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80 Hz versus 130 Hz subthalamic nucleus deep brain stimulation: Effects on involuntary movements

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Abstract

Background

Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) represents a valid therapeutic option for advanced Parkinson's disease (PD), leading to a significant amelioration of motor fluctuations and levodopa-induced involuntary movements (IM). This study address the issue of whether stimulation frequency may influence the control of IM in STN-DBS treated patients, comparing the effects of 80 Hz and 130 Hz STN-DBS frequencies in 10 parkinsonian patients with residual IM (dyskinesia in 6 cases and dystonia in 4 cases).

Methods

Patients were evaluated by means of the Rush Dyskinesias Rating Scale (blinded-video analysis) and Unified Parkinson's Disease Rating Scale at 4 different time-points: baseline, shortly after the switch of stimulation frequency from 130 Hz to 80 Hz, after 1 month and 12 months of chronic 80 Hz stimulation.

Results

IM improved in most subjects after the switch of stimulation frequency: dyskinesias improved in 6/6 subjects and dystonic features in 3/4 subjects after one month of 80 Hz stimulation. However, the 130 Hz STN stimulation was restored in 4 subjects during the following months, because of a gradual worsening of

parkinsonian symptoms. A sustained efficacy on motor features and IM was observed with 80 Hz stimulation frequency in the remaining patients.

Conclusions

In this limited cohort of STN-DBS patients, we observed an improvement of residual IM after the switch of stimulation frequency from 130 Hz to 80 Hz. However, a moderate worsening of parkinsonian symptoms was observed in a portion of patients, requiring to return at 130 Hz STN-DBS.

Keywords

Subthalamic nucleus deep brain stimulation;

Frequency;

80 Hz;

Dyskinesia;

Dystonia

1. Introduction

A frequency-dependent mechanism of action has been proposed for Subthalamic Nucleus (STN) Deep Brain Stimulation (DBS), starting from the clinical observation that frequencies ranging from 130 to 185 Hz can induce an amelioration of Parkinson's disease (PD) cardinal symptoms [1] and [2], while frequencies ≤ 20 Hz may induce a worsening of parkinsonian features [2]. STN-DBS usually lead to a significant improvement of motor fluctuations and involuntary movements (IM): stimulus-related dyskinesias can be frequently induced by increasing the intensity of stimulation in the first phases after surgery [3], while they usually disappear with time, resulting in a significant amelioration of peak-dose dyskinesias, diphasic dyskinesias and off-dystonias [2], [3] and [4].

Nevertheless, compared to the Globus pallidus pars interna (GPi) DBS, where a direct antidyskinetic effect has been postulated [5], the mechanisms of action of STN-DBS on IM are not completely understood; several factors may contribute to the amelioration of IM observed with STN-DBS, including the reduction of dopaminergic therapies [4]. However, an adequate control of IM can not always be achieved [6] and different stimulation strategies can be assessed, using a bipolar configuration, in order to deliver a more spatially focused electrical field [3], or activating an additional contact located dorsally to the STN, as suggested by Herzog et al. [6].

At the present time, no data have been reported on the possible role played by the switch of stimulation frequency in the control of IM. This approach has been proposed by Moreau et al. [7] and [8], who found a significant improvement of gait disturbances, freezing of gait [7] and dysarthropneumophonia [8] with a 60 Hz STN stimulation. Moreover, Brozova et al. [9] later confirmed these findings, while Ricchi et al. [10] suggested that similar effects could be obtained with a frequency of 80 Hz, which may represent a good compromise between axial symptoms improvement and the possible worsening of PD cardinal features associated to low stimulation frequencies.

In spite of these promising clinical results, the frequency modulation mechanisms of action still largely remain unclear [7], [8], [9] and [10]. In this context, in order to evaluate whether a frequency modulation approach may represent a possible alternative for DBS-treated patients with residual IM, we investigated the effects of two STN-DBS frequencies (80 Hz and 130 Hz) in 10 PD patients with IM not adequately controlled by the conventional parameters of stimulation.

2. Material and methods

2.1. Patients

Ten consecutive STN-DBS patients with residual IM were enrolled in the study, representing 9.4% of patients treated with STN-DBS in the previous 10 years and regularly followed-up at the outpatients clinic of our Hospital. Age at surgery was 59.4 ± 4.8 (mean \pm SD) years, age at PD onset was 48.6 ± 4.5 years, and the time interval since STN-DBS implant was 2.12 ± 1.3 years (range 9–40 months). Five patients were classified as having “peak dose dyskinesias” (choreic IM, preferentially involving upper limbs, reaching the maximum intensity more than 1 h after the levodopa dose administration); 1 patient was classified as having “diphasic dyskinesias” (IM with dystonic and ballistic features of the lower limbs, with a maximum expression shortly after the levodopa dose administration and at the end of its effect); 2 patients showed perioral dystonic features, that in one case worsened shortly after each levodopa dose administration, and in the other case did not show a clear association with the levodopa intake; 2 patients had a stable dystonic posture of the lower limb that did not change with levodopa administration.

2.2. STN procedure, stimulation parameters and pharmacological treatment at baseline

The bilateral stereotactical STN quadripolar electrode implantation (Electrode model 3389, Medtronic, Minneapolis, MN, USA) was performed according to the surgical procedure previously described elsewhere [11]. As shown in Table 1, at baseline 8 subjects were stimulated with a bilateral cathodic unipolar stimulation, 1 subject with bipolar stimulation on adjacent contacts on the left STN and cathodic unipolar stimulation on the right STN and 1 subject with bilateral bipolar stimulation on adjacent contacts; the frequency of STN stimulation was 130 Hz and the pulse width was 60 μ s for all patients. These STN patterns of stimulation represented the best clinical compromise, reached after several modifications of electrode active contacts, voltage, frequency, pulse width and pharmacological therapies. Pharmacological therapies are also reported in Table 1, as well as the total levodopa equivalent daily dose (LEDD).

Table 1
Baseline clinical and demographic main characteristics.

Patient	Type of motor complication	Clinical phenotype	UPDRS-III score "off"	STN Dx stimulation parameters	STN Sx stimulation parameters	LEDD	Pharmacological therapies
Patient #1 female	Peak dose dyskinesia	TD	31	Unipolar 2(-); 2.5 V; 60 μ s; 130 Hz	Bipolar 2(-)/1(+); 2.6 V; 60 μ s; 130 Hz	200 mg	Levodopa, amantadine
Patient #2 Female	Peak dose dyskinesia	AR	47	Bipolar 7(-)/6(+); 4.0 V; 60 μ s; 130 Hz	Bipolar 3(-)/2(+); 3.4 V; 60 μ s; 130 Hz	650 mg	Levodopa, pramipexole, amantadine
Patient #3 female	Peak dose dyskinesia	TD	76	Unipolar 3(-); 3.2 V; 60 μ s; 130 Hz	Unipolar 2(-); 3.2 V; 60 μ s; 130 Hz	400 mg	Levodopa
Patient #4 male	Peak dose dyskinesia	TD	39	Unipolar 7(-); 3.2 V; 60 μ s; 130 Hz	Unipolar 3(-); 3.1 V; 60 μ s; 130 Hz	400 mg	Levodopa, amantadine, clonazepam
Patient #5 male	Peak dose dyskinesia	TD	40	Unipolar 5(-); 3.4 V; 60 μ s; 130 Hz	Unipolar 2(-); 3.4 V; 60 μ s; 130 Hz	750 mg	Levodopa, pramipexole, amantadine
Patient #6 female	Diphasic dyskinesia	AR	37	Unipolar 6(-); 2.8 V; 60 μ s; 130 Hz	Unipolar 2(-); 2.6 V; 60 μ s; 130 Hz	700 mg	Levodopa, pramipexole, amitriptyline
Patient #7 female	Dystonia: lower limb	AR	56	Unipolar 7(-); 3.6 V; 60 μ s; 130 Hz	Unipolar 3(-); 3.6 V; 60 μ s; 130 Hz	550 mg	Levodopa, ropinorole, quietapine, duloxetine, delorazepam
Patient #8 male	Dystonia: lower limb	AR	48	Unipolar 5(-); 3.4 V; 60 μ s; 130 Hz	Unipolar 1(-); 3.6 V; 60 μ s; 130 Hz	620 mg	Levodopa, ropinorole
Patient #9 male	Perioral dystonia	TD	34	Unipolar 6(-); 3.0 V; 60 μ s; 130 Hz	Unipolar 2(-); 2.5 V; 60 μ s; 130 Hz	700 mg	Levodopa, entacapone, pramipexole
Patient #10 female	Perioral dystonia	TD	23	Unipolar 5(-); 3.0 V; 60 μ s; 130 Hz	Unipolar 1(-); 3.2 V; 60 μ s; 130 Hz	250 mg	Levodopa, rotigotine

TD: tremor dominant; AR: kinetic-rigid; LEDD: levodopa equivalent daily dose.

Table options

2.3. Study protocol

At baseline, patients were evaluated in two conditions: with the parameters of stimulation adjusted to obtain the best clinical effect at the usual 130 Hz frequency (Table 1), and after switching the frequency to 80 Hz, adjusting the voltage of stimulation in order to maintain constant the total energy delivered, according to the equation: TEED (1 s) = voltage² × frequency × amplitude/impedance [10]. No other changes of stimulation parameters or electrode contact were allowed during the entire duration of the study and baseline dopaminergic therapies were maintained stable during follow-up period. Unified Parkinson Disease Rating Scale (UPDRS) section-III and a video recording of IM were collected in both conditions and patients were also evaluated by means of UPDRS section-IV.

Following assessments were scheduled after 1 and 12 months of chronic 80 Hz stimulation. Evaluations were performed on individual time-length from levodopa intake, in order to assess the worse clinical presentation of IM, collecting video recording assessments of IM and UPDRS section-III and section-IV scores.

Patients who reported a clinical worsening with 80 Hz stimulation were switched back to 130 Hz before the end of follow-up and evaluated by means of UPDRS-III and -IV.

At the end of the study, a blinded video assessment was performed by a neurologist expert in movement disorders (M.G.R.), who scored the severity of dyskinesias and dystonias according to the Rush Dyskinesias Rating Scale (Rush DRS) [12]; the most disabling IM (dyskinesias or dystonias) and the score of the most affected district were considered in the analyses. The mean UPDRS-III tremor subscore (items 20, 21) and bradykinesia/rigidity subscore (items 22, 23, 24, 27, 28, 29, 30, 31) were also considered separately, as well as UPDRS-IV items 32 (dyskinesias duration) and 33 (dyskinesias severity).

Statistical analyses were performed using PASWStat 18 for Windows, considering a probability (p) values <0.05 as the statistical threshold; UPDRS and Rush DRS scores were compared by means of the non parametric Wilcoxon, Friedmann and Mann–Whitney U tests.

All subjects gave written informed consent to be included in this study.

3. Results

3.1. Short term and one-month results

At the first acute evaluation after the switch of stimulation frequency from 130 Hz to 80 Hz, 5 patients with dyskinesias and 1 patient with dystonia showed an improvement of IM (Table 2).

Table 2.

Rush Dyskinesias Rating Scale scores: blinded video evaluation at different follow-up, considering only the most affected district: 0/4: absent; 1/4: no interference with the rated task; 2/4: impairing voluntary movement, but the task is efficiently completed; 3/4: intense interfering with movement control, completing the task is greatly limited; 4/4: violent dyskinesias, impossible to complete the task.

Patients	Dyskinesias Rating Scale		Rush Dyskinesias Rating Scale			
	Clinical phenotype	Type of motor complication	130Hz Basal evaluation	80 Hz Basal evaluation	80 Hz 1st month	80 Hz 12th month
Patient #1 female	TD	Peak dose dyskinesia	3/4	2/4	1/4	2/4
Patient #2 female	AR	Peak dose dyskinesia	2/4	2/4	1/4	Switched to 130 Hz after 3 months
Patient #3 female	TD	Peak dose dyskinesia	2/4	1/4	0/4	Switched to 130 Hz after 2 months
Patient #4 male	TD	Peak dose dyskinesia	2/4	1/4	1/4	Switched to 130 Hz after 2 months

Patient #5 male	TD	Peak dose dyskinesia	2/4	1/4	1/4	Switched to 130 Hz after 1.5 months
Patient #6 female	AR	Diphasic dyskinesia	2/4	0/4	0/4	1/4
Patient #7 female	AR	Dystonia: lower limb	1/4	1/4	1/4	Switched to 130 Hz after 6 months
Patient #8 male	AR	Dystonia: lower limb	2/4	1/4	1/4	1/4
Patient #9 male	TD	Perioral dystonia	2/4	2/4	1/4	1/4
Patient #10 female	TD	Perioral dystonia	3/4	3/4	1/4	1/4

Table options

The Rush DRS mean score, obtained by the blinded video analysis, decreased from 2.0 ± 0.6 to 1.4 ± 0.8 ($p:0.02$).

After one month of chronic 80 Hz stimulation, IM were found to be improved in 9 out of 10 patients (6 patients with dyskinesias and 3 with dystonias); the Rush DRS showed a further decline from 1.4 ± 0.8 to 1.2 ± 0.4 ($p: 0.001$) and the mean score of UPDRS-IV significantly decreased from 10.37 ± 4.8 to 7.13 ± 3.7 ($p: 0.012$). The duration of dyskinesias (item 32) and the disability of dyskinesias (item 33) showed a marked improvement: item 32 average score decreased from 2.75 ± 0.6 to 1.19 ± 0.4 ($p: 0.01$) and item 33 average score decreased from 2.06 ± 0.5 to 1.12 ± 0.3 ($p: 0.02$).

No significant changes in the mean UPDRS-III score or in the separate assessment of tremor and bradykinesia/rigidity subscores were observed between 130 Hz and 80 Hz, neither at baseline, nor comparing the one-month condition with 130 Hz baseline values (Table 3). Tremor subscore initially showed a slight worsening after the switch of stimulation frequency from 130 Hz to 80 Hz (from 1.7 ± 1.4 to 2.1 ± 1.9 ; $p: 0.18$), then it remained substantially stable after one month of 80 Hz chronic stimulation (2.2 ± 1.8 ; $p: 0.14$). Bradykinesia/rigidity subscore did not change significantly after switching the stimulation frequency to 80 Hz at baseline (from 16.4 ± 4.4 to 16.4 ± 4.8 ; $p: 0.78$), while it showed a mild, not significant, worsening after one month of 80 Hz chronic stimulation (17.1 ± 4.3 ; $p:0.41$).

Table 3.

Mean UPDRS-III score, UDPRS-III bradykinesia/rigidity subscore, UPDRS-III tremor subscore at different follow-up assessments.

UPDRS-III score Bradykinesia/rigidity subscore Tremor subscore

Stim-off/med-off baseline score 44.0 ± 14.73 27.9 ± 8.8 4.3 ± 2.46

Baseline 130 versus 80 Hz $25.5 \pm 6.8 \rightarrow 25.7 \pm 6.7$ (p:0.82) $16.4 \pm 4.4 \rightarrow 16.4 \pm 4.8$ (p:0.78) $1.7 \pm 1.4 \rightarrow 2.1 \pm 1.9$ (p:0.18)

130 Hz (baseline) versus 80 Hz (1 month) $25.5 \pm 6.8 \rightarrow 26.4 \pm 6.4$ (p:0.53) $16.4 \pm 4.4 \rightarrow 17.1 \pm 4.3$ (p:0.41) $1.7 \pm 1.4 \rightarrow 2.2 \pm 1.8$ (p:0.14)

130 Hz (baseline) versus 80 Hz (12 months)* $24.9 \pm 6.3 \rightarrow 25.7 \pm 7.3$ (p:0.26) $16.2 \pm 4.6 \rightarrow 16.3 \pm 4.4$ (p:0.73) $1.45 \pm 1.2 \rightarrow 1.5 \pm 1.8$ (p:0.48)

Drop-out*: 130 Hz (baseline) versus 80 Hz (last visit) $26.3 \pm 5.3 \rightarrow 28.1 \pm 6.2$ (p:0.24) $16.6 \pm 3.2 \rightarrow 17.1 \pm 4.1$ (p:0.42) $1.95 \pm 2.4 \rightarrow 2.75 \pm 2.8$ (p:0.11)

*5/10 patients dropped-out before completing the 12 months follow-up assessment.

Table options

3.2. Long term results

Five patients showed a progressive worsening of PD motor symptoms and were switched back to 130 Hz stimulation frequency before completing the 12 months follow-up assessment, even if the IM improvement previously achieved was still present in 4 subjects (Table 2); the drop-out causes were tremor worsening (2 patients), bradykinesia and rigidity worsening (2 patients) and increased frequency of falls (1 patient).

80 Hz stimulation was maintained in 5 patients, who showed a sustained improvement of IM after 12 months, without worsening of PD motor symptoms: the Rush DRS mean score at 12 months was still lower than the baseline score (1.45 ± 0.4 versus 2.0 ± 0.6 ; p: 0.013), as well as the UPDRS-IV (8.4 ± 4.6 versus 10.37 ± 4.8 ; p: 0.007) and the dyskinesia duration (item 32) mean scores (1.6 ± 0.5 versus 2.75 ± 0.6 ; p: 0.007). Disability of dyskinesias (item 33) similarly showed a sustained improvement compared to baseline assessment (1.6 ± 0.6 versus 2.06 ± 0.5), even though the statistical threshold was not reached (p: 0.06).

In the group of patients who returned to 130 Hz stimulation, no significant changes were observed at the last visit at 80 Hz stimulation frequency in the total UPDRS-III score (from 26.3 ± 5.3 to 28.1 ± 6.2 ; p: 0.24) and in the bradykinesia/rigidity subscore (from 16.6 ± 3.2 to 17.1 ± 4.1 ; p: 0.42), while the comparison of UPDRS-III tremor subscores revealed a moderate, not significant, worsening (from 1.95 ± 2.4 to 2.75 ± 2.8 ; p: 0.11).

An additional evaluation was performed to assess whether patients who dropped-out from 80 Hz stimulation differed from those who did not drop-out. The two groups were compared for clinical characteristics at baseline: dropped-out patients showed a slightly higher UPDRS-III tremor subscore (1.95 ± 2.4 versus 1.45 ± 1.15), even if the statistical threshold was not reached ($p:0.13$); on the other hand, only little differences were observed in UPDRS-III mean score (24.7 ± 5.1 in the 80 Hz group; 26.3 ± 5.3 in dropped-out patients, ($p: 0.45$)), and in bradykinesia/rigidity UPDRS-III subscore (16.2 ± 4.3 in the 80 Hz group; 16.6 ± 3.2 in dropped-out patients ($p: 0.48$)).

4. Discussion

The aim of this study was to evaluate the effects of a frequency modulation approach (80 Hz versus 130 Hz STN-DBS) in 10 PD patients with residual dyskinesia or dystonia refractory to the conventional stimulation parameters.

According to the UPDRS-IV patient self-report and to a blinded video assessment of IM, dyskinesia improved in 6 subjects and dystonia in 3 subjects in the short term evaluation (1 month) and sustained beneficial effects on motor complications and dyskinesia duration were reported by 5 patients in a long-term evaluation (12 months), suggesting a beneficial effect of the new stimulation settings in the daily living activities and in quality of life. However, a gradual worsening of parkinsonian features was observed in 5/10 subjects, who returned to 130 Hz STN-DBS in the following months in spite of the persistent beneficial effect on IM.

Interestingly, dyskinetic or dystonic IM seemed to have different time-related responses to frequency changes: dyskinetic IM showed a rapid improvement, detected soon after the switch of stimulation frequency, while dystonic IM improved in most patients only after one month of 80 Hz chronic stimulation, according to a slower progressive modulation of basal ganglia (BG) activity in dystonic features. It is likely that several different mechanisms are involved in the antidyskinetic effect of STN-DBS [6], including both a post-operative levodopa dose reduction [4] and the possible restoration of a more physiological BG oscillatory pattern [1]. Nevertheless, the positive effect observed in this study with 80 Hz STN-DBS on persistent dyskinesias and dystonias might suggest that specific frequency of stimulation could interfere with the pathogenesis of IM. The clinical improvement achieved on IM did not wear off with time, as reported with 60 Hz and 80 Hz stimulation frequencies in gait disturbances [9] and [10], possibly suggesting different underlying pathogenetic mechanisms. However, the worsening of PD cardinal features observed in several subjects with 80 Hz stimulation frequency may suggest that a variable response could be observed with different stimulation frequencies in subgroups of PD patients. This mechanism of action is only speculative; it has been suggested that a modulation of the mesencephalic locomotor area might underlie the improvement of gait disturbances observed with 60 Hz and 80 Hz STN-DBS [7], [9] and [10]. Another hypothesis proposed by Moreau et al. [8] suggests that the electrical activity of basal ganglia neural circuits could be differently modulated by the frequency of stimulation. This last mechanism could hypothetically explain the results observed in our study, even though the preliminary positive effects of 80 Hz stimulation on IM need to be confirmed by further experimental and clinical data.

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