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ORIGINAL COMMUNICATION

Low-frequency subthalamic nucleus deep brain stimulation for axial symptoms in advanced Parkinson's disease

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Abstract Axial symptoms such as freezing of gait and falls are common manifestations of advanced Parkinson's disease (PD) and are partially responsive to medical treatment. High-frequency (≥130 Hz) deep brain stimulation (DBS) of the subthalamic nucleus (STN) is highly efficacious in ameliorating appendicular symptoms in PD. However, it is typically less effective in improving axial symptomatology, especially in the long term. We have studied the effects of low-frequency stimulation (LFS) (≤80 Hz) for improving speech, gait and balance dysfunction in the largest patient population to date. PD patients with bilateral STN-DBS and resistant axial symptoms were switched from chronic 130 Hz stimulation to LFS and followed up to 4 years. Primary outcome measures were total motor UPDRS scores, and axial and gait subscores before and after LFS. Bivariate analyses and correlation coefficients were calculated for the different conditions. Potential predictors of therapeutic response were also investigated. Forty-five advanced PD patients who had high frequency stimulation (HFS) for 39.5 ± 27.8 consecutive months were switched to LFS. LFS was kept on for a median period of 111.5 days before the assessment. There was no significant improvement in any of the primary outcomes between HFS and LFS, although a minority of patients preferred to be maintained on LFS for longer periods of time. No predictive factors of response could be identified. There was overall no improvement from LFS in axial symptoms. This could be partly due to some study limitations. Larger prospective trials are warranted to better clarify the impact of stimulation frequency on axial signs.

Keywords Deep brain stimulation · Gait · Low frequency · Subthalamic nucleus

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Introduction

Axial symptoms, such as freezing of gait (FOG), falls and hypophonia, are common manifestations of advanced Parkinson's disease (PD), ranging in frequency from 20–60 % depending on study type [3]. In PD patients there is a ninefold increase in falls [2], not infrequently leading to fractures, rendering them a major source of disability, dependence and morbidity. FOG, on the other hand, can also be seen even in the early stages of the disease [11] and can be associated with levodopa treatment, although it is

more common in the off medication state and with longer disease duration [10]. subthalamic nucleus-deep brain stimulation (STN-DBS) is an approved and robust symptomatic treatment for appendicular parkinsonian symptoms such as tremor, bradykinesia and rigidity, but its beneficial effects on axial symptoms remain controversial. Earlier reports and meta-analyses on patients who underwent STN-DBS suggested some improvement in postural instability and gait disturbance (PIGD) [1], with younger age and levodopa responsive axial symptoms as positive predictors [29]. However, this view has been more recently challenged from data coming from long-term follow-up studies [6, 7, 16, 21, 23] and those that evaluated STN vs. globus pallidus internus (GPi) DBS [9]. These studies have reported a progressive loss of stimulation benefit in regards to axial symptoms, but this worsening has been related to the progression of the disease rather than lack of DBS efficacy. Whether continued stimulation itself contributes to postural instability remains uncertain. Additionally, the recent Veterans Affairs study has indicated that patients with conventional STN-DBS may have an increased number of falls after surgery, at least compared to GPi-DBS [9], although this observation was not confirmed by their last results at 36 months [27]. In that latter study, STN and GPi surgery had the same outcomes in regards to axial subscores, as measured by the UPDRS part II and III.

STN stimulation for PD is usually delivered using high frequencies, typically in the range of 130–185 Hz. Although these frequencies have been shown to be the most efficacious in controlling tremor, rigidity and bradykinesia, their effects on axial symptoms have been less evident. To our knowledge, only three other studies with a limited number of patients and mixed results have attempted to evaluate the effects of low frequency stimulation (LFS), typically 80 or 60 Hz, on postural instability and falls in advanced PD patients [4, 18, 22].

In the present study we have analyzed the effects of high-frequency stimulation (HFS) and LFS in a subgroup of our population of PD patients with bilateral STN-DBS who developed troublesome axial features at variable time points after surgery. We sought to confirm and expand on previous positive reports from small open label studies that LFS could be beneficial in PIGD and identify any predictors of outcome.

Methods

Patients with idiopathic PD and HFS (130–185 Hz) of the STN, regularly followed up at the Toronto Western Hospital Movement Disorders Center, were involved in the study.

Patients were selected because of the presence of one or more of the following conditions after medical optimization and physiotherapy or speech-therapy: (a) early loss of axial improvement (less than 1 year) after STN DBS (b) loss of axial benefit after several years of STN DBS (c) no satisfactory benefit from conventional HFS despite optimization of medical treatment and physiotherapy (d) severe hypophonia, alone or in conjunction with other axial symptoms.

The patients included in the study were switched to LFS when all previous stimulation adjustments using HFS had failed to improve or stabilize axial symptoms. Voltage was increased at the same time in an attempt to keep the total electrical energy delivered (TEED) at a comparable level.

There was no predefined frequency of parameter adjustment using LFS rather than an as needed approach, however patients who could tolerate LFS without side effects were left on it long term.

Data were collected prospectively over the years in an open label way.

Statistical analysis

As primary outcome measures we used the total motor UPDRS scores, total axial subscores (items 18, 27–30) and gait subscores (item 29) before and after the switch to LFS at the last available visit, whereas secondary outcomes were the speech subscores (item 18), as well as the self-reported number of falls with high and LFS. The number of falls was extracted from clinic visit notes and classified as no falls, rare (<1/month), monthly (>1/month but <1/week), weekly (>1/week but <1/day) and daily (≥1/day). The TEED was calculated based on the formula: V^2 (Voltage)/R (Impedance) × (PW) pulse width × f (frequency) [15].

Exploratory analyses were conducted to identify potential predictors of a positive LFS response. The strength and magnitude of potential associations between two continuous features were explored using Spearman's rank correlation coefficient. The comparison of a single continuous feature across a binary categorical feature was performed using the Wilcoxon rank sum test, whereas the comparison across polytomous (>2) categorical features was performed using the Kruskal–Wallis test. The chi-square test, or where appropriate, Fisher's exact test were used to test categorical associations. Pre-post comparisons of continuous features were conducted using the Wilcoxon signed rank test. A p value of 0.05 was considered statistically significant. Continuous measures are presented as means and standard deviations, whereas categorical measures are presented as counts and percentages. The SAS software package version 9.3 was used for statistical analyses.

Results

Forty-five patients were involved in the study. There were 35 males (77.8 %) and ten females (22.2 %). Mean age was 59.5 ± 7.8 years and mean disease duration was 17.8 ± 5.7 years. All but one of them had bilateral STN stimulation. One of them had a third electrode placed in the left GPi, two patients had also unilateral pedunculopontine nucleus stimulation, one had undergone fetal mesencephalic tissue grafting in the past and one had a previous right pallidotomy.

Baseline (before STN-DBS surgery) data are shown in Table 1.

Motor outcomes with HFS

Patients had chronic HFS for 39.5 ± 27.8 months before changing to LFS. Their clinical characteristics after surgery are summarized in Table 1.

Based on the self-reported number of falls, 4.3 % of patients had no falls, 4.3 % only rare ones, 17.4 % would fall once a month, 34.8 % once per week, and 39.1 % at least once daily.

The patients' mean levodopa response was 36.2 ± 18.4 % at the last post-operative assessment. The TEED was (R/L) 16.8/16.2 μJ.

Motor outcome with LFS

Thirty-nine patients were switched to 80 Hz and six patients to 60 Hz. Patients were reassessed at a median follow-up time of 111.5 days (range: 1–1,513 days) after the frequency change.

There was no improvement in any of the primary outcome measures with LFS in the on medication state.

Main results with LFS are shown in Table 2.

The number of falls did not differ with LFS, although there was a trend for better outcomes with HFS ($p = 0.07$).

In regards to patients' self-reported perceived benefit, 13 patients (28.9 %) had transient benefit in gait and balance, 18 (24.4 %) had some benefit in speech and 21 reported no benefit whatsoever (Table 3).

With regard to side effects, 14 patients (31.1 %) reported worsening of tremor, four (8.9 %) had worsening of off dystonia, three (6.7 %) worsening gait, and one (2.2 %) upper limb paresthesias, whereas 23/45 (51.11 %) experienced no side effects (Table 3). However, seven patients (15.5 %) had to be switched back to 130-Hz stimulation within 48 h due to intolerable worsening of their symptoms (mainly tremor and gait). Overall, 12/45 patients remained on LFS, seven of them on 80 Hz, one of them on 65 Hz, three of them on 60 Hz and one on 50 Hz.

Table 1 Patients' clinical characteristics before surgery and at the last available follow-up with HFS of the STN

	Before STN DBS	130 Hz DBS
Motor UPDRS off/on meds (/108)	43.9/17.7	30.5/28.2
Axial subscore off/on meds (/20)	8.9/4.2	8.4/7.4
Gait subscore off/on meds (/4)	2.3/0.7	1.8/1.5
Freezing subscore off/on meds (/4)	2.2/0.7	1.6/1.3
Falls subscore off/on meds (/4)	1.3/0.7	0.9/1.2
LD response (%)	56.7	45
Speech (item 18) on meds	1.18	2.2
LEDD	1433.4	930.5

Data are presented as means

Table 2 Primary outcomes and speech outcome for HFS vs. LFS

	130 Hz STN DBS	80 Hz STN DBS	*p* value
Motor UPDRS on meds (/108)	28.2	31.9	0.79
Axial subscore on meds (/20)	7.4	7.6	1.00
Gait subscore on meds (/4)	1.5	1.7	0.77
Speech subscore on meds (/4)	2.2	2.1	0.77
TEED R/L (μJ)	167.9/162.3	94.0/95.4	<0.0001

Data are presented as means

Table 3 Self-reported improvements (even transient) and side effects with 80-Hz stimulation

Subjective symptoms	Improvement	Side effects
Balance and gait (*N*/%)	13/28.9	
Speech (*N*/%)	18/40	
None (*N*/%)	21/46.7	
Worsening balance and falls (*N*/%)		3/6.7
Worsening of dystonia (*N*/%)		4/8.9
Worsening of tremor (*N*/%)		14/31.1
Paresthesia (*N*/%)		1/2.2
None (*N*/%)		23/51.1

We performed a post hoc analysis of those 12 patients, who tolerated long term LFS, however results did not differ (Figs. 1, 2).

We employed bivariate analyses between the three primary outcome measures (motor UPDRS scores, axial and gait subscores) on 80 Hz in the on medication state. There was no association with either the preoperative levodopa response or the patients' disease duration at the time of change in the frequency of stimulation (correlation coefficient $r = 0.01$ and $r = 0.19$ for motor UPDRS with

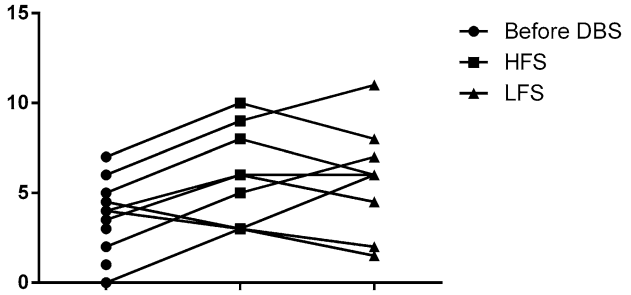

Fig. 1 Axial subscores in the ON medication condition, before DBS, using HFS and LFS. Results shown for the 12 patients who tolerated long term LFS

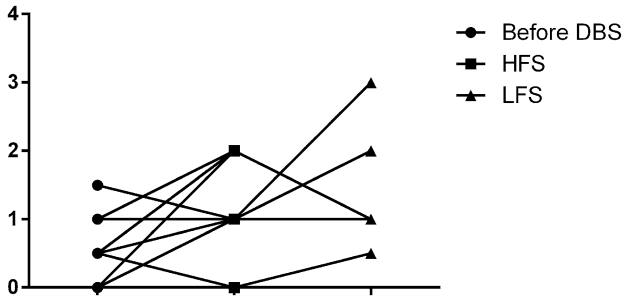

Fig. 2 Gait subscores in the ON medication condition, before DBS, using HFS and LFS. Results shown for the 12 patients who tolerated long term LFS

preoperative levodopa response and disease duration respectively, $r = -0.07$ and $r = 0.15$ for the axial subscore, $r = 0.02$ and $r = 0.12$ for gait, level of significance set at 0.05).

Discussion

This study presents the largest cohort of patients who were treated with LFS for medication and HFS-refractory axial symptoms. We did not find a significant improvement on axial symptoms from the switch to LFS, apart from isolated patients who subjectively benefited from it.

Our study provides further information on the use of LFS for axial symptoms in advanced PD. First, if LFS is at all effective, the gains from a symptom perspective are likely modest and not easily captured by standard clinical scales such as the motor UPDRS and its axial and gait subscores. Moreover, a substantial proportion of our patients were not able to tolerate LFS at all, or worsened on it compared to conventional 130 Hz stimulation.

Our study is in accordance with the one by Ricchi et al. [22] that assessed in a partially blinded fashion for up to 15 months 11 STN-DBS PD patients who were tried on 80 Hz stimulation. While there was an initial improvement in axial parameters by 1 month, this benefit had already worn off by 5 months.

However, our results are in conflict with those reported by Brozova et al. [4]. The authors followed-up nine STN-DBS PD patients in an open label study on 60 Hz for 8–12 weeks, after three other patients had failed to tolerate LFS due to worsening tremor, rigidity and gait. In these nine patients, the authors found an average 3.9 point improvement in the UPDRS part II scores, as well as speech, falling and walking subscores. However, total axial subscores worsened in two patients. An average voltage increase of 1.3 V bilaterally was required to sustain control of PD symptoms.

Moreau et al. [18] blindly assessed 13 PD patients on 130 and 60 Hz STN stimulation with different voltages but equivalent TEED. They found a beneficial effect of 60 Hz on freezing episodes during the stand–walk–sit test, while the UPDRS scores and subscores did not differ statistically between 60 and 130 Hz. They were able to maintain 85 % of their patients with LFS at 8 months of follow-up.

Overall, these studies support the conclusion that the UPDRS may not the most appropriate scale to assess gait and balance changes with surgical treatments also due to its lack of sensitivity. Using blindly assessed kinematic parameters, Moreau et al. [19] studied four patients with bilateral implants in the STN and the pedunculopontine (PPN) nucleus. They found that stride length demonstrated greater improvement in the on and off L-Dopa condition when using 60-Hz STN stimulation alone vs. 25-Hz PPN stimulation. Although the study was limited by the low number of patients, it shows the utility of more sophisticated methods of gait assessments when outcome magnitudes are more subtle.

In regards to the pathophysiology underlying the effects of STN stimulation on gait, it could either involve current spread to nearby structures or excitation of fibers to nearby locomotor areas, such as PPN. The former, although frequently reported and discussed in the pertinent literature, is unlikely given the fact that the STN and PPN are not in direct anatomical proximity. On the other hand, it is known that the PPN and STN are anatomically reciprocally connected and thus likely functionally coupled [5, 12, 13, 17, 20]. Furthermore, despite evidence that the PPN is critically involved in gait control, it is uncertain as to what the optimal or "healthy" firing frequency is, as alpha [24], beta [28] and gamma bands [14] have been reported to be generated in the PPN. However, driving the STN at frequencies in the beta band can make bradykinesia, and possibly gait worse [8]. As such it still remains elusive as to the optimal frequency window for DBS stimulation of the STN in refractory axial symptoms, if one postulates a direct effect of STN DBS on PPN. Recently Tsang et al. [25] employed individualized frequencies to PD patients

with externalized STN DBS leads at theta, beta and gamma bands. Intriguingly, gamma band DBS was as effective as conventional HFS in ameliorating parkinsonian symptoms, whereas theta and beta band DBS did not worsen their control, contrary to what was expected. These findings might open the way to customized DBS and suggest that many aspects of the functionality of cerebral oscillatory networks remain to be unraveled [26].

HFS of the STN using relatively high voltages, as frequently happens in daily clinical practice, might involve structures outside the STN and have deleterious effects on axial signs. However, it remains a mystery why in some patients these possible negative effects appear several months or years of continuous high-frequency stimulation and why the simple change of frequency can be beneficial.

The possible different responses to STN stimulation frequencies in PD patients raise also the question whether different PD phenotypes actually respond to a more individualized DBS treatment, as tremor frequently worsens with LFS and tremor predominant patients may require either an increase in voltage and/or L-Dopa dosage or be less suitable candidates for LFS overall.

Moreover, as some patients also experienced some subjective improvement in speech with LFS (or resolution of HFS-related speech impairment), we could propose a two-step stimulation approach for those affected with similar issues, i.e., switching from HFS to LFS when needed and in those patients who can tolerate it. There is also some evidence from previous studies that speech parameters can improve with LFS [30].

Our study findings should be viewed in light of its limitations. First, raters were different at subsequent office visits and assessments were not double-blinded. For outcome measures we used the standard motor UPDRS and the axial subscores to capture potential improvement in hypophonia and gait scores. Using patient questionnaires or falls diaries could have been a more sensitive outcome measure to assess for moderate but clinically important long-term benefits in axial symptom control. We did not use objective and more gait-specific assessment tools, such as the GaitRite gait analysis system, which may have provided further useful insights and captured more subtle changes in gait parameters. Finally, the TEED was not kept constant, despite our attempts to adjust for it. However, the real impact of the TEED using both low and high frequencies remains unclear and merits further investigation. Finally, a type II error cannot be excluded in our study, thereby failing to detect a subtle but real trend, due to an insufficient sample size and lack of statistical power.

In summary, despite the lack of clinical benefit, our study provides further insight into the intriguing use of LFS for axial symptoms in advanced PD. As there are currently no satisfactory therapeutic options for gait disturbances in PD, new treatment modalities are needed. For LFS to find its place as one such modality, larger, prospective, blinded trials are needed, focusing not only on common motor outcomes but also on detailed gait assessment. Establishing predictive factors for responders and potentially excluding patients which are unlikely to benefit, such as patients with tremor-dominant PD, will be another challenging but clinically meaningful task.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard The University Health Network Research Ethics Board approved the study. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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