Deep brain stimulation fine-tuning in Parkinson's disease: short pulse width effect on speech

Article (Accepted Version)

Deep brain stimulation fine-tuning in Parkinson's disease: short pulse width effect on speech

Margherita Fabbri,[1] MD, PhD, Federico Natale[2], SLT, Carlo Alberto Artusi[3], MD, Alberto Romagnolo[3], MD, Marco Bozzali[3,4,5], MD, PhD, Giovanni Giulietti[6], PhD, Isabel Guimaraes[7], SLT, PhD, Mario Giorgio Rizzone[3], MD, Anna Accornero[2], SLT, PhD, Leonardo Lopiano[3], MD, PhD, Maurizio Zibetti[3], MD, PhD

[1]Clinical Investigation Center CIC1436, Department of Clinical Pharmacology and Neurosciences, Parkinson Expert Centre and NeuroToul Center of Excellence in Neurodegeneration (COEN) of Toulouse; INSERM, University of Toulouse 3, CHU of Toulouse; Toulouse, France

[2]Department of Surgical Sciences, University of Turin, Turin, Italy

[3]Department of Neuroscience "Rita Levi Montalcini", University of Torino, Via Cherasco 15, 10124, Turin, Italy

[4]AOU Città della Salute e della Scienza di Torino

[5]Department of Neuroscience, Brighton & Sussex Medical School, University of Sussex, Brighton, East Sussex, United Kingdom.

[6]Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Via Ardeatina 306, 00179, Rome, Italy.

[7]Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Portugal; Department of Speech Therapy, Escola Superior de Saúde de Alcoitão, Estoril, Portugal

***Corresponding author**

Margherita Fabbri

Clinical Investigation Center CIC1436, Department of Clinical Pharmacology and Neurosciences, Parkinson Expert Centre and NeuroToul Center of Excellence in Neurodegeneration (COEN) of Toulouse; INSERM, University of Toulouse 3, CHU of Toulouse; Toulouse, France

E-mail: margheritafabbrimd@gmail.com

Phone: 0033- 0561776039

Paper word count: 2357

Abstract word count: 203

References: 13

Tables: 2

Supplementary material: Figure S1, Table S1 and Data Analysis

Key words: Parkinson's Disease, deep brain stimulation, short-pulse width, dysarthria;

Abstract

Background: subthalamic nucleus deep brain stimulation (STN-DBS) may have a detrimental effect on speech in Parkinson's disease (PD) patients and new stimulation technologies may help in addressing this issue.

Objective: to evaluate the STN-DBS acute effect of 30 μs pulse width (30PW) versus conventional 60 μs PW (60PW) on speech and identify the core features of voice modified by 30PW.

Methods: seven STN-DBS treated PD patients participated into a pilot cross-sectional study. Motor and speech performances were tested by means of both automatic analysis and blinded clinical evaluations in four stimulation conditions: 30PW and 60PW both at the usual amplitude and at an amplitude just below the threshold for stimulation-related side effects.

Results: at the threshold amplitude, 30PW stimulation improved speech intelligibility for both words ($p= 0.02$) and sentences ($p= 0.04$), without worsening motor performance. A lower but not statistically significant voice variability and instability and percentage of stuttering disfluencies was also observed. The beneficial effect of 30PW detected by automatic analysis, was confirmed by patients' perception.

Conclusions: STN-DBS treated patients experiencing low speech intelligibility may benefit from a 30PW stimulation trial at a higher amplitude. Deep characterization of PD speech profiles may help in a better application of recent DBS hardware advances.

Introduction

Up to 90% of patients with Parkinson's disease (PD) suffer from speech disorders - most typically hypokinetic dysarthria - which are characterized by hypophonia and dysprosody that worsen over disease progression [1]. While subthalamic nucleus deep brain stimulation (STN-DBS) is highly efficacious for the treatment of motor symptoms and complications in PD, its effects on speech are variable, multifactorial and in some cases detrimental [2]. Despite an improvement of voice tremor and loudness, speaking pitch variability, speech rate, intelligibility and diadochokinesis (DDK), tend to deteriorate one-to-five years after STN-DBS, depending on electrodes' position and pre-operative speech characteristics, with a significantly higher decline in intelligibility compared to that observed in medically treated patients [3, 4].

A beneficial acute and long-term effect of low frequency (LFS) and high voltage stimulation on speech intelligibility and laryngeal coordination has been suggested in few small-sampled studies [5, 6]. Thanks to technological advances, there are nowadays new devices available that allow to use pulse width (PW) settings < 60 μs. Recently, a small retrospective study has shown how a short PW setting may acutely expand the therapeutic window of STN-DBS treated patients [7], with consequent speech improvement which may last up to 6 months [8]. A pilot randomized cross-over study suggested that dysarthric PD patients who underwent STN-DBS in the previous 4 years may benefit of lower PW [9]. However, the characterization of speech disturbances and their management in DBS-treated PD patients is still matter of debate and identifying a therapeutic balance between motor and speech symptoms can be challenging.

In this cross-sectional pilot study, we evaluated specific modifications of speech parameters to an acute stimulation challenge with short PW in STN-DBS treated PD patients, with the aim of characterizing speech clinical and subclinical features that could benefit from this stimulation setting.

Patients and methods

Study protocol and patient recruitment

We performed a pilot cross-sectional study enrolling seven PD patients (two females, mean age 56.2±8.2 years, mean disease duration 11.1±3.1 years) who underwent DBS surgery with bilateral implantation of electrodes in the STN. PD patients have been consecutively recruited in agreement with the following inclusion criteria: a) at least six months of chronic STN stimulation, with stable treatment and stimulation parameters for longer than one month and bilateral monopolar stimulation at 130 Hz; b) Mini Mental State Examination score ≥ 26; c) implanted with a Boston Scientific Vercise PC or St. Jude Medical Infinity, which allowed short PW stimulation. The Local Ethical Committee approved the study and all patients provided a written informed consent.

Neuroimaging

All patients underwent a presurgical MRI scan and a postsurgical CT scan. In each patient, electrodes' location relative to a selection of deep brain structures was estimated combining CT and T2-weighted scans, which were first coregistered using ANTs [10], and then normalised in MNI space using Statistical-Parametric-Mapping-12 [11]. In each patient, the subthalamic nucleus, substantia nigra, and red nucleus (structures of interest) were segmented in MNI space using pBrain [12] (Figure S1, Supplementary material). The corticospinal tracts were extracted from the "JHU White-Matter Tractography Atlas" available in FSL (fsl.fmrib.ox.ac.uk/fsl/fslwiki) and overlaid to each individual T2-weighted scan in MNI space.

Assessment of patients

Patients were assessed in Medication Off (*M-Off*), after overnight withdrawal of antiparkinsonian medications. The stimulation frequency (130 Hz) and the active electrode (cathodic monopolar

stimulation) were maintained fixed, while PW (30 μs vs. 60 μs) and amplitude (usual vs. threshold for side effects) were manipulated.

The threshold amplitude was defined as 0.1 mA below the minimum amplitude determining any side effect persisting after 2 minutes of stimulation.

When considering 30μs stimulation (30PW), usual amplitude was adapted to maintain the same total electrical energy delivered (TEED) in 60μs conditions (60PW), as per the validated formula [(Voltage^2×Frequency×Pulse-width)/Impedance], after conversion of the stimulation current to voltage using individual contact impedances.

Four different stimulation settings were tested: i) 60PW with the usual amplitude (*Condition A*); ii) *30PW* with the usual amplitude *(Condition B)*; iii) *60PW* at threshold amplitude (*Condition C)*; iv) *30PW* at threshold amplitude, that was attained starting from the *baseline* amplitude of *Condition B* (*Condition D)*.

Each stimulation condition was maintained for at least 60 minutes before assessment.

During each condition we assessed: (a) 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, using the motor section of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS part III); (c) Patient Global Impression Improvement Scale (PGI-I). The following scales were also assessed, in the usual Med-On/Stim-On, 60PW condition: i) Quality of life in the dysarthric speaker questionnaire (QoL-DyS, Italian version); ii) MMSE and Schwab & England Scale (S&E) scores; iii) MDS-UPDRS part I-II and IV. L-dopa equivalent daily dose (LEDD) was calculated according to recognized standard conversion.

All voice and speech samples were recorded in a quiet hospital room using a tabletop cardioid condenser microphone, with a 15 cm mouth to microphone distance.

Data analysis

Detailed methods on speech acquisition and analysis are described in *Supplementary material file*. Overall, data were evaluated by means of both automatic analysis and blinded speech language therapist evaluation. The following parameters were considered: (a) Voice (pitch) quality; (b) Voice (pitch) variability; (c) Voice (pitch) instability; (d) Speech rate; (e) Speech intelligibility; (f) DDK; g) Stuttering dysfluencies.

Statistical analysis

The acute effect of 30PW *vs.* 60PW and of the threshold voltage *vs.* usual voltage was calculated by comparisons of speech and motor parameters, between different stimulation conditions using the Wilcoxon's signed ranked test. Spearman's rank correlation coefficient was used to assess the correlation between the motor response to stimulation and the speech response to PW changes. All analyses were performed with SPSS 25.0 (Chicago, IL) using two-tailed p-values with a 0.05 level of significance.

Results

Demographic, clinical and therapeutic data are detailed in Table 1. All patients, but one, had no clinically relevant speech impairment before DBS (Table S1).

All patients had an optimal motor response to stimulation (38.4±20.2% at the MDS-UPDRS part III comparing *M-Off* /Stim-On and presurgical *M-Off* conditions, p=0.018), a mild speech impairment as per the MDS-UPDRS 2.1 item at the post-DBS assessment which showed a *not homogeneous* trend of speech worsening if compared to MDS-UPDRS pre-DBS 2.1 item (Table 1), with a slight impact on QoL-DyS (Table 1). Speech impairment progressively appeared in the 3-6 months after DBS implantation, in all but two patients who remained stable (pt-1 and pt-5, see Table S1).

30PW effect at usual amplitude. Comparing speech parameters at 30PW *vs.* 60PW on the usual amplitude (Condition B *vs.* A), we did not find significant changes, with the exception of a lower

percentage of stuttering disfluencies (p=0.04). Concomitantly, we observed a higher voice variability, worse DDK, and a better clinician-based speech score, as per the MDS-UPDRS item 3.1, but these differences did not reach the statistical threshold (Table 2 and Table S1). Motor performance did not get worse (p= 0.21). Three patients reported a minimal subjective improvement of speech (PGI-I=3) while four reported no changes (PGI-I=4).

30PW effect at a threshold amplitude. Comparing speech parameters at 30PW *vs.* 60PW, at threshold *amplitude* (Condition D *vs.* C), we found a statistically significant improvement of speech intelligibility for both words (p= 0.02) and sentences (p= 0.04), with a better clinician-based speech score (p= 0.02). A lower voice variability and instability, better alternating motion rate AMR and sequential motion rate (SMR) DDK, and a lower percentage of stuttering disfluencies was also observed, but did not reach statistical significance (Table 2 and Table S1). Consistently, motor performances were globally unchanged. Four out of seven patients reported minimal subjective improvement of speech at the PGI-I. The most common side effects were facial muscle contractions (n=5) and dysarthria (n= 5), related to pyramidal tract activation (Table S1). No correlation was found among the motor improvement (ΔMDS-UPDRS-III) and speech intelligibility improvement.

Amplitude effect. Comparing usual vs. threshold amplitude, at the same PW (A vs. C and B vs. D), we noted: a) at 30 PW, there were no significant modification of speech parameters, along with a trend towards better motor effect with higher voltage (p= 0.09); b) at 60 PW, we found a significant worsening of AMR DDK (p= 0.03) and speech intelligibility (p= 0.02) at higher voltage, with a trend towards worsening of MDS-UPDRS item 3.1 (p= 0.08) (Table 2).

Discussion

In this pilot study, we observed that, in the absence of dopaminergic treatment, 30PW STN stimulation at threshold amplitude may acutely improve speech intelligibility for both sentences and

words, without negative effects on motor performance. The beneficial effect of short PW was confirmed by patients' perception.

We did not select patients based on a severe speech impairment after DBS implantation, to observe any clinical but also subclinical effect of 30PW, by means of acoustic analysis of speech, which would be able to detect changes that are not detectable by the MDS-UPDRS-based assessment. Indeed, the aim of this study was to observe any acute modification of speech parameters switching PW from 60 to 30, to identify which features of speech and voice could benefit from PW switching. All included patients had a slight and progressive worsening of speech 3-6 months after DBS implantation, except two who remained stable compared to pre-surgical condition. None of the patients presented an acute stimulation-induced dysarthria soon after the implantation. We chose to study patients in a short-medium term after DBS implantation (range 6-36 months), in order to avoid patients with severe axial symptoms related to disease progression, i.e. 5-10 after DBS.

Current hardware-related advances have increased the options of stimulation settings, providing a higher level of personalization of the DBS treatment. While more options may help achieve better clinical outcomes, they make identifying the best setting of individual stimulation parameters more challenging. Speech impairment, along with the treatment of axial symptoms, is one of the main unmet clinical needs in DBS-treated patients. In recent years, the use of PWs shorter than the usual 60μs lower limit has been investigated to increase selectivity of fibre stimulation. New stimulation opportunities allow to widen the PW range from 10 to 450 μs, with steps of 10 μs. Reduction of PW to 30μs could increase the therapeutic window, avoiding capsular side effects. This is due to a more precise current targeting on smaller-diameter axons, which are closer to the electrode than pyramidal tract fibres [13]. Concerning PD patients with stimulation-induced dysarthria, reduction of PW to 30μs has been shown to be effective in improving speech outcomes, with a sustained benefit at 6 months follow-up [8], while on patient with a longer DBS duration (up to 6.5 years), 30 PW seems to be a feasible option in terms of motor symptoms effect, but with no clear

improvement on speech impairment [8]. At current amplitude close to the side-effect threshold, 30PW seems to offer a benefit in terms of speech intelligibility, voice variability, instability and DDK. We argue that 30PW stimulation does not further affect the glottal function that is typically impaired in PD (e.g., incomplete glottal closure, hyperadduction of false vocal folds, anteroposterior hypercompression, and asymmetrical glottal movement). Concomitantly a lower percentage of stuttering disfluencies contributes to a better speech intelligibility. The exact mechanism by which short PW stimulation results in increasing the therapeutic windows remains to be fully elucidated in detail, but it seems that 30 PW is more effective in selectively targeting smaller-diameter axons in close vicinity of the stimulation contact due to differences in chronaxies. Avoiding capsular effect and targeting smaller-diameter axons seems to have a beneficial effect on the glottal function, but the mechanism still remains to be further investigated.

Due to the small sample of patients and the quite optimal position of all electrodes implanted, any consideration related to the relationship between electrodes position and 30PW effect (Table S1) remain speculative, though we may argue that a beneficial effect seems possible independently from a central or slightly lateral/medial position.

Thus, our pilot study suggests that DBS-treated patients who experience impaired speech intelligibility, mainly related to stuttering disfluencies, voice variability and instability, may benefit from a 30PW stimulation trial at a current amplitude close to the side effect threshold maintaining a satisfactory motor performance. Additionally, we observed a not statistically motor improvement at 30PW with a threshold stimulation amplitude. This could mean that our patients may have been previously undertreated due to the presence of mild dysarthria, and the 30PW setting is confirmed to be effective in increasing the therapeutic window. Of note, DBS duration in our patients is on average shorter than two and a half years, which has been suggested as a favourable criterion to predict the reversibility of stimulation-induced dysarthria using 30 PW DBS [9].

Main limitations of this pilot study include the small sample size, the cross-sectional design, the lack of randomization and the lack of pre-DBS acoustic analysis or Qol-Dys data that would have allowed to detect subclinical speech impairment. Pre-DBS data could have been helpful to answer the question whether 30PW stimulation is only correcting the deterioration due to 60PW stimulation or is actually improving PD-related aspects of dysarthria. At the same time, the speech intelligibility improvement we observed seems to be related to the 30PW stimulation and not to the amplitude increment, since it was present only at 30PW, while intelligibility worsened at threshold amplitude with 60PW.

Our preliminary findings need to be confirmed in larger cohorts of patients selected for their low speech intelligibility after DBS with a longitudinal design. The effect of 30PW should be better explored, both at low and threshold amplitude, in a longitudinal setting. Additionally, further studies are warranted to investigate the effect of combined low frequencies and low PW stimulation in either hemisphere, the left one being typically associated with speech impairment. This might result in tailored stimulation protocols for patients with stimulation-related speech dysarthria, similarly to previous observations in patients with asymmetric freezing of gait.

In conclusion, a thorough characterization of PD speech profiles may help a better application of recent DBS hardware-related advances for patients with specific speech impairment. The use of shorter PW stimulation in STN-DBS treated PD patients with impaired speech intelligibility deserves further investigation.

Acknowledgments:

The authors thank all the patients and their families for participating in this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest and Financial Disclosures

Dr. Fabbri no conflict of interest to report. Received travel grant from AbbVie

Federico Natale: no conflict of interest to report. No disclosures.

Dr. Artusi no conflict of interest to report. Received travel grants from Zambon and Abbvie, and educational grants from Ralpharma and Neuraxpharm.

Pr. Marco Bozzali no conflict of interest to report. Received honoraria for lecturing and travel grants from Biogen and Roche. He sits in a Advisory Board for Roche Pharmaceuticals.

Dr Giulietti has no disclosures.

Prof. Isabel Guimaraes: no conflict of interest to report. No disclosures.

Dr Romagnolo no conflict of interest to report. Received grant support and speaker honoraria from AbbVie, speaker honoraria from Chiesi Farmaceutici and travel grants from Lusofarmaco, Chiesi Farmaceutici, Medtronic,

and UCB Pharma.

Dr Rizzone has no conflict of interest to report. No disclosures.

Anna Accornero no conflict of interest to report. No disclosures.

Prof. Lopiano no conflict of interest to report. Received honoraria for lecturing and travel grants from Medtronic, UCB Pharma, and AbbVie.

Dr Zibetti no conflict of interest to report. Received grant support and speaker honoraria from AbbVie, speaker honoraria from Bial Pharmaceuticals and travel grants from Merz, Medtronic, Boston Scientific and UCB Pharma.

References

[1] S. Pinto, C. Ozsancak, E. Tripoliti, S. Thobois, P. Limousin-Dowsey, P. Auzou, Treatments for dysarthria in Parkinson's disease, The Lancet. Neurology 3(9) (2004) 547-56.
[2] L. Brabenec, J. Mekyska, Z. Galaz, I. Rektorova, Speech disorders in Parkinson's disease: early diagnostics and effects of medication and brain stimulation, J Neural Transm (Vienna) 124(3) (2017) 303-334.
[3] E. Tripoliti, P. Limousin, T. Foltynie, J. Candelario, I. Aviles-Olmos, M.I. Hariz, L. Zrinzo, Predictive factors of speech intelligibility following subthalamic nucleus stimulation in consecutive patients with Parkinson's disease, Movement disorders : official journal of the Movement Disorder Society 29(4) (2014) 532-8.
[4] E. Tripoliti, L. Zrinzo, I. Martinez-Torres, E. Frost, S. Pinto, T. Foltynie, E. Holl, E. Petersen, M. Roughton, M.I. Hariz, P. Limousin, Effects of subthalamic stimulation on speech of consecutive patients with Parkinson disease, Neurology 76(1) (2011) 80-6.
[5] C. Moreau, O. Pennel-Ployart, S. Pinto, A. Plachez, A. Annic, F. Viallet, A. Destee, L. Defebvre, Modulation of dysarthropneumophonia by low-frequency STN DBS in advanced Parkinson's disease, Movement disorders : official journal of the Movement Disorder Society 26(4) (2011) 659-63.
[6] M. Fabbri, M. Zibetti, G. Ferrero, A. Accornero, I. Guimaraes, M.G. Rizzone, A. Romagnolo, J.J. Ferreira, L. Lopiano, Is lowering stimulation frequency a feasible option for subthalamic deep brain stimulation in Parkinson's disease patients with dysarthria?, Parkinsonism & related disorders 64 (2019) 242-248.
[7] V. Dayal, T. Grover, P. Limousin, H. Akram, D. Cappon, J. Candelario, M. Salazar, E. Tripoliti, L. Zrinzo, J. Hyam, M. Jahanshahi, M. Hariz, T. Foltynie, The Effect of Short Pulse Width Settings on the Therapeutic Window in Subthalamic Nucleus Deep Brain Stimulation for Parkinson's disease, Journal of Parkinson's disease 8(2) (2018) 273-279.
[8] V. Dayal, A. De Roquemaurel, T. Grover, F. Ferreira, M. Salazar, C. Milabo, J. Candelario-McKeown, L. Zrinzo, H. Akram, P. Limousin, T. Foltynie, Novel Programming Features Help Alleviate Subthalamic Nucleus Stimulation-Induced Side Effects, Movement disorders : official journal of the Movement Disorder Society 35(12) (2020) 2261-2269.
[9] V. Dayal, T. Grover, E. Tripoliti, C. Milabo, M. Salazar, J. Candelario-McKeown, D. Athauda, L. Zrinzo, H. Akram, M. Hariz, P. Limousin, T. Foltynie, Short Versus Conventional Pulse-Width Deep Brain Stimulation in Parkinson's Disease: A Randomized Crossover Comparison, Movement disorders : official journal of the Movement Disorder Society 35(1) (2020) 101-108.
[10] B.B. Avants, C.L. Epstein, M. Grossman, J.C. Gee, Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain, Medical image analysis 12(1) (2008) 26-41.
[11] K.J. Friston, Ashburner, J. T., Kiebel, S. J., Nichols, T. E., & Penny, W. D., Statistical Parametric Mapping: The Analysis of Functional Brain Images., Academic Press (2011).
[12] J.V. Manjón, A. Bertó, J.E. Romero, E. Lanuza, R. Vivo-Hernando, F. Aparici-Robles, P. Coupe, pBrain: A novel pipeline for Parkinson related brain structure segmentation, NeuroImage. Clinical 25 (2020) 102184.
[13] M.M. Reich, F. Steigerwald, A.D. Sawalhe, R. Reese, K. Gunalan, S. Johannes, R. Nickl, C. Matthies, C.C. McIntyre, J. Volkmann, Short pulse width widens the therapeutic window of subthalamic neurostimulation, Annals of clinical and translational neurology 2(4) (2015) 427-32.

LEGEND FOR TABLES

Table 1. Demographic, clinical, therapeutic and speech characteristics of DBS patients. 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; MMSE: Mini mental state examination; S&E: 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.

Table 2. Speech and voice response to PW and voltage changes. Med Off: Medication Off; Oral diadockocinesis: number of /pa/, /pata/, /pataka/5 seconds; 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%.

SUPPLEMENTARY MATERIAL

Table S1. Detail of single patient demographic, clinical, motor and speech features in Med On/Stim On and during the stimulation challenge test (Med Off, *60PW at usual amplitude - Condition A*, *30PW at* usual amplitude - *Condition B*; *60PW* at a threshold amplitude - *Condition C and 30PW* at threshold amplitude - *Condition D)*; (*) at MedOn/StimOn (130Hz and 60PW);

Figure S1. Electrode positioning. The figure shows axial, coronal and sagittal slices (from top to bottom panels) of each patients' presurgical T2-weighted scan coregistered to postsurgical CT images in MNI space. Subcortical nuclei of interest were segmented from each individual normalised T2-weighted scan, while the corticospinal tract was imported from the "JHU White-Matter Tractography Atlas" available in FSL (fsl.fmrib.ox.ac.uk/fsl/fslwiki). Electrodes' reconstruction (white) was based on the hyperdense signal they cause on CT images. The subcortical regions of interest, i.e., the STN (red), substantia nigra (green) and red nucleus (yellow)

were represented using false colours. All the electrodes resulted within the STN, with minor difference among patient, including a slightly lateral position for patient #2, #4, #5 and #7 concerning the left electrode and a slightly anterior/lateral position for patient #3 concerning the right electrode.

	Patients with DBS (n=7)
Age	56.2 ± 8.2
Women (n/total (%))	2/7 (28.5%)
Age at disease onset (y)	44.8 ± 5.9
Disease duration (y)	11.1 ± 3.1
Age at DBS (y)	54 ± 9
Months after DBS	14.4 ± 10.2
LEDD before surgery (mg)	1129.3 ± 85.2
LEDD after surgery (mg)	530.7 ± 116.2
Stimulation voltage	
R_STN/L_STN at 60 µs (Condition A), mA	2.5 ± 0.9 / 2.5 ± 0.8
R_STN/L_STN at 30 µs (Condition B), mA	3.1 ± 0.8 / 3.2 ± 0.9
R_STN/L_STN at 60 µs (Condition C), mA	3.7 ± 1.1 / 3.6 ± 1.1
R_STN/L_STN at 30 µs (Condition D), mA	4.4 ± 1.3 / 4.7 ± 1.5
Electrode position* **Ventral n. (%)***	 2 (28%)
MMSE	29.6 ± 0.8
S&E (ON)	95.7 ± 7.9
MDS-UPDRS I**	6.4 ± 4.2
MDS-UPDRS II total score pre-DBS** **item 2.1 (speech) pre-DBS**** **MDS-UPDRS II total score post-DBS**** **item 2.1 (speech) post-DBS**** **MDS-UPDRS item 3.1 (speech) pre-DBS**** **item 3.1 (speech) post-DBS****	13.4 ± 5.6 0.6 ± 0.8 12.9 ± 4.1 1.3 ± 1.1 1.2 ± 0.7 1.7 ± 0.9
MDS-UPDRS III pre-DBS (Med Off) **MDS-UPDRS III pre-DBS (Med On)** **MDS-UPDRS III post-DBS (Med Off/Stim On 60PW)**	51.8 ± 10.8 20 ± 5.8 30.1 ± 8.6^
MDS-UPDRS IV (pre DBS) **MDS-UPDRS IV**	9.7 ± 1.6 3.6 ± 2.8^
QoL-Dys Total Score	54 ± 24
Speech characteristics	*14 ± 10*
Situational difficulty	*13 ± 10*
Compensatory strategies	*14 ± 10*
Perceived reactions of others	*6 ± 4*

Table 1. Demographic, clinical, therapeutic and speech characteristics of DBS patients.
LEDD: levodopa equivalent daily dose (no patient was taking benzodiazepine or antipsychotic treatment) ; R_STN: right subthalamic nucleus; L_STN: left subthalamic nucleus; MMSE: Mini mental state examination; S&E: 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, all but one patients use ring stimulation; (**): in the MedOn/Stim On condition at 60PW; (^): $p < 0.05$ comparing with pre-DBS

	Med-Off				Pulse width effect (*P-values*)	Pulse width effect (*P-values*)	Amplitude effect at 30PW (*P-values*)	Amplitude effect at 60PW (*P-values*)
	Usual voltage		Threshold amplitude		*A vs. B*	*C vs. D*	*B vs. D*	*A vs. C*
Pulse width setting	**PW60 (A)**	**PW30 (B)**	**PW60 (C)**	**PW30 (D)**				
Voice quality								
Average F_0	162.1 ± 7.3	166.1 ± 2.7	162.1 ± 5.1	155.6 ± 5.5	0.87	0.75	0.40	0.87
Voice variability								
F_0SD	2.1 ± 0.6	4.2 ± 2.4	7.8 ± 3.1	6.1 ± 1.9	0.13	0.5	0.61	0.09
Voice instability								
(jitter)	0.36 ± 0.06	0.41 ± 0.03	0.7 ± 0.4	0.5 ± 0.1	0.31	0.87	0.31	0.50
Speech rate								
First paragraph	5.2 ± 1.4	5.3 ± 1.4	5.5 ± 1.9	5.2 ± 1.5	0.87	0.50	0.86	0.49
Second paragraph	4.4 ± 1.3	4.8 ± 0.9	4.8 ± 0.9	4.9 ± 0.9	0.40	0.61	0.93	0.61
DDK								
/pa/	4.5 ± 1.8	3.7 ± 1.3	3.5 ± 1.7	4.1 ± 1.8	0.06	0.17	0.31	**0.03**
/pata/	2.3 ± 0.5	2.2 ± 0.3	2.1 ± 0.6	2.3 ± 0.3	0.46	0.21	0.20	0.24
/pataka/	1.6 ± 0.2	1.7 ± 0.1	1.6 ± 0.4	1.8 ± 0.2	0.18	0.25	0.18	0.89
Speech Intelligibility								
Word list (%)	92 ± 2	89 ± 2	84 ± 2	90 ± 1	0.18	**0.02**	0.40	**0.02**
Intelligibility read. (sentence)	7.0 ± 0.5	7.0 ± 0.3	6.6 ± 0.5	7.1 ± 0.6	0.83	**0.04**	0.59	0.14
Stuttering disfluences (%)	2.0 ± 1.7	0.9 ± 0.9	1.4 ± 0.9	1.0 ± 1.0	**0.04**	0.41	0.48	0.40
Mean Int (dB)	68.7 ± 3.9	69.7 ± 6.0	69.3 ± 6.8	69.1 ± 5.4	0.84	0.92	0.83	0.09
Amplitude perturbation Shimmer (%)	4.2 ± 2.6	4.2 ± 2.7	4.1 ± 2.5	4.8 ± 2.5	0.91	0.86	0.85	0.09
MDS-UPDRS III	31.2 ± 8.8	33.4 ± 10.4	28.7 ± 7.9	26.9 ± 7.6	0.21	0.40	0.09	0.49
MDS-UPDRS item 3.1	1.4 ± 1.3	0.7 ± 0.8	1.9 ± 1.1	0.9 ± 0.9	0.06	**0.02**	0.56	0.08

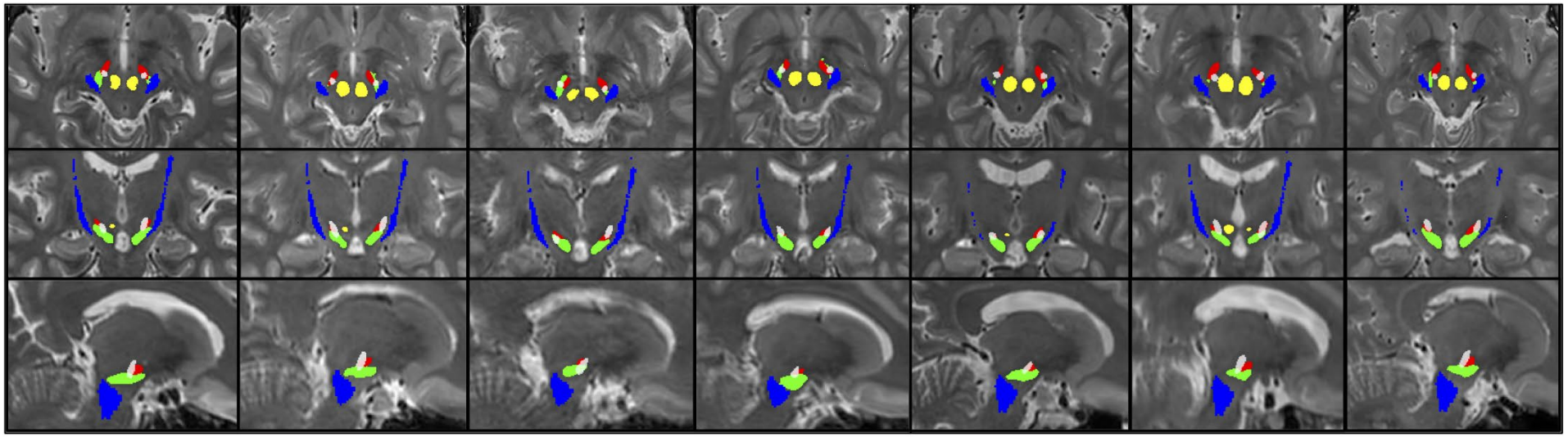
Table 2. Speech and voice response to PW and Amplitude changes. Med Off: Medication Off; Oral diadockocinesis: number of /pa/. /pata/. /pataka/5 seconds; Speech rate: syllables/sec. Available values for vocally healthy subjects with same age: Average F0 (men: 128 ± 36; women: 198 ± 44); speech rate: 3–6 syllables/sec; DDK: 5–7 syllables/sec; Hz; Jitter:<1%;

	Pt-1	Pt-2	Pt-3	Pt-4	Pt-5	Pt-6	Pt-7
DBS duration, months	17	10	13	12	7	36	6
LEDD pre-DBS, mg	1150	1300	1100	1100	1120	1115	1020
LEDD post-DBS, mg	600	650	475	450	360	680	500
Stimulation configuration	L. C+ 2-3-4- (ring) R. C+ 13-14-15- (ring)	L. C+ 5-6-7- (ring) R. C+ 13-14-15- (ring)	L. C+ 5-6-7- (ring) R. C+ 13-14-15- (ring)	L. C+ 5-6-7- (ring) R. C+ 10-11-12- (ring)	L. C+ 5-6-7- (ring) R. C+ 13-14-15- (ring)	L. C+ 3- R. C+ 11(B, C)-	L. C+ 5-6-7- (ring) R. C+ 13-14-15- (ring)
Electrodes position	Both centered the STN (anterior-motor part)	R: centered the STN (anterior-motor part) L: slightly lateral position	R: slightly anterior/lateral position L: centered the STN (anterior-motor part)	R: centered the STN (anterior-motor part) L: slightly lateral position	R: centered the STN (anterior-motor part) L: slightly lateral position	R: centered the STN (anterior-motor part) L: slightly medial position	R: centered the STN (anterior-motor part) L: slightly lateral position
R_STN/L_STN at 60 µs (Condition A), mA	2.6/ 2.3	2.5/ 1.8	2.5/ 2.5	1.3/ 1.2	1.9/2.5	4/3.3	3.13.61
R_STN/L_STN at 30 µs (Condition B), mA	3.6/ 3.2	3.5/ 2.5	3.5/3.1	2.5/ 2.4	2.6/ 3.5	5.6/ 4.5	4.3/ 5
R_STN/L_STN at 60 µs (Condition C), mA	3.6/ 3.3	3.8 / 4.3	3/ 2.5	1.8/ 1.6	2.3/ 3.1	4.2 /4.1	3.3/ 3.8
R_STN/L_STN at 30 µs (Condition D), mA	5.3/ 4.9	5.2/ 6	4.6/ 3.8	2/ 1.8	3.4/ 4.5	5.8/ 5.8	4.8/ 5.8
MDS-UPDRS II total score pre-DBS **item 2.1 (speech) pre-DBS** **item 2.1 (speech) post-DBS** **MDS-UPDRS II total score post-DBS** **Item 3.1 (speech) pre-DBS*** **Item 3.1 (speech) post-DBS*** **QoL-Dys Total Score**	10 2 2 17 3 3	17 0 1 12 1 2	12 0 1 10 1 1	8 0 1 9 1 1	9 1 0 11 1 1	14 1 3 20 1 3	24 0 1 12 1 1

	90	55	53	50	17	78	36
MDS-UPDRS III pre-DBS (Med Off)	51	61	55	34	51	67	46
MDS-UPDRS III post DBS	40	29	21	26	23	36	44
A, PW60	40	34	23	22	29	34	50
B, PW30	24	16	25	32	28	39	33
C, PW60	23	20	22	21	28	40	30
D, PW30							
MDS-UPDRS IV (pre DBS)	10	9	9	12	10	7	11
MDS-UPDRS IV	1	6	2	2	1	8	5
AEs							
C, PW60	Dysarthria	Facial muscle contraction/Dysarthia	Dysarthria	Facial muscle contraction/Dysarthia	Minimal facial musc contraction	Facial muscle contraction/Dysarthia	Diplopia, Facial muscle contraction
D, PW60	Dysarthria	Facial muscle contraction/Dysarthia	Dysarthria	Facial muscle contraction/Dysarthia	Minimal faial musc contraction	Facial muscle contraction/Dysarthia	Diplopia Facial muscle contraction
Speech parameters							
Voice quality, Average Fo							
A	240.9	104.6	175.9	231.5	135.8	117.3	128.4
B	221.8	108.4	184.4	220.9	173.8	134	118.9
C	199.2	127.3	159.9	209	170.4	156.5	111.9
D	216.1	113.6	143.3	214.4	132.5	140.2	129.3
Voice variability, F_0SD							
A	1.3	0.9	3.3	2.2	4.4	1.5	1.3
B	2.1	1.1	2.9	2.9	13.9	1.1	5.3
C	1.4	1.6	2	22.9	12.9	1.7	11.8
D	1.4	1.8	2.3	13.8	19.5	1.4	2.3
Voice instability, Jitter							
A	0.21	0.28	0.23	0.59	0.26	0.29	0.65
B	0.29	0.29	0.26	0.43	0.23	0.36	1.06
C	0.21	0.19	0.22	0.59	0.29	0.53	2.59

D	0.28	0.45	0.46	0.62	0.24	0.38	0.84
Speech rate							
First paragraph							
A	4.2	6.9	5.9	3.2	4.2	6.5	5.5
B	3.3	6.9	5.9	4	4.4	6.5	6.1
C	2.8	7.9	6.3	2.9	5.2	6.4	6.8
D	3.7	8.1	5.8	4.4	4.3	4.8	5.8
Second paragraph							
A	4.5	6.2	5.2	3.6	3.6	2.4	5.2
B	4	6.4	5.3	3.9	4	4.9	4.9
C	4.9	5.8	5	2.8	4.7	4.7	5.3
D	4.8	6.4	4.8	3.9	4	4.7	6.1
DDK							
/pa/							
A	4.4	3.4	7.2	3	6.6	3.8	2.8
B	4	3.6	5.2	1.8	5.6	2.8	3
C	2.2	3.4	6	1.8	5.6	3.2	2.2
D	3.4	5	6	3	6.4	2.2	2
/pata/							
A	2.2	2	3.4	2.2	1.8	2	2.6
B	2.4	1.8	2.6	1.8	2.6	2	2.2
C	1.2	1.6	2.6	1.4	2.6	2.2	2.6
D	2.2	2.4	2.8	2.2	2.6	2	2.2
/pataka/							
A	2	1.6	1.8	1.4	1.4	1.6	1.6
B	1.8	1.8	1.8	1.6	1.6	1.6	1.8
C	1.4	1.6	1.8	0.8	1.6	1.8	2.2
D	1.8	2.2	1.8	1.6	1.8	1.6	1.8
Speech Intelligibility							
Word list (%)							
A	71	98	99	97	92	86	98
B	55	97	98	91	90	93	96
C	37	97	98	92	88	84	88
D	56	98	99	98	94	92	93
Intelligibility read. (sentence)							
A	2.2	9.4	9.6	6.8	7.8	4.6	8.4
B	1.6	8.4	9.8	8	7.8	5.6	7.6
C	1.6	7.8	9.4	7.2	7.8	4.6	7.6
D	2.4	9	9.8	7.2	7.8	5.4	8
Stuttering disfluences (%)							

A	1.5	1.5	0.5	1.5	1	5.5	2.5
B	1.5	0.5	0.5	0	0.5	2.5	0.5
C	2.5	0.5	0.5	2	0.5	1.5	2
D	1	0.5	0	1	0.5	3	1
Mean Int (dB)							
A	67.5	73.3	70.0	71.8	63.3	64.0	71.1
B	65.4	72.4	71.6	77.6	59.3	73.6	68.1
C	63.9	78.5	70.0	71.7	57.4	72.5	71.4
D	64.9	77.5	66.4	72.6	61.6	72.6	68.1
Amplitude perturbation Shimmer (%)							
A	2.8	1.9	3.2	4.3	2.5	9.7	4.8
B	4.2	1.9	3.3	2.8	2.6	4.6	10.0
C	3.4	1.5	2.7	3.4	3.9	4.1	9.5
D	4.2	1.9	9.6	4.6	2.6	5.0	5.8
MDS-UPDRS item 3.1							
A	3	2	0	1	0	3	1
B	2	1	0	0	0	1	1
C	3	2	1	2	0	3	2
D	2	0	0	1	0	2	1



Patient #1 Patient #2 Patient #3 Patient #4 Patient #5 Patient #6 Patient #7

Corticospinal tract Subthalamic nucelus Substantia nigra Red nucleus Electrode