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RESEARCH ARTICLE

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ABSTRACT: Background: Subthalamic nucleus deep brain stimulation (STN-DBS) effectively treats motor symptoms and quality of life (QoL) of advanced and fluctuating early Parkinson's disease. Little is known about the relation between electrode position and changes in symptom control and ultimately QoL.

Objectives: The relation between the stimulated part of the STN and clinical outcomes, including the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS) and the quality-of-life questionnaire, was assessed in a subcohort of the EARLYSTIM study.

Methods: Sixty-nine patients from the EARLYSTIM cohort who underwent DBS, with a comprehensive clinical characterization before and 24 months after surgery, were included. Intercorrelations of clinical outcome changes, correlation between the affected functional parts of the STN,

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and changes in clinical outcomes were investigated. We further calculated sweet spots for different clinical parameters.

Results: Improvements in the UPDRS III and Parkinson's Disease Questionnaire (PDQ-39) correlated positively with the extent of the overlap with the sensorimotor STN. The sweet spots for the UPDRS III ($x = 11.6$, $y = -13.1$, $z = -6.3$) and the PDQ-39 differed ($x = 14.8$, $y = -12.4$, $z = -4.3$) ~3.8 mm.

Conclusions: The main influence of DBS on QoL is likely mediated through the sensory-motor basal ganglia loop. The PDQ sweet spot is located in a posteroventral spatial location in the STN territory. For aspects of QoL, however, there was also evidence of improvement through stimulation of the other STN subnuclei. More research is necessary to customize the DBS target to individual symptoms of each patient.

Key Words: Parkinson's disease; deep brain stimulation; subthalamic nucleus deep brain stimulation; quality of life

Clinical experience has shown that deep brain stimulation of the subthalamic nucleus (STN-DBS) is an effective method for treating motor symptoms in Parkinson's disease (PD). Randomized controlled trials comparing STN-DBS to best medical treatment showed an improvement in motor symptoms between 28% and 41%[1] measured with the Unified Parkinson's Disease Rating Scale (UPDRS III) motor score without medication. Even the nonmotor symptoms that often occur in the context of PD can be improved by DBS[2]: 23% in the Non-Motor Symptoms Questionnaire and 33% in the Non-Motor Symptoms Scale.[3] Moreover, quality of life (QoL), a measure that summarizes various aspects of motor and nonmotor symptoms in the form of a self-assessment, improves significantly.[2-6] Although the positive effects of DBS on all these symptom domains could be demonstrated robustly, the question of the exact topography of the area to be stimulated remains elusive, especially for improvement in QoL. Sweet spots, defined as the optimal DBS target for motor symptoms, have been reported.[7-10] However, an optimal stimulation target associated for improvement in QoL has not been established so far. First data were provided by Dafsari and colleagues, who showed that an improvement in QoL depends on more anterior and ventral positioning of active contacts.[2] Further, Petry-Schmelzer and colleagues[3] showed an association between an improvement in mood and apathy as part of QoL and a stimulation in the ventral border region of the STN and within the sensorimotor STN. Because the STN resides at the intersection of Forel's and Meynert's axes,[11] the term "anterior/posterior" or "dorsal/ventral" is ambiguous. For this paper, as most reports in the neurosurgical literature, we adopt Forel's nomenclature, that is, refer to a superior (toward M1) position with the term "dorsal" and a frontal (toward the frontal pole) position with the term "anterior." Furthermore, it is crucial to note that there is no evidence of septa actually dividing the STN into motor, associative, or limbic domains; the cortical inputs of the structure rather result in a functional gradient that loosely follows its main axis.[11] When speaking of the sensorimotor/associative/limbic functional zones of the structure, we apply the parcellation defined (based on structural connectivity) in Ewert and colleagues.[12]

Here, we used data from the EARLYSTIM cohort[13] to investigate the relationship between the localization of the STN-DBS electrodes and improvement in clinical parameters, particularly QoL. The major advantage of this cohort over previously used (and mostly retrospective) cohorts[8,14-17] is the meticulous clinical characterization over a period of 2 years after stimulation. To examine the STN-DBS effect, we considered the clinical parameters that improved most with DBS, namely motor aspects and QoL. Although STN-DBS does not have a very strong effect on depressive symptoms, this symptom complex is clinically highly relevant for QoL aspects,[18] and therefore, we included it in our considerations. Furthermore, in individual patients, changes in depressive symptoms have been related to contact placement in the past.[19]

This study first aims at investigating whether stimulation of the sensorimotor STN is preferable to other STN subdivisions for improving not only motor symptoms but also the QoL. Second, it aims at defining sweet spots for improvement in QoL compared to the ideal stimulation position for improving motor aspects.

Patients and Methods

Study Design and Participants

We investigated a sample of 69 patients from the EARLYSTIM cohort, a multicenter, randomized controlled trial conducted in France and Germany.[13] The original study cohort recruited 251 patients (age <61 years) with PD with a minimum disease duration of 4 years, disabling motor fluctuations lasting for up to 3 years, and at least 50% levodopa responsiveness randomized for STN-DBS or best medical treatment. Of the 124 implanted patients, 69 patients from 12 centers had accessible and technically complete pre- and postoperative imaging (preoperative T1-weighted image and a postoperative magnetic resonance imaging or

computed tomography with sufficient image quality for localization of the electrodes) and clinical assessment. Postoperative scans were acquired within 1 week after surgery. The stimulation target was chosen by each center according to its best medical practice. The algorithm for optimizing the stimulation parameters has been published elsewhere.[20] The primary outcome for the optimization was an improvement due to motor aspects. The detailed study protocol of the EARLYSTIM has been published previously.[21] The ethics committee of the Kiel Medical Faculty (CAU) approved the study protocol (A 121/06) and the specific subproject reported here (D 492/19). All patients provided written informed consent before randomization.

Clinical Assessment

Clinical assessments were performed before surgery in an off-medication state and at 24 months follow-up, including the UPDRS (UPDRS II—worst condition; UPDRS III—Med off/Stim ON; UPDRS IV), the time spent with good mobility and without troublesome dyskinesia (ON-time without dyskinesia) and depressive symptoms through the Beck's Depression Inventory (BDI) II score and the Montgomery–Åsberg Depression Rating Scale (MADRS). The levodopa equivalent daily dose (LEDD) was calculated following the approach of Tomlinson and colleagues.[22] The summary index of the Parkinson's Disease Questionnaire (PDQ-39_SI) was used to measure aspects of QoL.

DBS Electrode Localization and Estimation of the Stimulation Volumes

Image preprocessing (coregistration, normalization, and brainshift correction) and DBS electrode localization have been performed using the Lead-DBS toolbox (http://www.lead-dbs.org[15]). The electric fields and the stimulation volumes derived from these were estimated in native space and transferred to Montreal

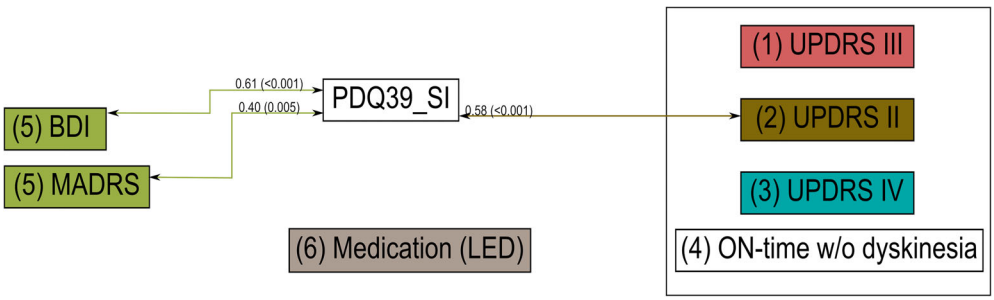

FIG. 1. Intercorrelation structure and FDR-corrected *P*-values (in brackets) of changes in motor aspects following STN-DBS with changes in life quality. Two groups of outcomes affect quality of life (QoL): motor disease severity and depressive symptoms. Only significant correlations ($P < 0.05$, FDR corrected) with QoL are shown. For other correlations, see Supplementary Table S1. Spearman's correlation coefficients are given. BDI, Beck's Depression Inventory; FDR, false discovery rate; LED, levodopa equivalent dose; MADRS, Montgomery–Åsberg Depression Rating Scale; PDQ, Parkinson's Disease Questionnaire; QoL, quality of life; SI, summary index; STN-DBS, subthalamic nucleus deep brain stimulation; UPDRS, Unified Parkinson's Disease Rating Scale.

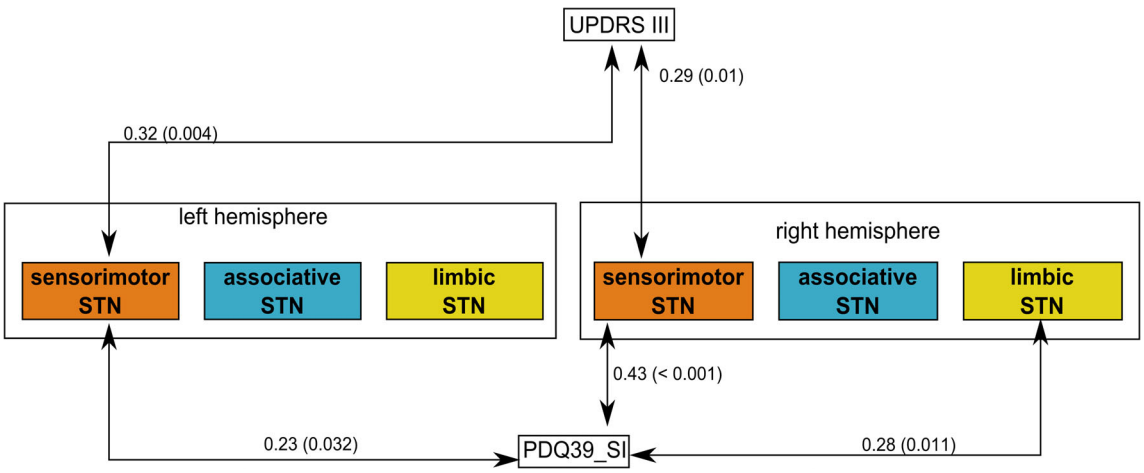

FIG. 2. Schematic representation of significant correlations between stimulation volume-STN overlaps and improvements in motor function (UPDRS III) and QoL (PDQ-39_SI numbers represent Spearman's correlation coefficients and permuted *P*-values [in brackets]). A correlation matrix showing the same data can be found in Appendix S1. PDQ, Parkinson's Disease Questionnaire; QoL, quality of life; SI, summary index; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 1 *Baseline characteristics and means (±SD) of clinical scores at baseline and 24 months follow-up of the sample analyzed here (DBS cohort, n = 69) and of the excluded patients from the EARLYSTIM cohort (n = 55)*

	Included patients (n = 69)			Excluded patients (n = 55)	
	Mean ± SD or number of patients (d)	Absolute improvement (*P*-value)	Percentage improvement		Difference between groups
Age (y)	52.8 ± 6.8			53.4 ± 6.33	0.669[a]
Gender—number (%)					0.834[b]
Male	53 (76.8)			41	
Female	16 (23.2)			14	
Duration of Parkinson's disease (y)	7.4 ± 3.2			7.3 ± 2.7	0.653[a]
Dyskinesia					
Number of patients (%)	43 (62.3)			41	0.178[b]
Motor fluctuations					
Number of patients (%)	68 (98.5)			53	0.584[b]
Treatment with levodopa					
Number of patients (%)	62 (89.9)			49	1.00[b]
Duration (y)	4.9 ± 3.8			4.5 ± 2.6	0.917[a]
Levodopa equivalent daily dose (mg)					
Baseline	897 ± 385	379 (<0.001[c])	42.3	946 ± 447	0.525[c]
24 months follow-up	518 ± 326				
Treatment with dopamine agonist					
Number of patients (%)	64 (92.8)			54	0.226[b]
Duration (y)	6.1 ± 3.2			5.8 ± 2.8	0.821[a]
UPDRS II (worst condition)					
Baseline	15.8 ± 6.6	4.8 (<0.001[a])	30.4	14.2 ± 5.4	0.231[a]
24 months follow-up	11.0 ± 5.2				
UPDRS III					
Baseline (Med off)	35.3 ± 10.8	17.7 (<0.001[c])	50.1	31.7 ± 11.9	0.091[c]
24 months follow-up (Med off/Stim ON)	17.6 ± 9.8				
UPDRS IV					
Baseline	5.4 ± 3.0	3.0 (<0.001[a])	55.6	6.1 ± 3.4	0.354[a]
24 months follow-up	2.4 ± 1.9				
ON-time[a]					
Baseline	10.8 ± 4.6	−2.0 (0.014[c])	18.5	9.8 ± 4.7	0.272[c]
24 months follow-up	12.8 ± 4.4				
MADRS					
Baseline	7.7 ± 6.6	0.6 (0.407[a,e])	7.8	5.9 ± 4.6	0.252[a]
24 months follow-up	7.1 ± 5.8				

(Continues)

TABLE 1 *Continued*

	Included patients (n = 69)			Excluded patients (n = 55)	
	Mean ± SD or number of patients (d)	Absolute improvement (*P*-value)	Percentage improvement		Difference between groups
BDI					
Baseline	10 ± 6.1	1.0 (0.308[a,e])	10	10 ± 4.7	0.801[a]
24 months follow-up	9 ± 6				
PDQ-39_SI					
Baseline	28.5 ± 13.4	4.6 (0.049[c])	16.1	32.2 ± 12.9	0.117[c]
24 months follow-up	23.9 ± 13.4				

Improvements after STN-DBS are given as absolute and percentage values for the subgroup analyzed in this study.
[a]*P*-value of Wilcoxon test.
[b]*P*-value of Fisher's test.
[c]*P*-value of *t* test.
[d]ON-time without troublesome dyskinesia.
[e]Intragroup changes only. Compared with the best medical treatment group, the difference is significant.
Abbreviations: SD, standard deviation; DBS, deep brain stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; BDI, Beck's Depression Inventory; PDQ, Parkinson's Disease Questionnaire; SI, summary index.

Neurosciences Institute (MNI) space based on the individual optimized stimulation parameters using a finite element method approach established within the SimBio-FieldTrip pipeline.[14] A detailed description of this pipeline can be found in Appendix S1.

Quantification of Neuroanatomical Placement and Sweet Spot Calculation

As a quantification for the neuroanatomical placement of DBS electrodes, we calculated the overlaps between individual stimulation volumes and the atlas-defined STN[12] as implemented in Lead group[23] separately for the left and the right hemispheres.

The sweet spot calculation is based on an effect image (=stimulation volumes × absolute clinical improvement) and a voxel-wise one sample *t* score to estimate the degree to which the particular voxel would account for clinical improvement (*t*-image). Only voxels covered by at least 10 stimulation volumes were retained in the model. Rather, we aimed to provide a weighted map of clinical effects that was rather inclusive and then validated the map on out-of-sample (unseen) data points by applying leave-one-out cross-validation. To analyze both sensitivity and specificity of the leave-one-out cross-validation approach for our sweet spot models, we calculated the receiver operator characteristic (ROC) curve across specific sweet spot thresholds. A detailed description of this pipeline can be found in Supplementary Material S2.

Statistical Analysis

The strongest contrast for clinical outcomes is a comparison of the preoperative medication-off and the postoperative medication-off and stimulation-on situation. We chose this contrast because the postoperative medication off/Stim ON state is the one that our patients experience as the worst in real life, as the stimulator is not switched off after successful implan2wtation. For the clinical baseline, follow-up, and improvement scores that were not normally distributed, we used nonparametric procedures (Shapiro–Wilk tests), otherwise *t* tests. We calculated Spearman's correlation coefficients between clinical improvement scores and performed a false discovery rate correction[24] adjusting the *P*-values for 28 tests (see Supplementary Table S1; Fig. 1). Correlation coefficients between the overlap of stimulation volume and STN atlases and clinical improvement scores were calculated using Spearman's rho and tested for significance using permutation tests (see Supplementary Table S2; Fig. 2). An α level of 0.05 was chosen. Sweet spot analysis (*t* test) was validated through a leave-one-patient-out correlation (see sweet spot calculation) with permutation test. All statistical analyses were conducted using R statistics (version 3.3.1[25]).

Results

Patient Characteristics

In this study, we included 69 patients (53 men) with idiopathic PD from the EARLYSTIM cohort, who

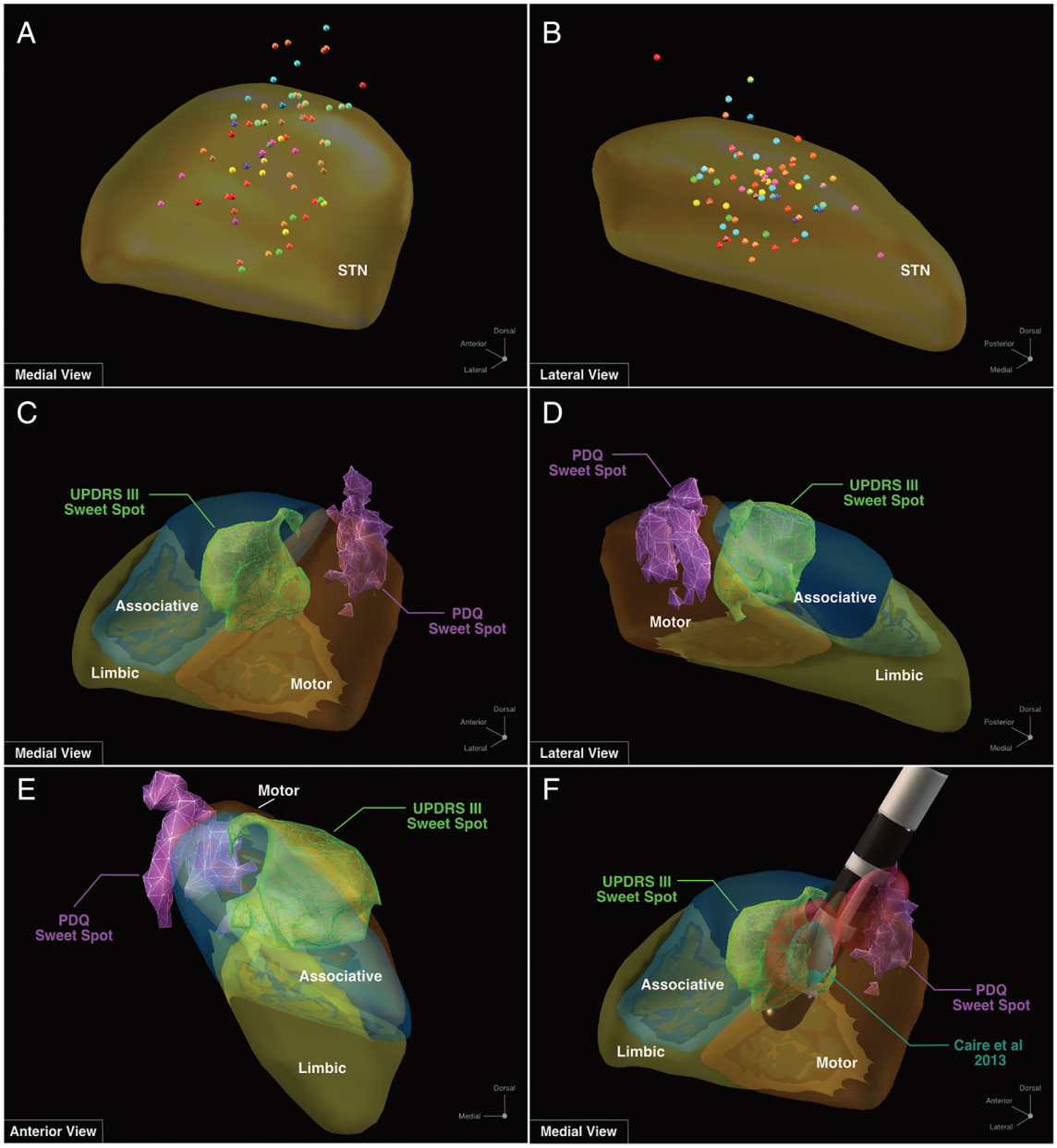

FIG. 3. Distribution of the active contacts colored for the different centers in a (**A**) medial and (**B**) lateral view. Sweet clusters (maximum 15% of the *t*-values) for UPDRS III (green blob) and PDQ-39_SI (purple blob) exemplary in the right hemisphere in a (**C**) medial, (**D**) lateral, and (**E**) anterior view. Comparing our motor sweet spot to sweet spots published previously, we found high agreement and small distances between them. As an example, we show the motor sweet spot defined by us and the coordinate calculated in a meta-analysis by Caire et al[31] (**F**) together with an exemplary directional electrode with two simulated volumes stimulating both sweet clusters. The Euclidian distance between their midpoints was 1.04 mm. PDQ, Parkinson's Disease Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale.

underwent STN-DBS. We had to exclude 55 patients of the original per-protocol population (n = 124) because of lack of access to the imaging or clinical data (N = 43) or insufficient pre- or postoperative imaging quality (N = 12). Demographic characteristics and a comparison between the subgroup included here and the excluded patients are summarized in Table 1. We found no significant differences between the groups and can therefore assume that the cohort analyzed here represents the entire EARLYSTIM cohort. All clinical scores except the BDI and MADRS score showed a significant improvement after STN-DBS.

Improvement in Clinical Outcomes and Their Intercorrelations

Outcomes with a high clinical relevance which are known to undergo significant changes with DBS and which are surrogates for different behavioral domains were selected: we found a significant improvement for

TABLE 2 *Sweet spots for the clinical improvement scores and correlation coefficients of the leave-one-patient-out cross-validation method.*

	Left hemisphere						Right hemisphere					
	Sweet spot results				Cross-validation results		Sweet spot results				Cross-validation results	
	X	*y*	*z*	*t*	R	*P*	*x*	*y*	*z*	*t*	R	*P*
UPDRS II	−14.7	−12.6	−4.3	5.88	**0.28**	**0.009**	15.0	−10.9	−3.7	4.92	0.00	0.482
UPDRS III	−12.3	−13.1	−7.2	9.30	**0.28**	**0.005**	11.6	−13.1	−6.3	8.27	**0.19**	**0.049**
UPDRS IV	−12.5	−12.8	−7.0	6.47	0.08	0.238	12.6	−11.5	−6.7	5.19	0.04	0.364
ON-time[a]	−9.4	−12.8	−1.9	1.71	−0.40	0.001	14.1	−13.7	−9.6	1.44	−0.28	0.015
MADRS	−14.9	−16.8	−8.7	2.37	0.01	0.451	11.7	−16.1	−12.5	2.24	−0.41	0.001
BDI	−13.6	−14.2	−11.6	2.33	−0.15	0.104	14.8	−12.2	−5.2	3.02	−0.05	0.329
LEDD	−13.6	−9.8	−4.8	3.29	−0.12	0.202	11.0	−12.2	−7.4	2.66	−0.18	0.108
PDQ-39_SI	−13.6	−13.7	−2.8	4.18	0.10	0.206	14.8	−12.4	−4.3	5.72	**0.26**	**0.013**

Here, we report the *P*-values of permutation tests. Significant values ($P < 0.05$) are printed in bold. Note that in a leave-one-out cross-validation design, negative correlation coefficients are not meaningful (represents a null finding) and were therefore not FDR corrected. Coordinates are reported in MNI space.

[a]ON-time without troublesome dyskinesia.

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; BDI, Beck's Depression Inventory; LEDD, levodopa equivalent daily dose; PDQ, Parkinson's Disease Questionnaire; SI, summary index; FDR, false discovery rate.

motor symptoms (UPDRS III, UPDRS II, ON-time without dyskinesia), LEDD and PDQ-39_SI (Table 1). Clinical scores for depression (BDI and MADRS) were added as they were significantly improved compared to the best medical treatment for the whole EARLYSTIM cohort[13] and as depression has consistent influence on QoL.[26]

The intercorrelations between clinical improvement scores (Fig. 1; Supplementary Table S1) suggested a complex interaction: UPDRS subscales were intercorrelated except for complications in therapy not being correlated with disease severity. This is meaningful, as the two aspects are not necessarily related at this stage of disease severity. It is also tempting to look at the variables that do not correlate. First, ON-time without dyskinesia and LEDD reduction did not correlate with any of the other variables. Second, the two depression parameters did not correlate with the UPDRS subscales (except for a significant correlation between the MADRS and UPDRS II) and ON-time without dyskinesia. This suggests that the change in the two behavioral dimensions, motor disease severity and mood, was not closely related, in agreement with prior results.[19]

Because of the multicenter nature of this study, we used a univariate ANOVA (one-way analysis of variance) to examine systematic differences between centers in LEDD reduction and UPDRS III. To ensure the robustness of the ANOVA, we included only centers with more than 4 subjects. No significant differences were found (LEDD: F6, 49 = 1.302, $P = 0.274$; UPDRS-III: F6, 50 = 1.396, $P = 0.235$).

Correlation between Clinical Improvements and DBS Localization

We hypothesized that the influence of DBS on the different outcomes could have been mediated by modulating one or more of the subdivisions of the STN, namely the sensorimotor, associative, and limbic functional zones that are integrated into the three cortex-basal ganglia loops. We must emphasize that in reality, the basal ganglia loops rather work along a gradient/continuum and loops are highly interconnected on multiple levels—but the applied model of three divisions would still serve as a useful simplified model here. Therefore, we used the tripartite separation of the STN into its subareas[12] and studied the correlation of the overlap of the individual stimulation volume with the anatomical target area (Supplementary Table S2). We found significant correlations between the extent of the overlap with the sensorimotor STN and the improvement along the UPDRS III (left: r = 0.32, $P = 0.004$; right: r = 0.29, $P = 0.010$) and the PDQ-39 SI (left: r = 0.23, $P = 0.032$; right: r = 0.43, $P < 0.001$). The correlation between the improvement in the UPDRS II and the sensorimotor STN overlap was significant only when both hemispheres were included (r = 0.21, $P = 0.044$). The overlap with the limbic STN was significantly correlated with the PDQ-39_SI (r = 0.28, $P = 0.011$) for the right hemisphere (Fig. 2; Supplementary Table S2).

- As observed in Figure 3, the vast majority of active contacts are within or very close to the boundary of the STN. There were no active contacts placed in

Substantia nigra pars reticulata (SNr) and very few above the STN but still within an acceptable distance.

Sweet Spots

Table 2 presents the peaks of sweet spot areas. We found significant out-of-sample correlations between the predicted average *t* score and the clinical improvement scores for UPDRS III in both hemispheres (left: $R^2 = 0.28$, $P = 0.005$; right: $R^2 = 0.19$, $P = 0.049$) as well as for PDQ-39_SI for the right hemisphere (PDQ_SI: $R^2 = 0.26$, $P = 0.013$) and for UPDRS II for the left hemisphere ($R^2 = 0.28$, $P = 0.009$) (Table 2). The peak maxima of *t*-maps (sweet spots) for UPDRS III and PDQ-39 differed on the left side by 4.6 mm and on the right side by 3.8 mm. Figure 3 shows the position of the two clusters in the right hemisphere that are close to the border between the motor and associative zones (ie, corresponding to a premotor location) and within the center of the motor area, respectively. ROC curve revealed an area under the curve of 0.64 and 0.57 for the right and left sweet spot models of PDQ, respectively, whereas for UPDRS these were 0.58 and 0.66, respectively, for the right and left sweet spot models.

Discussion

QoL is influenced by many factors. The aim of this study was to better understand the role of the DBS-electrode location for changes in motor severity (UPDRS III) and QoL (PDQ-39). We calculated the sweet spots of STN-DBS effects for the two outcome parameters of the EARLYSTIM cohort, investigated the relationship between the overlap of individual stimulation volumes and functional subzones of the STN and various clinical improvement scores, and inferred that the larger the stimulated part of the sensorimotor STN is, the higher is the improvement in motor severity and QoL.

Relationship between Changes in Clinical Parameters Due to DBS

The relationship between changes in the clinical parameters through DBS does not seem to be well investigated, as usually only the relationships at baseline are analyzed.[18,27] However, some studies have also looked for the correlations between the changes in the clinical parameters. These showed low[28] to moderate[17] correlations between the overall QoL and the UPDRS III. Due to the finding that the effect of DBS on disease severity is not very strongly associated with a change in QoL, it makes sense to consider these two very important parameters for the patient separately when analyzing the effect of DBS.

Electrode Placements Influence Motor Aspects and Quality of Life

Certainly, clinicians would like to know the most efficient spot for stimulation. If different spots have different effects, they would like to choose for individualized treatment, by either electrode placement or DBS programming. Indeed, the analysis of the relationships between different improvement scores has shown that, at the individual patient level, STN-DBS does not affect all parameters in the same direction and with the same intensity. In our study, UPDRS III and QoL were influenced by the topographic distribution of the stimulation volumes with respect to the STN anatomy. For motor improvements, this has been shown repeatedly,[9,14,17,29,30] and sweet spots defined for the best improvement in motor aspects, including the one we defined here, fall closely together.[7,9,31] Similarly, our results suggest that the extent of an improvement in disease severity (UPDRS III) was mainly influenced by stimulation of the sensorimotor STN area. Overlaps with other parts of the STN had no statistical relationship with improvement in motor symptoms. As previously reported in most studies,[9,31,32] the sweet spot related to motor symptoms was within the premotor functional zone of the STN, which would correspond to cortical input by the supplementary motor area.[15,23] We must emphasize that in reality, the basal ganglia loops rather work along a gradient/continuum and loops are highly interconnected on multiple levels. Instead, the functional zones of the STN should be considered as a continuum with cross talk between loops on inter alia, cortical, striato-cortical, thalamo-cortical, and nigro-striatal levels. In the classical anatomical literature, a parcellation into five regions (premotor and oculomotor zones) has conventionally been described.[33] However, the STN receives input from almost all regions of the frontal cortex and even from the primary sensory cortex in its most posterior part.[34]

For nonmotor parameters, there is also early evidence for a valid relationship between the stimulated STN part and the amount of clinical improvement.[2,3] However, the evidence is far from being as advanced as for the relationship between the stimulated STN part and improvement in motor aspects of the disease. Furthermore, some reports associated changes in nonmotor symptoms with stimulating the sensorimotor STN,[35,36] potentially because the motor loop is most affected in early PD and DBS has the strongest effect on affected circuits. Therefore, by rebalancing the affected motor loops, nonmotor effects could emerge due to the aforementioned cross talk between loops.[35]

Furthermore, modulating the anterior regions of the left STN has been associated with a detrimental effect on mood, whereas modulating the same site on the right hemisphere, as well as modulating the motor circuits on both sides, was associated with beneficial

effects on mood.[19] In agreement with these findings, the optimal stimulation site corresponding to improvements in QoL we estimated here resided within the right sensorimotor part of the STN. This is consistent with the finding of a lateralization toward the nondominant brain hemisphere for emotional processing.[37] Again, this site corresponds precisely to the loop that is most affected in (especially early-stage) PD and to the region in which most elevated pathological β-power has been reported.[10] Again, alluding to the notion that only what is broken can be fixed, modulating the most affected loop could lead to the best overall improvement in symptoms and associated benefits in QoL.[36] In agreement, a previous study investigated the interaction between the stimulation site and mood and apathy, whereby especially aspects of mood are included in the PDQ, and concluded that above-average improvement in these symptoms could be observed at within the sensorimotor parts of the STN.[3] Instead, improvements in neither mood/apathy, attention/memory, nor sleep/fatigue were associated with more antero-medial stimulation sites (associate/limbic domains). Again, our sample consists of patients in the early stages of the disease, and it has been concluded previously that the sensorimotor loop degenerates first in PD.[38,39] Because DBS presumably mainly improves loop functions whose related nigral cells have already started to degenerate, here, we add to the accumulating evidence that the optimal target for improving nonmotor symptoms is also located in the motor part of the STN (references 3,42; for a summary of this line of reasoning, see reference 41). For instance, Irmen et al reported that STN-DBS to the motor functional zone not only improved PD motor symptoms but also normalized overly risk-averse decision behavior in PD.[36] Further, there is evidence that stimulation of the nonmotor parts of the STN may lead to cognitive and neuropsychiatric *disturbances* rather than improvements.[40-42] Therefore, at this stage of the research, we conclude that stimulation of the sensorimotor STN increases the perceived QoL. This hypothesis could be supported by analyzing larger cohorts of patients, with some of them having their stimulated contacts within the nonmotor regions and thus would have less improvement in their nonmotor functions (or even nonmotor disturbances). Another aspect to be discussed is a possible selection bias of those patients considered for DBS. An indication for DBS is given only if a patient is severely affected motor-wise and medical treatment does not provide sufficient improvement. The presence of nonmotor symptoms that significantly affect QoL is therefore not a necessary condition for DBS and not present in all patients.

Limitations

Patients included in our study are in a relative early stage of the disease. This must be considered when interpreting the results of this study. Therefore, to confirm the interpretations, it is essential to replicate the results in a sample stimulated at an advanced stage of the disease. Even better would be a prospective study of a large sample to increase the chance for a subsample of patients with a more antero-ventro-medial contact stimulation. This could be used to systematically compare the differences in the DBS effect on the various outcome parameters.

In the past, different methods to calculate sweet spots for clinical outcomes have been used (references9 and[43-46]; for an overview, see reference 47). Here, we chose a comparatively simple weighting method (by calculating *t* scores against zero) but used it to cross-predict out-of-sample results not observed by the model (leave-one-out cross-validation design).

Electrode localizations from neuroimaging data (which in our case were heterogeneous and collected at different centers) are subject to slight inaccuracies resulting from brain shift, coregistration processes, and similar neuroimaging problems.[32] We applied a modern pipeline, specifically created for electrode localizations, that aims at addressing these issues using strategies such as multispectral normalization,[48] phantom-validated electrode localizations,[49] and correction for brain shift.[15] However, despite these efforts, a certain degree of inaccuracy must be assumed.[50]

We describe a similar sweet spot location as most other studies for the motor aspects of PD (for a recent review, see reference 36). New methods of sweet spot calculation have recently been proposed, and future studies may further refine our findings and compare statistical methods to the one applied here. Statistically, a *t* test model comparing to zero has been criticized, in the past, because most patients improve and, therefore, *t*-values will always be positive.[47] However, because we used the *t*-values only as a surrogate parameter for our maps and not as an indicator of voxel-wise statistical significance, this problem is only of little importance.

The applied model for calculating the stimulation volumes is considered rather simple in comparison to more elaborate axon-cable-based or pathway-activation-based concepts.[51,52] Although more elaborate models have recently been introduced within the field of open-source research,[53] at present, our methodology is limited to estimating the stimulation volume based on the electric field norm (for a comparison of stimulation volume shapes using different models including our approach, which represents a good first-order approximation, see reference 54).[54]

Motor as well as nonmotor symptoms contribute to QoL.[55,56] It has been shown that nonmotor symptoms are even strongly correlated to QoL than motor symptoms[18,57]: urinary symptoms, sleep, and fatigue, which are not covered by our scales, significantly contribute to

QoL[56] EARLYSTIM did not assess nonmotor symptoms with an adequate scale[58] as this was not yet available at the time of the study planning. However, having detailed data on these aspects would possibly help explain a larger part of the QoL changes and thereby might better help explain the sweet spot relations.

Finally, our results stem from an exploratory post hoc analysis of data prospectively collected in a randomized trial. Imaging data could not be retrieved from all patients, so a subset is analyzed here. Multiple outcome parameters were related to electrode placement and stimulation volumes, leading to multiple comparisons. Effect sizes of expected relationships between clinical outcomes and placement were not clear up front, so only post hoc power calculations could be performed.

Conclusion

The study suggests that the improvement in QoL of PD with STN-DBS is mediated mainly through stimulating the sensory-motor loop of the basal ganglia in early PD with fluctuations. However, the sweet spot for QoL is still different from the one for motor symptoms measured with the UPDRS III and is located in a posteroventral spatial location in the STN territory. This location represents the center of the STN. This may indicate that stimulation of other loops than the sensory motor is additionally involved. This needs confirmation by independent cohorts. If confirmed, a different stimulation point to specifically improve different aspects of QoL would be a valuable tool for this treatment.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author (acting on behalf the Earlystim steering committee) upon reasonable request.

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Supporting Data

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