 80 Hz were tremor dominant, whereas only one of eight patients who benefited from 80 Hz stimulation displayed a tremor dominant phenotype.

The pathophysiologic mechanisms involved in the effects of frequency modulation remain to be elucidated. One hypothesis concerns the current spread to structures around the STN area, possibly to fibers projecting to the PPN, because the direct low-frequency stimulation of the human PPN produces gait improvement.[11] Alternatively, different DBS frequencies may boost disease impaired local activity in the gamma band (60-90 Hz) within the basal-ganglia cortical loop.[19]

In conclusion, in this study we have shown that reducing the stimulation frequency from 130 Hz to 80 Hz has a transient positive effect on gait impairment in STN DBS treated patients; however, the objective benefit achieved by stimulation at 80 Hz is not clearly maintained over time.

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