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Deep brain stimulation of the subthalamic nucleus in severe Parkinson's disease: relationships between dual-contact topographic setting and 1-year worsening of speech and gait

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Abstract

Background

Subthalamic nucleus (STN) deep brain stimulation (DBS) alleviates severe motor fluctuations and dyskinesia in Parkinson's disease, but may result in speech and gait disorders. Among the suspected or demonstrated causes of these adverse effects, we focused on the topography of contact balance (CB; individual, right and left relative dual positions), a scantily studied topic, analyzing the relationships between symmetric or non-symmetric settings, and the worsening of these signs.

Method

An observational monocentric study was conducted on a series of 92 patients after ethical approval. CB was specified by longitudinal and transversal positions and relation to the STN (CB sub-aspects) and totalized at the patient level (patient CB). CB was deemed symmetric when the two contacts were at the same locations relative to the STN. CB was deemed asymmetric when at least one sub-aspect differed in the patient CB. Baseline and 1-year characteristics were routinely collected: (i) general, namely, Unified Parkinson's Disease Rating Scores (UPDRS), II, III motor and IV, daily levodopa equivalent doses, and Parkinson's Disease Questionnaire of Quality of Life (PDQ39) scores; (ii) specific, namely scores for speech (II-5 and III-18) and axial signs (II-14, III-28, III-29, and III-30). Only significant correlations were considered ($p < 0.05$).

Results

Baseline characteristics were comparable (symmetric versus asymmetric). CB settings were related to deteriorations of speech and axial signs: communication PDQ39 and UPDRS speech and gait scores worsened exclusively with symmetric settings; the most influential CB sub-aspect was symmetric longitudinal position.

Conclusion

Our findings suggest that avoiding symmetric CB settings, whether by electrode positioning or shaping of electric fields, could reduce worsening of speech and gait.

Keywords: DBS, Symmetry, STN, Speech, Gait, Parkinson's disease

Introduction

Deep brain stimulation (DBS) is an adjuvant treatment of Parkinson's disease for patients who shows motor fluctuations and dyskinesia despite optimal medication [27]. The most often targeted structure is the subthalamic nucleus (STN) and its close neighborhood [33]. STN DBS coupled with medication adjustment improves quality of life, which might revert to preoperative values some years after implantation [11] notably because of the progressive nature of the disease. Yet difficulties in managing both medication and DBS remain [69]. The location of electrode contacts is important [54]:

a “sweet spot” is sought, which may be the superolateral STN, either anterior or posterior, the zona incerta (ZI), or the fields of Forel [68]. Briefly, STN DBS could work by local inhibitory and distant excitatory electric modulation [24], while the clinical effects look like local lesioning, but this latter is associated with risks of ballism [2, 40]. In any event, patients may experience negative outcomes mainly in a deterioration of dopamine-resistant axial symptoms, such as impaired speech [1], freezing of gait and postural instability [47, 56, 91], and also deterioration of behaviors [13, 53, 79, 87, 88]. The mechanisms of STN DBS combined with medication, which underline these signs, are not set. Speech deterioration has been attributed to contacts in the left hemisphere medially to the STN [82], or close to the internal capsule [23, 44, 66], or to poor preoperative conditions, cognitive factors [78] and speech intelligibility [82], or to the participation of the supplementary motor area (SMA) [77]. The cause of the worsening of gait, particularly dopamine-resistant [85] and less frequent in younger patients [5], is unknown, but might be limited using unilateral right STN stimulation [56]. The interest of pedunculopontine nucleus DBS to alleviate gait troubles specifically must be confirmed [86], and notably before becoming a complementary and/or synergistic DBS target.

DBS impacts neural circuits mainly by reversible modulation, merging positive, predominant, and negative effects, and to some extent by a lesioning effect. Although a permanent subthalamic lesioning effect of electrodes is not demonstrated, worsening of cognition — working memory or verbal fluency, is reported when probes, respectively, cross the caudate [90] or the left superior frontal gyrus [4]. Furthermore, the role of dual stimulation is more complex than the sum of two unilateral stimulations, unilateral DBS itself having bilateral effects [16]. Dopamine (dopa) alone can also worsen speech, particularly in females, linked with levodopa-induced dyskinesia [12], and dopa alone like STN-DBS can aggravate postural control [17]. The relevance of the topographic symmetry of dual contacts has attracted less interest, suggesting a negative role [50]. Yet, dysarthria following bilateral lesioning is well-known for pallidotomy in Parkinson’s disease [19], and historically for thalamic ventrointermediate nucleus lesioning in essential tremor [32], which is also still an issue for DBS [42]. We set out to study the relationships between the symmetry or asymmetry of contact balance (CB; individual, right and left relative dual positions) and clinical effects, ~~one~~ 1 year after implantation, in a

consecutive observational series of 92 patients. Unified Parkinson's Disease Rating Scores (UPDRS) and Parkinson's Disease Questionnaire of Quality of Life (PDQ39) sub-scores were analyzed. In this retrospective study, speech worsening was described from routine clinical assessments of UPDRS II-5 and III-18, although specific scales, used prospectively, might have been more efficient [83]. Gait worsening was described by UPDRS II-14 freezing, III-28 posture, III-29 postural stability, and III-30 walk items. We hypothesized that symmetric STN DBS of right and left cortico-subcortical controls would impair more axial functions than asymmetric settings, while maintaining significant clinical benefit. The symmetry or asymmetry of CB was determined in 3D relative to the STN, and concerned the effective contact used at 1-year. CB was studied overall (patient-CB) and in three sub-aspects, two positions, namely, longitudinal (antero-posterior) and transversal (around the STN in the coronal plane), and the relation to STN. The goal was to identify CB settings related to deteriorations of speech or gait following STN DBS and medication modifications.

Materials and methods

Clinical material

Ninety-two patients with severe Parkinson's disease, treated by STN DBS coupled with optimal medication, were retrospectively included from January 2004 to December 2020 in a monocentric observational study (ethical approval 2020/CE103, South-East VI; agreement approved March 3, 2021). The selection criteria were bilateral implantation, neurologic assessments at 1-year, and specification of the left and right effective contacts used in chronic stimulation. Of the series of 168 patients operated over the period, 38 were excluded because of other positionings (ventral intermediate nucleus of thalamus 18, internal globus pallidus 13, posterior zona incerta 7). Of the 130 remaining patients, 38 were excluded because of missing data (no specification of the contacts used for chronic stimulation).

The electrodes were implanted under local ($n = 73$) and general ($n = 19$) anesthesia following institutional approval (Expert Center for Parkinson's disease). The electrodes used were Medtronic model 3389 ($n = 78$) and Abbott model 6170 ($n = 14$, the last patients of the series; the three facets of contacts were used, equivalent to one contact). The two contacts no. 2 and no. 3, located above the

distal contact (no. 1 was deepest), were the most often used effective contacts, in respectively 47.8% and 27.2% (the numbers of contacts were normalized irrespective of specific industrial features). The intended target was the sensorimotor territory of the STN, superior and lateral.

The longitudinal position along the STN (anterior–posterior location) was planned to consider anatomical constraints that restricted the straight-lead positioning: systematic entrance through the 2nd frontal gyrus; avoidance of sulci, vessels, ventricles, and caudate nucleus. The electrodes were implanted using an already published technique [20] using double guide-tube, semi-micro-electrode recording, and positioning of one contact or two adjacent contacts in the optimal region covering the target (STN and ZI) with step-by-step x-rays controls, and final securitization to the skull (microplates plus silastic cap). We also used cerebrospinal fluid tight guide tubes, with punctiform opening of the dura. The targeting was not intended to be asymmetric up to January 2010. After our initial findings, [50], we began a paradigm shift in which the contact contralateral to the most severe hemibody, usually where the disease began, was intended to be positioned slightly posteriorly to the contralateral contact (see below). The final effective contact, i.e., the one used at 1-year after implantation, was detected from the electrode artifact on a postoperative CT-scan [36] registered with the preoperative structural MRI (White Matter Attenuated Inversion Recovery sequence, WAIR; Magnetom Sonata and Avanto 1.5 Tesla, Siemens, Germany; stereotactic, frame secured to the head; coronal acquisition, 30 joined slices, voxel = $0.5 \times 0.5 \times 2 \text{ mm}^3$) on which were manually segmented the subthalamic structures for the surgery. One neurosurgeon (JJL) did all the manual segmentations of the 92 patients. Briefly, most subthalamic structures, such as STN, Forel's fields, ZI, red nucleus and substantia nigra, were manually contoured (Iplan 3.0®, BrainLab, Germany) on coronal images [18, 20, 48, 93] (Fig. 1). Each contour was determined according to WAIR spontaneous contrasts, and the relative location of structures, aided by a high resolution MRI atlas (isotropic voxels of 0.250 mm side) with the same contrasts [48, 49, 51]. The electrode artifact was detected from high resolution CT-scan with reconstructed isotropic voxels of 0.4 mm side (dual energy acquisition; LightSpeed, GE HealthCare, IL, USA). All image datasets of each individual were co-registered with the surgical software (Iplan 3.0®, BrainLab, Germany) using rigid method (mutual information).

Practically the effective contact location slightly deviated from the intended target because of the limited accuracy of surgical positioning, related to stereotactic instrument precision, electrode rigidity, cerebrospinal fluid leakage, securing of electrode, geometrical accuracy of images and the smallness of subthalamic structures. Consequently, only the location of effective contacts was further analyzed. For each hemisphere, the STN-centered subthalamic region was subdivided according to the STN axis defined from the antero-inferomedial pole to the postero-superolateral pole (Fig. 2). The contact (length 1.5 mm, diameter 1.3 mm) was located according to its longitudinal and transversal positions, and its relation to the STN (Fig. 2), namely: (i) longitudinal positions, anterior (ant), intermediate-anterior (intant), intermediate-posterior (intpost) and posterior (post); (ii) transversal positions, supero-lateral (suplat), inferolateral (inflat), inferomedial (inftmed) and superomedial (supmed); (iii) STN relation, in, out, and edge.

This allowed a precise, 3D, volumetric, individualized, topographic analysis of dual contact settings (Fig. 3).

We noted age (year), sex, disease duration (year) at surgery, and daily levodopa equivalent dose (LED, mg). The patients underwent the following examinations at baseline, preoperatively, and at 1-year (the higher the score, the worse the condition): the Hoehn & Yahr (H&Y) on-period score; the UPDRS III motor score and the III-18 speech, III-28-posture, III-29 postural stability, and III-30 walk subscores; the UPDRS II self-evaluation of the activities of daily life (II-ADLs) on-period score; the UPDRS II-5 speech and II-14 freezing of gait on- and off-period scores; the UPDRS IV, dyskinesia (A32 & A33 items) and fluctuations (B39 item), scores; the Parkinson's Disease Questionnaire of Quality of Life scores (PDQ39, eight groups of items; index expressed in %), mobility 1–10, activities of daily living 11–16, emotional well-being 17–22, stigma-depression 23–26, social support 27–29, cognition 30–33, communication 34–36, and bodily discomfort 37–39. The UPDRS III score was specified during an acute levodopa challenge in two conditions: DOPA-OFF (after 12 h of withdrawal of all antiParkinsonian medication) and DOPA-ON (1 h after acute administration of 150% of the usual morning levodopa dose), at baseline and 1-year without stimulation to calculate the dopa effect $(DOPA-OFF - DOPA-ON) / DOPA-OFF$, at 1-year, DOPA-OFF, without and with stimulation to

calculate the stim effect $(\text{STIM-OFF} - \text{STIM-ON}) / \text{STIM-OFF}$, and the overall effect $(\text{DOPA-OFF} - \text{STIM-OFF} - \text{DOPA-ON} - \text{STIM-ON}) / \text{DOPA-OFF} - \text{STIM-OFF}$. We focused on the deteriorations of speech (III-18; II-5, on- and off-periods) and gait signs, freezing, posture, stability and walk (III-28-29-30; II-14, on- and off-periods).

The baseline and 1-year clinical characteristics are given in Table 1.

Limitations

This individual patient anatomy approach enabled a precise, personalized, 3D mapping of the subthalamus, however at the cost of a significant perioperative workload with about ~~two~~ 2 hours of manual mapping, which compares unfavorably with the time of classical surgical targeting based on dot-landmarks and relative coordinates. The resulting high geometric accuracy (infra millimetric) must be put also into perspective taking into account the efforts of interpretation of gray-values, even with the assistance of a high resolution MRI atlas (see above), notably because of partial volume effect due to the small sizes of structures (see, e.g., [30]). Yet, this time cost at surgery, shorten dramatically the 3D topographic analysis of effective contacts, because the mapping was already available for each individual. Especially, each individual space being its own anatomical reference, prior group normalization was useless, while preserving the possibility to use other statistical approaches, such as atlas-coordinate-based group analysis of contacts.

Methods

The CB was specified irrespective of the hemisphere, i.e., the mirror left-right or right-left settings were not distinguished. Indeed, the number of possible combinations would have precluded statistical analysis. Symmetry was defined as when the right and left contacts were at the same locations relative to the STN. Asymmetry was defined as when this was not the case. Three longitudinal, three transversal and three STN relation CB sub-aspects were defined (Supplementary material A and Fig. 4), namely: (i) longitudinal CB, symmetric posterior (sym-post), symmetric non-posterior (sym-non-post), and asymmetric (asym-L); (ii) transversal CB, symmetric superolateral (sym-suplat), symmetric non-superolateral (sym-non-suplat), and asymmetric (asym-T); (iii) STN relation CB, symmetric out (sym-out), symmetric non-out (sym-non-out), and asymmetric (asym-N).

The three sub-aspects grouped by patient, defined the patient CB, which was either symmetric (sym-p) or asymmetric (asym-p); asymmetry meant that at least one sub-aspect was asymmetric.

The clinical characteristics were subdivided into general, namely demographic data, H&Y score on-period, UPDRS III motor total, II-ADLs on-period, IV, LED and PDQ39 scores, and specific, namely speech (UPDRS III-18 and II-5) and gait (UPDRS III-28, III-29, III-30, II-14). They were studied according to patient CB and CB sub-aspects. At 1-year, we considered only significant variations ($p < 0.05$) and only if all the settings were accessible to statistical analysis, enabling comparison; instances when data was short ($n = 1$) were also excluded from the analysis.

Continuous variables were expressed as mean and standard deviation. The assumption of normal distribution was examined by the Shapiro-Wilk test. For continuous variables (such as UPDRS and PDQ39), the comparisons between CB settings were made with analysis of variance (ANOVA), or the Kruskal-Wallis test when conditions to apply ANOVA were not met. Homoscedasticity (equality of variances) was analyzed by Bartlett's test. When appropriate (i.e., omnibus p -value less than 0.05), post-hoc tests were applied on two-by-two multiple comparisons: Tukey-Kramer after ANOVA and Dunn after Kruskal-Wallis. Comparisons concerning categorical variables used chi-squared or Fisher's exact tests followed by Marascuilo's procedure for multiple comparisons. Paired comparisons for within group analyses (baseline vs. 1-year) were conducted with the paired Student test or Wilcoxon test. All analyses were generated with Stata software, version 15.0 (StataCorp, College Station, USA). A two-sided p value of less than 0.05 was considered to indicate statistical significance. As analyses were exploratory, the individual p -values are reported, (i) without systematically applying mathematical correction (except as stated above), and (ii) according to several published studies [6, 70], but (iii) with special attention to the magnitude of differences and to clinical relevance [22].

Results

At 1-year, the clinical overview was as follows: the motor symptoms improved (DOPA-OFF—STIM-ON—DOPA-OFF [baseline] $21.2 \pm 33.8\%$, stim effect $38.4 \pm 16.7\%$, overall

effect $62.3 \pm 14.5\%$), the motor complications (i.e., dyskinesia and fluctuations) were reduced, the LED decreased (-201.7 ± 573.5 mg), while motor symptoms without stimulation, DOPA-OFF and -ON, worsened, and the dopa effect decreased (Supplementary material B, C, D, E). The left and right voltages (normalized irrespectively of specific industrial features), respectively 2.87 ± 0.95 volts and 2.85 ± 0.99 volts, were comparable.

Distributions of CB

The most frequent CB sub-aspects were symmetric, post longitudinal (47 out of 92, 51%), suplat transversal (71 out of 92, 77%), and out (38 out of 92; 41%) and non-out (41 out of 92, 44%). The most frequent patient-CB was symmetric (64 out of 92, 69%), mainly post/suplat/out (21 out of 64) and non-post/suplat/non-out (20 out of 64)). The detailed distribution is given in Table 2.

Clinical effects according to CB

The detailed mean values (\pm standard deviation) of clinical items, at baseline and 1-year after electrode implantation, according to patient-CB, and CB sub-aspects, are in the supplementary material (supplementary material B, C, D, E). The synthesis of statistically significant results represented qualitatively, such as improvement or worsening of scores and values, is shown in the supplementary material F.

General characteristics

At baseline, the general characteristics were comparable. However, higher PDQ39 scores were related to CB conditions: (i) cognition with symmetric, patient CB and (out and non-out) STN relation, (ii) social support with symmetric suplat and asymmetric transversal CB, and (iii) communication with symmetric out and asymmetric STN relation. Lower dopa effect was related to symmetric non-suplat transversal CB.

At 1-year, the LED decreased slightly more with asymmetric patient CB but increased, exclusively with symmetric non-out and asymmetric STN relation CBs. Symmetric, patient CB and transversal-CB were related to higher PDQ39 cognition scores. In addition, symmetric suplat and asymmetric transversal-CB were related to higher UPDRS III score, without stimulation, DOPA-OFF.

As regards the variations, LED decreased exclusively with symmetric non-out CB. Symmetric patient-CB was related to worsening of H&Y score. Either symmetric or asymmetric patient CB ~~were~~ was related to worsening of ADLs. Almost all CBs were related to improvement of UPDRS-IV scores, except for asymmetric longitudinal and symmetric non-suprat transversal sub-aspects. PDQ39 scores improved with (i) symmetric patient CB, for emotional well-being, stigma, and bodily discomfort, (ii) symmetric post longitudinal CB for stigma, (iii) symmetric suprat transversal CB for activities of daily living, emotional well-being, stigma, and bodily discomfort, and (iv) symmetric out STN relation for stigma and bodily discomfort. Symmetric, patient CB, and suprat transversal and out STN relation CBs were related to worsening of PDQ39 communication scores.

The variations of UPDRS III scores, without stimulation, symmetric and asymmetric patient CB, and STN relation CB settings were related to a decrease in the dopa effect. This also specifically concerned two symmetric sub-aspects, the post and non-post longitudinal, and the suprat transversal. In addition, all patient CB settings were related to worsening, DOPA-OFF and -ON, without stimulation; this also specifically concerned symmetric (post and non-post) longitudinal CB, and symmetric suprat and asymmetric transversal CB. For the STN relation CB, symmetric out and non-out in DOPA-OFF, and all membership CB settings in DOPA-ON, were related to worsening without stimulation. All patient CB and all longitudinal CB settings were related to - stim effect lower than dopa-effect -, which also specifically concerned the symmetric suprat and asymmetric transversal, and the symmetric (out and non-out) STN relation sub-aspects.

Speech

Baseline and 1-year speech characteristics were comparable, except for higher III-18 scores, respectively, DOPA-OFF with symmetric (post and non-post) longitudinal, and DOPA-ON STIM-ON with asymmetric transversal sub-aspects.

As regards the II-5 scores, all patient CB settings and symmetric (post and non-post) longitudinal CB were related to worsening (on and off periods), as were symmetric suprat and asymmetric transversal CBs. Concerning STN relation CB, all settings and symmetric (out and non-out) were related, respectively, with worsening of II-5 on and II-5 off scores.

As regards the III-18 scores, only symmetric patient CB, and post longitudinal, suplat transversal and out STN relation sub-aspects were related to worsening of dopa effect. All patient CB settings, symmetric post longitudinal, symmetric suplat transversal, and asymmetric STN relation sub-aspects were related to worsening of stim effect (lower than the dopa₋effect). Without stimulation, all patient CB and all STN relation CB settings were related to worsening, DOPA-OFF and -ON, along with all longitudinal and transversal sub-aspects, DOPA-OFF, and symmetric (post and non-post) longitudinal, symmetric suplat and asymmetric transversal sub-aspects, DOPA-ON.

Gait

Baseline and 1-year axial signs were comparable, without stimulation, except for higher DOPA-ON III-29 postural stability scores and lower dopa₋effect, with symmetric out and asymmetric STN relation CB.

As regards the II-14 freezing scores, all patient CB settings, symmetric suplat transversal and symmetric (out and non-out) STN relation sub-aspects were related to worsening.

As regards the dopa effect and stim effect of III-28 posture, III-29 postural stability and III-30 walk scores, all patient CB settings, symmetric (post and non-post) longitudinal CB, and symmetric (out and non-out) STN relation sub-aspects were related to - stim effect lower than dopa effect -.

Symmetric, patient CB and non-post longitudinal CB were related to improvement of dopa effect for III-29 postural stability. Conversely, all patient CB settings, symmetric post longitudinal CB, symmetric suplat and asymmetric transversal CB, and symmetric out and asymmetric STN relation CB were related to worsening of dopa effect, for III-30 walk. Without stimulation, symmetric, patient CB, (post and non-post) longitudinal CB, suplat transversal CB, and non-out STN relation CB were related to worsening of III-29 postural stability, DOPA-OFF. Asymmetric patient CB, symmetric post longitudinal CB and symmetric-out STN relation CB were related to worsening of III-28 posture, DOPA-ON. Asymmetric patient CB was related to worsening of III-29 postural stability, DOPA-ON. All patient CB settings, symmetric (post and non-post) longitudinal CB, symmetric suplat and asymmetric transversal CB, and all STN relation CB settings were related to worsening of III-30 walk, DOPA-ON.

Discussion

Our findings show tangible relationships between speech and gait deteriorations and dual-contact balance (Fig. 5, supplementary material F). The key finding was that a symmetric setting appeared to promote an axial adverse effect, irrespective of confounding variables (see e.g. [1] for speech). The most influential CB sub-aspect seemed the symmetric longitudinal, which was exclusively related to worsening of speech (UPDRS II-5, on and off periods; III-18, DOPA ON, dopa₋effect and stim₋effect) and gait (UPDRS III), and motor score (III-total).

Despite the limits of our monocentric observational study, notably the absence of a control group, both general and specific baseline characteristics of patients, with either with symmetric or asymmetric settings, were comparable enabling meaningful interpretation of data. The personalized 3D MRI--based subthalamic mapping by hemisphere, irrespective of probabilistic anterior-commissure — posterior-commissure (AC-PC) relative coordinates, let us optimize the topographic analysis, as far as possible, considering the detailed architecture of the STN and its neighborhood.

At the patient level, only the Hoehn and Yahr score and the communication score (items 34--36; PDQ39), deteriorated exclusively with symmetric settings. Conversely, symmetry was related to improvement of emotional well-being, stigma, and bodily discomfort (PDQ39, 17--22, 23--26, 37--39) illustrating the merged positive-negative effects of DBS. During acute DBS challenge, we did not observe any relationship between CB settings and speech or gait worsening (average values) that could have supported direct causality. Only the decrease in dopa effect on speech (III-18) was related to the symmetric condition, suggesting cross effects between dopa and DBS. Paradoxically, posture (III-28) and postural stability (III-29), DOPA-ON, worsened exclusively with the asymmetric setting, suggesting a predominant negative dopa effect on postural controls [17], whereas dopa effect during III-29 postural stability challenge, improved exclusively with symmetric settings (supplementary material F3).

Topographic CB sub-aspects revealed worsening effects on communication, speech, and gait that correlated exclusively with symmetric settings. From the non-acute assessments, communication

(PDQ39, 34--36) worsened with the symmetric, suplat, and out CBs. On the other hand, activities of daily living, emotional well-being, stigma, and bodily discomfort improved exclusively with symmetric, respectively, suplat, suplat, post-suplat-out, and suplat-out (merged positive-negative effects) CBs. Speech (UPDRS II-5) worsened with symmetric settings during, on and off periods according to longitudinal sub-aspect, and in off period according to STN relation sub-aspect. Freezing (UPDRS II-14) worsened, on period, with the symmetric, suplat and STN relation, sub-aspects. On the other hand, fluctuations (UPDRS IV, B39) were reduced exclusively with the symmetric longitudinal sub-setting (merged positive-negative effects). From the acute challenges, III-motor worsened with, STIM-OFF, the symmetric, longitudinal, suplat, and STN relation sub-aspects. Speech (III-18) worsened with, DOPA-ON STIM-OFF, the symmetric longitudinal, and specifically for dopa effect with post, suplat, and out sub-aspects. The stim effect worsened alone with the post and suplat symmetric settings. Posture (III-28) worsened, DOPA-ON STIM-OFF, with the symmetric post and out settings. Postural stability (III-29) worsened, DOPA-ON STIM-OFF, with the symmetric, longitudinal, suplat, and STN relation sub-aspects. Walk (III-30) worsened, DOPA-ON STIM-OFF (and dopa effect), with the symmetric longitudinal sub-aspect.

It is known that STN-DBS can harm the ability to accelerate speech, which is often faster, at baseline, than in healthy controls [46]. Speech deterioration, and notably hypokinetic dysarthria, is also very frequent in Parkinson's disease independent of DBS [15] and worsens with the disease with no significant effect of dopa [21]. However, dopa and symmetric CBs seem to interact, as suggested by the correlations between symmetric setting and DOPA-ON condition (Fig. 5, supplementary material F). In addition, the dopa effect was reduced exclusively with almost all symmetric settings (patient CB, post longitudinal, suplat transversal, and out STN relation sub-aspects). The STN functional territories could also partially explain the negative role of symmetric longitudinal sub-aspect on speech. Two common models of functional segregation can be used based on the relative location of territories: a transversal model, where the associative territory is lateral and the limbic medial [29, 60, 62], and a longitudinal model where the associative territory is above and posterior to the limbic [35, 41]. Because the most frequent CB patterns were symmetric, post/suplat/out, and non-post/suplat/non-out

(Table H2), the related neural correlates should, respectively, be exclusively sensorimotor including projecting fibers (transversal model), or mixed, sensorimotor (post-out) and associative (non-post/non-out) (longitudinal model) (Fig. 6). Caudal zona incerta DBS, which also affects speech [71], is very close to STN-DBS post/sup/out contacts (Fig. 6), and is very likely included in the volume of tissue activated [10] considering the mean voltages in our series. The symmetric posterior setting could also directly and symmetrically impact oro-pharyngo-laryngeal controls of the sensorimotor and SMA-related territories [67]. The worsening of PDQ39 communication with symmetric settings, highlights the possible role of projecting fibers and/or the interaction between dysarthria and circuits related to social aspects of Parkinson's disease [65].

The gait deterioration, exclusively during the II-14 on-period, with symmetric transversal and STN relation CBS (Fig. 5, supplementary material F), could illustrate entanglement with dopa effect during motor fluctuations [3]. The negative impact of symmetric settings on freezing could be explained by a bilateral brain dysfunction, even with right-hemisphere controls predominating [63]. Interestingly, the dopa effect improved solely on III-29 postural stability with symmetric settings (patient CB and non-post longitudinal CB; supplementary material F3), suggesting a positive influence on the dopa effect for this symptom.

Globally, over 1-year of DBS coupled with optimized medication, general modifications occurred, whatever the CB settings: LED and dyskinesia decreased, as expected, the dopa effect decreased with an increase of DOPA-OFF and -ON scores at 1-year, while the difference decreased (baseline $70.0 \pm 12.4\%$, 1-year $59.5 \pm 18.5\%$, average decrease $-10.8 \pm 17.9\%$). The stim-effect, $38.4 \pm 16.7\%$, was systematically lower than the dopa effect (average decrease $19.1 \pm 21.0\%$). Our values of [dopa—stimulation] effects at 1-year (ON versus OFF, including the stim-effect) are comparable to meta-analysis [84]. The variety of therapeutic effects reported in recent or large series [25, 26, 28, 39, 43, 52, 61, 74, 80, 81, 88, 89, 92], including our series, impedes detailed analysis, although salient features are shared (i.e., a very frequent lack of very limited improvement of on-period ADLs scores and PDQ39 index (Fig. 7). Long-term DBS also shows a worsening of UPDRS III total and quality of life scores [8, 11]. The DBS effect also depends on the preoperative motor baseline [14]. The overall

evidence (Fig. 5, supplementary material F) suggests that pathophysiologic circuits changed differentially according to CB settings over 1-year, all other things being equal, worsening scores during acute dopa challenge tests. This could be supported by post-DBS structural and functional plasticity of STN in Parkinson's disease [34, 57, 76] and the pallidum in dystonia [59, 72].

The merged positive–negative effects illustrate the still untangled complexity of nodal-based systems overlapping on the STN, such as non-motor circuits [7, 45, 88]. In addition, in vivo imaging of the DBS effect showed the implication of the primary motor cortex (M1) and supplementary motor area (SMA) [31, 37], temporal cortices [38], the globus pallidus internus, thalamus, and deep cerebellar nuclei, and the deactivation of M1, putamen, and cerebellum [75], and the brainstem following electrode positioning during the “lesioning effect” [37]. It was also found that DBS increased the connectivity of the cortico-thalamo-cerebellar network, and contrary to dopamine [58].

In conclusion, the symmetric dual-contact setting, notably the longitudinal aspect, seems to interfere negatively with speech and gait controls, suggesting that the asymmetric setting could mitigate these adverse effects. Further studies integrating the complexity and diversity of effects, location, and disease, at the individual level, notably through a functional connectivity approach based on volume of tissue activated, should refine our understanding of dual-contact settings. For the time being, the complexity of nodal-based circuitry is a hindrance to understanding speech and gait worsening. Probe lesioning effects should also be considered, together with the lateralization of DBS effect [55]. Because asymmetric positioning can be difficult to achieve surgically, whatever the methods of targeting and electrode implantation, the deformation of the shape of electric field using directional contacts could likely surrogate asymmetric contact setting, as it already enables relevant therapeutic tuning [9, 73]. New DBS options, such as non-continuous, beta-based adaptive DBS, should also be considered [64], considering the specific features of the right and left hemispheres.

Supplementary information

A, Specification of contact balance (CB); B, Table of patient CB; C, Table of longitudinal CB; D, Table of transversal CB; E, Table of STN relation CB; F, Baseline, 1-year and variation of clinical

characteristics (general F1, speech F2, and gait F3) according to patient CB and sub-aspects, longitudinal and transversal positions, and STN relation.

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Author contribution

Conceptualization, JJJ, YEO, AM; methodology, BP, JJJ, YEO; validation, YEO, ML, DM, JJJ; formal analysis, JJJ, YEO, BP; investigation, YEO, AM, ML, BD, PD, DM, FD, JJJ; resources, YEO, BC, AS, JC, AM, BD, PD, JJJ; data curation, YEO, DM, JC, FD; writing—original draft preparation, JJJ, YEO, AM; writing-review and editing, YEO, AM, BP, ML, BC, JC, AS, RC, BD, PD, FD, JJJ; visualization, JJJ, YEO, BP; supervision, JJJ; project administration, BP; All authors have read and agreed to the published version of the manuscript.

Declarations

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee: Ethical approval 2020/CE103, South-East VI; agreement approved March 3, 2021.

Informed consent statement

Informed consent was obtained from all the subjects involved in the study, or their representative.

Competing interests

The authors ~~have declare~~ no ~~financial or proprietary competing~~ interests ~~in any material discussed in~~ ~~this article~~.

Comments

Although deterioration of speech and gait occurring in Parkinson disease (PD) patients over time is a well-known phenomenon; it occurs with or without deep brain stimulation (DBS) surgery and is

frequently observed even in patients whose cardinal PD symptoms improve after surgery. Higher incidence of speech and gait worsening after bilateral surgical interventions has been known for decades, but the connection of this phenomenon to specific electrode contact locations, and especially their symmetry, remains unclear. The authors of this large cohort study make a strong argument that symmetry of contact may be contributing, or directly causing, deterioration of axial issues and speech, but at the same time notice that this may occur with remarkable improvement in other PD symptoms. The question therefore remains if the intentional placement of DBS electrodes in asymmetric locations would eliminate negative effects on speech and gait while maintaining high efficacy for other motor PD manifestations, and whether quality of life in operated PD patients will be higher or lower with alternative electrode setups. It would probably be naïve to expect a panacea-like surgical intervention that would cure a complex neurodegenerative disorder with a simple delivery of electrical impulses, but it is definitely worth trying when it comes to optimization of our surgical approaches and technical nuances. I must admit that I never paid attention to intentional or unintentional symmetry of my implanted DBS electrodes; after reading this study, I would start doing it now.

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Fig. 1 Manual segmentation of subthalamic structures (Iplan ®, BrainLab, Germany): subthalamic nucleus, yellow; Forel 'fields, green; zona incerta, deep red; substantia nigra, dark blue; nucleus of ansa lenticularis, orange; raw image without filtering, and raw contours (up to subpixel, 0.25 mm side) according to contrasts and relative locations of structures

Fig. 2 Location of effective contacts. **A**- 3D view showing the three inclinations, from the anterior-commissure (AC) — posterior-commissure (PC) orthogonal planes, of the subthalamic nucleus (STN, yellow) axis (dotted line); (AM, antero-inferomedial point; PS, postero-superolateral point; substantia nigra, sn, red nucleus, rn, and zona incerta, zi). **B** Longitudinal (**B**) and **C** transversal (**C**) positions and **D** STN relation (**D**) showing the four longitudinal, anterior (ant), intermediate-anterior (intant), intermediate-posterior (intpost) and posterior (post), and the four transversal, supero-lateral (suplat), inferolateral (inflat), inferomedial (infmed), and superomedial (supmed), positions, and the three STN relation, in, out and edge; reconstructed sections along the STN axis, longitudinal or pseudo-sagittal (left), transversal or pseudo-coronal (intermediate and right); STN, yellow, zi, purple, sn, dark gray, rn, red

Fig. 3 Effective contact location (same patient as in Fig. 1): **(A)** anterior 3D view (reconstructed from the personalized contours; Iplan®, BrainLab, Germany) of the subthalamic nucleus (stn, yellow, transparent), substantia nigra (sn, dark blue), red nucleus (rn, red), fields of Forel (ff, green) showing the STN axis (yellow segment) and the right (R) and left (L) effective contacts at 1-year (red cylinders); **(B)** Longitudinal (left column; AM, antero-inferomedial point of the STN axis, yellow segment) and transversal (right column) locations of the left (top row) and right (bottom row) effective contacts (red cylinders); reconstructed MRI sections from the WAIR sequence with the contours of structures (see text; same slice orientation than Fig. 2), the left contact was intermediate-posterior (int-post), superomedial (supmed) and in, and the right contact was intermediate-posterior (int-post), superolateral (suplat) and in

Fig. 4 STN relation CB: sym-out, sym-non-out, and asym-N

Fig. 5 Clinical characteristics that worsened significantly according to patient CB and sub-aspects: orange square (■) symmetric; black square (■) asymmetric; light blue background in DOPA-ON condition

Fig. 6 Most frequent CB settings and STN functional territories. The most frequent CB settings, post/suplat/out (black circle; $n=21$, out 64 symmetric patient CB), and non-post/suplat/non-out (white circle; $n=20$, out 64 symmetric patient CB) are overlaid on two models, transversal (**A**, top) and longitudinal (**B**, bottom) functional models of segregations of sensorimotor (SM), associative (A), and limbic (L) territories of the subthalamic nucleus; left columns, 3D, anterior (above) and superior (below), views; right columns, coronal sections at the 1/3-posterior point and midpoint point along the anterior-commissure — posterior-commissure line. The two models are embedded in the STN volume of an MRI atlas ([49]). The segregation was meticulously done manually (Amira 6.0, Thermo Fischer Scientific, USA), according to the literature (see text), based on aspect ratios

Fig. 7 DBS-medication outline of 14 series of patients with severe Parkinson's disease: series ≥ 90 patients, or ≥ 2015 and ≥ 30 patients; values are expressed as percentage from the raw mean values (negative value means improvement); LED baseline (percentage of 1400 mg); LED decrease (percentage of baseline); Δ ADLs baseline (off-period—on-period/-off-period); Δ ADLs stim on at 1-year (off-period—on-period/-off-period); Δ ADLs off-period (off-period_baseline—off-period_1year/-off-period_baseline); Δ ADLs on period (on-period_baseline—on-period_1-year/-on-period_baseline); Δ PDQ39 index (1-year—baseline/-1-year); dopa effect, baseline (off—on/-off), 1-year stim-off, 1-year stim-on; stim effect dopa-off, at 1-year (stim-off—stim-on/-stim-off), and baseline—1-year (baseline—stim-on-1-year/-baseline); vertical white bars are proportional to the number of values and centered on the mean; missing values are set to zero

Table 1: Baseline and 1-year, characteristics of the 92 patients (n =collected data); SD, standard deviation

Table 1 Baseline and 1 year, characteristics of the 92 patients (n =collected data); SD, standard deviation

Characteristics		Baseline		1 year	
		Mean \pm SD	n	Mean \pm SD	n
Age (year)		60.86 \pm 6.85	92		
Gender (female)		42	92	n.a.	
Disease duration (year)		10.4 \pm 3.8	92		
LED (mg)		1230.1 \pm 480.2	87	1037.6 \pm 540	80
Hoehn & Yahr score	On-period	1.78 \pm 0.88	83	2.13 \pm 0.75	73
	Off-period	2.36 \pm 0.74	86	2.51 \pm 0.86	77
ADLs (UPDRS II)	On-period	4.68 \pm 4.02	80	9.80 \pm 5.56	70
	Off-period	16.36 \pm 5.57	81	15.97 \pm 6.68	69
UPDRS	A32 (%)	1.76 \pm 1.02	90	0.22 \pm 0.61	81
IV-dyskinesia	A33 (disability)	1.67 \pm 1.12	90	0.13 \pm 0.49	81

UPDRS IV-fluctuations	B39 (%off)	1.59 ± 0.67	91	1.04 ± 0.65	81
	Index (100%)	35.48 ± 13.09	52	28.40 ± 14.14	38
	Mobility 1 & 10	18.05 ± 8.83	71	15.59 ± 8.80	47
	Activities of daily living 11 & 16	9.8 ± 4.68	70	7.59 ± 4.25	47
	Emotional well-being 17 & 22	8.87 ± 4.96	64	7.47 ± 4.44	44
PDQ39	Stigma-depression 23 & 26	6.34 ± 3.46	70	4.27 ± 3.51	48
	Social support 27 & 29	2.41 ± 2.69	65	1.85 ± 2.22	42
	Cognition 30 & 33	4.67 ± 2.74	71	4.26 ± 2.55	49
	Communication 34 & 36	3.46 ± 2.15	67	4.26 ± 2.53	49
	Bodily discomfort 37 & 39	5.76 ± 2.97	67	4.66 ± 2.83	48
UPDRS III motor (total)	DOPA-OFF	31.70 ± 11.29	91	37.92 ± 13.75	89
	DOPA-ON	9.60 ± 5.74	91	15.54 ± 9.86	60
	Dopa effect (%)	70.05 ± 12.46	90	59.50 ± 18.55	60
UPDRS II-5 speech	On-period	0.45 ± 0.74	91	1.48 ± 1.09	81
	Off-period	1.12 ± 0.95	90	1.81 ± 1.02	80
UPDRS III-18 speech	DOPA-OFF	0.79 ± 0.67	92	1.33 ± 0.87	90
	DOPA-ON	0.51 ± 0.63	91	1.18 ± 0.86	61
	Dopa effect (%)	36.61 ± 52.33	61	10.03 ± 38.86	54
UPDRS II-14 freezing	On-period	0.18 ± 0.47	83	0.45 ± 0.76	73
	Off-period	1.03 ± 1.19	83	1.07 ± 1.10	72
UPDRS III-28 posture	DOPA-OFF	1.38 ± 0.92	92	1.51 ± 0.97	90
	DOPA-ON	0.75 ± 0.74	91	1.00 ± 0.99	61
	Dopa effect (%)	46.70 ± 42.63	78	32.43 ± 41.51	52
III-29 postural stability	DOPA-OFF	0.79 ± 0.82	92	1.12 ± 0.96	90
	DOPA-ON	0.34 ± 0.48	91	0.58 ± 0.69	61
	Dopa effect (%)	55.74 ± 47.94	58	49.14 ± 44.30	49
UPDRS III-30 walk	DOPA-OFF	1.67 ± 1.04	92	1.67 ± 1.00	90
	DOPA-ON	0.30 ± 0.51	91	0.68 ± 0.73	61
	Dopa effect (%)	82.31 ± 28.22	84	57.93 ± 36.91	55

Table 2 Distributions of settings according to CB sub-aspects and patient CB (n =number of patient)

CB sub-aspects		<i>n</i>
Longitudinal position	Sym-post	47
	Sym-non-post	39
	Asym-L	6
Transversal position	Sym-suplat	71
	Sym-non-suplat	4
	Asym-T	17
STN relation	Sym-out	38
	Sym-non-out	41
	Asym-N	13
Patient CB		<i>n</i>
Symmetric	Post/suplat/out	21
	Non-post/suplat/non-out	20
	Post/suplat/non-out	12
	Non-post/suplat/out	7
	Post/non-suplat/out	3
	Non-post/suplat/non-out	1
	Total	64
Asymmetric	Asymmetric/asymmetric/asymmetric	4
	Asymmetric/asymmetric/out	4
	Asymmetric/suplat/asymmetric	4
	Asymmetric/suplat/non-out	3
	Asymmetric/suplat/out	3
	Non-post/asymmetric/asymmetric	3
	Non-post/asymmetric/non-out	2
	Non-post/asymmetric/out	1
	Non-post/suplat/asymmetric	1
	Post/asymmetric/non-out	1
	Post/asymmetric/out	1
Post/suplat/asymmetric	1	
Total	28	