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Original Article

Subthalamus stimulation in Parkinson disease: Accounting for the bilaterality of contacts

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Abstract

Background: Deep brain stimulation (DBS) in Parkinson's disease uses bi-hemispheric high-frequency stimulation within the subthalamus, however, the specific impacts of bilaterality of DBS are still not clear. Thus, we aimed to study the individual-level clinical impact of locations of right-left contact pair-up accounting for each subthalamic nucleus (STN) anatomy.

Methods: Contact locations and effects at 1 year were studied retrospectively in an unselected series of 53 patients operated between 2004 and 2010. Location of contacts was defined relatively to the main axis of STN used to map longitudinal and transversal positions, and STN membership (out meaning out-of-STN). Contact pairings were described via three methods: (i) Unified contact location (UCL) collapsing DBS into an all-in-one contact; (ii) balance of contact pair-up (BCPU), defined as symmetric or asymmetric regardless of laterality; (iii) hemisphere-wise most frequent contact pair-up (MFCP) regardless of BCPU. Clinical data were: mean levodopa equivalent dose, Unified Parkinson's Disease Rating Scale (UPDRS) motor score III without medication, UPDRS II and III speech sub-scores, UPDRS II freezing sub-score, 1 year versus preoperative values, with and without levodopa. Ad-hoc two-sided tests were used for statistical analysis.

Results: Worsening speech, was more frequent for UCL_out patients and when the left MFCP contact was rear and/or superolateral, however, it less frequent for BCPU-asymmetric patients. Worsening freezing was more frequent when the right MFCP contact was rear and superolateral.

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Conclusions: These results point to strategies for minimizing dysarthria and freezing as adverse effects of DBS.

Key Words: Bilateral, deep brain stimulation, Parkinson's disease, Subthalamic nucleus

INTRODUCTION

Bilateral high-frequency chronic deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an efficient treatment for motor complications in advanced Parkinson's disease[1,23,24] and a promising option for younger patients.[30] Motor efficiency, commonly quantified as the percent reduction of Unified Parkinson's Disease Rating Scale motor score III (UPDRS III; from 0 to 108, where higher values equate to more severe symptoms) without medication, ranges, on average, from 35.8 to 61% [Figure 1a]. This broad variability across studies is difficult to explain but fits with the inter-individual variability observed in daily practice. It depends on several parameters that, although not fully grasped, include phenotype of Parkinson's disease, comorbidities, age, duration and severity of disease, sociofamilial context, goal-directed postoperative management, surgical lesion, electrode design, current delivery, contact positioning, and specificity of the anatomo-functional environment of each individual. Motor improvement seems to rely mainly on STN modulation,[1] which also triggers adverse effects such as deterioration in speech intelligibility,[8,33] particularly in the posterior region of the STN,[17] whereas pitch voice modifications,[16] such as gait worsening,[28] seem less frequent with posterior (caudal) zona incerta. Adverse effects are rarely documented. Approximately 46% of studies report adverse event data, of which 62.5% report speech worsening and 37.5% postural worsening, both of which are independent of aggregate motor efficiency [Figure 1b]. The overall mechanism of action of STN DBS is still intriguing.[2,7,9,23,24] Location of contacts is likely a pivotal factor given the functional segregation of the STN[22,15,12] and its anatomic environment.[21] New DBS technologies will likely help factor in the specificity of individual anatomy and functionality.[11] In practice, STN DBS involves the STN and its close vicinity because clinical improvement has been reported within an anteroposterior area encompassing the superior border of the STN,[39] the fields of Forel, and the zona incerta.[3,10,27,35] Globally, the explanation of the clinical effects of bilateral STN DBS is simplified as if the location of the effective right and left contacts is symmetrical and collapsible into a unique location including the STN and its close environment.

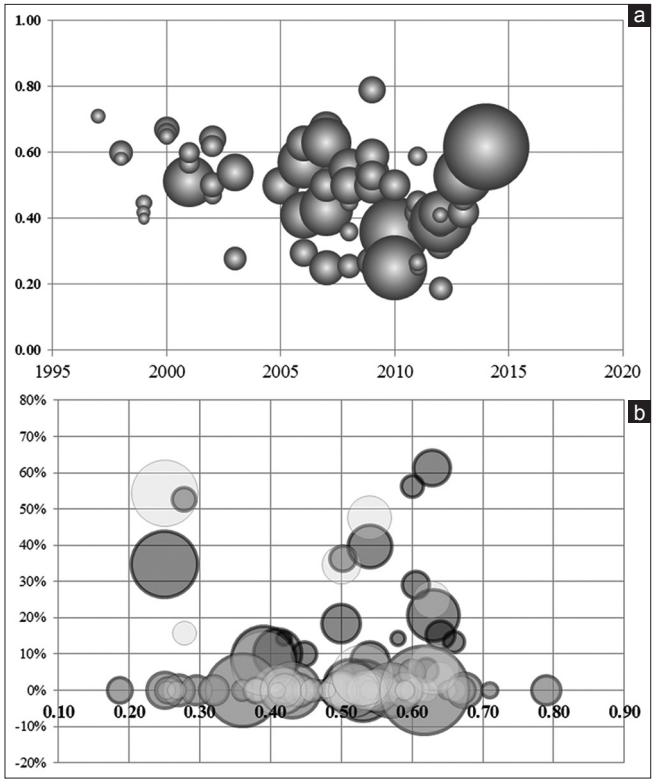


Figure 1: Overview of literature from 1994 to 2014: Bilateral, high-frequency, chronic deep brain stimulation (DBS) of the subthalamic nucleus (STN), or "STN DBS." (a) Percent reduction of Unified Parkinson's Disease Rating Scale motor score III (y-axis) according to the year of publication; the circle size is proportional to number of patients in the series (*n* = 72). (b) Distribution of stimuli-induced adverse effects (y-axis; percentage of patients with speech worsening, grey circles, or postural worsening, white circles; circle size is proportional to number of patients in the series) according to the percent drop in Unified Parkinson's Disease Rating Scale motor score III without medication (x-axis) in the series (40 and 41 did not reported stimuli-induced adverse effects, respectively for speech and posture; out of 72)

We hypothesized that accounting for each individual right-left contact pair-up could be relevant to study either positive or adverse clinical effects for further personalization of electrode targeting and optimization of pulse settings. Here, we performed a single-center cross-sectional cohort study of 53 consecutive unselected patients, analyzing aggregate motor efficiency, dysarthria, and freezing according to the location of effective contacts used in chronic conditions at 1 year post-surgery. In addition, we analyzed the influence of age, gender, voltage, and drug modifications. We assumed an optimal compromise between medical treatment and bilateral DBS for each individual. Location of effective contacts was blinded from clinical results. Each right-left pair-up

of effective contacts was specified according to STN landmarks, enabling two analyses, namely, a unified approach, where right-left contact pair-up was simplified, resulting in a unique location for each individual, and a bilateral approach, describing the balance of right-left contact pair-up for each patient and accounting for differences between the right and left hemispheric locations.

MATERIALS AND METHODS

Patients

Clinical data on 53 Parkinson's patients (two left-handed) operated consecutively between June 2004 and September 2010 were studied retrospectively after first securing Institutional Review Board approval. Bilateral subthalamic DBS (Lead 3387©, Kinetra©; Medtronic, USA) implantation was carried out according to the preoperative magnetic resonance imaging (MRI) anatomic mapping and intraoperative micro-recordings and clinical assessment (rigidity, tremor, speech) using semi-micro stimulation (MicroGuide Pro™; Alpha Omega, Israel) following an already published technique.[6,18] The four lead contacts were usually positioned as follows (double obliquity avoiding vessels, sulci, ventricles, striatum; entry point within the second frontal gyrus): Contact 0 (distal) within the STN, typically near the center; contact 1 within the lateral and superior region of the STN, at the frontier or outside, i.e., within the fields of Forel or zona incerta; contact 2 within the fields of Forel or zona incerta; contact 3 (proximal) within the inferior portion of the ventral-lateral thalamus. Contact number 1 was placed on the optimal site allowing efficacy on symptoms with a low current value (usually between 0.2 and 1 mA) and no or little adverse effects with a high current value (usually above 2 mA), using semi-micro electrodes. The final locations of the right and left electrodes, particularly in the anteroposterior position, depended on anatomy (limiting the options for secured trajectories), intraoperative assessments, and technical concerns such as mechanical accuracy of stereotactic tools. Brain shift was negligible with this technique (X-ray and computed tomography (CT)-scan controls; recumbent position; cerebrospinal-fluid-air-proof dura opening). All patients attended regular follow-up with senior institutional neurologists at least 1 year after the surgery to optimize their medication and pulse settings. UPDRS II, III, and IV sub-scores at 1 year post-implantation were collected [Table 1].

Motor efficiency on the targeted motor symptoms was calculated on UPDRS III motor score, and expressed as percent improvement, in Dopa-OFF condition (MedOFF) at 1 year: StimOFF1yr – StimON1yr/StimOFF1yr; Dopa challenge, DopaOFF, 12 hours after withdrawal of antiparkinsonian drugs; StimOFF, 1 hour after turning

Table 1: Demographic data of the 53 Parkinson's patients operated on consecutively between June 2004 and September 2010; (a) Baseline characteristics; (b) 1-year follow-up

	Values
(a) Baseline characteristics	
Age (years) (mean±SE)	60.9±7.4
Gender, *n* (%)	
Male	30 (56.6)
Duration of Parkinson's disease (years) (mean±SE)	10.9±4.3
UPDRS IV duration of "Dyskinesia" sub-score (*n*=53), duration (mean±SE)	1.7±1.0
UPDRS IV duration of "off phases" sub-score (*n*=53), duration (mean±SE)	1.6±0.7
Treatment with levodopa (*n*=53), dose (mean±SE)	960.2±434.4
Treatment with dopamine agonist (*n*=37), dose (mean±SE)	182.7±176.6
Levodopa-equivalent daily dose (mg) (mean±SE)	1182.3±411
UPDRS III global (mean±SE)	
Med ON	8.4±4.9
Med OFF	29.6±9.8
UPDRS II speech sub-score (mean±SE)	
Med ON	0.4±0.7
Med OFF	0.9±0.9
UPDRS III speech sub-score (mean±SE)	
Med ON	0.4±0.6
Med OFF	0.7±0.7
UPDRS II freezing sub-score (mean±SE)	
Med ON	0.2±0.5
Med OFF	1.0±1.2
(b) 1 year follow-up	
Levodopa-equivalent daily dose (mg) (mean±SE)	1051.3±566
UPDRS IV duration of "Dyskinesia" sub-score (*n*=53), duration (mean±SE)	0.2±0.7
UPDRS IV duration of "off phases" sub-score (*n*=53), duration (mean±SE)	1.0±0.7
UPDRS III global (*n*=53) (mean±SE)	
Med ON Stim ON	14.0±8.3
Med ON Stim OFF	14.9±10.0
Med OFF Stim ON	22.9±10.2
Med OFF Stim OFF	37.7±13,2
Score improvement (*n*=53) (Med OFF, *n*)	
Low, <30%	12
Moderate, (30%, 50%)	28
High, >50%	13
UPDRS II speech sub-score, chronic (*n*=53) (mean±SE)	
Med ON	1,6±1,0
Med OFF	1.7±0,9
UPDRS III speech sub-score, acute (*n*=53) (mean±SE)	
Med ON Stim ON	1.5±0.9
Med ON Stim OFF	1.3±0.8
Med OFF Stim ON	1.5±0.8
Med OFF Stim OFF	1.4±0.8

Contd...

Table 1: Contd...

	Values
UPDRS II freezing sub-score, chronic (n=53) (mean±SE)	
Med ON	0.5±0.7
Med OFF	1.1±1.2

UPDRS: Unified Parkinson's Disease Rating Scale, Med On: With medication, Med OFF: Without medication, Stim ON: Bilateral deep brain stimulation ON with the effective contacts used in chronic conditions 1 year after surgery, SE: Standard error

off the stimulator; stimON, using the chronic parameters at 1 year (substantial clinical improvement; compromise with any adverse effects; optimized dopatherapy). Mean percent UPDRS III improvement in Dopa-OFF condition was 37.1% [Table 1b]. Disease severity increased over 1 year, with UPDRS III score in DopaOFF-StimOFF conditions varying from 29.6 ± 9.8 to 37.7 ± 13.2 (paired t-test; $P < 0.001$). For group analysis, percent DBS motor improvement was segregated into three classes [Table 1b] as low, <30%, 12 patients (22.6%); moderate, from 30 to 50%, 28 patients (52.8%), and high, >50%, 13 patients (24.5%). UPDRS IV sub-scores on dyskinesia and off-phases at 1 year were significantly reduced [Table 1a; $P < 0.001$]. We used UPDRS II and III sub-scores describing speech and freezing [Table 1S]: 0, no speech problems or freezing; 1, slight symptoms; 2, mild symptoms; 3, moderate symptoms; 4, severe symptoms. Speech was explored with and without medication as follows: 1-year versus preoperative values of UPDRS II speech sub-score based on spontaneous fluctuations (or chronic condition) and UPDRS III speech sub-score in acute condition; at 1 year, stimON versus stimOFF. Freezing was quantified as follows: 1-year versus preoperative values of UPDRS II freezing sub-score based on spontaneous fluctuations when walking (or chronic conditions) with and without medication. Modifications in UPDRS sub-scores on speech and freezing were segregated into three classes according to two modalities: Option A, less sensitive to worsening, improvement, ≤0; no change [0, 1] or 0.5–1; worsening >1; option B more sensitive to worsening, improvement, ≤0; no change, [0, 1] or 0.5; worsening, ≥1. Patient distribution according to these criteria is reported in Table 2.

Right-plus-left 1-year effective contacts (n = 106) were: 10 times contact 0 (9.4%), 49 times contact 1 (46.2%), and 42 times contact 2 (39.6%), thus, 95.3% of contacts were within the subthalamus; and 5 times contact 3 (4.7%). The average (±SEM; median) and min–max 1-year voltage values (monopolar stimulation 102 times out of 106; 130 Hz) of right and left contacts were 2.92 V (±0.98; 2.80), 1.00–6.30 and 2.98 V (±0.87; 2.80), 1.30–6.30, respectively, with no significance difference between the two sides (P = 0.58, paired t-test). For further analysis, voltage difference, left minus right, and absolute value of difference for each individual (mean ± SEM; median; min–max) were calculated as: Left minus right = 0.06 V (±0.76; 0.00), min − 2 V, ma × 2.80 V; the absolute value of difference 0.44 V (±0.62; 0.20), min 0 V, ma × 2.80 V. Mean variation in levodopa equivalent drugs (LED) expressed as percent LED variation, i.e. preoperative dose – 1-year postoperative dose/preoperative dose (n = 50, 3 missing data) was 0.1 ± 0.5 (min = −1.7; max = 0.8), with a positive value indicating a drop in LED. For further analysis, the percentages of LED variation were segregated into three classes: <−30%, significant rise, 8 patients; [−30%, 30%], no significant change, 23 patients; >30%, significant drop, 19 patients.

Location of effective contacts according to subthalamic nucleus landmark

Location of effective contacts (chronic stimulation 1 year after electrode implantation) was determined for the right and left hemispheres. Each contact was identified on postoperative CT scan[13] co-registered with preoperative MRI (Iplan©, BrainLab, Germany). STN had already been contoured preoperatively on coronal stereotactic MRI slices acquired with a dedicated anatomic sequence called White Matter Attenuated Inversion Recovery (WAIR), at 2-mm slice thickness and a pixel size of 0.56 × 0.56 mm^2. The main STN axis running laterally and superiorly was used as reference to specify contact location. This axis was determined on preoperative MRIs using tri-planar and 3D display (Iplan©, BrainLab, Germany). The geometric characteristics of the right and left STN, respectively, were: Mean length of main axis, 9.96 mm (±1.76; min, 6.91; max 13.75) and 9.46 mm (±1.60; min, 5.79; max 13.13); mean volume, 0.14 cm^3 (±0.04; min, 0.06; max 0.23) and 0.13 cm^3 (±0.04; min, 0.06; max 0.22). The anatomic space around the main axis was parceled for further analysis [Figures 2 and 3]. It was subdivided into 4 longitudinal anteroposterior subdivisions along the axis, i.e., front, intermediate-anterior (InterAnt), intermediate-posterior (InterPost), and rear, and 4 transversal subdivisions in the plane perpendicular to axis, i.e. superolateral (SupLat), superomedial (SupMed), inferolateral (InfLat) and inferomedial (InfMed). Contacts were attributed to several subdivisions as each contact was mapped because a 3-mm-diameter circle to integrate geometric errors and contact dimensions (length, 1.5 mm: Diameter, 1.3 mm). Thus, a total 7 longitudinal and 8 transversal, discrete, contact locations were defined: 4 longitudinal primary, Front, InterAnt, InterPost and Rear; 3 longitudinal combined, InterAnt/Front, InterPost/InterAnt and Rear/InterPost; 4 transversal primary, SupLat, InfLat, InfMed and SupMed; 4 transversal combined, SupLat/InfLat, InfLat/InfMed, SupMed/InfMed, and SupLat/SupMed. Contact location was also specified according to STN contour defining STN membership, i.e. within (In), at the frontier (Frontier), or outside (Out) the STN. Hence, for each patient, right and left contact locations were characterized by longitudinal and transversal positions

Table 2: Distribution of patients according to the modifications of Unified Parkinson's Disease Rating Scores, following bilateral subthalamic deep brain stimulation: option A, less sensitive to worsening; option B, more sensitive to worsening; (a) Unified Parkinson's Disease Rating Scores II speech sub-score; (b) Unified Parkinson's Disease Rating Scores III speech sub-score; (c) Unified Parkinson's Disease Rating Scores freezing sub-score

	n
(a) Modifications of UPDRS II speech sub-score	
1 year versus preoperative, Med ON (*n*=48)	
Option A	
Improvement, ≤0	13
No change, 0.5-1	16
Worsening, >1	19
Option B	
Improvement, ≤0	13
No change, 0.5	0
Worsening, ≥1	35
1 year versus preoperative, Med OFF (*n*=47)	
Option A	
Improvement, ≤0	14
No change, 0.5-1	22
Worsening, >1	11
Option B	
Improvement, ≤0	14
No change, 0.5	2
Worsening, ≥1	31
(b) Modifications of UPDRS III speech sub-score	
1 year versus preoperative, Med ON (*n*=50)	
Option A	
Improvement, ≤0	14
No change, 0.5-1	20
Worsening, >1	16
Option B	
Improvement, ≤0	14
No change, 0.5	4
Worsening, ≥1	32
1 year versus preoperative, Med OFF (*n*=53)	
Option A	
Improvement, ≤0	20
No change, 0.5-1	21
Worsening, >1	12
Option B	
Improvement, ≤0	20
No change, 0.5	4
Worsening, ≥1	29
1 year, Med ON (*n*=45)	
Option A	
Improvement, ≤0	13
No change, 0.5-1	22
Worsening, >1	10
Option B	
Improvement, ≤0	13
No change, 0.5	5
Worsening, ≥1	27
1 year, Med OFF (*n*=53)	
Option A	
Improvement, ≤0	22
No change, 0.5-1	22
Worsening, >1	9
Option B	
Improvement, ≤0	22
No change, 0.5	4
Worsening, ≥1	27
(c) Modifications of UPDRS II freezing sub-score	
1 year versus preoperative, Med ON (*n*=47)	
Option A	
Improvement, ≤0	35
No change, 0.5-1	9
Worsening, >1	3
Option B	
Improvement, ≤0	35
No change, 0.5	0
Worsening, ≥1	12
1 year versus preoperative, Med OFF (*n*=48)	
Option A	
Improvement, ≤0	31
No change, 0.5-1	10
Worsening, >1	7
Option B	
Improvement, ≤0	31
No change, 0.5	0
Worsening, ≥1	17

Med On: With medication, Med OFF: Without medication, UPDRS: Unified Parkinson's Disease Rating Scale

and STN membership, thus yielding per-individual discrete contact locations. Most contacts at 1 year were in intermediate or posterior superolateral position and at the frontier or outside the STN [Figure 4 and Table 2S].

We defined a unified contact location (UCL) of right and left contacts for each patient because the so-called "STN DBS" unifies right and left contacts assuming no significant asymmetry. The 53 patients were regrouped according to simplified longitudinal (Front, Intermediate, and Rear) and transversal (SuperoLateral, SupLat UCL; Non-SuperoLateral, Non-SupLat UCL) locations (LonTranUCL) [Figure 5a]. The rationale for segregating into SupLat UCL and Non-SupLat UCL was that the subthalamic superolateral region is one of most common locations of effective contacts.[3] We individualized a sub-series of 36 patients fitting the most frequent LonTranUCL. Broadly speaking, the most frequent

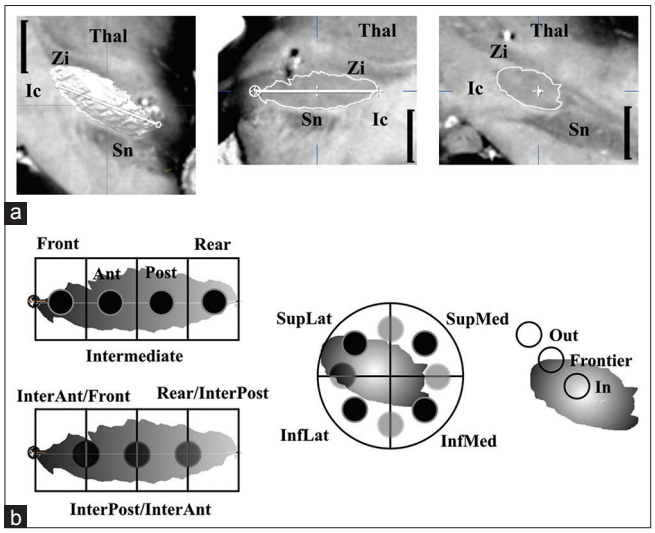


Figure 2: Subdivisions of the anatomic space centered on the subthalamic nucleus (STN). (a) Triplanar 4.7 T MRI of an anatomic specimen (black vertical bar = 5 mm): frontal view (left), anterior commissure–posterior commissure aligned, of the STN (3D, white) located below the thalamus (Thal) and zona incerta (Zi), above the substantia nigra (Sn), and medially to the internal capsule (Ic); longitudinal (intermediate) and transversal (right) sections running through the main axis of STN (white line) and the midpoint (white cross) of the longitudinal axis, respectively. (b) Longitudinal (left) and transversal (intermediate) subdivisions (primary locations, black dots; combined locations, gray dots) and STN membership (right) used to locate the effective contacts (see text for abbreviations)

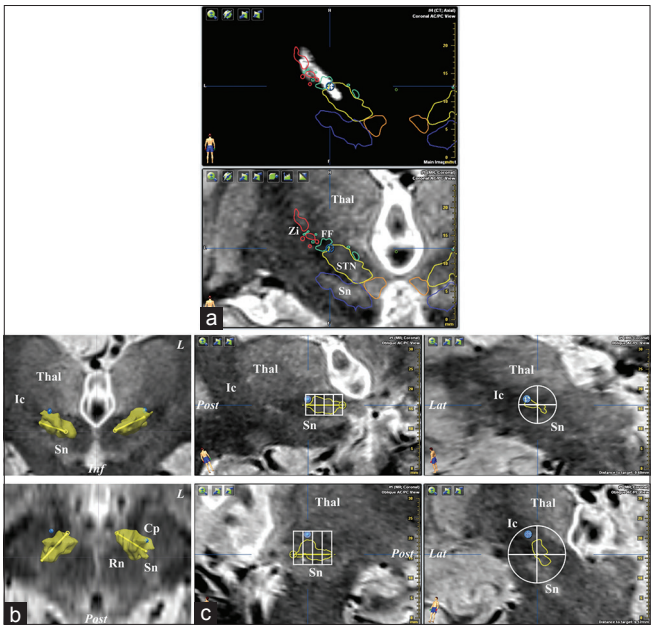


Figure 3: Example (patient #53, see Table 3) of effective contact location used at 1-year post-surgery (1.5 T MRI). (a) Coronal CT-scan (top) and MRI (bottom) slices (perpendicular to anterior commissure–posterior commissure line; light-green dot) running through the effective contact (blue circle; contact 1) of the left electrode (white artefact); co-registered; showing the position of the contact at the superior and lateral boundary of the subthalamic nucleus (STN). Thalamus (Thal), zona incerta (Zi), substantia nigra (Sn), and fields of Forel (FF) are shown. (b) Frontal (top; inferior, Inf) and superior (bottom; posterior, Post) views (left, L) of the right and left subthalamic nucleus (yellow): main axis of the nucleus (yellow line) and the effective contacts (blue dots) are shown; Thalamus (Thal), zona incerta (Zi), substantia nigra (Sn), and internal capsule (Ic). (c) Reconstructed images (left hemisphere, top row; right hemisphere, bottom row) along the main axis of the STN (left column; posterior, Post) and perpendicular to the axis (right column; lateral, Lat) showing contact locations according to longitudinal and transversal subdivisions (white grid) and STN membership (white circle grid): left contact, Rear longitudinal position, SupLat transversal position, and Frontier STN membership; right contact, InterAnt position, SupLat transversal position, and Out STN membership

LonTranUCL was Intermediate or Rear UCL and SupLat UCL. The 53 patients were also regrouped according to STN membership (MembUCL) as In, Out, In-Out, and Frontier MembUCL [Figure 5a]. From the sub-series of 36 patients fitting the most frequent LongTranUCL, we selected 25 patients fitting the most frequent global longitudinal and transversal locations and STN membership (GlobalUCL). Details of the LonTranUC, MembUCL, and GlobalUCL groups of contact pair-ups can be found in the supplementary material [Table 3S].

Balance of contact pair-up (BCPU) was defined as symmetric or asymmetric regardless of laterality (R-L BCPU was not differentiated from L-R BCPU), and was determined for longitudinal, transversal, and STN membership aspects [Figure 5b and Table 4S]. The distribution of BCPU for the 53 patients was simplified and fell into 6 raw conditions [Tables 3 and 5S] that were further pooled into BCPU-asymmetric (17 patients), BCPU-sym-Rear-SupLat-Out (most frequent symmetric condition, 15 patients) and BCPU-sym-other (21 patients). Details of longitudinal, transversal, and STN membership BCPU can be found in the supplementary material.

We studied the left or right hemisphere-wise laterality of most frequent contact pair-ups (MFCP) regardless of either symmetric or asymmetric BCPU [Figure 5c and 4c; Table 6S]: First, only rear-longitudinal MFCP, named 1-MFCP; second, 1-MFCP and SupLat-transversal MFCP, named 2-MFCP; third, 2-MFCP and out-STN-membership MFCP, named 3-MFCP.

Data analysis

Statistical analysis was performed using Stata software version 13 (StataCorp, College Station, TX). Data were presented as mean ± standard deviation (SD) or median (interquartile range) for continuous data and as number of patients and associated percentages for categorical parameters. Comparisons between independent groups were analyzed using the Chi-squared test or Fisher's exact test for categorical variables followed, when appropriate, by Marascuillo's procedure, and analysis of variance (ANOVA) or Kruskal–Wallis test for quantitative variables, with normality verified by the Shapiro–Wilk test and homoscedasticity verified by the Bartlett test. When appropriate, post-hoc multiple comparisons tests were proposed (Tukey-Kramer

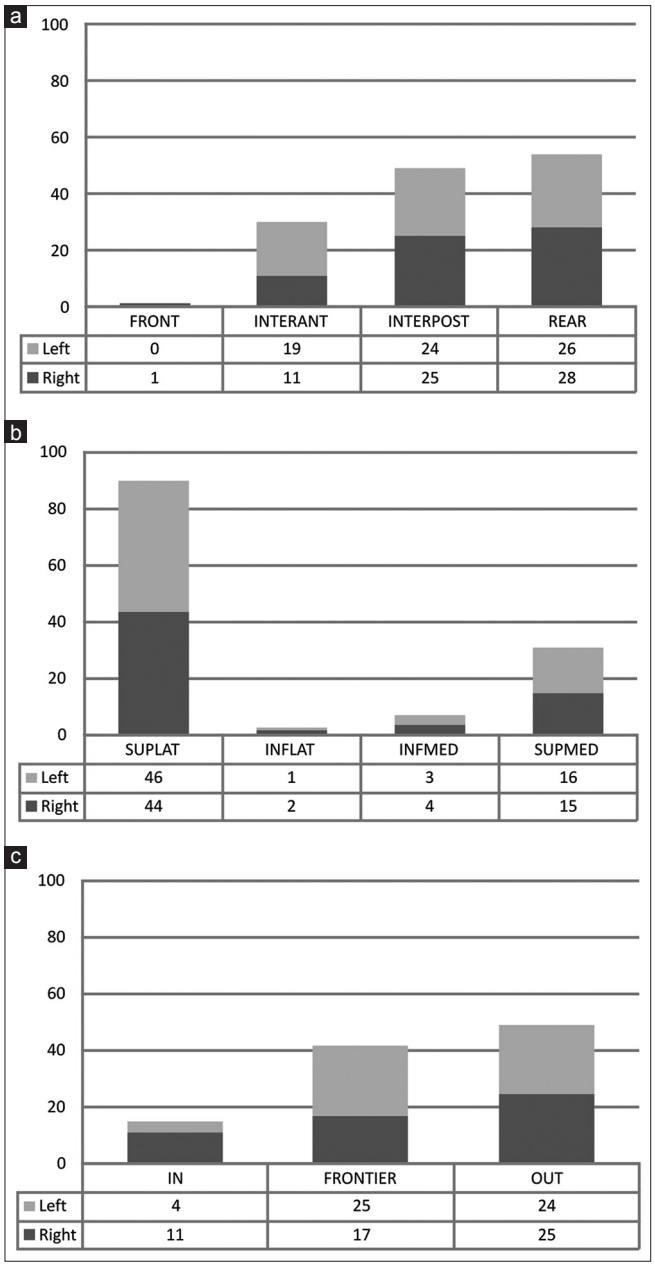


Figure 4: Overall contact locations of the 53 patients according to longitudinal (a) and transversal (b) positions and STN membership (c); sums >53 for the right-plus-left contacts result from multiple attributions of contacts overlapping different locations (see text)

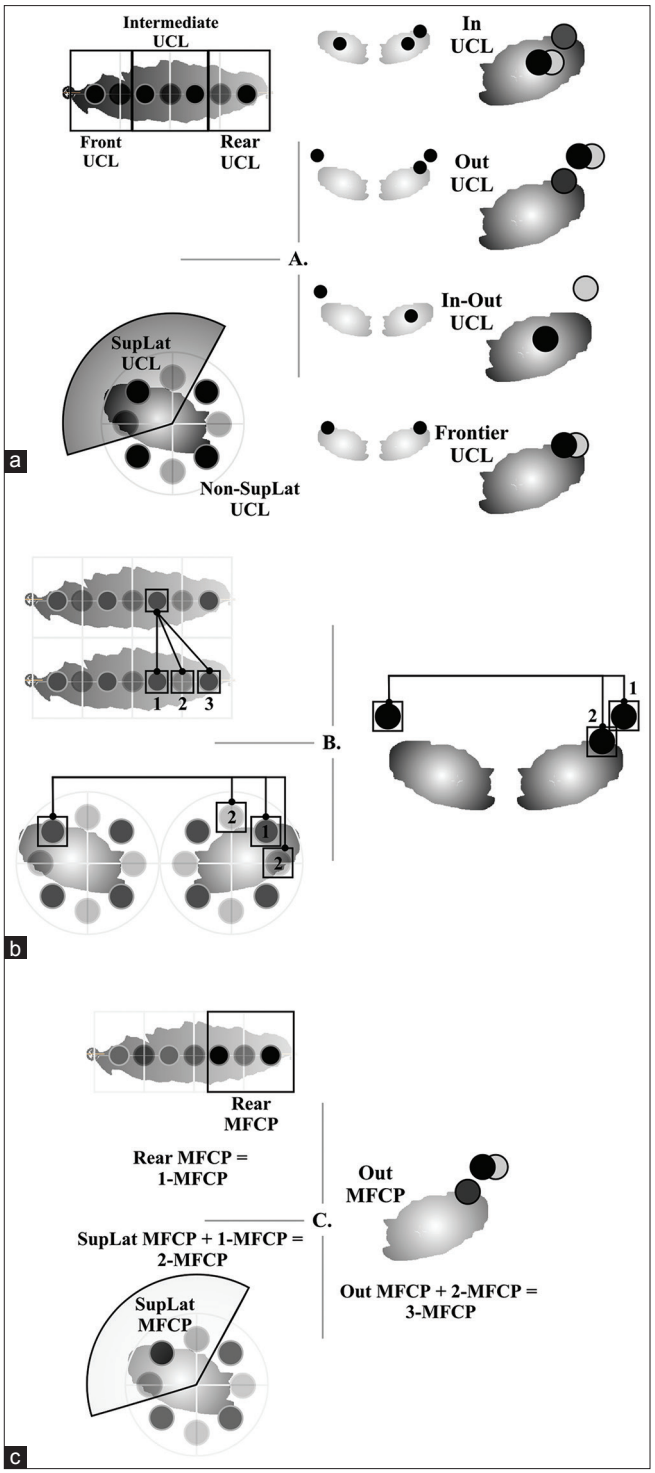


Figure 5: The three methods of contact location according to longitudinal location, transversal location and STN membership: (a) Unified Contact Location (UCL); (b) Balance of Contact Pair-up (BCPU); (c) Most Frequent Contact Pair-up (MFCP)

after ANOVA and Dunn for Kruskal-Wallis). Non-parametric tests were often preferred due to sample size. For paired comparisons, a paired *t*-test or Wilcoxon test was used for quantitative data and a Stuart–Maxwell test for qualitative parameters. All tests were two-sided, with a type-I error set at $\alpha = 0.05$, without mathematical correction.[29]

RESULTS

We did not find differences in UPDRS III motor score, voltage, age, or gender according to UCL [Tables 7S and 8S]; whereas mean LED dose at 1-year was higher for MembUCL_Out patients than other MembUCL patients ($P = 0.03$; 51 patients; Table 7S], i.e., 1075 mg [800–1750] for MembUCL_Out vs 800 mg [675–1400] for MembUCL_Frontier, 663 mg

Table 3: Conditions of balance of balance of contact pair-up of the 53 patients, according to longitudinal and transversal location and STN membership

BCPU condition		Longitudinal			Logical operation	Transversal			Logical operation	STN membership			Patients
Raw	Grouped	Rear	Not-rear	Asymmetric		SupLat	Not-SupLat	Asymmetric		Out	Not-out	Asymmetric	
BCPU0	Asymmetric			Yes	Or			Yes	Or			Yes	17
BCPU1	Symmetric-rear-supLat-out	Yes			And	Yes			And	Yes			15
BCPU2	Symmetric-other	Yes				Yes					Yes		8
BCPU3		Yes					Yes			Yes			4
BCPU4			Yes			Yes				Yes			3
BCPU5			Yes			Yes					Yes		6

BCPU: Balance of contact pair-up, STN: Subthalamic nucleus

[450–1100] for MembUCL_In, and 500 mg [450–850] for MembUCL_In-Out. UPDRS III speech sub-score worsening (1-year versus preop) was more frequent for MembUCL_Out patients with medication ($P = 0.005$, most frequent patients, $n = 33$; option B, sensitive to worsening; Table 8S).

We did not find differences in UPDRS III motor score, voltage, age, and gender according to BCPU [Tables 9S and 10S]; whereas mean preoperative LED dose was higher for BCPU-sym-Rear-SupLat-Out patients than other BCPU patients ($P = 0.03$; 53 patients; Table 9S), at 1438 mg [1175-1650] for BCPU-sym-Rear-SupLat-Out vs 1125 mg [975–1300] for BCPU-sym-other, and 1030 mg [650–1550] for BCPU-asymmetric. BCPU-asymmetric patients had less speech sub-score worsening, with medication, with either UPDRS III (at 1-year; $P < 0.05$, $n = 46$; option A, less sensitive to worsening; versus BCPU-sym-Rear-SupLat-Out and BCPU-sym-other) or UPDRS II (1 year vs preop; $P < 0.05$, $n = 48$; option B, sensitive to worsening; vs the others) [Table 10S].

We did not find differences in voltage and age according to MFCP [Tables 11S and 12S], whereas mean preoperative LED dose of right contact was higher for 1-MFCP (rear MFCP) patients than other patients, at 1306 mg [980–1550] for 1-MFCP (rear MFCP) vs 975 mg [650–1250] ($P = 0.03$; 53 patients; Table 11S). We also found that females presented more 3-MFCP (rear-SupLat-out MFCP), either right-wise ($P = 0.03$; $n = 53$) or left-wise ($P = 0.05$, $n = 53$) [Table 11S]. The left contact of MFCP was associated with more frequent speech worsening in different conditions [Table 12S]: (i) 1-MFCP (rear) patients, 1 year vs. preop (option A, less sensitive to worsening), UPDRS II speech sub-score worsening with medication ($P = 0.01$, $n = 48$), and UPDRS III speech sub-score without medication ($P = 0.04$, $n = 53$); (ii) 2-MFCP (rear-SupLat) patients, 1 year vs. preop, UPDRS II speech sub-score worsening with medication (option B, sensitive to worsening; $P = 0.02$, $n = 48$), and at 1 year, UPDRS III speech sub-score worsening without medication (option A, less sensitive to worsening; $P = 0.02$, $n = 48$); (iii) 3-MFCP (rear-SupLat-out) patients, at 1 year, UPDRS III speech sub-score worsening with medication (option A, less sensitive to worsening; $P = 0.05$, $n = 46$). The right contact of 1-MFCP (rear) patients was also associated with more frequent speech worsening, 1 year vs. preop, UPDRS II speech sub-score with medication (option B, sensitive to worsening; $P = 0.048$, $n = 48$). The right contact of 2-MFCP (rear-SupLat) patients was associated with more frequent UPDRS II freezing sub-score worsening, 1 year vs. preop, without medication (option A, less sensitive to worsening; $P = 0.03$, $n = 48$).

The full results are summarized in Figure 6.

DISCUSSION

Our results show that the precise location of effective contacts within the subthalamic region, regardless of the method used for location analysis, i.e. UCL, individual balance of contact pair-ups, or individual hemisphere-wise most frequent contact pair-up, does not explain the degree of motor improvement (UPDRS III). Consequently, the only key factor would be location within the subthalamic region, provided the contact is located within, at the frontier, or above the STN. These results are consistent with other studies reporting effective contact location, using different methods, at different locations in the subthalamic region (see Supplementary material) or even as far as the internal capsule.[37] Nevertheless, high percentage drops in UPDRS III motor score have been reported when the contact is located within the STN, whether associative or sensorimotor, compared with the zona incerta,[37] suggesting that STN DBS should be more efficient on motor symptoms, at least those evaluated by UPDRS.[1,34] The importance of involvement of the sensorimotor component of the STN[32,38] within the volume of electric stimulation commonly estimated as a sphere of 2–5 mm radius[36] is not challenged by our results (≈86% of contacts here were located at the boundary

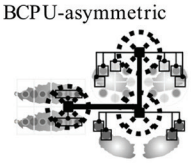
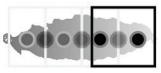
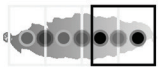
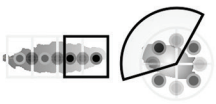
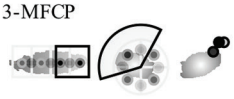
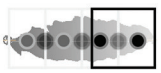
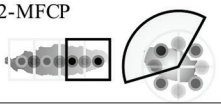
Groups of patients			Patients (n)	Significant results				
UCL	MembUCL_Out 		53 33 (out of most frequent, 36)	higher mean LED dose at 1-Year more frequent speech worsening	1 year versus preop	acute (UPDRS III speech sub-score)	with medication	Option B, sensitive to worsening
BCPU	BCPU-sym-Rear-SupLat-Out 	3 classes	53	higher mean preoperative LED dose				
	BCPU-asymmetric 		46	less frequent speech worsening	at 1-year	acute (UPDRS III speech sub-score)	with medication	option A, less sensitive to worsening
		6 classes	48		1 year versus preop	chronic (UPDRS II speech sub-score)		Option B, sensitive to worsening
MFCP	1-MFCP 	right	53	higher mean preoperative LED dose				
	3-MFCP 	right and left				female		
	1-MFCP 		48			chronic (UPDRS II speech sub-score)	with medication	option A, less sensitive to worsening
			53		1-year vs preop	acute (UPDRS III speech sub-score)	without medication	option A, less sensitive to worsening
	2-MFCP 	left	48	more frequent speech worsening		chronic (UPDRS II speech sub-score)	with medication	option B, sensitive to worsening
			53		at 1 year	acute (UPDRS III speech sub-score)	without medication	option A, less sensitive to worsening
	3-MFCP 		46					
	1-MFCP 		48			chronic (UPDRS II speech sub-score)	with medication	option B, sensitive to worsening
	2-MFCP 	right	48	more frequent freezing worsening	1-year vs preop	Chronic (UPDRS II freezing sub-score)	without medication	option A, less sensitive to worsening

Figure 6: Synthesis of results (see text for details)

or outside the STN) nor the results of Welter *et al.*[37] (contacts were within the associative and sensorimotor parts), as it is very likely that corticosubcorticothalamic loops are modulated directly by contacts within or at the boundary of the STN or indirectly by outside contacts placed on corticosubthalamic white matter fibers crossing the zona incerta below the thalamus.[19] Our results add support to the functional segregation proposed by Yelnik *et al.*[38] because most contacts were located superiorly, posteriorly, and laterally relative to STN. Interestingly, we observed that out-STN patients, whether with right or left locations unified (MembUCL_Out patients) or symmetric Rear-SupLat-Out balance pair-ups (BCPU-sym-Rear-SupLat-Out patients) have higher

postoperative LED at 1 year than patients with other contact locations. A tentative explanation would be that electric modulation does not activate dopaminergic release as much as direct STN stimulation, although we cannot rule out an influence of disease severity, as suggested by the increase of UPDRS III baseline (dopa off–stim off) in our series, and our relatively elderly population of mean age 60.9 whereas recent series studied younger patients.[30,37]

We also found that contacts located outside the STN seemed associated with more frequent speech worsening, regardless of the hemisphere and balance contact pair-up (acute test with medication versus preoperative scores). It appears as though electric stimulation plus dopamine functionally disrupts speech circuitry, specifically categorical fluency.[17] Speech intelligibility is also lower when using acute high-voltage STN stimulation compared to low-voltage protocols,[34] possibly because high voltage modulates circuits located outside STN. We have also found that speech deterioration is reduced, with medication, when the right and left contacts are not symmetrical, suggesting that symmetric stimulation conditions more heavily deteriorate speech controls. We found that the left contact (only 2 left-handed patients out of 53) seems particularly involved in this stimuli-induced adverse effect, confirming published results by Tripoliti *et al*.[33] and Sjöberg *et al*.[31] Speech worsening also seems to be influenced by anteroposterior and mediolateral location because we observed more dysarthria for posterior and lateral locations; however, medial and anterior contact positions appear to be equally involved.[33,34] This variability could be related to the patient studied and the method of contact location analysis used.

In regards to freezing worsening, we observed that regardless of STN membership, patients with the right contact located posteriorly and laterally were more prone to worsening. We hypothesize that fibers ascending from the pedunculopontine nucleus (PPN) toward the substantia nigra compacta, STN, pallidum, and thalamus[25,26] and fibers projecting from the substantia nigra reticulata and the internal globus pallidus[26] could be influenced by electric field. More data are needed to understand the laterality of effects. Clinical DBS studies have also reported that unilateral PPN stimulation contralateral to the most severely-affected side of the body seems to improve falls[20] and modulate contralateral or bilateral inferior limb muscular activity during the steady state of gait.[4] Dorsal STN stimulation modulates gait velocity assessed during acute tests, using cerebellar loops.[14] Other lateralized differentiated effects have been reported such as the reduction of motor disability, axial scores and levodopa daily dose, lower if the right contact is more anterior[37] and left STN DBS seems to lead to more improved mood.[5]

CONCLUSIONS

Right-left contact pair-up could be an important factor for optimization of DBS electrode targeting and electric stimulation parameter, in severe Parkinson's disease, and for efforts to gain a sharper understanding of the precise mechanisms of effects. Neurologists should aim to position right and left contacts asymmetrically to the STN landmark to minimize speech worsening. In particular, the left contact should not be in posterior, superior, and lateral position. The data reported here could be used for surgical targeting and proposed to neurologists as postoperative electrical settings if contacts are remotely selectable and anatomical location is known.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL 2

Subthalamus deep brain stimulation in parkinson's disease: Accounting for the bilaterality of contacts

Table 1S: Assessments of speech and freezing: (1) Speech, 1-year vs preoperative values of UPDRS II speech sub-score based on spontaneous fluctuations (or chronic condition), with and without medication, and of UPDRS III speech sub-score in acute condition with and without medication; (2) Speech at 1 year, stimON vs stimOFF, with and without medication; (3) Freezing, 1-year vs preoperative values of the UPDRS II freezing sub-score based on spontaneous fluctuations when walking (or chronic condition) with and without medication

Assessment	Period	Type		Condition	Abbreviation
Speech	1-year vs preoperative values	UPDRS II speech sub-score based on spontaneous fluctuations (or chronic condition)	with medication	MedON_StimON1y_vsPreop	SpeeChro_MedON_1yvsPreop
			without medication	MedOFF_StimON1y_vsPreop	SpeeChro_MedOFF_1yvsPreop
		UPDRS III speech sub-score in acute condition	with medication	MedON_StimON1year – vsPreop	SpeeAcc_MedON_1yvsPreop
			without medication	MedOFF_StimON1year – vsPreop	SpeeAcc_MedOFF_1yvsPreop
	1 year		with medication	MedON_StimON1year_vsStimOFF1year	SpeeAcc_MedON_1y
			without medication	MedOFF_StimON1year_vsStimOFF1year	SpeeAcc_MedOFF_1y
Freezing	1-year vs preoperative values	UPDRS II freezing sub-score based on spontaneous fluctuations when walking (or chronic condition)	with medication	MedON_StimON1year_vsPreop	FreeChro_MedON_1yvsPreop
			without medication	MedOFF_StimON1year_vsPreop	FreeChro_MedOFF_1yvsPreop

Table 2S: Individual right and left effective contact locations of the 53 patients according to longitudinal and transversal positions and STN membership

Patient	Left hemisphere			Right hemisphere		
	Longitudinal position	Transversal position	STN membership	Longitudinal position	Transversal position	STN membership
1	REAR/INTERPOST	SUPLAT	FRONTIER	REAR	SUPLAT/SUPMED	OUT
2	INTERPOST/INTERANT	SUPLAT/SUPMED	FRONTIER	REAR	SUPLAT/SUPMED	FRONTIER
3	INTERPOST/INTERANT	SUPLAT	OUT	INTERPOST	SUPLAT	IN
4	INTERANT	SUPLAT/SUPMED	IN	INTERPOST/INTERANT	SUPLAT	FRONTIER
5	INTERPOST/INTERANT	SUPLAT	FRONTIER	REAR	SUPLAT	OUT
6	REAR	SUPLAT	FRONTIER	REAR/INTERPOST	INFMED/INFLAT	IN
7	INTERANT	SUPMED	OUT	INTERPOST/INTERANT	SUPLAT	FRONTIER
8	REAR	SUPLAT	OUT	REAR	SUPMED	OUT
9	INTERPOST	SUPLAT/SUPMED	OUT	REAR	SUPMED	OUT
10	INTERANT	SUPLAT	FRONTIER	INTERPOST	SUPLAT	OUT
11	INTERPOST	SUPLAT	OUT	INTERANT/FRONT	SUPMED	IN
12	REAR/INTERPOST	SUPMED	OUT	REAR/INTERPOST	SUPLAT/SUPMED	IN
13	REAR	SUPMED/INFMED	OUT	INTERPOST	INFMED	FRONTIER
14	INTERPOST	SUPLAT	OUT	INTERPOST/INTERANT	SUPLAT	IN
15	REAR	SUPLAT/SUPMED	OUT	INTERPOST	SUPMED	OUT
16	INTERPOST/INTERANT	SUPLAT/SUPMED	OUT	INTERANT	SUPLAT	OUT
17	INTERPOST	SUPLAT/SUPMED	OUT	INTERPOST	SUPLAT/SUPMED	FRONTIER
18	REAR	SUPLAT	FRONTIER	INTERPOST	SUPLAT	FRONTIER
19	REAR	SUPLAT	FRONTIER	REAR	SUPLAT	FRONTIER
20	INTERPOST	SUPLAT	FRONTIER	INTERPOST	SUPLAT	OUT
21	REAR	SUPLAT	OUT	REAR	INFLAT	IN
22	INTERPOST	SUPLAT	FRONTIER	INTERANT	SUPLAT	OUT
23	INTERPOST/INTERANT	SUPLAT	FRONTIER	REAR/INTERPOST	SUPLAT	OUT
24	INTERPOST/INTERANT	SUPLAT	FRONTIER	INTERPOST/INTERANT	SUPLAT	FRONTIER

Contd...

Table 2S: Contd...

Patient	Left hemisphere			Right hemisphere		
	Longitudinal position	Transversal position	STN membership	Longitudinal position	Transversal position	STN membership
25	REAR	SUPLAT	OUT	INTERPOST	SUPLAT	FRONTIER
26	REAR	SUPLAT	OUT	INTERPOST	SUPLAT	OUT
27	REAR	SUPLAT	OUT	REAR	SUPLAT	OUT
28	REAR	SUPLAT	OUT	REAR	SUPMED	OUT
29	REAR/INTERPOST	SUPLAT	FRONTIER	REAR	SUPLAT/SUPMED	OUT
30	INTERANT	SUPLAT/SUPMED/ INFMED/INFLAT	IN	INTERANT	SUPLAT	FRONTIER
31	REAR	SUPLAT/SUPMED	FRONTIER	REAR	INFMED	OUT
32	INTERANT	SUPLAT	FRONTIER	INTERPOST/INTERANT	SUPLAT	FRONTIER
33	REAR/INTERPOST	SUPLAT	FRONTIER	INTERPOST	SUPLAT	IN
34	REAR	SUPLAT	OUT	REAR/INTERPOST	SUPLAT	OUT
35	INTERANT	SUPLAT	FRONTIER	REAR/INTERPOST	SUPLAT/SUPMED	IN
36	INTERANT	SUPMED	FRONTIER	REAR	SUPLAT	OUT
37	REAR/INTERPOST	SUPLAT	OUT	REAR	SUPLAT	FRONTIER
38	INTERPOST/INTERANT	SUPLAT	IN	REAR	SUPLAT	FRONTIER
39	INTERPOST	SUPLAT	OUT	REAR	SUPLAT	OUT
40	INTERANT	SUPLAT/SUPMED	FRONTIER	INTERPOST	SUPLAT	FRONTIER
41	INTERANT	SUPLAT	FRONTIER	REAR	SUPLAT	OUT
42	REAR	SUPMED	OUT	REAR	SUPLAT	OUT
43	REAR	SUPLAT	OUT	REAR/INTERPOST	SUPLAT	OUT
44	REAR	SUPLAT	FRONTIER	REAR	SUPLAT/SUPMED	IN
45	REAR/INTERPOST	SUPLAT	FRONTIER	INTERPOST	SUPMED/INFMED	IN
46	REAR	SUPLAT	OUT	REAR	SUPLAT	FRONTIER
47	INTERPOST/INTERANT	INFMED	IN	REAR	SUPLAT	IN
48	REAR	SUPLAT	FRONTIER	INTERPOST	SUPLAT	FRONTIER
49	INTERPOST/INTERANT	SUPLAT/SUPMED	FRONTIER	REAR	SUPLAT/SUPMED	OUT
50	INTERPOST/INTERANT	SUPLAT	FRONTIER	INTERPOST/INTERANT	SUPLAT/SUPMED	FRONTIER
51	REAR	SUPMED	OUT	REAR	SUPLAT	OUT
52	REAR	SUPLAT	OUT	REAR	SUPLAT	OUT
53	REAR	SUPLAT	FRONTIER	INTERANT	SUPLAT	OUT

Longitudinal positions: Frontal (FRONT), intermediate anterior (INTERANT), intermediate posterior (INTERPOST) and posterior (REAR); transversal positions: superolateral (SUPLAT), Inferolateral (INFLAT), Inferomedial (INFMED) and superomedial (SUPMED); STN membership, within (IN), at the frontier (FRONTIER) or outside (OUT) the STN. (See text for details)

Table 3S: Unified Contact Location (UCL) summarizing right and left contact positions of each patient ($n=53$) according to the simplified longitudinal (Front, Intermediate and Rear) and transversal (Supero-Lateral and Non-Supero-Lateral) locations and STN membership: 14 (1 to 14) longitudinal and transversal UCLs; 4 STN-membership UCLs (in, Out, Frontier and In-Out) (See text for details)

Patient	Left hemisphere		Right hemisphere		UCL	
	Longitudinal simplification	Transversal simplification	Longitudinal simplification	Transversal simplification	LongTrans	Memb
1	Rear	Superolateral	Rear	Superolateral	13	Out
2	Intermediate	Superolateral	Rear	Superolateral	5	Frontier
3	Intermediate	Superolateral	Intermediate	Superolateral	3	In-Out
4	Intermediate	Superolateral	Intermediate	Superolateral	3	In
5	Intermediate	Superolateral	Rear	Superolateral	5	Out
6	Rear	Superolateral	Rear	Non-Superolateral	12	In
7	Intermediate	Non-Superolateral	Intermediate	Superolateral	1	Out
8	Rear	Superolateral	Rear	Non-Superolateral	14	Out
9	Intermediate	Superolateral	Rear	Non-Superolateral	6	Out

Contd...

Table 3S: Contd...

patient	Left hemisphere		Right hemisphere		UCL	
	Longitudinal simplification	Transversal simplification	Longitudinal simplification	Transversal simplification	LongTrans	Memb
10	Intermediate	Superolateral	Intermediate	Superolateral	3	Out
11	Intermediate	Superolateral	Front (InterAnt-Front)	Non-Superolateral	4	In-Out
12	Rear	Non-Superolateral	Rear	Superolateral	9	In-Out
13	Rear	Non-Superolateral	Intermediate	Non-Superolateral	8	Out
14	Intermediate	Superolateral	Intermediate	Superolateral	3	In-Out
15	Rear	Superolateral	Intermediate	Non-Superolateral	11	Out
16	Intermediate	Superolateral	Intermediate	Superolateral	3	Out
17	Intermediate	Superolateral	Intermediate	Superolateral	3	Out
18	Rear	Superolateral	Intermediate	Superolateral	10	Frontier
19	Rear	Superolateral	Rear	Superolateral	13	Frontier
20	Intermediate	Superolateral	Intermediate	Superolateral	3	Out
21	Rear	Superolateral	Rear	Non-Superolateral	12	In-Out
22	Intermediate	Superolateral	Intermediate	Superolateral	3	Out
23	Intermediate	Superolateral	Rear	Superolateral	5	Out
24	Intermediate	Superolateral	Intermediate	Superolateral	3	Frontier
25	Rear	Superolateral	Intermediate	Superolateral	10	Out
26	Rear	Superolateral	Intermediate	Superolateral	10	Out
27	Rear	Superolateral	Rear	Superolateral	13	Out
28	Rear	Superolateral	Rear	Non-Superolateral	14	Out
29	Rear	Superolateral	Rear	Superolateral	13	Out
30	Intermediate	Non-Superolateral	Intermediate	Superolateral	1	In
31	Rear	Superolateral	Rear	Non-Superolateral	14	Out
32	Intermediate	Superolateral	Intermediate	Superolateral	3	Frontier
33	Rear	Superolateral	Intermediate	Superolateral	10	In
34	Rear	Superolateral	Rear	Superolateral	13	Out
35	Intermediate	Superolateral	Rear	Superolateral	5	In
36	Intermediate	Non-Superolateral	Rear	Superolateral	2	Out
37	Rear	Superolateral	Rear	Superolateral	13	Out
38	Intermediate	Superolateral	Rear	Superolateral	5	In
39	Intermediate	Superolateral	Rear	Superolateral	5	Out
40	Intermediate	Superolateral	Intermediate	Superolateral	3	Frontier
41	Intermediate	Superolateral	Rear	Superolateral	5	Out
42	Rear	Non-Superolateral	Rear	Superolateral	9	Out
43	Rear	Superolateral	Rear	Superolateral	13	Out
44	Rear	Superolateral	Rear	Superolateral	13	In
45	Rear	Superolateral	Intermediate	Non-Superolateral	11	In
46	Rear	Superolateral	Rear	Superolateral	13	Out
47	Intermediate	Non-Superolateral	Rear	Superolateral	2	In
48	Rear	Superolateral	Intermediate	Superolateral	10	Frontier
49	Intermediate	Superolateral	Rear	Superolateral	5	Out
50	Intermediate	Superolateral	Intermediate	Superolateral	3	Frontier
51	Rear	Non-Superolateral	Rear	Superolateral	9	Out
52	Rear	Superolateral	Rear	Superolateral	13	Out
53	Rear	Superolateral	Intermediate	Superolateral	10	Out

Table 4S: Longitudinal and transversal balance of contact pair-up (BCPU): Symmetric longitudinal BCPU means same or overlapped or adjacent longitudinal subdivisions (3 combined and 4 raw subdivisions); symmetric transversal BCPU means same or overlapped transversal subdivisions

Symetric and asymetric conditions of longitudinal balance gathering			Left subdivision						
			Frontal	InterAnt/ Front	InterAnt	InterPost/ InterAnt	InterPost	Rear/ InterPost	Rear
			■□□□	■■□□	□■□□	□■■□	□□■□	□□■■	□□□■
Right subdivision	Frontal	■□□□	symmetric	symmetric	symmetric	asymmetric	asymmetric	asymmetric	asymmetric
	InterAnt/Front	■■□□	symmetric	symmetric	symmetric	symmetric	symmetric	asymmetric	asymmetric
	InterAnt	□■□□	symmetric	symmetric	symmetric	symmetric	symmetric	asymmetric	asymmetric
	InterPost/InterAnt	□■■□	symmetric	symmetric	symmetric	symmetric	symmetric	symmetric	symmetric
	InterPost	□□■□	asymmetric	symmetric	symmetric	symmetric	symmetric	symmetric	symmetric
	Rear/InterPost	□□■■	asymmetric	asymmetric	symmetric	symmetric	symmetric	symmetric	symmetric
	Rear	□□□■	asymmetric	asymmetric	asymmetric	asymmetric	symmetric	symmetric	symmetric

Transversal balance gathering			Left subdivision							
			SupLat	SupLat/ InfLat	InfLat	InfLat/InfMed	InfMed	SupMed/ InfMed	SupMed	SupLat/ SupMed
			↗	→	↘	↓	↙	←	↖	↑
Right subdivision	SupLat	↗	symmetric	symmetric	asymmetric	asymmetric	asymmetric	asymmetric	asymmetric	symmetric
	SupLat/InfLat	→	symmetric	symmetric	symmetric	asymmetric	asymmetric	asymmetric	asymmetric	asymmetric
	InfLat	↘	asymmetric	symmetric	symmetric	symmetric	asymmetric	asymmetric	asymmetric	asymmetric
	InfLat/InfMed	↓	asymmetric	asymmetric	symmetric	symmetric	symmetric	asymmetric	asymmetric	asymmetric
	InfMed	↙	asymmetric	asymmetric	asymmetric	symmetric	symmetric	symmetric	asymmetric	asymmetric
	SupMed/InfMed	←	asymmetric	asymmetric	asymmetric	asymmetric	symmetric	symmetric	symmetric	asymmetric
	SupMed	↖	asymmetric	asymmetric	asymmetric	asymmetric	asymmetric	symmetric	symmetric	symmetric
	SupLat/SupMed	↑	symmetric	asymmetric	asymmetric	asymmetric	asymmetric	asymmetric	symmetric	symmetric

Table 5S: Individual balance of contact pair-up (BCPU) of the 53 patients, ordered according to 6 BCPU conditions (see text)

Patient	Raw aspect of BCPU			Simplified aspect of BCPU			BCPU condition
	longitudinal	Transversal	Membership	longitudinal	Transversal	Membership	
11	INTERPOST-INTERANT/FRONT	asymmetric	asymmetric	Not-Rear	asymmetric	asymmetric	0
35	asymmetric	SUPLAT-SUPLAT/ SUPMED	FRONTIER-OUT	asymmetric	Supero-Lateral	Out	0
53	asymmetric	SUPLAT	FRONTIER-OUT	asymmetric	Supero-Lateral	Out	0
7	INTERANT-INTERPOST/ INTERANT	asymmetric	OUT-FRONTIER	Not-Rear	asymmetric	Out	0
14	INTERPOST-INTERPOST/ INTERANT	SUPLAT	asymmetric	Rear	Supero-Lateral	asymmetric	0
3	INTERPOST/ INTERANT-INTERPOST	SUPLAT	asymmetric	Rear	Supero-Lateral	asymmetric	0
21	REAR	asymmetric	asymmetric	Rear	asymmetric	asymmetric	0
8	REAR	asymmetric	OUT	Rear	asymmetric	Out	0
41	asymmetric	[2]	FRONTIER-OUT	asymmetric	Supero-Lateral	Out	0
6	REAR-REAR/INTERPOST	asymmetric	FRONTIER-IN	Rear	asymmetric	Not-Out	0
12	REAR-INTERPOST	SUPMED-SUPLAT/ SUPMED	asymmetric	Rear	Not Supero-Lateral	asymmetric	0
45	REAR/INTERPOST-INTERPOST	asymmetric	FRONTIER-IN	Rear	asymmetric	Not-Out	0
36	asymmetric	asymmetric	FRONTIER-OUT	asymmetric	asymmetric	Out	0
28	REAR	asymmetric	OUT	Rear	asymmetric	Out	0
51	REAR	asymmetric	OUT	Rear	asymmetric	Out	0
42	REAR	asymmetric	OUT	Rear	asymmetric	Out	0
47	INTERPOST/INTERANT-REAR	asymmetric	IN	Rear	asymmetric	Not-Out	0
34	REAR-REAR/INTERPOST	SUPLAT	OUT	Rear	Supero-Lateral	Out	1
29	REAR/INTERPOST-REAR	SUPLAT-SUPLAT/ SUPMED	FRONTIER-OUT	Rear	Supero-Lateral	Out	1
20	INTERPOST	SUPLAT	FRONTIER-OUT	Rear	Supero-Lateral	Out	1
17	INTERPOST	SUPLAT/SUPMED	OUT-FRONTIER	Rear	Supero-Lateral	Out	1
23	INTERPOST/INTERANT-REAR/ INTERPOST	SUPLAT	FRONTIER-OUT	Rear	Supero-Lateral	Out	1
1	REAR/INTERPOST-REAR	SUPLAT-SUPLAT/ SUPMED	FRONTIER-OUT	Rear	Supero-Lateral	Out	1
27	REAR	SUPLAT	OUT	Rear	Supero-Lateral	Out	1
5	INTERPOST/INTERANT-REAR	SUPLAT	FRONTIER-OUT	Rear	Supero-Lateral	Out	1
26	REAR-INTERPOST	SUPLAT	OUT	Rear	Supero-Lateral	Out	1
25	REAR-INTERPOST	SUPLAT	OUT-FRONTIER	Rear	Supero-Lateral	Out	1
43	REAR-REAR/INTERPOST	SUPLAT	OUT	Rear	Supero-Lateral	Out	1
37	REAR/INTERPOST-REAR	SUPLAT	OUT-FRONTIER	Rear	Supero-Lateral	Out	1
49	INTERPOST/INTERANT-REAR	SUPLAT/SUPMED	FRONTIER-OUT	Rear	Supero-Lateral	Out	1
39	INTERPOST-REAR	SUPLAT	OUT	Rear	Supero-Lateral	Out	1
52	REAR	SUPLAT	OUT	Rear	Supero-Lateral	Out	1
46	REAR	SUPLAT	OUT-FRONTIER	Rear	Supero-Lateral	Out	2
44	REAR	SUPLAT-SUPLAT/ SUPMED	FRONTIER-IN	Rear	Supero-Lateral	Not-Out	2
33	REAR/INTERPOST-INTERPOST	SUPLAT	FRONTIER-IN	Rear	Supero-Lateral	Not-Out	2
48	REAR-INTERPOST	SUPLAT	FRONTIER	Rear	Supero-Lateral	Not-Out	2
38	INTERPOST/INTERANT-REAR	SUPLAT	IN-FRONTIER	Rear	Supero-Lateral	Not-Out	2
19	REAR	SUPLAT	FRONTIER	Rear	Supero-Lateral	Not-Out	2
2	INTERPOST/INTERANT-REAR	SUPLAT/SUPMED	FRONTIER	Rear	Supero-Lateral	Not-Out	2
18	REAR-INTERPOST	SUPLAT	FRONTIER	Rear	Supero-Lateral	Not-Out	2

Contd...

Table 5S: Contd...

Patient	Raw aspect of BCPU			Simplified aspect of BCPU			BCPU condition
	longitudinal	Transversal	Membership	longitudinal	Transversal	Membership	
9	INTERPOST-REAR	SUPLAT/ SUPMED-SUPMED	OUT	Rear	Not Supero-Lateral	Out	3
15	REAR-INTERPOST	SUPLAT/ SUPMED-SUPMED	OUT	Rear	Not Supero-Lateral	Out	3
13	REAR-INTERPOST	SUPMED/ INFMED-INFMED	OUT-FRONTIER	Rear	Not Supero-Lateral	Out	3
31	REAR	SUPLAT/ SUPMED-INFMED	FRONTIER-OUT	Rear	Not Supero-Lateral	Out	3
16	INTERPOST/ INTERANT-INTERANT	SUPLAT-SUPMED/ SUPLAT	OUT	Not-Rear	Supero-Lateral	Out	4
10	INTERANT-INTERPOST	SUPLAT	FRONTIER-OUT	Not-Rear	Supero-Lateral	Out	4
22	INTERPOST-INTERANT	SUPLAT	FRONTIER-OUT	Not-Rear	Supero-Lateral	Out	4
40	INTERANT-INTERPOST	SUPLAT/ SUPMED-SUPLAT	FRONTIER-FRONTIER	Not-Rear	Supero-Lateral	Not-Out	5
30	INTERANT	SUPLAT/ SUPMED-SUPLAT	IN-FRONTIER	Not-Rear	Supero-Lateral	Not-Out	5
50	INTERPOST/INTERANT	SUPLAT-SUPLAT/ SUPMED	FRONTIER	Not-Rear	Supero-Lateral	Not-Out	5
32	INTERANT-INTERPOST/ INTERANT	SUPLAT	FRONTIER	Not-Rear	Supero-Lateral	Not-Out	5
4	INTERANT-INTERPOST/ INTERANT	SUPLAT/ SUPMED-SUPLAT	IN-FRONTIER	Not-Rear	Supero-Lateral	Not-Out	5
24	INTERPOST/INTERANT	SUPLAT	FRONTIER	Not-Rear	Supero-Lateral	Not-Out	5

Table 6S: Left-hemisphere-wise and right-hemisphere-wise most frequent contact pair-up (MFCP): rear-longitudinal MFCP, or 1-MFCP; 1-MFCP and SupLat-transversal MFCP, or 2-MFCP; 2-MFCP and out-STN-membership MFCP (3-MFCP); yes means that the contact fits the MFCP criteria (e.g. patient 12, the left contact fits 1-MFCP and the right contact fits 2-MFCP); * symmetric for the MFCP condition (see text for details)

Patient	Left-hemisphere-wise MFCP			Right-hemisphere-wise MFCP		
	Rear or Rear/ Interpost or Interpost: 1-MFCP	1-MFCP and SupLat or SupLat/SupMed or SupLat/InfLat: 2-MFCP	2-MFCP and Out or Out-Frontier or Frontier-Out: 3-MFCP	Rear or Rear/ Interpost or Interpost: 1-MFCP	1-MFCP and SupLat or SupLat/SupMed or SupLat/InfLat: 2-MFCP	2-MFCP and Out or Out-Frontier or Frontier-Out: 3-MFCP
1	yes*	yes*	yes*	yes*	yes*	yes*
2				yes	yes	
3				yes	yes	
4						
5				yes	yes	yes
6	yes*	yes		yes*		
7						
8	yes*	yes	yes	yes*		
9	yes*	yes	yes	yes*		
10				yes	yes	yes
11	yes	yes	yes			
12	yes*			yes*	yes	
13	yes*	yes	yes	yes*		
14	yes	yes	yes			
15	yes*	yes	yes	yes*		
16						
17	yes*	yes*	yes*	yes*	yes*	yes*
18	yes*	yes*		yes*	yes*	
19	yes*	yes*		yes*	yes*	

Contd...

Table 6S: Contd...

Patient	Left-hemisphere-wise MFCP			Right-hemisphere-wise MFCP		
	Rear or Rear/ Interpost or Interpost: 1-MFCP	1-MFCP and SupLat or SupLat/SupMed or SupLat/InfLat: 2-MFCP	2-MFCP and Out or Out-Frontier or Frontier-Out: 3-MFCP	Rear or Rear/ Interpost or Interpost: 1-MFCP	1-MFCP and SupLat or SupLat/SupMed or SupLat/InfLat: 2-MFCP	2-MFCP and Out or Out-Frontier or Frontier-Out: 3-MFCP
20	yes*	yes*	yes*	yes*	yes*	yes*
21	yes*	yes	yes	yes*		
22	yes	yes	yes			
23				yes	yes	yes
24						
25	yes*	yes*	yes*	yes*	yes*	yes*
26	yes*	yes*	yes*	yes*	yes*	yes*
27	yes*	yes*	yes*	yes*	yes*	yes*
28	yes*	yes	yes	yes*		
29	yes*	yes*	yes*	yes*	yes*	yes*
30						
31	yes*	yes	yes	yes*		
32						
33	yes*	yes*		yes*	yes*	
34	yes*	yes*	yes*	yes*	yes*	yes*
35				yes	yes	yes
36				yes	yes	yes
37	yes*	yes*	yes*	yes*	yes*	yes*
38				yes	yes	
39	yes*	yes*	yes*	yes*	yes*	yes*
40				yes	yes	
41				yes	yes	
42	yes*			yes*	yes	yes
43	yes*	yes*	yes*	yes*	yes*	yes*
44	yes*	yes*		yes*	yes*	

Table 7S: Analysis of voltage difference (left minus right hemisphere), medication (levodopa equivalent grugs, LED; classes, < -30%, significant rise, [-30%, 30%], no significant change, >30 %, significant drop), age and gender according to unified contact location (UCL), longitudinal and transversal location (LonTran) and STN membership (Memb), and LonTran and Memb (Global); *, statistically significant

Patients (*n*)	UCL	Voltage difference	Medication (LED dose)				Age	Gender
			Preop	1-year	Percentage of variation (Preop -1-Year/Preop)			
					Dose	Class		
All patients (53)	LonTran	0.88 (53)	0.32 (53)	0.14 (51)	0.69 (51)	0.97 (51)	0.80 (53)	0.91 (53)
	Memb	0.69 (53)	0.17 (53)	0.03 (51)*	0.2 (51)	0.43 (51)	0.48 (53)	0.28 (53)
Most frequent LonTran UCL (36)	LonTran	0.71 (36)	0.17 (36)	0.36 (34)	0.95 (34)	0.95 (34)	0.88 (36)	0.76 (36)
	Memb	0.65 (36)	0.14 (36)	0.13 (34)	0.54 (34)	0.47 (34)	0.54 (36)	0.12 (36)
Most frequent Global UCL (25)	Global	0.83 (25)	0.2 (25)	0.45 (24)	0.54 (24)	0.90 (24)	0.36 (25)	0.43 (25)

Table 8S: Analysis of UPDRS III motor score (Dopa-OFF condition: StimOFF – StimON / StimOFF; n.a. not applicable) and UPDRS speech and freezing sub-scores (option A, less sensitive to worsening; option B, more sensitive to worsening) according to unified contact location (UCL), longitudinal and transversal (LonTran) location and STN membership (Memb), and LonTran and Memb (Global); *, statistically significant

Patients (*n*)	UPDRS III global motor score improvement	Difference of UPDRS sub-scorings describing speech and freezing	UCL	Speech						Freezing	
				Chronic (UPDRS II speech sub-score)		Acute (UPDRS III speech sub-score)				Chronic (UPDRS II freezing sub-score)	
				1 year vs preop		1 year vs preop		1 year		1 year vs preop	
				Med ON	Med OFF	Med ON	Med OFF	Med ON	Med OFF	Med ON	Med OFF
				SpeeChro_ MedON_1yvs Preop	*SpeeChro_ MedOFF_1yvs Preop*	*SpeeAcc_ MedON_1yvs Preop*	*SpeeAcc_ MedOFF_1yvs Preop*	*SpeeAcc_ MedON_1y*	*SpeeAcc_ MedOFF_1y*	*FreeChro_ MedON_1yvs Preop*	*FreeChro_MedOFF_1yvs Preop*
	P value (number of patients)			*P* value (number of patients)							
All patients (53)	0.63 (53)	Option A	LonTran	0.74 (48)	0.96 (47)	0.61 (50)	0.19 (53)	0.20 (46)	0.22 (53)	0.68 (47)	0.64 (48)
	0.80 (36)		Memb	0.62 (48)	0.92 (47)	0.66 (50)	0.94 (53)	1 (46)	0.62 (53)	0.34 (47)	0.07 (48)
Most frequent LonTran UCL (36)	0.91 (36)		LonTran	0.36 (32)	0.96 (32)	0.43 (33)	0.50 (36)	0.12 (30)	0.64 (36)	0.57 (32)	0.42 (32)
	0.92 (36)		Memb	0.43 (32)	0.45 (32)	0.10 (33)	0.78 (36)	0.80 (30)	0.78 (36)	0.53 (32)	0.12 (32)
Most frequent Global UCL (25)	0.46 (25)		Global	0.74 (23)	1 (23)	0.96 (24)	0.38 (25)	1 (22)	0.76 (25)	0.55 (23)	0.65 (23)
All patients (53)	n.a.	Option B	LonTran	0.52 (48)	0.70 (47)	0.95 (50)	0.26 (53)	0.30 (46)	0.23 (53)	0.69 (47)	0.69 (48)
			Memb	0.45 (48)	0.69 (47)	0.18 (50)	0.55 (53)	0.74 (46)	0.19 (53)	0.48 (47)	0.06 (48)
Most frequent LonTran UCL (36)			LonTran	0.24 (32)	1 (32)	0.35 (33)	0.47 (36)	0.48 (30)	0.63 (36)	0.78 (32)	0.65 (32)
			Memb	0.38 (32)	0.75 (32)	0.005 (33)*	0.07 (36)	0.62 (30)	0.78 (36)	0.41 (32)	0.06 (32)
Most frequent Global UCL (25)			Global	0.28 (23)	0.93 (23)	0.83 (24)	0.09 (25)	1 (22)	0.76 (25)	0.86 (23)	0.93 (23)

Table 9S: Analysis of voltage difference (left minus right hemisphere), medication (Levodopa equivalent drugs, LED; classes, <−30%, significant rise, (−30%, 30%), no significant change, >30%, significant drop), age and gender according to balance of contact pair-up (BCPU) with 6 classes (BCPU0 to BCPU5, see text for details) or 3 classes (BCPU-asymmetric, BCPU-sym-Rear-SupLat-Out, and BCPU-sym-other; *, statistically significant

Patients (*n*)	BCPU	*P* value (number of patients)						
		Voltage difference	Medication (LED dose)				Age	Gender
			Preop	1-year	Percentage of variation (Preop -1-Year/Preop)			
					Dose	Class		
All patients (53)	6 classes	0.65 (53)	0.11 (53)	0.28 (5)	0.17 (50)	0.11 (50)	0.63 (53)	0.31 (53)
	3 classes	0.53 (53)	0.03 (53)*	0.15 (50)	0.43 (50)	0.11 (50)	0.62 (53)	0.16 (53)

Table 10S: Analysis of UPDRS III motor score (Dopa-OFF condition: StimOFF – StimON / StimOFF; n.a. not applicable) and UPDRS speech and freezing sub-scores (option A, less sensitive to worsening; option B, more sensitive to worsening) according to balance of contact pair-up (BCPU) with 6 classes (BCPU0 to BCPU5, see text for details) or 3 classes (BCPU-asymmetric, BCPU-sym-Rear-SupLat-Out, and BCPU-sym-other; *, statistically significant

Patients (*n*)	UPDRS III global motor score improvement	Difference of UPDRS sub-scorings describing speech and freezing	BCPU	Speech						Freezing	
				Chronic (UPDRS II speech sub-score)		Acute (UPDRS III speech sub-score)				Chronic (UPDRS II freezing sub-score)	
				Chronic (UPDRS II speech sub-score)		1-year vs preop		1 year		1-year vs preop	
				Med ON	Med OFF	Med ON	Med OFF	Med ON	Med OFF	Med ON	Med OFF
				SpeeChro_ MedON_1yvs Preop	*SpeeChro_ MedOFF_1yvs Preop*	*SpeeAcc_ MedON_1yvs Preop*	*SpeeAcc_ MedOFF_1yvs Preop*	*SpeeAcc_ MedON_1y*	*SpeeAcc_ MedOFF_1y*	*FreeChro_ MedON_1yvs Preop*	*FreeChro_ MedOFF_1yvs Preop*
	***P* value (number of patients)**			***P* value (number of patients)**							
All patients (53)	0.92 (53)	Option A	6 classes	0.11 (48)	0.59 (47)	0.23 (50)	0.39 (53)	0.38 (46)	0.94 (53)	0.64 (47)	0.97 (48)
	0.92 (53)		3 classes	0.30 (48)	0.77 (47)	0.52 (50)	0.21 (53)	0.05 (46)*	0.48 (53)	0.60 (47)	0.99 (48)
	n.a.	Option B	6 classes	0.05 (48)*	0.99 (47)	0.28 (50)	0.11 (53)	0.74 (46)	0.84 (53)	0.76 (47)	1 (48)
			3 classes	0.12 (48)	0.77 (47)	0.38 (50	0.21 (53)	0.24 (46)	0.62 (53)	0.37 (47)	1 (48)

Table 11S: Analysis of voltage difference (left minus right hemisphere), medication (Levodopa equivalent drugs, LED; classes, < -30%, significant rise, [-30%, 30%], no significant change, >30%, significant drop), age and gender according to left-hemisphere-wise or right-hemisphere-wise laterality of the most frequent contact pair-ups (MFCP): first, only rear-longitudinal MFCP, named 1-MFCP, second, 1-MFCP and SupLat-transversal MFCP, named 2-MFCP, and third, 2-MFCP and out-STN-membership MFCP, named 3-MFCP; *, statistically significant

Patients (*n*)	hemisphere-wise	MFCP	Voltage difference	Medication (LED dose)				Age	Gender
				Preop	1-year	Percentage of variation (Preop - 1-Year/Preop)			
						dose	class		
			P value (number of patients)						
All patients (*n*=53)	left	1-MFCP	0.95 (53	0.78 (53)	0.48 (50)	0.66 50)	0.92 (50)	0.56 (53)	0.19 (53)
		2-MFCP	0.91 (53)	0.92 (53)	0.92 (50)	0.92 (50)	1 (50)	0.17 (53)	0.16 (53)
		3-MFCP	0.39 (53)	0.71 (53)	0.39 (50)	0.48 (50)	0.93 (50)	0.12 (53)	0.05 (53)*
	right	1-MFCP	0.95 (53)	0.03 (53)*	0.49 (50)	0.83 (50)	0.79 (50)	0.12 (53)	0.40 (53)
		2-MFCP	0.78 (53)	0.20 (53)	0.40 (50)	0.28 (50)	0.79 (50)	0.42 (53)	0.85 (53)
		3-MFCP	0.97 (53)	0.37 (53)	0.46 (50)	0.24 (50)	0.47 (50)	0.93 (53)	0.03 (53)*

Table 12S: Analysis of UPDRS III motor score (Dopa-OFF condition: StimOFF – StimON / StimOFF; n.a. not applicable) and UPDRS speech and freezing sub-scores (option A, less sensitive to worsening; option B, more sensitive to worsening) according to left-hemisphere-wise or right-hemisphere-wise laterality of most frequent contact pair-ups (MFCP): first, only rear-longitudinal MFCP, named 1-MFCP, second, 1-MFCP and SupLat-transversal MFCP, named 2-MFCP, and third, 2-MFCP and out-STN-membership MFCP, named 3-MFCP; *, statistically significant

Patients (n)	hemisphere-wise	MFCP	UPDRS III global motor score improvement	Difference of UPDRS sub-scorings describing speech and freezing	Speech						Freezing	
					Chronic (UPDRS II speech sub-score)		Acute (UPDRS III speech sub-score)				Chronic (UPDRS II freezing sub-score)	
					1-year vs preop		1-year vs preop		1 year		1-year vs preop	
					Med ON	Med OFF	Med ON	Med OFF	Med ON	Med OFF	Med ON	Med OFF
					SpeeChro_ MedON_1yvs Preop	*SpeeChro_ MedOFF_1yvs Preop*	*SpeeAcc_ MedON_1yvs Preop*	*SpeeAcc_ MedOFF_1yvs Preop*	*SpeeAcc_ MedON_1y*	*SpeeAcc_ MedOFF_1y*	*FreeChro_ MedON_1yvs Preop*	*FreeChro_ MedOFF_1yvs Preop*
			p value (number of patients)		p value (number of patients)							
All patients (n=53)	left	1-MFCP	0.80 (53)	A	0.01 (48)*	0.93 (47)	0.82 (50)	0.04 (53)*	0.56 (46)	0.17 (53)	0.43 (47)	1 (48)
				B	0.006 (48)	0.88 (47)	1 (50)	1 (53)	0.22 (46)	0.43 (53)	0.95 (47)	0.99 (48)
		2-MFCP	0.75 (53)	A	0.06 (48)	0.51 (47)	0.48 (50)	0.02 (53)*	0.14 (46)	0.28 (53)	0.39 (47)	0.43 (48)
				B	0.02 (48)*	0.07 (47)	0.82 (50	0.90 (53)	0.21 (46)	0.66 (53)	0.56 (47)	0.58 (48)
		3-MFCP	0.13 (53)	A	0.34 (48)	1 (47)	0.49 (50)	0.23 (53)	0.05 (46)*	0.49 (53)	1 (47)	0.27 (48)
				B	0.15 (48)	0.52 (47)	0.30 (50)	0.48 (53)	0.35 (46)	0.67 (53)	0.93 (47)	0.93 (48)
	right	1-MFCP	1 (53)	A	0.16 (48)	1 (47)	0.90 (50)	1 (53)	1 (46)	0.81 (53)	0.53 (47)	0.26 (48)
				B	0.048 (48)*	1 (47)	1 (50)	1 (53)	0.37 (46)	1 (53)	0.67 (47)	0.70 (48)
		2-MFCP	0.93 (53)	A	0.71 (48)	0.47 (47)	0.19 (50)	0.34 (53)	1 (46)	0.20 (53)	0.87 (47)	0.03 (48)*
				B	0.51 (48)	0.22 (47)	0.48 (50	0.21 (53)	0.82 (46)	0.38 (53)	0.78 (47)	0.82 (48)
		3-MFCP	0.45 (53)	A	0.30 (48)	0.30 (47)	0.63 (50)	0.42 (53)	0.35 (46)	0.35 (53)	1 (47)	0.84 (48)
				B	0.19 (48)	0.59 (47)	0.91 (50)	0.39 (53)	0.64 (46)	0.44 (53)	0.94 (47)	0.51 (48)