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Feasibility of local field potential-guided programming for deep brain stimulation in Parkinson's disease: A comparison with clinical and neuro-imaging guided approaches in a randomized, controlled pilot trial

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ABSTRACT

Background: Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective treatment for advanced Parkinson's disease (PD). Clinical outcomes after DBS can be limited by poor programming, which remains a clinically driven, lengthy and iterative process. Electrophysiological recordings in PD patients undergoing STN-DBS have shown an association between STN spectral power in the beta frequency band (beta power) and the severity of clinical symptoms. New commercially-available DBS devices now enable the recording of STN beta oscillations in chronically-implanted PD patients, thereby allowing investigation into the use of beta power as a biomarker for DBS programming.

Objective: To determine the potential advantages of beta-guided DBS programming over clinically and image-guided programming in terms of clinical efficacy and programming time.

Methods: We conducted a randomized, blinded, three-arm, crossover clinical trial in eight Parkinson's patients with STN-DBS who were evaluated three months after DBS surgery. We compared clinical efficacy and time required for each DBS programming paradigm, as well as DBS parameters and total energy delivered between the three strategies (beta-, clinically- and image-guided).

Results: All three programming methods showed similar clinical efficacy, but the time needed for programming was significantly shorter for beta- and image-guided programming compared to clinically-guided programming ($p < 0.001$).

Conclusion: Beta-guided programming may be a useful and more efficient approach to DBS programming in Parkinson's patients with STN-DBS. It takes significantly less time to program than traditional clinically-based programming, while providing similar symptom control. In addition, it is readily available within the clinical DBS programmer, making it a valuable tool for improving current clinical practice.

1. Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective therapy for patients with advanced Parkinson's disease (PD) [1]. However, STN-DBS remains a poorly standardized therapy and prone to treatment failures that may occur because of inappropriate patient selection, lead misplacement, or inadequate postoperative management [2]. Programming in DBS is key to postoperative management, which remains a highly-specialized, long, and iterative clinical process [2]. Poor programming can severely compromise clinical outcomes after DBS, potentially leading to both suboptimal motor improvement and stimulation-related side effects [3]. With the increasing complexity of DBS devices, any tools with features that reduce the programming burden for clinicians and patients are urgently needed.

Abbreviations: CT, computed tomography; DBS, deep brain stimulation; LFP, local field potentials; MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III; PSD, power spectral density; PW, pulse width; STN, subthalamic nucleus; SWI, susceptibility-weighted images; TEED, total electrical energy delivered; TFP, time for programming.

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Electrophysiological studies in unmedicated PD patients undergoing STN-DBS have shown prominent synchronization in the beta (β) frequency band (13–30 Hz) [4]. This synchronization was estimated as power in the spectral density (PSD) of STN local field potentials (LFP), where it appears as a β-peak. In recent years, converging evidence has suggested that β power is associated with the severity of PD motor symptoms [5–12]. STN β power has been shown to be inversely correlated with the severity of rigidity and bradykinesia, and to be suppressed by dopaminergic medication [13]. Furthermore, the reduction in STN β power with medication correlated with the reduction in motor symptoms. Clinically effective STN DBS has also been shown to reduce β power that reappears after withdrawal of stimulation. Accordingly, β power has been discussed as a potential therapeutic tool to improve DBS treatment through β power-assisted programming [5–12].

Estimation of STN β power is already used to guide lead placement and has been studied for subsequent contact selection [14]. However, the intraoperative approach does not account for likely perioperative lead rotation, which occurs within 24 h after surgery [15]. Furthermore, recording of β-power from chronically implanted devices has been limited to experimental devices such as Activa PC + S or RC + S (Medtronic, PLC) [16] or to externalised leads in a very limited number of patients [5–12]. However, the advent of commercially available neurostimulators that are capable of recording and analysing LFPs from chronically implanted electrodes months after DBS surgery has made it possible to investigate the role of LFP recordings in clinical practice [17].

The aim of this study is to evaluate the potential of beta-guided programming, a novel technology based on the use of beta power recordings, to optimize DBS programming through contact and parameter selection compared to conventional methods.

2. Material and Methods

2.1. Study design

We designed our study as a randomized, blinded, three-arm, crossover clinical trial. The primary endpoints were differences in symptom control and time to program (TFP) between different programming paradigms. Pre-specified secondary endpoints were differences in total electrical energy delivered (TEED), rate of adverse events and stimulation parameters (i.e. amplitude, frequency, pulse width). As this was a feasibility study, all eligible patients were enrolled during the prespecified study period, accordingly no fixed sample size was set. The local ethics committee approved the study (Ethik-Kommission der Medizinischen Fakultät Würzburg, ref: 94/210-me), which was conducted in accordance with the Declaration of Helsinki. All patients signed a written informed consent to participate in the study. The study was registered with the German Clinical Trials Register (registration number DRKS00030350).

2.2. Participants

All patients were diagnosed with idiopathic PD according to the UK Parkinson Disease Brain Bank criteria. All patients had received bilateral STN-DBS at our center three months prior to enrollment (study period: January to December 2021).

2.3. Surgical procedure

The surgical procedure has previously been described [18]. In brief, the DBS electrode used was Sensight (Medtronic, PLC), comprising eight platinum–iridium contacts of 1.5 mm each in a 1-3-3-1 configuration and a contact-to-contact separation of 0.5 mm. The intended coordinates for STN (i.e., 12 mm lateral, 2 mm posterior, 4 mm ventral to the mid-commissural point) were adjusted according to individual delineation of the STN on T2-weighted and susceptibility-weighted images (SWI) (Magnetom Trio, Siemens Healthcare) and verified by intraoperative microelectrode recordings and stimulation.

2.4. Study assessments

Study assessments were performed during routine in-patient care, three months after DBS surgery. First, we performed a cranial stereotactic computed tomography (CT) scan to rule out surgical complications and to determine the exact placement of the leads. We also discontinued all dopaminergic medications for >12 h (MedOFF) and long-acting dopamine agonists for >72 h. The next morning, the stimulator was turned off for 3 h (StimOFF) and we assessed the patient's clinical status using the Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III). Each patient then underwent programming for DBS, which was either clinically, image (i.e., anatomically), or beta power (i.e., electrophysiologically) guided. A detailed description of each programming paradigm is provided below. Each programming paradigm was tested on a different day, and the order of testing was block-randomized in advance for each patient. After 30 min of stimulation, patients were clinically reassessed using the MDS-UPDRS III. All examinations were videotaped and later evaluated by three independent movement disorder experts (CD, TO, and TM) who were blinded to the stimulation paradigm. Due to the limitations of assessing rigidity via video, we used an adapted version of the MDS-UPDRS III that excluded the rigidity items. We endeavored to maintain a double-blind study design; however, inherent variations across programming sessions potentially introduced biases. Despite our best efforts to uphold blinding, we acknowledge these as potential weak points in the study protocol. During a standard follow-up visit three months post-initial programming, patient feedback, amendments to the assigned DBS program, and overall satisfaction were recorded. This follow-up data was retrospectively analyzed to provide initial insights into the possible long-term efficacy of the programming paradigms.

We documented the TFP, stimulation parameters, and side effects for each programming paradigm. All stimulation paradigms were stored on the patient's implantable pulse generator and could be selected for chronic stimulation at the end of the study. An additional standard follow-up visit was conducted three months after the initial programming session. During this visit, we collected patient feedback on the assigned DBS program, documented any changes made, and assessed overall satisfaction. Formal MDS-UPDRS III testing was not conducted at this visit. It's important to note that these follow-up visit data were subsequently analyzed retrospectively to provide preliminary insights on the long-term effectiveness of the programming paradigms. The study procedure is shown in Fig. 1.

2.5. Programming paradigms: clinically-, image- and beta-guided programming

The clinically- and image-guided programming has been described in detail elsewhere [18]. Briefly, clinically guided programming (i.e., slightly shortened monopolar review) was performed by a DBS expert (PC) in the MedOFF condition for both hemispheres, assessing rigidity. The four contact levels were first assessed non-directionally for effect thresholds (i.e., symptom reduction in the contralateral limb) and side effect thresholds by gradually increasing the amplitude by 0.5 mA and then narrowing in 0.1 mA increments.

Contact levels with directional contacts (the middle two) were tested both individually and in combination, following the same testing procedure as with other contact levels. To optimize efficiency, we skipped single testing of directional contacts with high effect thresholds if other combination or single contacts seemed preferential (better therapeutic window) in the ring-mode-testing. The most effective contact or combination of contacts was selected for final adjustments to the settings, which were titrated based on clinical response and patient feedback. The TFP included the entire procedure, excluding the time for obtaining the

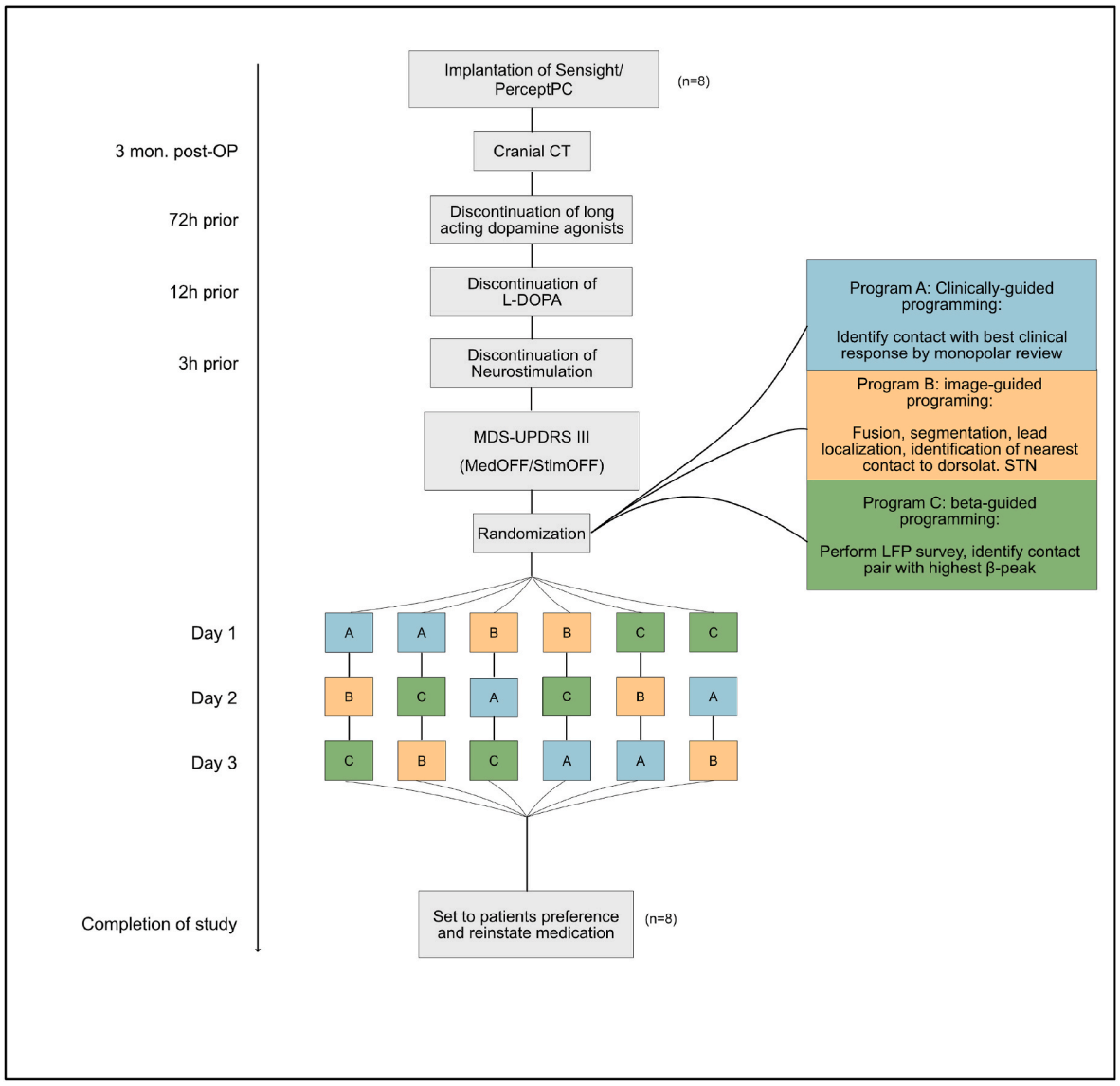

Fig. 1. Study flow. A randomized, sham-controlled, prospective, crossover design was utilized, during which participants returned to the laboratory for three consecutive visits. Each visit was identical apart from the condition of stimulation received.
A = clinically-guided programming; B = image-guided programming; C = beta-guided programming.

CT scan.

For the image-guided programming, preoperative 3 T MRI scans performed under general anesthesia (T1-MPRAGE sagittal 1 mm, T2-TSE axial 2 mm, T2 SWI image axial isotropic 1.15 mm) and postoperative cranial stereotactic CT scans were imported into the Brainlab Elements (Brainlab, Munich, Germany). Images were fused using an automated software algorithm and accuracy was visually verified. The STN, substantia nigra, and red nucleus were automatically segmented by the software and corrected as necessary based on the SWI or T2 image series.

Postoperative CT was used to determine the depth, laterality, and rotation of the electrodes. The GuideXT element in the Brainlab Elements Suite was used to identify the individual contacts directed toward the dorsolateral part of the STN. Projected contact settings were programmed along with default parameters for pulse width (PW; 60 μs) and frequency (130 Hz). The amplitude was clinically set at 0.5 mA below the threshold for adverse effects. If necessary, PW and frequency values were adjusted to manage adverse effects or inadequate tremor control. The TFP included the time required to load the image series, perform planning, print the anatomical plan, and program the device.

For the beta-guided programming, we focused on the β power. We relied on the built-in algorithm of the device (Percept PC, Medtronic, PLC) to compute the STN β power and performed all electrophysiological analyses with the Medtronic Clinician Programmer. We first allowed the evaluation of potentially artifact-contaminated measurements (i.e., PSD) through the setup option in the Brain Sense Setup screen. We then ran the "Brain Sense Survey" and obtained a bipolar PSD for each given pair of leads. This was done for segmented contacts only.

Each evaluation took up to 1 min; if a telemetry problem occurred, the evaluation was repeated. During this time (i.e., during the "Brain Sense Survey"), patients sat comfortably in a chair in a well-lit room with their eyes open and were instructed to relax, remain silent, and not control any symptom (e.g., tremor). We then evaluated all PSDs from the Brain Sense Survey for plausibility of the PSD and for the presence of an elevated β power, which was presented as a peak in the β frequency range (β peak). The algorithm differentiates between two types of measurements: 'level' and 'segments'. Level measurements capture LFPs from all possible bipolar combinations of all non-segmented contacts and segmented contacts on the respective level amalgamated to a single omnidirectional virtual contact. This measurement was performed to establish verticality in the beta signal. On the other hand, Segments

Measurement concentrated exclusively on the segmented contacts, specifically excluding ring contacts 0 and 3. Although this approach does not cover all potential pairs, it examines all feasible ones. The pairs considered include each segmented contact with its immediate neighbors such as 1a/1 b, 1a/1c, 1a/2a, and so forth. The primary goal of the segments measurement is to detect horizontal directionality in the beta signal. If more than one β-peak was detected, we selected the peak in the "low beta" range (<20 Hz). This was done separately for each hemisphere under MedOFF/StimOFF conditions. The contact pair with the highest β-peak in the bipolar montage was selected for stimulation and the current equally shared between those contacts. For example, if the pair 9a and 9 b had the highest β-peak, the resulting stimulation settings were as follows: C+, 9a- (50%), 9 b- (50%). The stimulation amplitude was set clinically. We increased the stimulation amplitude in 0.5 mA steps until side effects occurred. The final stimulation amplitude was set 0.5 mA below this side effect threshold. As for the other paradigms, the default PW and frequency (60 μs and 125 Hz) were used initially and adapted to clinical needs: PW was once adjusted to 40 μs to manage stimulation-induced dysarthria, and the frequency was modified in 8/29 programs to account for persisting tremor. The programming process is illustrated in Fig. 2A and B.

2.6. Titration of stimulation amplitude to β power: beta titration

In a subgroup of patients, we performed an additional investigation and tested the clinical efficacy of β-power-based stimulation amplitude selection. Owing to both technical constraints, which restrict the specific method to the two central levels of contacts, and instances of insufficient signal quality, this approach was feasible for only 5/8 patients. This limits the generalizability of our results. For beta titration, we decided to maintain the contacts, PW, and frequency settings used for the initial beta-guided programming, but we adjusted the stimulation amplitude according to the spectral power suppression of an a priori selected β-frequency range, namely the β-peak. This range and all

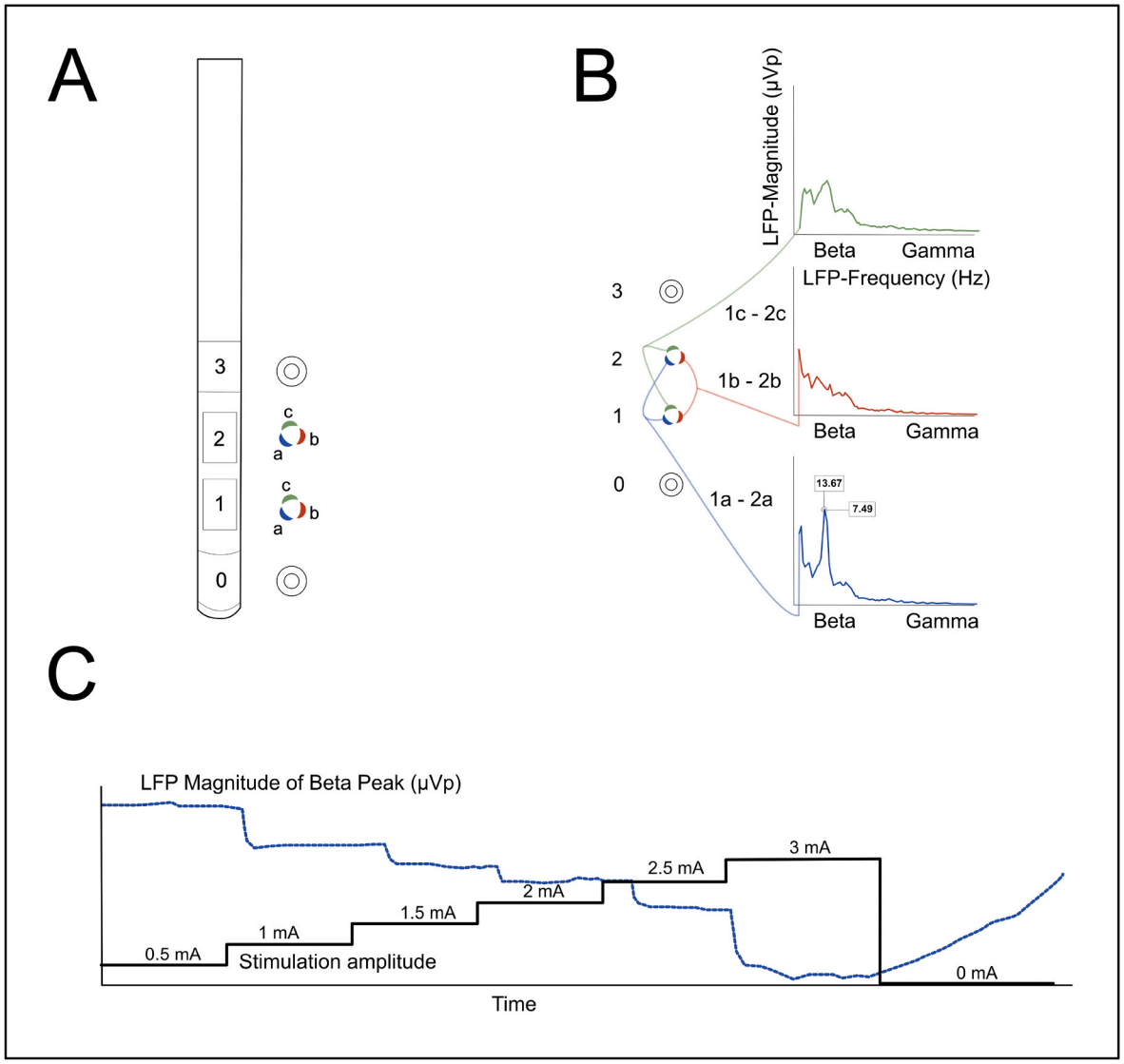

Fig. 2. Schematic illustration of the basic steps for initial beta-guided programming and subsequent beta titration. **(A)** The layout of the local field potentials (LFP) sensing electrode with two ring contacts on the top and bottom level and two levels with directional contacts in the middle. **(B)** Three exemplary power spectral densities (PSD) over different contacts (green, orange and blue). In this example, there is a pronounced beta peak over contacts 1a-2a (blue line). **(C)** With the stimulation amplitude plotted against the beta peak magnitude of the selected beta peak. By gradually increasing the amplitude of stimulation, there was a reduction in beta power. The suppression of beta power reached its maximum at 3 mA. After cessation of stimulation, the beta power quickly reappeared. Note that this is a schematic illustration of the process and does not contain actual sensing data. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

electrophysiological analyses were performed using the built-in algorithm of the device (Percept PC, Medtronic, PLC) and the Medtronic Clinician Programmer. We first turned off the stimulation bilaterally for 30 min and repeated a "Brain Sense Survey" to ensure the presence and consistency of the results (i.e., the β-peak). We then proceeded to the "Brain Sense Setup" and performed a "Signal Test" to allow a directional selection of the contact pair with the most prominent β-peak. Note that this step limited the contact selection to the middle two segmented contacts, as it was only possible to sense around (i.e., one contact above and one contact below) the stimulating contact. Once the β-peak was selected, we switched to the Brain Sense display, where we started LFP streaming. This command displays the spectral power of the selected frequency range over time and allows the assessment of changes with increasing stimulation amplitude. For each side, we proceeded in a standardized manner and performed a 30-s recording in StimOFF, followed by a gradual increase in stimulation amplitude in 0.5 mA steps. After each increase, we observed the power dynamics for 60 s. We repeated this procedure until a steady (i.e., over 60 s) suppression of the displayed power was achieved. Suppression was defined as >75% reduction of the original power. Note that this is a visual and qualitative assessment, as there is no numerical scale for this feature in the Medtronic Clinician Programmer. This process is illustrated in Fig. 2C.

For this additional examination, patients were examined a second time on the afternoon of the beta-guided programming, after the regular study examinations for that day had been completed. Because of the extended testing time required for these patients (which included more hours in the MedOFF condition), we limited the comparison to beta titration versus the initial beta-guided programming (i.e., they were not compared to the clinical or image-guided programming groups).

2.7. Statistical analysis

For every programming paradigm, we computed a measure of clinical improvement that we named percent (%) symptom control. This was computed as follows:

$$1 - \left(\frac{MDS - UPDRSIIImedOFF/stimON}{MDS - UPDRSIIImedOFF/stimOFF} \right) \times 100 \qquad \text{Equation 1}$$

The TEED was approximated by Equation (2) [19], where I = current in Amperes, pw = PW in sec, f = frequency, and R = resistance. This equation was adapted for directional contacts according to the information provided by Medtronic. The TEED for directional contact settings (TEED_directional) is equal to the product of pulse width (pw) in seconds, frequency (f) in Hertz, and the sum of the squares of the products of resistance (R) in Ohms and current (I) in Amperes for each contact, i, from 1 to n.

$$TEED = I(A)^2 \times pw(sec) \times f(Hz) \times R(\Omega) \qquad \text{Equation 2}$$

$$TEED\ directional = \mathrm{pw(sec)} \times \mathrm{f(Hz)} \times \Sigma\left\{ \left(\mathrm{R}(\Omega)\_\mathrm{i} \times \mathrm{I(A)}\_\mathrm{i} \right)\hat{2} \right\} \text{ for i} = 1 \text{ to n} \qquad \text{Equation 3}$$

We used JASP (jasp-stats.org) for statistical analyses. The extent of symptom control (%), TFP, TEED, stimulation amplitude, frequency, and PW were compared across the three study arms via Friedman test and post-hoc testing using the Wilcoxon signed-rank. An alpha level of 0.01 was chosen as significant. *P*-values were adjusted by comparing a family of three using Holm's method. The null hypothesis of all analyses was that there were no measurable differences between the study arms, i.e., clinically-, image-, and beta-guided programming. Significant results against the null hypothesis are documented with corresponding p-values, estimates of effect size and its precision in terms of 95% confidence intervals (CI). Results are presented as mean ± standard deviation.

3. Results

3.1. Patient cohort

Eight patients implanted at our center participated in the study (seven men and one woman; age 59.1 ± 7.2 years; disease duration 10.2 ± 4.2 years). All patients were treated with bilateral STN-DBS and received a Medtronic device (Sensight leads and Percept PC, Medtronic, PLC). Demographic data and stimulation settings are summarized in Table 1.

3.2. Symptom control

All three programming paradigms showed similar clinical efficacy after 30 min of stimulation (Fig. 3A). Specifically, the improvement in motor scores was 57.66 ± 12.95% for clinically-guided programming, 57.21 ± 11.26% for image-guided programming, and 65.18 ± 13.97% for beta-guided programming. Neither Friedman test nor post hoc testing revealed significant differences. In a retrospective analysis of the three-month follow-up visits, all eight patients reported maintaining their assigned DBS program and expressed overall satisfaction. Two patients had minor amplitude adjustments (+0.2 mA for one patient in the clinically-guided and +0.3 mA for one patient in the beta-guided group) for enhanced symptom control.

3.3. Programming time

Both image- and beta-guided programming showed a clear and significant reduction in TFP compared to clinically-guided programming (Fig. 3B) in Friedman test ($p = 0.002$) and post hoc testing (clinically-vs. image-guided programming: $p < 0.001$, Cohen's d: 2.345, CI95%: 19.6/56.8); clinically-vs. beta-guided programming: $p < 0.001$, Cohen's d: 2.909 CI95%: 27.6/54.8). Post hoc comparison between image- and beta-guided programming was not significant. In absolute values, the mean duration of programming was 60 ± 11.99 min for clinically-guided, 27 ± 8.24 min for image-guided, and 19 ± 4.17 min for beta-guided programming (Fig. 3B).

3.4. Stimulation settings and power consumption

There were no significant differences in amplitude, frequency, PW, or TEED between clinical, image, or beta-guided programming. Comparisons of TEED and amplitude are highlighted in Fig. 3C and D, while frequency and PW are summarized in Table 1.

3.5. Beta titration

Titration of stimulation amplitude based on suppression of pathologic beta bands was possible in five of eight patients. The stimulation amplitude selected after beta titration was below the side effect threshold in all patients. The clinical data for beta titration are summarized in Table 1. Beta titration improved symptom control in four out of five patients, while one patient showed a worsening of symptom control (−12%). Fig. 3 shows symptom control after beta titration compared to initial beta-guided programming and illustrates individual performance.

4. Discussion

Our study results show that beta-guided stimulation may be a promising new strategy to reduce the programming burden for Parkinson's patients with STN DBS. This method outperforms the gold standard, clinically based programming, and matches the current alternative, image-based programming, in terms of programming time, while resulting in similar symptom control. It is important to note that the efficacy evaluation was conducted 30 min after parameter settings,

Table 1
Demographic data and stimulation settings.

Patient Age/ Sex	Disease Duration (y)	Programming paradigm	Symptom control (%)	TFP (min)	TEED (μJ)	Amplitude (mA) Right/Left	Frequency (Hz) Right/Left	Pulse width (μs) Right/ Left	Cathode Right/Left
60/m	7	MR	72.9	41	140.4	3/3	130	60	11/0
		AN	64.8	32	376.7	3.7/4.5	180	60	11/3 (78%), 2 b (16%), 2c (6%)
		BS	65.79	18	222.9	3.5/2.8	125	60	9 b (50%),10 b (50%)/1c (50%),2c (50%)
		BT	80.49	–	264.6	4.0/2.8	125	60	9 b (50%),10 b (50%)/1c (50%),2c (50%)
64/m	12	MR	57.5	62	291.6	3/4.5	180	60	9a,9 b, 9c (33%)/2 b
		AN	46.1	37	164.7	4/4.7	130/180	60	10a, 10 b, 10c (33%)/1 b (74%),1a (26%)
		BS	41.3	12	142.9	4/5.3	125	60	9 b (50%),10 b (50%)/1a (50%), 1c (50%)
		BT	–	–	–	–	–	–	–
53/m	5	MR	62.5	77	233.1	4.2/3.3	130	60	11/2a,2 b, 2c (33%)
		AN	65.7	26	429.5	5.9/4.5	130	60	10 b (42%), 11 (58%)/1a (22%), 1 b (42%), 2a (13%), 2 b (22%)
		BS	75.0	18	137.3	4/3.1	125	60	9 b, 10 b (50%)/1c, 2c (50%)
		BT	75.0	–	157,9	4.0/3.5	125	60	9 b, 10 b (50%)/1c, 2c (50%)
45/m	16	MR	43.2	65	171.79	1.9/4.5	130	40	10 b (40%), 10c (60%)/0
		AN	64.4	15	497.6	4.8/4.8	180	60	10 b (53.3),10c (13.3), 11 (33.3/2 b (21.4%),2c (57.1),3 (21.4%))
		BS	72.5	27	86.4	2/2	125	60	9a, 10a (50%)/1a, 2a (50%)
		BT	77.5	–	553.5	3.0/6.5	125	60	9a/1a
69/m	17	MR	45.7	60	131.3	2.8/3	130	60	10 b, 10c (50%)/2a,2 b, 2c (33%)
		AN	42.2	26	63.9	1.2/2.6	130	60	10 b (47.4%),10c (21.0),11 (31.6)/1a (76%),1 b (24%)
		BS	59.1	18	211.8	4/3.5	125	60	9 b, 10 b (50%)/1c, 2c (50%)
		BT	–	–	–	–	–	–	–
63/f	7	MR	70.8	70	249.6	4/4	130	60	9a (24%),10a (76%)/1c (24%),2c (76%)
		AN	43.4	15	149.8	2.5/3.6	130	60	10 b (23.0),10c (46.15),11c (30.8)/2a (35.8),2 b (10.0),2c (32.1),3 (22.1)
		BS	80.0	20	207.7	4.1/3.3	125	60	9a,9c,10a,10c (25%)/1a,2a (50%)
		BT	–	–	–	–	–	–	–
55/m	7	MR	40.6	45	106.7	2.2/2.5	130/180	60	10 b (35%),11 (65%)/3
		AN	69.5	32	272.3	2.9/4.1	180	60	10a (15.9%), 10c (43.2%), 11 (40.9%)/2a,2 b, 2c (33%)
		BS	50.0	21	288.2	3.8/3.5	125	60	9 b,10 b (50%)/1a, 2a (50%)
		BT	58.3	–	229.5	3.0/3.5	125	60	9 b,10 b (50%)/1a, 2a (50%)
64/m	11	MR	67	62	452.3	2.6/6	185	60	10a/2a,2 b, 2c (30%)
		AN	61.3	33	201.9	2.1/3.9	130/185	60	11/2a (15%), 2c (35%), 3 (50%)
		BS	77.8	18	250.0	3.9/3.5	125	60	9c,10c (50%)/1c,2c (50%)
		BT	66.6	–	312.1	4.5/3.8	125	60	9c,10c (50%)/1c,2c (50%)

AN, anatomic programming (i.e., image-guided); BS, brain sense (i.e. initial beta-guided programming); BT, beta titration (took place on the same day after initial BS); MR, monopolar review (i.e., clinically-based programming); TFP, time needed for programming; TEED, total electrical energy delivered. The preferred stimulation program chosen by each patient at the end of the study is underlined, providing an indirect measure of comfort associated with each programming approach.

providing initial evidence for the feasibility of this approach. Using a commercially available patient programmer, beta-guided programming can be easily incorporated into routine clinical practice, providing a simplified bedside solution for achieving optimal symptom control without adverse effects and with a reasonable time commitment.

4.1. Symptom control, energy consumption and beta titration

We have shown that beta-guided programming of DBS resulted in symptom control that was equivalent or superior to both clinically and image-guided programming (Fig. 3A). Monopolar review has been the gold standard for DBS programming for decades and has supported the discovery of novel and optimized stimulation settings under experimental conditions [20]. However, this approach is highly operator dependent and poorly standardized, which may lead to suboptimal results in routine clinical practice [2]. In an attempt to standardize DBS programming, a previous report by Fernández-García and colleagues showed similar clinical outcomes after monopolar review and beta-based programming as computed intraoperatively in ten PD patients undergoing STN-DBS surgery [14]. Although this approach is interesting, it may be compromised by immediate postoperative rotation of the electrodes, resulting in inadvertent stimulation of areas outside the STN [15].

In recent years, computational models have been developed to support DBS programming, with results showing comparable clinical outcomes compared to clinically based programming [18,21–23]. In addition to further confirming these results, we demonstrate equal clinical efficacy between beta- and image-guided DBS programming, thus further supporting the reliability of a programming paradigm based on STN β power (Fig. 3A).

To further characterize potential differences between programming paradigms and to rule out a possible confounding effect on clinical efficacy due to increased energy consumption, we compared both stimulation parameters and TEED and found no differences (Fig. 3C). We hypothesize that similar symptom control was primarily related to similar efficacy and was not confounded by higher current delivery.

An intriguing finding in our study was that despite employing different programming techniques, which led to the selection of different contacts (see Table 1 and Supplementary Fig. 1), all three methods provided comparable clinical outcomes. This observation suggests that multiple contact configurations can be efficacious in patients undergoing DBS, which highlights a key issue - the lack of

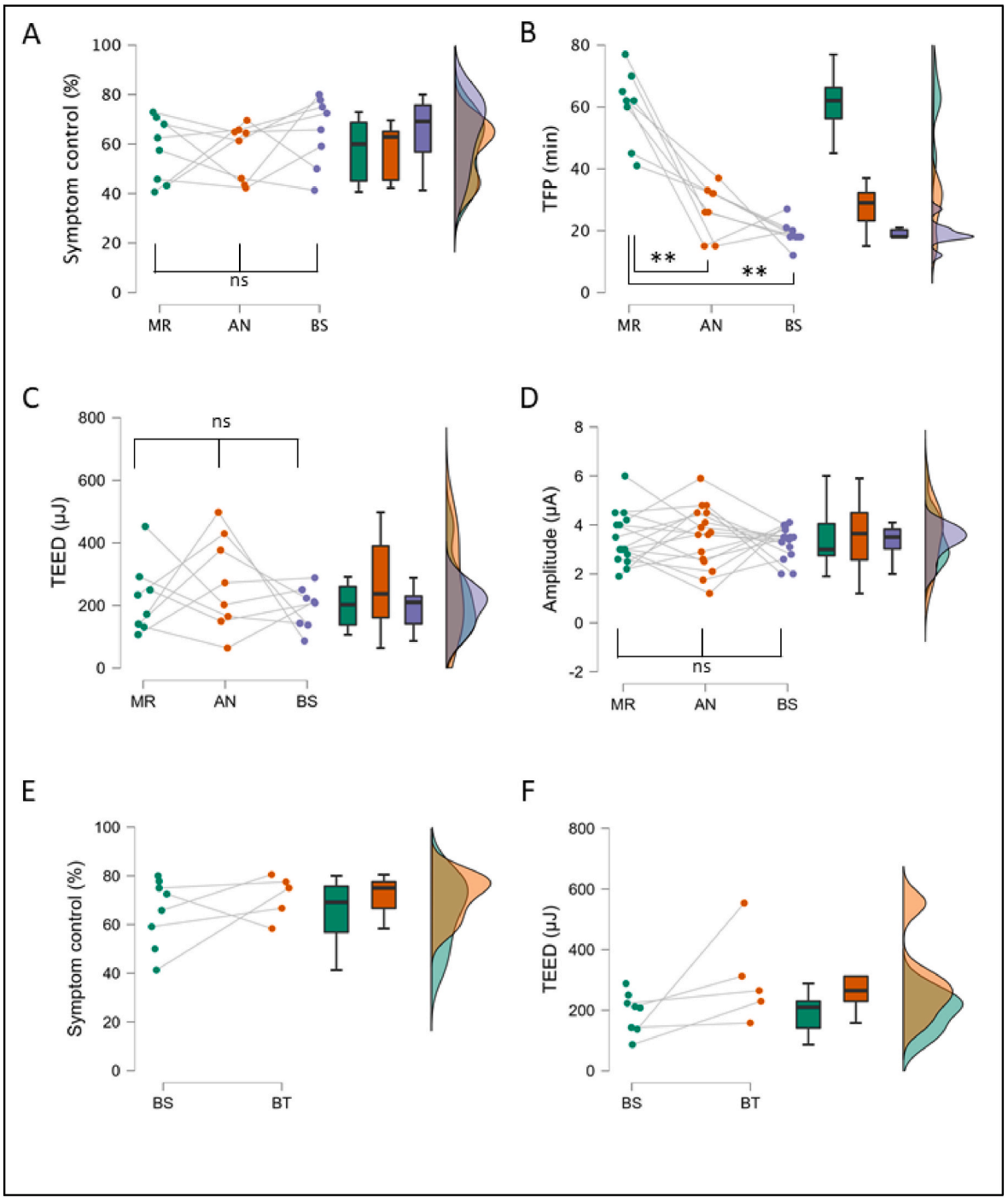

Fig. 3. **(A)** Percentage of motor score improvement between the StimOFF and StimON condition, with no significant differences. Note that this analysis was performed in the MedOFF condition to account for stimulation effects only. **(B)** Image- (AN, orange) and beta-guided programming (BS, purple) both needed significantly less TFP vs. clinically-guided programming (MR, green) (both $p < 0.001$ in ANOVA and Post Hoc testing). Of note, the standard deviation in the BS group was markedly small, indicating a very robust programming time of around 20 min. No significant differences between the groups were found for TEED **(C)**, stimulation amplitude **(D),** or any of the stimulation parameters (see also Table 1). The performance of the beta titration (BT) is summarized with the symptom control **(E)** and TEED **(F)** compared to initial beta-guided programming. As described in the Material and Methods, not all patients could be programmed with BT.
AN, anatomic programming (image-guided programming); BS, brain sense (beta-guided programming); BT, beta titration; MR, monopolar review (clinically-guided programming); TEED, total electrical energy delivered; TFP, time for programming. **$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

consensus among different programming types about the optimal contact selection.

Several factors could underlie this observation. Firstly, there might be a non-linear relationship between contact location and clinical outcome, where multiple contacts could potentially influence the same neural circuits or pathways. Secondly, the variability in individual responses to stimulation could result in some patients having a broader therapeutic window, which would allow different contacts to provide effective symptom control. Lastly, the clinical outcome measures used in this study might have limitations in sensitivity, making it challenging to

detect subtle differences between the effects of different contact configurations. Beta titration is a tool to potentially avoid STN overstimulation. We investigated this possibility in a subset of patients and showed that adjusting the stimulation amplitude with beta titration did not cause any side effects. Beta titration also resulted in a further improvement in symptom control in four of the five patients who underwent beta titration compared to the initial beta-guided programming (Fig. 3).

While our data demonstrates some potential for Beta Titration in improving symptom control and avoiding STN overstimulation, it is important to consider that this was a highly selective group, and this method was only applicable in a subset of this cohort (5/8). Although beta-guided DBS programming demonstrated reliable and robust usability, the sub-feature Beta Titration, which involves titrating the stimulation amplitude based on the beta-signal, was only investigated on an exploratory basis. This limits the generalizability of the results of the Beta Titration. In future investigations, it would be beneficial to include detailed frequency analyses of the beta peak frequencies used for programming each patient, as this information could provide valuable insights for understanding the effects of beta-titration on symptom control and optimization of DBS programming strategies.

4.2. Time required for programming

We demonstrated that DBS programming using either β-sensing or anatomical images significantly reduced programming time compared to conventional clinically guided programming (Fig. 3B). Of note, TFP with β-guided programming was extremely consistent (Fig. 3B) and limited to 18 ± 4 min (6/8 patients were programmed within 20 min or less).

This result is of great clinical relevance as the TFP has a direct impact on the daily routine in a DBS center. Shorter and more efficient DBS programming may allow more patients to be treated per day, which would reduce waiting lists and ultimately improve patient well-being, as long as comparable outcomes are achieved. In particular, the introduction of directional DBS requires a simplification of programming to reduce the clinical burden [2]. Software used for image-guided programming can shorten the TFP [18,22], as reflected in our data. However, this requires an additional platform and increases the financial cost, as it requires some expertise in neuroanatomy. DBS programming based on β-power can be performed at the bedside with a commercially available clinician programmer, reducing the financial and time burden.

4.3. Longterm impressions

In a retrospective analysis of the three-month follow-up data, we found that all eight patients adhered to their assigned program with overall satisfaction. Adjustments in the amplitude were noted in two patients for improved symptom control. However, these findings were based on patient reports and clinical impression, not on formal MDS-UPDRS III testing. Therefore, they provide preliminary, cautionary evidence that the effects of acute programming may persist over time. Given the limitations of this retrospective analysis, these observations should be interpreted with caution. More comprehensive and systematic studies are required to fully elucidate the long-term effectiveness of these programming paradigms.

4.4. Limitations

Our study has several limitations. First, the small sample size is related to the limited enrollment because few PD patients agreed to use a sensor device (i.e., Sensight and Percept PC, Medtronic, PLC). In our center, patients are offered different available DBS systems, and many chose a rechargeable system over the non-rechargeable Percept PC, despite its sensing capabilities. Second, only acute motor effects in the MedOFF state were evaluated, and therefore long-term side effects cannot be excluded. Third, beta titration was only available in a subset of patients in our study, so these beta titration-related observations remain anecdotal and need to be confirmed in larger dedicated studies. However, this demonstrates that the sensing process as such is highly dependent on good signal quality, which can easily be affected by a variety of artifacts. It is easy to imagine that closed-loop neurostimulation, which depends on robust sensing quality at all times, will pose a particular challenge to hardware and software. Fourth, as part of our clinically guided programming strategy, we skipped single testing of directional contacts with high effect thresholds if other contacts seemed preferential in the ring-mode-testing, which could potentially result in missing an effective segmented contact; however, our experience suggests that this is rarely the case if the whole ring does not yield good symptom control. Fifth, due to the nature of the study design, dopamine agonist withdrawal times may have varied across the three programming conditions, with potential for longer withdrawal periods for the second and third conditions. While the order of conditions was randomized to minimize any potential impact, we acknowledge this as a limitation of our study. Lastly, despite the strategies employed to maintain patient blinding, we acknowledge potential limitations in our blinding process. The inherent differences in systematic testing of contacts in traditional clinical programming versus selected contacts in imaging and neurophysiology programming may have provided cues to the assigned programming strategy. Nevertheless, we believe the measures taken minimized potential bias and ensured a reasonable level of concealment for the study's purposes.

5. Conclusion

Beta-guided programming using local field potentials with β-power calculation is a promising approach to optimize DBS programming in Parkinson's disease patients with STN-DBS. This study demonstrates the potential to significantly reduce programming time while achieving similar symptom control compared to conventional strategies, based on a 30-min evaluation. Its integration into the clinical DBS programmer makes it a readily accessible tool for improving current DBS programming practices.

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Data availability statement

Original data is available from the authors upon request and under respect of patient anonymity.

CRediT authorship contribution statement

Tobias Binder: Conceptualization, Methodology, Investigation, Data curation. **Florian Lange:** Methodology, Investigation, Formal analysis, Visualization, Writing – original draft. **Nicolò Pozzi:** Data curation, Investigation, Writing – review & editing. **Thomas Musacchio:** Investigation. **Christine Daniels:** Investigation. **Thorsten Odorfer:** Investigation. **Patrick Fricke:** Investigation. **Cordula Matthies:** Investigation, Supervision. **Jens Volkmann:** Investigation, Supervision. **Philipp Capetian:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, review and editing of manuscript, Supervision, Project administration.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:FL reports grants from Boston Scientific all outside the submitted work.CM reports no competing interests.JV reports grants and personal fees from Medtronic, personal fees from St. Jude, grants and personal fees from Boston Scientific, personal fees from UCB, personal fees from Merz, personal fees from Allergan, personal fees from TEVA, personal fees from Novartis, personal fees from AbbVie and personal fees from Grünenthal, all outside the submitted work.PC reports personal fees from Medtronic, personal fees and grants from Boston Scientific, personal fees and grants from Brainlab, all outside the submitted work.All other authors report no competing interests.

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Appendix A. Supplementary data

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