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Is lowering stimulation frequency a feasible option for subthalamic deep brain stimulation in Parkinson's disease patients with dysarthria?

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A R T I C L E I N F O

Keywords:
Parkinson's disease
Deep brain stimulation
Low frequency stimulation
Dysarthria

A B S T R A C T

Background: The long-term effect of subthalamic nucleus deep brain stimulation (STN-DBS) on dysarthria can be detrimental. A transient beneficial effect of low-frequency stimulation (LFS) has been reported.

Objective: to investigate if the magnitude of dysarthria could predict the effect of LFS on speech in STN-DBS PD patients and to verify whether the benefit is maintained over time.

Methods: a cohort study, comparing 10 PD patients with severe speech impairment (MDS-UPDRS item 3.1 ≥ 3) with 10 PD patients with mild speech impairment (MDS-UPDRS item 3.1 ≤ 2), all submitted to STN-DBS. Patients were tested in: MED OFF/STIM OFF, MED OFF/STIM ON (130 Hz, high frequency stimulation [HFS]), MED OFF/STIM ON (60 Hz - LFS) and MED ON with both HFS and LFS. The following was assessed in all conditions: voice (fundamental frequency and jitter), speech (articulatory diadochokinesis [DDK], pitch variability, rate and intelligibility) and motor performance (MDS-UPDRS-III).

Results: LFS compared to no stimulation and HFS, in the absence of L-dopa effect, significantly improved DDK and speech intelligibility for sentence, among patients with severe speech impairment. During the L-dopa effect, comparing LFS *vs.* HFS, there was a significant improvement of speech intelligibility in both groups.

Five patients with severe speech impairment opted to maintain LFS. After six months, speech benefit was maintained but treatment adjustments were required.

Conclusions: LFS may offer both an immediate and long-lasting improvement of speech in a subgroup of STN-DBS patients with severe speech impairment during HFS. Nevertheless, its effect on motor symptoms may not be preserved over time.

1. Introduction

Speech disorders affect nearly 70% of Parkinson's disease (PD) patients [1]. Parkinsonian hypokinetic dysarthria is characterized by hypophonia and dysprosody that worsen with the progression of the disease due to breath, phonation and articulation dysfunction [1]. Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a common adjunct surgical treatment for the motor symptoms of PD, typically recommended for patients who have developed motor fluctuations and entered the advanced disease stage [2]. Although STN-DBS has been shown to be highly effective for cardinal motor symptoms associated with PD [2], its effects on speech are variable, multifactorial and sometime detrimental [3]. After one to five years since STN-DBS, in spite of an improvement of voice tremor and loudness, speaking pitch variability [4], articulatory diadochokinesis [5], speech rate and intelligibility tend to deteriorate, depending also on electrodes position and pre-operative speech characteristics [6]. Indeed, the most significant predictive factors for deterioration of speech intelligibility are lower preoperative speech intelligibility, longer disease duration, and a medially placed left active electrode contact [6]. Additionally, the concomitant effect of L-dopa and stimulation due to their effect on dyskinesias and respiratory control [7,8] and the disease progression could negatively affect the speech outcome among STN-DBS treated patients. Taken as a whole, the role of STN-DBS in parkinsonian

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dysarthria and its management are still a matter of debate. Hypokinetic dysarthria can severely impact PD patients QoL and speech worsening can counterbalance the motor benefits of STN-DBS [9,10]. A beneficial acute effect of low frequencies stimulation (LFS) and high voltages on speech intelligibility, articulation, general grade of dysarthria and laryngeal coordination has been suggested in few small-sampled studies, with no follow-up data available [11–13].

Our primary aim was to evaluate if the severity of dysarthria could predict the effect on speech to an acute stimulation challenge with LFS in STN-DBS treated PD patients and to assess whether the benefit obtained with LFS, when present, could be maintained over time without parkinsonian aggravation. As secondary aim, we also explored the concomitant acute effect of levodopa (l-dopa) and LFS on speech and voice.

2. Patients and methods

2.1. Study protocol and patient recruitment

We performed a cohort study, in which we compared PD patients (UK Brain Bank criteria [14]) with severe dysarthria, who represented the cases (([Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale (UPDRS) item 3.1 ≥ 3, in the Medication On/Stimulation On condition [*M-On/S-On*] [15]) versus PD patients with mild dysarthria, who represented the controls (MDS-UPDRS item 3.1 ≤ 2 in *M-On/S-On*), all treated with STN-DBS for at least 3 years. From a cohort of 183 PD patients, 10 patients with severe dysarthria were consecutively recruited and individually matched for gender, age and age at disease onset with 10 patients with mild dysarthria. Among patients with severe dysarthria, one had a bilateral bipolar stimulation and one a unilateral bipolar stimulation. Among patients with mild dysarthria, one patient had a unilateral bipolar stimulation and one a 180 Hz frequency stimulation. All other patients had a bilateral monopolar stimulation at 130 Hz. A descriptive comparison of speech and voice parameters of all patients in the Medication Off/Stimulation Off (*M-Off/S-Off)* condition, with the published available parameters, i.e. jitter, DDK and average $F_{0,}$ of vocally healthy subjects with same age and gender, was also performed. PD patients with dementia [16] were excluded. The Local Ethical Committee approved the study and all patients provided a written informed consent.

2.2. Neurosurgical procedure

2.2.1. STN-DBS surgery was performed as previously described with quadripolar leads (electrode

Model 3389; Medtronic, Minneapolis, MN), with a bilateral lead implantation based on magnetic resonance imaging (MRI)/computed tomography (CT) image fusion for anatomical targeting, intraoperative electrophysiological recording and microstimulation [17]. Postoperative MRI was performed to confirm electrode positioning and to exclude surgical complications in all patients.

2.2.2. Assessment of patients

Baseline: Patients were assessed in the following conditions: M-Off/S-On_130 Hz, M-Off/S-Off, M-Off/S-On_60 Hz, M-On/S-On_60 Hz and M-On/S-On_130 Hz. M-Off condition was reached after at least 12 h from the last l-dopa intake. Each stimulation condition was maintained for at least 60 min before assessment. For the M-On condition, each patient was evaluated 45–60 min after the intake of the usual morning l-dopa dose.

The equivalent voltage for LFS was calculated for each patient using the total electrical energy delivered (TEED) formula [15]: TEED (1s) = voltage^2 x frequency x amplitude/impedance.

During each condition we assessed: (a) speech performance by means of digital recordings of a steady vowel production (vowel/a/, repeated three times), an oral reading performance and a set of repetitive syllables (/pa/,/pata/,/pataka/) for all patients; (b) motor disease severity and gait performance by means of the MDS-UPDRS part III and the Timed up and go test (TUG), respectively; (c) dyskinesias severity by means of the Modified Abnormal Involuntary Movement Scale (mAIMS); (d) the Clinical Global Impression Improvement Scale (CGI-I). The following scales were also assessed: a) the Quality of life in the dysarthric speaker questionnaire (QoL-DyS, Italian version) [18]; b) the New freezing of gait questionnaire (NFG-Q) [19]; c) the MDS-UPDRS part I-II and IV. l-dopa equivalent daily dose (LEDD) was calculated according to recognized standard conversion [20].

All voice and speech samples were recorded in a quiet hospital room using a tabletop unidirectional microphone (Fame, MS- 1800S) attached to a preamplifier (M-Audio Fast Track Pro, preamp, USB) and a desktop computer running *Audacity software version 2.1.2* (Free software Foundation Europe, Hamburg, Germany). Five separate perceptual files were completed with all stimuli presented at the same sound pressure levels. A 500 ms silence between single words and sentences was kept.

Follow-up: If at baseline CGI-I during M-On/S-On_60 Hz vs. M-On/S-On_130 Hz was ≤3 (slight to great improvement), the patient was maintained on LFS and follow-up visits were scheduled after two weeks (clinical assessment, i.e. MDS-UPDRS part III and CGI-I) and six months (clinical and acoustic analysis of speech).

2.2.3. Data analysis

All speech samples were copied to a computer (recorded at 44 kHz and down sampled to 24 kHz, 16 bits, mono), edited into individual files and screened for extraneous noise using Audacity by a speech language therapist (SLT) who examined the recordings in a randomized fashion and was blind to the participants' demographics, stimulation, and clinical status. Acoustically, the waveform, spectrogram, pitch, intensity, and the formants of each sustained vowel were visually observed using the Praat 5.1 software downloaded from http://www.praat.org. The F_0 (Hz) and jitter (local, %) of the vowel/a/, were analysed with a moving window with at least 1-sec. The voice report in the Praat software was used. The mean pitch samples (periods) used were between 122 and 125 (95% CI 107–137). The signal length analysis of each different therapeutic condition did not vary significantly ($p < 0.05$), thus we could exclude an analysis bias. Voice onset and offset were removed and only the stable steadiest portion of the vowel/a/was selected for the analysis. The limits used for vowels F0 tracking was set at 60–400 Hz for both genders.

The following parameters were analysed: (a) Voice (pitch) quality: the average fundamental frequency (F_0) in Hertz; (b) Voice (pitch) variability: the F_0 standard deviation (SD); (c) Voice (pitch) instability: jitter (local, %). All parameters were analysed in all vowels in the three moments; (d) Speech rate (syllables/sec of the first and the last paragraph of a phonetically balanced text, of respectively 46 and 41 syllables); (e) Speech intelligibility, measured as: (i) the percentage of words from a list of 50 words correctly understood by two independent SLT blinded to patients' conditions, who rated speech in a randomized fashion; (ii) a VAS scale (from zero to 10, being 10 the best score) evaluated by a blinded SLT, who scored speech intelligibility during a text reading; (f) Articulatory diadochokinesis (DDK): the number of syllables,/pa/(alternating motion rate, AMR, articulatory movement of the jaw combined with the lips),/pata/and/pataka/(sequential motion rate, SMR, articulatory movement of the jaw combined with the lips and the anterior and posterior parts of the tongue), at a fast rate during 5 s each. For speech intelligibility three word-lists were randomly used. Each list included 50 bi-syllabic words, 20 with simple structure (CVCV) and 30 with complex structure (VCCV, CVCCV, CCVCV, CCVCCV, CCVCCV, CCVVCCV, CCCVCCV).

2.2.4. Statistical analysis

Clinical and demographic characteristics were summarized as mean ± standard deviation or percentages, as appropriate. Two group

Table 1
Demographic, clinical, therapeutic and speech characteristics of DBS patients. Severe speech impairment: PD patients with MDS.UPDRS ≥3; Mild speech impairment: PD patients with MDS.UPDRS 2.1 ≤ 2; Values are presented as mean ± SD, if not otherwise specified. LEDD: levodopa equivalent daily dose; R_STN: right subthalamic nucleus; L_STN: left subthalamic nucleus; NFG-Q: New freezing of gait questionnaire; MMSE: Mini mental state examination; SE: Schwab and England Scale (MED ON/STIM ON); QoL-DyS: Quality of life in the dysartrhic speaker questionnaire (total score range: 0–160, higher score = higher impact); (*): Electrode position was been classified as "ventral" if the active contact was one of the two most ventral contacts. Among patients with severe speech impairment, one had a bilateral bipolar stimulation and one a unilateral bipolar stimulation. Among patients with mild speech impairment, one patient had a unilateral bipolar stimulation and one a 180 Hz frequency stimulation. All the other patients had a bilateral unipolar stimulation at 130 Hz. Statistical significant p values are in bold character.

	Severe dysarthria (n = 10)	Mild dysarthria (n = 10)	p-values
Age (y)	65.3 ± 6.1	63.5 ± 5.7	0.589
Women (n/total (%))	3/10 (33%)	3/10 (33%)	1
Age at disease onset (y)	46.3 ± 6.6	43.6 ± 7.1	0.367
Disease duration (y)	19 ± 5.2	19.9 ± 4.9	0.645
Age at DBS (y)	58.4 ± 5.7	56.7 ± 8.1	0.487
Months after DBS	82 ± 42	81.1 ± 36.7	0.912
LEDD before surgery (mg)	1180.7 ± 436	1045 ± 337	0.723
LEDD after surgery (mg)	812 ± 610	680 ± 420	0.623
Stimulation Voltage			
R_STN/L_STN at 130 Hz	3.4 ± 0.7/ 2.8 ± 08	3.4 ± 0.5/3.4 ± 0.4	0.976
R_STN/L_STN at 60 Hz	4.8 ± 1/ 4.2 ± 1	5 ± 0.7 5.1 ± 0.6	0.076
Electrodes position *			
Ventral n (%)	4 (40%)	4 (40%)	1
MMSE	27 ± 1.7	28.6 ± 1.2	0.323
NFG-Q	13.8 ± 7.4	6.4 ± 8.1	0.048
SE (ON)	81 ± 11	86 ± 6.9	0.223
MDS-UPDRS-I	11.3 ± 3.6	11.4 ± 5	1
MDS-UPDRS-II	22.5 ± 6.1	18.2 ± 4	0.123
MDS-UPDRS-III	27.2 ± 9.8	22.2 ± 9.7	0.332
MDS-UPDRS-IV	5 ± 3.6	1.6 ± 2.2	**0.035**
QoL-DyS, total score	49 ± 22.6	16.2 ± 16	**0.001**
Speech characteristics	19.2 ± 7.3	7.2 ± 6	**0.001**
Situational difficulty	14.8 ± 6.4	4.4 ± 2.9	**0.002**
Compensatory strategies	5.3 ± 7.8	2.6 ± 6.1	0.278
Perceived reactions of others	9.5 ± 9.5	2 ± 3.3	< **0.002**

comparisons were performed using Mann-Whitney *U* test. The acute effect of LFS was calculated by comparisons between different therapeutic conditions using the Wilcoxon's signed ranked test, applying the Bonferroni's correction for multiple comparisons. The effect size of each therapeutic comparison, based on the mean difference for each comparison and adjusted bootstrap percentile interval as 95% confidence interval with 10,000 replicates, to avoid normal approximation, was also calculated (Table S1). All the analyses were performed with SPSS 23.0 (SPSS, Chicago, IL) using two-tailed p-values with a level of significance of 0.05.

3. Results

Demographic, clinical and therapeutic data of the patients are detailed in Table 1.

No differences were found for pre- and post-surgical LEDD, MMSE, STN-DBS treatment duration (almost 7 years), voltage intensity and MDS-UPDRS part I-II-III. Conversely, patients with severe speech impairment had a slightly worse MDS-UPDRS-IV and NFG-Q scores and a more severe QoL-DyS score (Table 1).

Comparing men and women there were no differences in motor, voice, and speech variables in all therapeutic conditions, except for voice quality (average F_0), that was higher among women, as expected. Thus, further analyses were carried out without stratifying by gender.

M-Off/S-Off condition. With no L-dopa and no stimulation, voice instability (Jitter) and DDK of all patients was worse if compared to vocally healthy subjects values with same age (Table 2) [21–23]. No differences were found for average F_0 analysing men, women and Groups separately [(data not showed; patients with severe speech impairment: men 138 ± 30; women: 172 ± 20; patients with mild speech impairment, men: 128 ± 29; women: 178 ± 30)]. DDK and speech intelligibility was worse in patients with severe compared to mild speech impairment ($p < 0.05$).

We describe below speech, voice and motor parameters changes in different therapeutic conditions (Table 2). Effect size results are detailed in Table S1 (Supplementary material).

Effect of HFS. HFS (M-Off/S-On_130 Hz vs M-Off/S-Off) did not significantly change voice and speech parameters, apart for a slight significant improvement of DDK and an increment of F_0 in patients with mild speech impairment (Table 1). Concomitantly, motor performances significantly improved by 40 ± 25% and 45 ± 12% at the MDS-UPDRS-III in patients with severe and mild speech impairment, respectively and an improvement of TUG (Table 2) was noted.

Effect of LFS. LSF (M-Off/S-On_60 Hz vs M-Off/S-Off) significantly improved SMR (syllable/pata/and/pataka) in both groups, and speech intelligibility for sentences in patients with severe speech impairment and speech intelligibility for words in patients with mild speech impairment (Table 2). Concomitantly motor performances significantly improved by 39 ± 22% and 42 ± 12% at the MDS-UPDRS-III in all patients, respectively with improvement of TUG only in patients with severe speech impairment (Table 2).

Effect of LFS vs HFS, without L-dopa. Comparing condition M-Off/S-On_130 Hz vs. M-Off/S-On_60 Hz, we found: a) a statistically significant improvement of DDK (syllable/pataka/), speech intelligibility for sentences and MDS-UPDRS item 3.1 in patients with severe speech impairment; b) no changes for voice and speech parameters in patients with mild speech impairment with level of voice instability maintained within acceptable values (< 1%) in both conditions; d) no significant changes in motor performances or dyskinesias development in both groups (Table 2).

Effect of LFS vs. HFS, with L-dopa. Comparing condition M-On/S-On_60 Hz vs. M-On/S-On_130 Hz, we found: a) a statistically significant improvement of speech intelligibility for sentences in both groups; b) a slight though significant reduction of speech rate of the first paragraph in patients with mild speech impairment; c) no significant changes in motor performance or dyskinesias development in both groups (Table 2).

L-dopa effect. No significant speech modification was revealed after L-dopa intake with both stimulation frequency (M-Off/S-On_60 Hz vs. M-On/S-On_60 Hz and M-Off/S-ON_130 Hz vs. M-On/S-On_130 Hz), with the exception of a slight worsening of DDK in patients with mild speech impairment (Table 2).

The TEED was held constant and no clinical manifestation of current diffusion was observed.

Patients with mild speech impairment reported no subjective speech improvement with LFS in MED ON (mean CGI-I = 4) and none of them maintained LFS. Conversely, five patients with severe speech impairment reported subjective speech improvement with LFS (CGI-I score was 2 for all but one patient who scored 3) and were maintained on LFS. Follow-up data of these patients were as follows (Fig. 1):

a) At two-weeks follow-up: one patient was switched back to HFS, due to wearing-off and severe resting tremor reappearance and one patient was switched at 80 Hz stimulation, due to worsening of tremor and blepharospasm appearance. Of the three patients who

Table 2
Speech and voice response to LFS (60 Hz), HFS (130 Hz) and L-dopa in combination with stimulation. Oral diadockocinesis: number of/pa/,/pata/,/pataka/5 s; Speech rate: syllables/sec. Available values for vocally healthy subjects with same age: Average F0 (men: 128 ± 36; women: 198 ± 44); speech rate: 3–6 syllables/sec; DDK: 5–7 syllables/sec; Hz; Jitter: < 1%; For one patient with severe speech impairment, speech intelligibility analysis by means of sentences reading was not possible as speech was not understandable. Two patients with severe speech impairment and one patients with mild speech impairment did not tolerate M-Off/S-Off condition for more than 30 min due to the severity of motor symptoms. Statistical significant p values are in bold character.

	Patients with severe dysarthria (n = 10)										
	MEDICATION-OFF			MEDICATION-ON		Stimulation effect (*P-values*)		Medication effect (*P-values*)		Frequency effect (*P-values*)	
	STIMULATION-OFF (A)	*STIMULATION-ON* 130 Hz *(B)*	*STIMULATION-ON* 60 Hz *(C)*	*STIMULATION-ON* 60 Hz *(D)*	*STIMULATION-ON* 130 Hz *(E)*	60 Hz *(A vs C)*	130 Hz *(A vs B)*	60 Hz *(C vs D)*	130 Hz *(B vs E)*	*MED-OFF (C vs B)*	*MED-ON (D vs E)*
Voice quality											
Average F_0 (Hz)	148.6 ± 32.5	150.1 ± 47.5	154.6 ± 29.1	158.4 ± 30.8	144.1 ± 45.6	.667	.921	.223	.831	1	.533
Voice variability											
F_oSD	7.1 ± 6.1	17.6 ± 6.1	9.1 ± 8	10.9 ± 9.4	12.3 ± 7.3	.721	.623	1	.623	.063	.834
Voice instability											
(Jitter)	1.2 ± 1.3	1.1 ± 1.2	0.9 ± 0.5	0.8 ± 0.5	0.9 ± 0.7	.545	.141	.234	.434	.476	.865
Speech rate											
First paragraph	4.5 ± 1.4	4.4 ± 1.1	4.5 ± 1.2	4.4 ± 1.2	4.4 ± 1.2	.623	.222	.932	.113	.545	.243
Second paragraph	3.9 ± 1.1	4.1 ± 1.3	4.4 ± 1.4	4.1 ± 1.1	4.4 ± 1.1	.222	.622	.643	.322	.756	.857
Oral diadochokinesis											
/pa/	2.9 ± 1	3.5 ± 0.9	3.2 ± 0.7	3.5 ± 0.8	3.2 ± 1.3	.051	.734	.322	.865	.554	.333
/pata/	1.8 ± 0.7	2 ± 0.6	2 ± 0.5	2.1 ± 0.6	2.4 ± 0.5	**.017**	.822	.422	.134	.235	.876
/pataka/	1.3 ± 0.5	1.4 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	± 0.2	**.041**	.323	.143	.765	**.012**	.545
Speech intelligibility											
Word list (%)	74.4 ± 20	82.6 ± 12.5	91.5 ± 8.5	88.6 ± 6.8	80 ± 9.3	.083	.933	.732	.222	.143	.046
Sentence	5.6 ± 1.5	5.8 ± 2	8.1 ± 1.3	7.5 ± 1.4	4.5 ± 2.2	**.023**	.433	.445	.122	**.014**	**.013**
mAIMS	1.3 ± 1.3	1.5 ± 1.5	1 ± 1.1	4.3 ± 4	5.1 ± 5.5	.534	.521	**.012**	.154	.934	.743
TUG (sec)	25.1 ± 11.4	18 ± 8	15.8 ± 8.6	13.6 ± 7.1	15.8 ± 8.6	**.017**	**.018**	**.018**	.064	.934	.965
MDS-UPDRS-III	60.1 ± 15.1	33.8 ± 11.7	35 ± 11.5	22.2 ± 14.8	24.8 ± 9.1	**.007**	**.004**	.059	**.032**	.754	.454
MDS-UPDRS item 3.1	2.4 ± 0.5	1.8 ± 0.4	2.3 ± 0.8	1.5 ± 0.5	2.2 ± 0.6	.059	.082	.082	.434	**.011**	**.031**

	Patients with mild dysarthria (n = 10)										
	MEDICATION-OFF			MEDICATION-ON		Stimulation effect (*P-values*)		Medication effect (*P-values*)		Frequency effect (*P-values*)	
	STIMULATION-OFF (A)	*STIMULATION-ON* 130 Hz *(B)*	*STIMULATION-ON* 60 Hz *(C)*	*STIMULATION-ON* 60 Hz *(D)*	*STIMULATION-ON* 130 Hz *(E)*	60 Hz *(A vs C)*	130 Hz *(A vs B)*	60 Hz *(C vs D)*	130 Hz *(B vs E)*	*MED-OFF (C vs B)*	*MED-ON (D vs E)*
Voice quality											
Average F_0 (Hz)	133.7 ± 28.1	150.3 ± 39.2	152.4 ± 39.2	156.3 ± 33.2	152.7 ± 40.1	**.012**	**.023**	.957	.523	.624	.458
Voice variability											
F_oSD	15 ± 14.4	16.9 ± 12.3	13.4 ± 15.5	11.8 ± 12.4	11.2 ± 15.4	.865	.967	.967	.235	.854	.976
Voice instability											
(Jitter)	0.7 ± 0.6	0.8 ± 0.8	0.8 ± 0.7	0.5 ± 0.4	0.4 ± 0.4	.545	.756	.244	.243	.764	.956
Speech rate											
First paragraph	4.2 ± 1	4.5 ± 0.6	4.5 ± 0.7	4.5 ± 0.7	4. 9 ± 0.8	.532	.334	.524	.113	.522	**.032**
Second paragraph	3.8 ± 1	4.3 ± 1	4.3 ± 0.7	4.1 ± 0.8	4.5 ± 0.6	.965	.145	.224	.322	.134	.076
Oral diadochokinesis											
/pa/	3.9 ± 0.7	4.1 ± 0.5	4.1 ± 0.4	3.7 ± 0.7	4.1 ± 0.7	.234	.143	.625	.865	.545	.112
/pata/	2.1 ± 0.6	2.5 ± 0.4	2.6 ± 0.4	2.5 ± 0.5	2.4 ± 0.2	**.035**	**.034**	.854	.134	.423	.224
/pataka/	1.5 ± 0.4	1.7 ± 0.2	1.9 ± 0.3	1.7 ± 0.3	1.7 ± 0.2	**.017**	.134	**.035**	.765	.051	.622
Speech intelligibility											
Word list (%)	84.5 ± 11.8	91.7 ± 4.6	90 ± 5	91.6 ± 3.4	88.8 ± 9.6	**.038**	.243	.732	.222	.722	.323
Sentence	8.5 ± 1.5	8.4 ± 2	8 ± 3	9.2 ± 0.8	7.7 ± 2.2	.465	.334	.323	.122	.634	**.031**
mAIMS	0.7 ± 1.3	0.1 ± 0.3	0.4 ± 0.8	4.4 ± 5	3.3 ± 3.5	.945	.564	**.041**	**.022**	.864	.675
TUG (sec)	22.1 ± 18.8	9.3 ± 4.1	12.3 ± 6.5	8.6 ± 2.3	9.1 ± 3	.073	**.012**	**.013**	.234	.645	.967
MDS-UPDRS-III	61 ± 13	32 ± 8	35.6 ± 12.4	19.5 ± 8.5	20.9 ± 9.3	**.005**	**.005**	**.007**	**.012**	.643	.244
MDS-UPDRS item 3.1	1.3 ± 0.8	1.2 ± 0.6	1.4 ± 0.7	1.1 ± 0.6	1.4 ± 0.8	.135	.543	.998	.976	.123	.084

maintained the 60 Hz stimulation, two needed to increase L-dopa dose (delta LEDD: 130 mg and 50 mg, respectively) due to wearing-off and rest tremor reappearance;

b) At 6-months follow-up: the patient switched to 80 Hz after two weeks maintained such frequency. One other patient stimulated at 60 Hz frequency was switched to 80 Hz due to wearing-off worsening. Two patients maintained 60 Hz stimulation and an adjustment of oral therapy was required for one of them (delta LEDD: 100 mg).

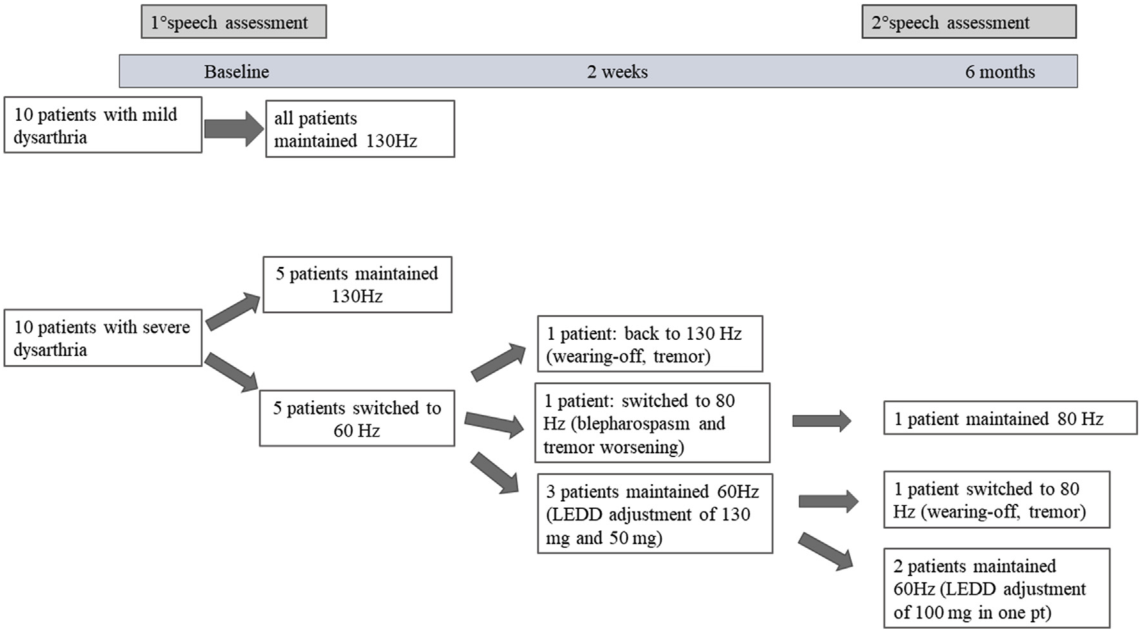

Fig. 1. Follow-up of patients who maintained a low frequency stimulation.LEDD: levodopa equivalent daily dose.

Acoustic analysis of speech of the four patients who kept a frequency stimulation ≤80 Hz revealed no significant difference of speech parameters and motor performance (p range: 0.07–0.2) if compared to baseline M-On/S-On_60 Hz. Equally the CGI-I did not reveal any significant change.

4. Discussion

In this study, we assessed the acute effect of LFS on PD patients with different grades of speech impairment in order to verify if the magnitude of dysarthria could predict the effect of LFS on speech and motor symptoms. LFS improved speech intelligibility for sentences both in the absence of L-dopa effect, and with concomitant L-dopa intake, among patients with severe speech impairment, chronically stimulated with conventional HFS. Among patients with mild speech impairment, a statistically significant improvement of speech intelligibility for words reading was also detected with LFS, though it was not clinically meaningful according to the CGI-S, as those patients had a mild speech impairment at HFS.

A jitter value $<$ 1% is considered normal [24]. Although the results failed to indicate any statistically significant difference in voice instability, under the effect of LFS, some trends were noted. Indeed, in patients with severe speech impairment, the voice instability (jitter magnitude) decreased from indices considered pathological with no stimulation or HFS without L-dopa (1.2 ± 1.3 in M-Off/S-Off and 1.1 ± 1.2 in M-Off/S-On at 130 Hz, respectively) to normal values, under LFS effect (0.9 ± 0.5 in M-Off/S-On at 60 Hz). A steady vowel production elicits a stationary process of the articulatory-laryngeal system [25] and reflects the sound produced by the vocal folds. Thus, it may be speculated that LFS contributes to a better muscular vocal fold control of phonation in STN-DBS treated PD patients with severe speech impairment and, to a lesser extent, in patients with mild speech impairment.

LFS compared to no stimulation and to HFS, in the absence of L-dopa effect, significantly improved DDK among patients with mild and severe dysarthria alike and speech intelligibility for sentences only in patients with severe dysarthria. LFS versus HFS, with L-dopa intake, reduced speech rate in PD patients with mild speech impairment and improved speech intelligibility for sentence in both groups, although the improvement of intelligibility was clinically meaningful only for patients with severe dysarthria. Interestingly, HFS did not have an acute detrimental effect on speech in both groups. However, a detrimental acute effect of HFS on voice instability and speech intelligibility was found at baseline in the two patients who maintained LFS 60 Hz at follow-up (data not showed). When chronically maintained, LFS seem to keep providing a benefit on speech, though often requiring therapeutic adjustment due to tremor or motor fluctuations reappearance.

We included PD patients with different levels of speech impairment in order to verify if lower frequency of stimulation could be a feasible option in the management of both DBS-treated patients with severe and mild dysarthria. Indeed, since also mild dysarthria can affect patient's perceived QoL, we aimed to verify if fine-tuning of stimulation parameters could be attempted also among these patients without losing an optimal control of motor symptoms. In this case, acute switching to LFS gave a statistically significant though not subjectively meaningful improvement of speech intelligibility only for words reading or for sentence, while M-Off or M-On, respectively. It has been suggested that an apparent improvement of axial signs with LFS is likely to appear only among patients who have a detrimental effect with HFS [26]. In agreement with this hypothesis, we found a more evident and clinically meaningful benefit of LFS at follow-up among patients with severe speech impairment who presented a detrimental effect of HFS on speech. On the contrary, patients with mild speech impairment are not likely to benefit from LFS. As the volume of activated tissue depends on stimulation voltage, it has been suggested that LFS and high voltage can activate some critical mesencephalic structures, especially the mesencephalic locomotor area and the fasciculus cerebellothalamicus, that are conversely inhibited by chronic HFS resulting in dysarthria worsening [27]. Our findings confirm this hypothesis. However, it may happen that LFS does not maintain its effect on motor symptoms [28,29] with consequent reappearance or worsening of motor fluctuations or tremor in few months, thus requiring stimulation or medication adjustment. The reason why such a benefit is not maintained over time remains to be clarified. Chronic HFS of the STN seems to cause long-term adaptation in the sensorimotor network, which results in reduced expression of subthalamic beta band oscillations and neural synchrony [30]. It would also be worth investigating if long-lasting LFS is related to phenomena of neuronal adaptation, in order to verify if cyclic stimulation frequency, i.e. a nocturnal HFS and a daily LFS, could prevent the occurrence of long-term tolerance to LFS. Alternatively, if patients do not tolerate LFS over time, due to the worsening of motor symptoms that cannot be stabilized by medication adjustment the occasional and transient use of LFS could be considered, based on patients' needs.

As expected for advanced PD patients, L-dopa intake did not give an additional benefit on speech impairment [31]. At the same time, dyskinesias increment after L-dopa intake is probably not sufficient or not severe enough to influence respiratory control and consequently affect speech, as it could be expected for DBS patients who have an optimal motor control [32].

The rate of L-dopa motor complications was higher among patients with severe speech impairment. However, among those patients, motor complications were more severe, though not significantly (data not shown), even before DBS and the motor effect of stimulation was significant in both groups. These data, along with the neuroimaging confirmation and the absence of stimulation-induced pyramidal side effects, support a correct position of the active contact.

The findings of our study are firstly limited by the lack of blinding for the neurological assessment which was maintained only for SLT evaluations. Secondly, recordings were not performed in an acoustic laboratory setting. Nevertheless, the quality and reliability of the recordings were evaluated by a SLT. Moreover, it should be considered that a feasible, sensitive and standardized tool for dysarthria assessment among PD patients has not been defined yet. Herein we adopt a brief and informative protocol for automatic acoustic assessment of DBS-treated PD patients. Further studies with larger samples should be performed to elaborate a standardized protocol for pre and post-surgical speech assessment of PD patients.

In conclusion, the acute switching to LFS seems to be a feasible option for STN-DBS patients with severe speech impairment at HFS. The possible application of alternative and new stimulation options that can widen the therapeutic window such as the use of short pulse width, directional leads or adaptive stimulations should also be investigated among DBS treated PD patients with severe speech impairment.

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Authors’ contributions

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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Dr. Maurizio Zibetti: 1A, 2C; 3B

Giulia Ferrero:1C, 2B; 3A; Anna Accornero: 1C, 2B; 3B; Isabel Guimaraes: 2A, 2C, 3B;

Dr. Mario Giorgio Rizzone: 1A, 2C; 3B;

Dr. Alberto Romagnolo: 1A, 3B;

Prof. Joaquim J Ferreira: 1A, 3B;

Prof. Leonardo Lopiano: 1A, 1B, 3B;

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Appendix A. Supplementary data

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