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Intraoperative Local Field Potential Beta Power and Three-Dimensional Neuroimaging Mapping Predict Long-Term Clinical Response to Deep Brain Stimulation in Parkinson Disease: A Retrospective Study

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ABSTRACT

Background: Directional deep brain stimulation (DBS) leads allow a fine-tuning control of the stimulation field, however, this new technology could increase the DBS programming time because of the higher number of the possible combinations used in directional DBS than in standard nondirectional electrodes. Neuroimaging leads localization techniques and local field potentials (LFPs) recorded from DBS electrodes implanted in basal ganglia are among the most studied biomarkers for DBS programing.

Objective: This study aimed to evaluate whether intraoperative LFPs beta power and neuroimaging reconstructions correlate with contact selection in clinical programming of DBS in patients with Parkinson disease (PD).

Materials and Methods: In this retrospective study, routine intraoperative LFPs recorded from all contacts in the subthalamic nucleus (STN) of 14 patients with PD were analyzed to calculate the beta band power for each contact. Neuroimaging reconstruction obtained through Brainlab Elements Planning software detected contacts localized within the STN. Clinical DBS programming contact scheme data were collected after one year from the implant. Statistical analysis evaluated the diagnostic performance of LFPs beta band power and neuroimaging data for identification of the contacts selected with clinical programming. We evaluated whether the most effective contacts identified based on the clinical response after one year from implant were also those with the highest level of beta activity and localized within the STN in neuroimaging reconstruction.

Results: LFPs beta power showed a sensitivity of 67%, a negative predictive value (NPV) of 84%, a diagnostic odds ratio (DOR) of 2.7 in predicting the most effective contacts as evaluated through the clinical response. Neuroimaging reconstructions showed a

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sensitivity of 62%, a NPV of 77%, a DOR of 1.20 for contact effectivity prediction. The combined use of the two methods showed a sensitivity of 87%, a NPV of 87%, a DOR of 2.7 for predicting the clinically more effective contacts.

Conclusions: The combined use of LFPs beta power and neuroimaging localization and segmentations predict which are the most effective contacts as selected on the basis of clinical programming after one year from implant of DBS. The use of predictors in contact selection could guide clinical programming and reduce time needed for it.

Keywords: Deep brain stimulation (DBS), directional leads, local field potentials (LFPs), neuroimaging, subthalamic nucleus

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Deep brain stimulation (DBS) with target in the subthalamic nucleus (STN), is more effective than medications alone in patients with advanced Parkinson disease (PD) in controlling motor symptoms and in terms of quality of life.[1] Moreover, patients may benefit from DBS even with a short disease duration if complications occur.[2] Since the first evidence of efficacy of stimulation at high frequency of the thalamic ventral intermedius in suppressing parkinsonian tremor, which marked the beginning of the modern era of DBS,[3] the technology behind DBS has seen an incredible amount of progress. Advances in technologies concern electrode configurations, current delivery method, types of stimulation, and parameters of stimulation.[4–6] A new frontier of DBS is the directional stimulation provided by directional electrodes. These types of leads have radially segmented contacts that allow the stimulation field to be moved in the horizontal plane or shaped using anodes and cathodes to steer the current in a specific direction. The more versatile shaping of the electrical field widens the therapeutic window, reduces the current needed for therapeutic effects, and allows a more precise tailoring of the stimulation parameters.[7,8] On the contrary, this new technology could increase the DBS programming time because of the higher number of the possible combinations than in the standard nondirectional electrodes.[9] The clinical programming of DBS is a time-consuming, trial and error process because the monopolar evaluations of each contact's therapeutic window still represent the gold standard in initial programming.[10] Considering the use of directional electrodes, eight contacts per hemisphere, 16 total contacts, 12 of which are segmented, the number of possible combinations in terms of contact selections and stimulation parameters exponentially increases. The lack of guidelines is another issue in clinical programming, indeed only algorithms shared by DBS center are available.[10,11] Hence, professional experience plays a fundamental role in clinical programming. The risk of suboptimal programming is to classify patients as nonresponders but not all possible combinations have been tested because of the limited time availability. Therefore, the use of methods that can guide the neurologist in the programming phase to optimize the time needed and improve symptom controls could be an important support to clinical practice and can lead to improvements in terms of patient outcomes. Traditionally, local field potentials (LFPs) recorded from DBS electrodes implanted in basal ganglia were among the most studied electrophysiological biomarkers for DBS programming. STN LFPs beta power is related to hypokinetic motor state, and both dopaminergic medication and high frequency DBS can suppress this pathologically enhanced activity in patients with PD.[12–15] Moreover, LFPs predict the most efficient stimulation contacts and may provide a useful tool to facilitate the selection of the optimal contact for directional DBS.[16] Neuroimaging reconstructions and localizations of DBS leads allow to localize the contacts with respect to the anatomy of basal ganglia of the patients and to discriminate which contacts are localized within the STN. The anatomical localization of DBS contacts provide useful information about the effective contacts for clinical programming.[17] Research is focusing on defining biomarkers to guide DBS programming in patients with PD, with the LFPs power and the neuroimaging reconstruction being the most suitable for this purpose.[18,19] This retrospective study aimed to evaluate whether the combination of LFP beta power and neuroimaging reconstructions can provide useful information for contact selection for DBS programming in patients with PD.

MATERIALS AND METHODS

We designed a multicenter, observational, retrospective study. We retrospectively enrolled patients from the Outpatients Movement Disorder Clinic of A. Gemelli University Hospital Foundation IRCSS, Campus Bio-Medico University Hospital Foundation, University of Rome "Tor Vergata", IRCCS Neuromed Institute, and St John the Baptist Hospital according to defined inclusion and exclusion criteria. The study was approved by the institutional review board of A. Gemelli University Hospital Foundation IRCSS. In this retrospective study, patients underwent standard clinical practice and the data that were available according to standard

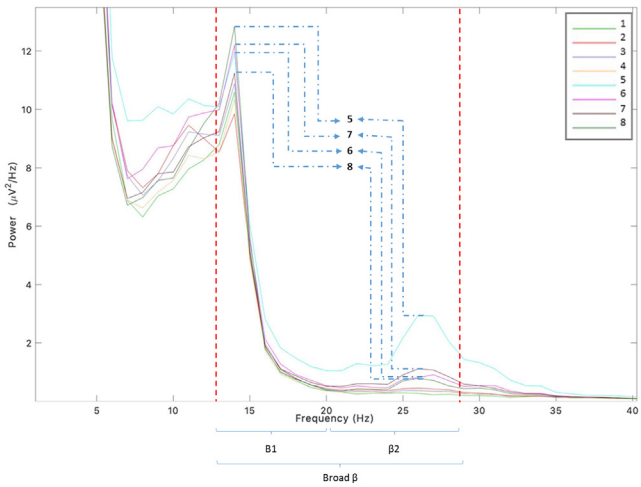

Figure 1. Representation of LFPs power registered from each of the eight contacts of the right lead in patient 3. The dashed red lines delimit the broad beta band (13–29 Hz); within this range, the first four contacts with the highest beta power were selected (5-7-6-8) to evaluate the predictive value for clinical programming. [Color figure can be viewed at www.neuromodulationjournal.org]

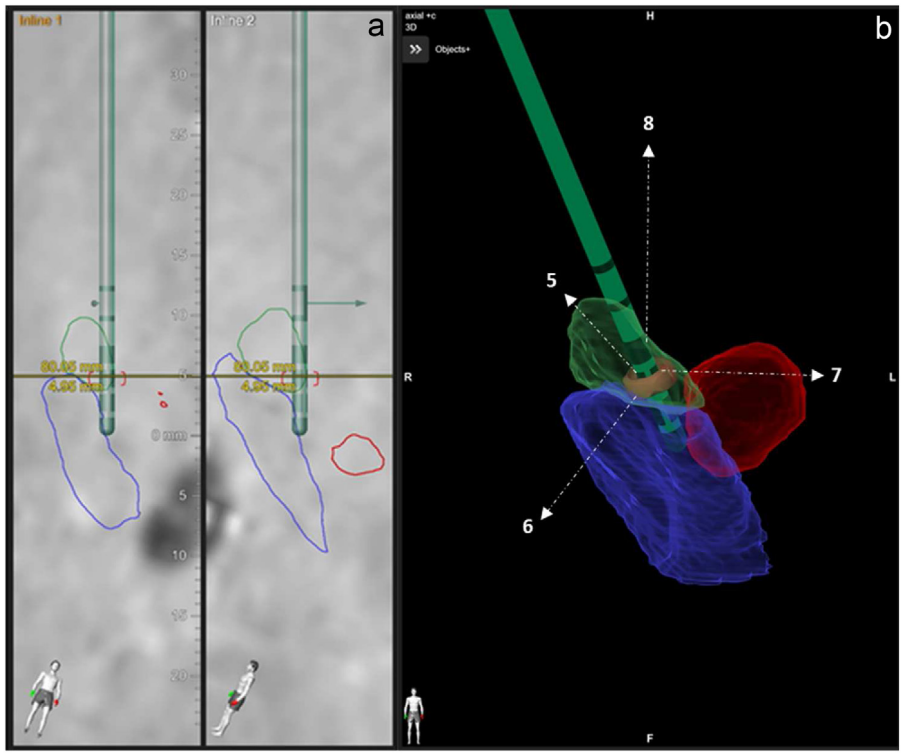

Figure 2. Reconstruction, using Brainlab, of the right lead position in patient 3. This image represents the position of right lead and position of the eight contacts with respect to the anatomical reconstruction of patient's basal ganglia anatomy. Contacts number 5-6-7-8 are positioned within the subthalamic nucleus. a. Reconstruction of lead position through elements anatomical mapping. b. Lead and contact position in the 3D anatomical reconstruction of basal ganglia anatomy. Green: subthalamic nucleus, red: red nucleus, blue: SNr substantia nigra. [Color figure can be viewed at www.neuromodulationjournal.org]

clinical practice were analyzed. Inclusion criteria were diagnosis of idiopathic PD according to the UK Brain Bank criteria, ongoing treatment with bilateral DBS of the STN, availability of LFPs intraoperative recordings, and availability of parameters of stimulation after one year from implant. Exclusion criteria were unavailability of intraoperative registrations of LFPs beta power and unavailability of parameters of clinical programming after one year from implant.

The type of IPG DBS system implanted was Boston Vercise (Boston Scientific Corporation, Marlborough, MA) octopolar directional model DB2202 for all patients, with the exception of patient 14's left lead, which was a linear octopolar lead. LFP recordings were made with Micromed (Micromed S.p.A., Treviso, Italy) SystemPLUS 98 and Micromed sam32FO cartridge. The duration of the recorded LFP signal was of 180 seconds for each patient. During DBS surgery LFPs were recorded from all contacts. The cannula was used as a common reference and LFPs were recorded from all contacts with a monopolar configuration. Signals were recorded for seven patients under general anesthesia and for the remaining seven patients during awake surgery.

The LFPs analysis was performed using the Brainstorm Toolbox in Matlab[20] (The Math Works Inc, Natick, MA) and in-house Matlab code. Offline data preprocessing was performed using Brainstorm and included 1) visual inspection for rejection of possible artefactual activity; 2) DC removal; 3) 50-Hz notch filter; and 4) bandpass filter between 1 and 150 Hz (linear phase finite impulse response filter). We computed the normalized power spectrum density through standard fast Fourier transform approach (Welch procedure: average of nonoverlapped windows with a duration of 2 seconds) for the following frequency bands: 1) delta: 2 to 4 Hz; 2) theta: 5 to 7 Hz; 3) alpha: 8 to 12 Hz; 4) beta1: 13 to 20 Hz; 5) beta2:

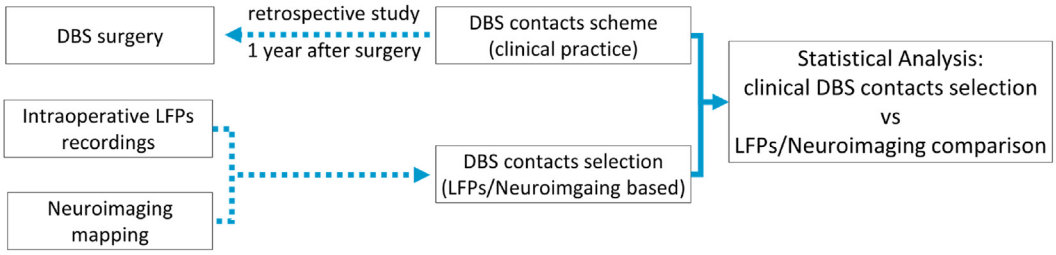

Figure 3. Study scheme. Data were analyzed retrospectively after 1 year from DBS surgery. Contacts selected in the clinical practice were compared with the contacts showing the highest beta band power in the intraoperative LFPs recording and with the contacts localized within the STN in the neuroimaging reconstruction. [Color figure can be viewed at www.neuromodulationjournal.org]

Table 1. Patient's Characteristics: Age, Disease Duration, Hoehn and Yahr Stage, Type of Anesthesia During the Registration of LFPs in Enrolled Patients, and Preoperative and Postoperative Unified Parkinson's Disease Rating Scale part III (UPDRS III) Score Under Different Conditions.

ID	Age, y	Disease duration, y	Hoehn and Yahr Stage	General anesthesia	UPDRS III							
					Preoperative				Postoperative			
					OFF-MED	ON-MED	OFF-MED	OFF-STIM	OFF-MED	ON-STIM	ON-MED	OFF-STIM	ON-MED	ON-STIM
1	55	11	3	No	52	19	N/A		N/A		N/A		16	
2	58	12	2	No	N/A	N/A	20		16		16		14	
3	56	14	3	Yes	49	25	63		47		36		33	
4	68	17	2.5	No	60	N/A	60		28		N/A		13	
5	51	14	3	Yes	55	30	60		41		41		27	
6	57	9	4	Yes	N/A	33	N/A		N/A		N/A		15	
7	57	12	3	No	33	12	N/A		N/A		N/A		10	
8	65	10	2	Yes	N/A	N/A	23		17		18		15	
9	45	8	2	No	34	14	32		19		20		9	
10	65	20	3	Yes	48	N/A	48		20		N/A		10	
11	50	10	4	Yes	70	26	65		39		42		30	
12	49	14	3	No	62	N/A	62		26		N/A		16	
13	64	12	2	No	52	N/A	52		24		N/A		12	
14	55	9	3	Yes	N/A	N/A	48		34		32		24	

N/A, not available.

21 to 29 Hz; 6) broad beta (13-29 Hz); and 7) gamma (narrow gamma band): 30 to 60 Hz. Normalized spectrum activity was derived from each directional contact through normalization of the individual peak activity from the whole frequency band of interest using the Brainstorm function *Spectrum Normalization*,[21] which derives at each source location and for each frequency band the ratio of how much the signal in the frequency band contributes to the total power of the source signal. For each lead, to lower the possible contact selection combination at least by 50%, among the eight contacts, we selected the first four with the highest value in the broad beta band (13–29 Hz) as possible predictors for clinical response as evaluated after clinical programming (Fig. 1).

Anatomical segmentations of basal ganglia and the position of the leads were obtained through Brainlab Elements software (Brainlab AG, Munich, Germany). This software allows to identify the leads' position and orientation and the position of the contacts in the patient's anatomical reconstructions of basal ganglia. This information was obtained through three functions:

- elements image fusion: automatically fuses patient's preoperative magnetic resonance imaging (MRI) and postoperative computed tomographies (CTs) and coregister patient's imaging;
- anatomical mapping: visualizes patient specific anatomy from the uploaded patient's imaging and obtains an MRI-based segmentation of structures in the basal ganglia region;
- leads localization: detects the localization and orientation of the leads based on postoperative CT artifact and shows, in three dimension (3D), individual lead contacts in the patient's own anatomy, obtaining a 3D display of the lead within the target anatomy.

In this study, we evaluated the predictive value for clinical programming of the contacts localized within the STN in the anatomical reconstruction obtained through Brainlab Elements (Fig. 2).

The clinical programming parameters were obtained after one year from the implant (Fig. 3). Whether the contacts with the greatest beta power of the LFPs and contacts located within the STN in neuroimaging reconstructions matched contacts selected for clinical programming after one year from implant was assessed. Statistical analysis of the results obtained was carried out and the following performance measures of a test were evaluated: accuracy, true positives, false positives, false negatives, true negatives, sensitivity, false negative rate, false positives rate, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, false omission rate, diagnostic odds ratio (DOR), false discovery rate, negative predictive value (NPV), F1 score.

To identify which method among LFPs recordings, data deriving from neuroimaging, and the combination of the two was able to identify the largest possible number of clinically effective contacts for programming and not to exclude contacts that instead proved effective in clinical programming, sensitivity, NPV, and DOR for the three data sets examined were compared.

RESULTS

Fourteen patients (8 male/6 female) were enrolled, with a mean age of 57 years (±6.8). The average duration of the disease at the time of implantation was 12 years (±3.3). The data relating to the scores of the Unified Parkinson's Disease Rating Scale part III

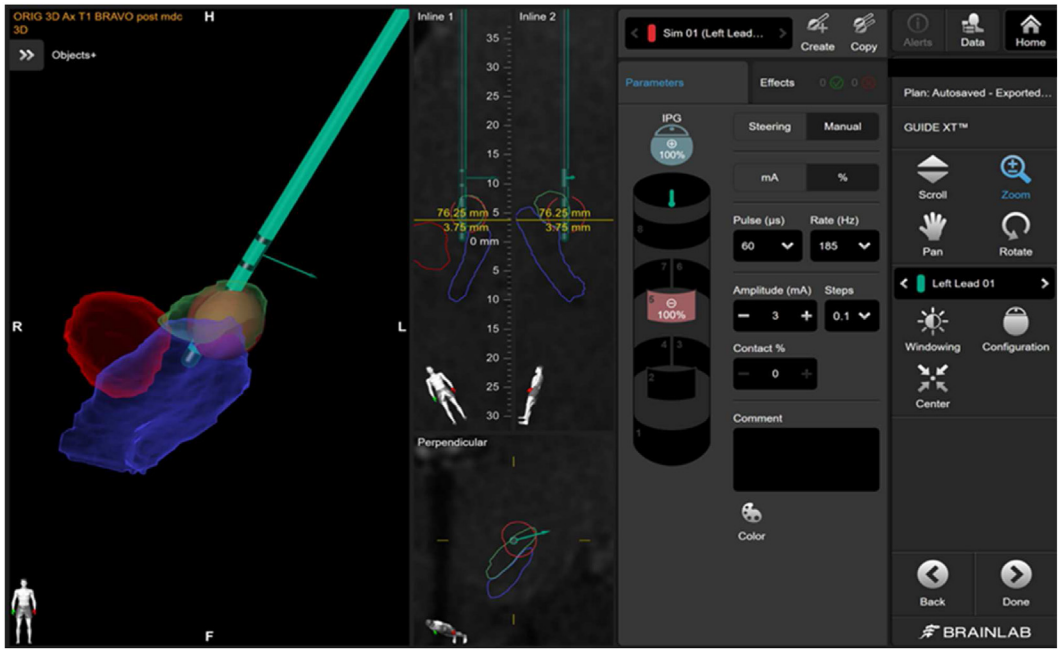

Figure 4. Brainlab reconstructions of the DBS lead positioning in the STN and display of parameter regulation for stimulation. [Color figure can be viewed at www.neuromodulationjournal.org]

were obtained in the preoperative stage in the without antiparkinsonian medication (OFF-MED) and under antiparkinsonian medication (ON-MED) conditions and in the postoperative stage in the OFF-MED/with DBS switched OFF (OFF-STIM), OFF-MED/with DBS switched ON (ON-STIM), ON-MED/OFF-STIM, ON-MED/ON-STIM conditions. Table 1 reports the data regarding age, disease duration, Hoehn and Yahr stage, and the type of anesthesia performed during the registration of LFPs in enrolled patients.

Through the Brainlab platform (Brainlab AG, Munich, Germany) the reconstructions of the electrode position in the target were obtained (Fig. 2). This platform allows also visualization, in a dynamic way, of the changes of the electric field

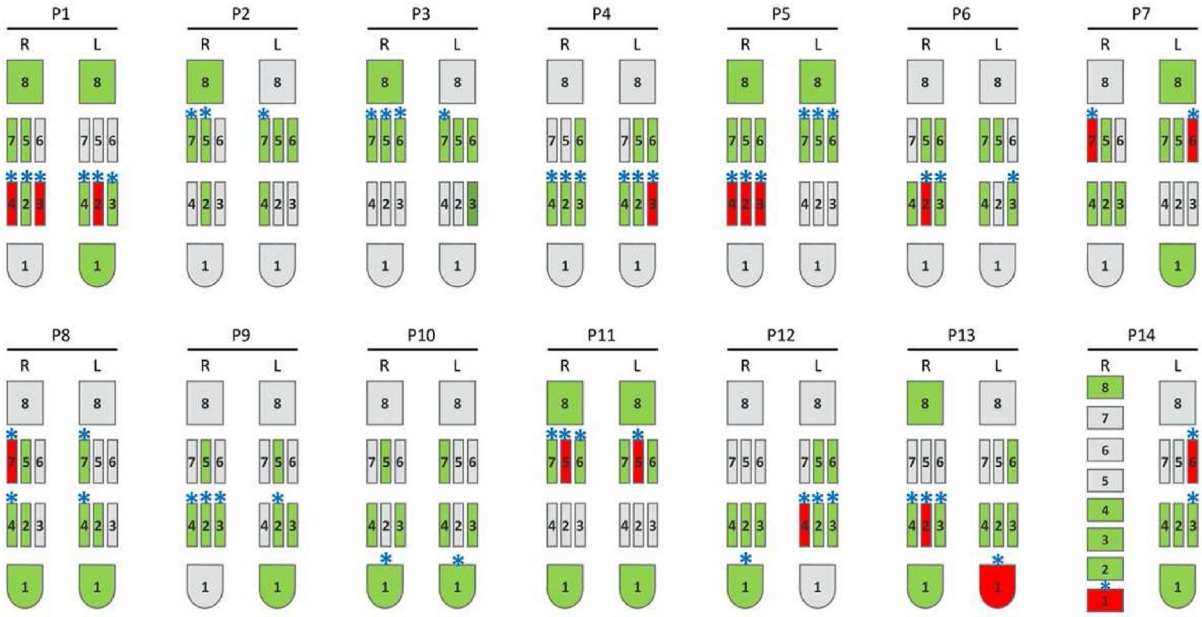

Figure 5. DBS programing scheme compared with LFPs recordings. The image shows for each of the 14 patients (from patient P1 to patient P14), the left (L) and right (R) electrodes with the eight contacts (from 1 to 8). Patient P14 has a linear octopolar electrode on the right and a directional octopolar electrode each on the right and on the left. *Contacts selected using standard clinical programing; green contacts indicate the first four contacts with the highest LFPs beta band power for each electrode; red contacts represent contacts selected using standard clinical programming but not selected among the first four contacts with the highest LFPs beta band power for the corresponding electrode. [Color figure can be viewed at www.neuromodulationjournal.org]

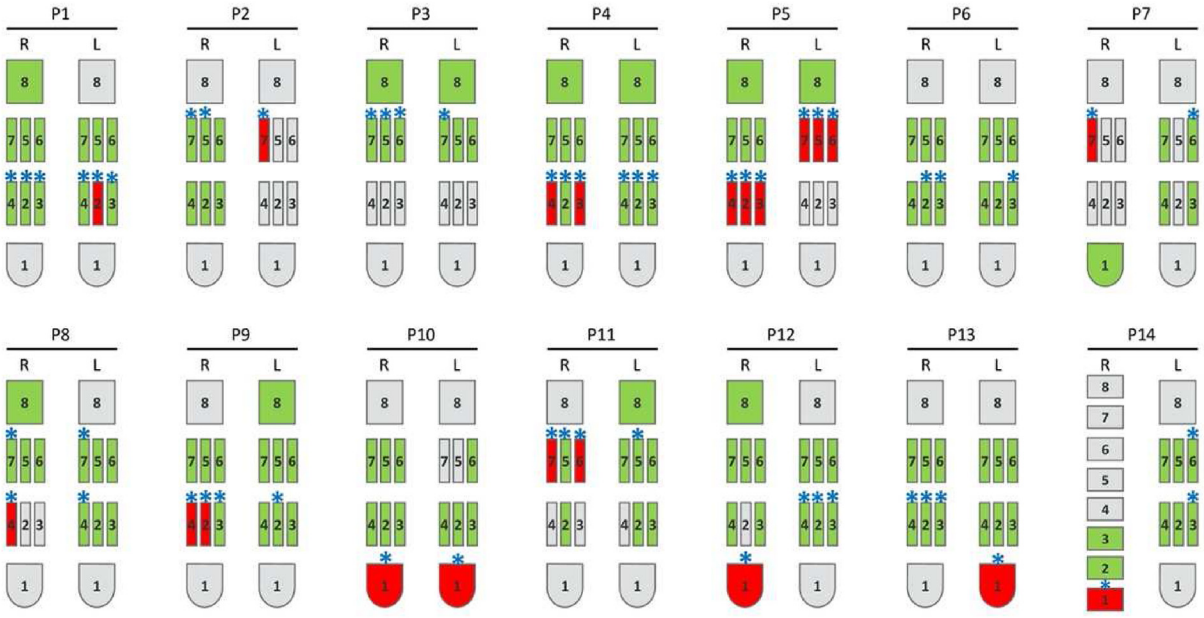

Figure 6. DBS programing scheme compared with neuroimaging reconstruction. The image shows the left (L) and right (R) electrodes with the eight contacts (from 1 to 8) for each of the 14 patients (from patient P1 to patient P14). Patient P14 has a linear octopolar electrode on the right and a directional octopolar electrode on the left. *Contacts selected through standard clinical programing; green contacts are the contacts localized within the STN; red contacts are the contacts selected using standard clinical programming but localized outside the STN [Color figure can be viewed at www.neuromodulationjournal.org]

around active contacts according to the parameters of stimulation (Fig. 4).

The data relating to the clinical programming of the DBS at one year from the implant were then compared with the data relating to the LFP recordings obtained intraoperatively (Fig. 5), the data relating to neuroimaging reconstructions (Fig. 6) and with both data sets (Fig. 7).

Analysis of data obtained by the recordings with LFPs showed a sensitivity of 67%, a NPV of 84%, a DOR of 2.7 (Table 2).

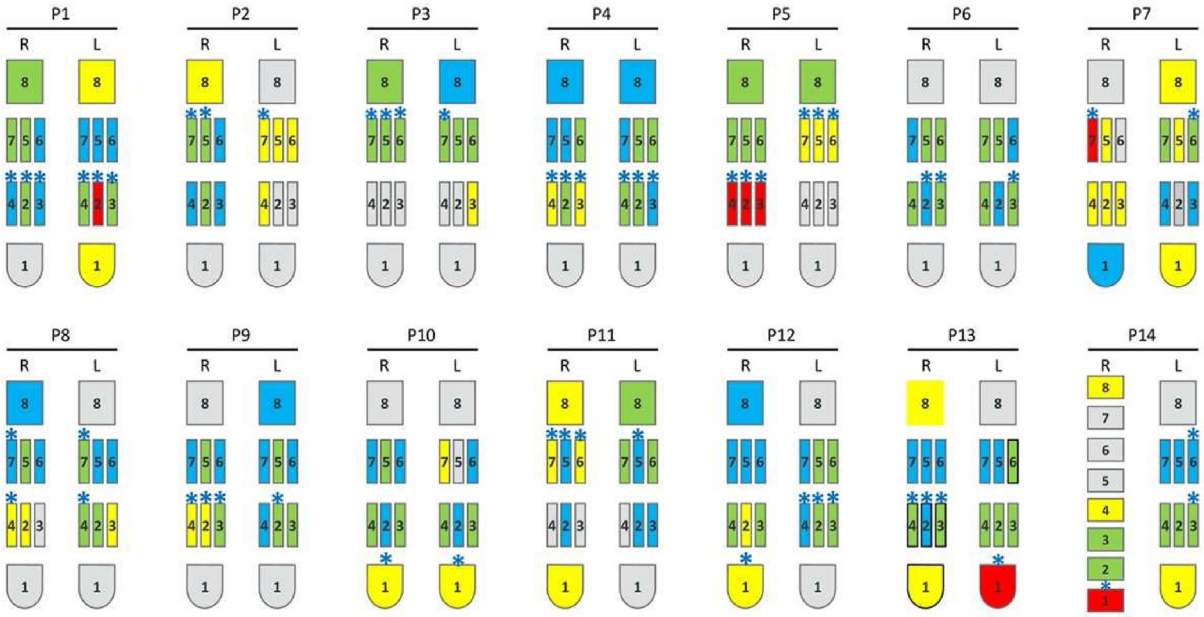

Figure 7. DBS programing scheme compared with the neuroimaging reconstructions and LFPs recordings. The image shows the left (L) and right (R) electrodes with the eight contacts (from 1 to 8) for each of the 14 patients (from patient P1 to patient P14). Patient P14 has a linear octopolar electrode on the right and a directional octopolar electrode on the left. *Contacts selected using standard clinical programing; yellow contacts indicate the first four contacts with the highest LFPs beta band for each electrode; blue contacts are the contacts localized within the STN; green contacts represent the contacts with both highest LFPs beta band and localization within the STN; red contacts represent the contacts selected using standard clinical programming but are localized outside the STN and without LFPs high beta band power. [Color figure can be viewed at www.neuromodulationjournal.org]

Table 2. Statistical Analysis and Comparison of the Data Obtained From Clinical Programming With LFPs Beta Power Band.

Confusion matrix	Clinical programming +	Clinical programming –	Total	Predictive values		
Beta band +	37 (TP)	73 (FP)	110	34% (PPV)	66% (FDR)	59% (ACC)
Beta band –	18 (FN)	96 (TN)	114	16% (FOR)	84% (NPV)	
Total	55	169	224			
	67% (SEN)	43% (FPR)	1.56 (LR+)	2.7 (DOR)	0.45 (F1 score)	
	33% (FNR)	57% (SPC)	0.58 (LR–)			

ACC, accuracy; FDR, false discovery rate; FN, false negative; FNR, false negative rate; FOR, false omission rate; FPR, false positives rate; FP, false positive; LR–, negative likelihood ratio; LR+, positive likelihood ratio; PPV, positive predictive value; SEN, sensitivity; SPC, specificity; TN, true negative; TP, true positive.

Analysis of the data obtained from the neuroimaging reconstructions showed a sensitivity of 62%, an NPV of 77%, and a DOR of 1.20 (Table 3).

The combined use of the two methods showed a sensitivity of 87%, an NPV of 87%, and a DOR of 2.7 (Table 4).

The type of anesthesia (general anesthesia vs awake surgery) performed did not influence the diagnostic performance of LFPs beta power; indeed, the DOR, the sensitivity, and the NPV showed no statistical difference between the two groups ($p = 0.4$). In the group with patients who underwent general anesthesia, DOR was 2.45, sensitivity 67%, and NPV 84%. In the group of patients with the awake surgery procedure DOR was 2.3, sensitivity 67%, and NPV 84%. However, we did not perform a power analysis, considering the retrospective nature of the study,[22,23] hence this observation requires verification with further prospective studies.

DISCUSSION

DBS with target in the STN bilaterally is an effective therapy for the control of motor symptoms in patients with advanced PD, in whom drug therapy is no longer sufficient for adequate symptom control. Optimal clinical programming is crucial to reach the best clinical outcome in terms of reduction of motor symptoms and improvement in the quality of life. Since the beginning, DBS technology have seen an extraordinary progress, allowing the programming possibilities to be further customized to meet the needs of individual patients. However, this entailed an increase in programming complexity, leading to a potentially infinite number of possible parameter combinations for programming, with the need to reserve a great amount of time to programming for each individual patient.

This might be overcome in the future through more advanced systems for automatic DBS programing through artificial intelligence algorithms.[24]

To date, in the clinical practice it is often difficult to dedicate the time necessary for programming a single patient, considering the multiple daily clinical commitments. Therefore, the risk is to not test all the possible most effective combinations offered by the DBS devices because of the lack of time. Moreover, the lack of shared stimulation guidelines, apart from protocols based on the experience of individual centers, is another obstacle to optimize clinical programming time.

Hence, the use of methods that can guide the clinical programming, shortening the time needed, are of considerable interest. Intraoperative LFPs recorded at the STN level are well suited for this purpose, because they are considered a neurophysiological biomarker of the hypokinesia of PD.

Modern software technologies return to the clinician in real time, during the programming phase, the 3D anatomical reconstructions of the basal ganglia, allowing identification of the contacts of the electrodes that are positioned within the STN, when STN is the nucleus chosen as a target for DBS.

The combined use of these two methods could, therefore, guide the clinician in choosing the contacts potentially more effective to use in the programming phase.

The objective of this retrospective study was to identify which method between the registration of intraoperative LFPs, the study with neuroimaging, and the combination of the two can identify the greatest number of clinically effective contacts to focus on during programming. The combined use of data deriving from the study of LFPs and neuroimaging showed sensitivity values and a NPVs more favorable than the data obtained from LFPs recordings and neuroimaging alone. The combination of the data deriving from the two methods showed a DOR of 2.7, therefore the use of the two methods together is a good predictor for the selection of contacts effective in the clinical planning phase. This predictor showed a high sensitivity (87%) indicating the ability to identify a high number of potentially clinically effective contacts. Furthermore, the high NPV (87%)

Table 3. Statistical Analysis and Comparison of the Data Obtained From Clinical Programming With Neuroimaging Reconstructions.

Confusion matrix	Clinical programming +	Clinical programming –	Total	Predictive value		
Neuroimaging +	34	97	131	26% (PPV)	74% (FDR)	47% (ACC)
Neuroimaging –	21	72	93	23% (FOR)	77% (NPV)	
Total	55	169	224			
	62% (SEN)	57% (FPR)	1.08 (LR+)	1.2 (DOR)	0.36 (F1 score)	
	38% (FNR)	43% (SPC)	0.90 (LR–)			

Neuroimaging + are contacts localized within the STN in neuroimaging reconstructions; Neuroimaging – are contacts located outside the STN.
ACC, accuracy; FDR, false discovery rate; FNR, false negative rate; FOR, false omission rate; FPR, false positives rate; LR–, negative likelihood ratio; LR+, positive likelihood ratio; PPV, positive predictive value; SEN, sensitivity; SPC, specificity.

Table 4. Statistical Analysis and Comparison of the Data Obtained From Clinical Programming With LFPs Beta Power and Neuroimaging Reconstructions.

Confusion matrix	Clinical programming +	Clinical programming –	Total	Predictive value		
Neuroimaging and/or Beta band +	48	121	169	28% (PPV)	72% (FDR)	43% (ACC)
Neuroimaging and beta band –	7	48	55	13% (FOR)	87% (NPV)	
Total	55	169	224			
	87% (SEN)	72% (FPR)	1.22 (LR+)	2.7 (DOR)	0.42 (F1 score)	
	13% (FNR)	28% (SPC)	0.45 (LR–)			

ACC, accuracy; FDR, false discovery rate; FNR, false negative rate; FOR, false omission rate; FPR, false positives rate; LR–, negative likelihood ratio; LR+, positive likelihood ratio; PPV, positive predictive value; SEN, sensitivity; SPC, specificity.

indicates an ability to exclude only truly ineffective contacts. Hence, neither neuroimaging techniques nor LFPs alone should be used individually to orient clinical programming. These results lay the foundations for the use of this combined predictor as a screening test when programming DBS with STN target.

Therefore, it could be considered in the initial programming phase, which contacts have a higher value in the beta band power of LFPs and a localization in STN in neuroimaging reconstructions and start testing the clinical efficacy of these contacts. In this way, the time required for first programming could be significantly reduced, which is beneficial for both clinician and patient. Even in the subsequent programming phase, the same technique could guide the necessary adjustments in the stimulation parameters, shortening the time necessary for programming also in this phase. One possible limitation of the use of intraoperative recorded LFPs as a parameter to guide subsequent programming phase is the rotation of the lead in the first few months after surgery. This retrospective study analyzed patients after one year from positioning, therefore the rotations should have occurred, however the LFPs showed high accuracy in predicting favorable contact selection for clinical programming. Recent sensing technology allows to obtain real time recording of the LFPs even after surgery in chronically implanted patients, these LFPs data could be compared with the ones obtained in the intraoperative recording, and a mismatch between them could mark a displacement of leads after surgery.

The main limitations of the study are the small number of the samples and the retrospective design, which does not allow to obtain all the data available. Therefore, further studies are needed to confirm the proposed approach.

CONCLUSIONS

This study has shown that contacts with higher value in the beta band power of LFPs and located within the STN identified through neuroimaging reconstructions have a high probability of being the contacts with the best clinical response in the programming phase. Conversely, contacts that do not show a high value in the beta band power of the LFPs and are not located within the STN in the neuroimaging reconstructions have a low probability of being selected in the clinical planning phase. The combined use of information deriving from intraoperative LFPs recordings and neuroimaging reconstructions can therefore be considered as an investigative protocol to guide the clinician for orientation during clinical programming and to reduce the time required to identify the contacts that have the most favorable clinical response both in the initial programming phase and for subsequent programming.

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Authorship Statements

Lazzaro di Biase contributed to the conception and execution of the study, clinical data collection, execution and review of the statistical analysis, and writing and review of the manuscript. Carla Piano, Francesco Bove, and Tommaso Tufo contributed to the execution of the study, clinical and intraoperative data collection, review of the statistical analysis, and review of the manuscript. Lorenzo Ricci and Maria Letizia Caminiti contributed to the execution of the study, clinical data collection, execution and review of the statistical analysis, and writing and review of the manuscript. Alessandro Stefani, Fabio Viselli, Nicola Modugno, Rocco Cerroni, Paolo Calabresi, Anna Rita Bentivoglio, and Vincenzo Di Lazzaro contributed to the execution of the study, clinical data collection, review of the statistical analysis, and review of the manuscript. All authors approved the final manuscript.

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