RESEARCH ARTICLE

Local Field Potentials Predict Motor Performance in Deep Brain Stimulation for Parkinson's Disease

CME

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ABSTRACT: Background: Deep brain stimulation (DBS) is an effective treatment option for patients with Parkinson's disease (PD). However, clinical programming remains challenging with segmented electrodes.

Objective: Using novel sensing-enabled neurostimulators, we investigated local field potentials (LFPs) and their modulation by DBS to assess whether electrophysiological biomarkers may facilitate clinical programming in chronically implanted patients.

Methods: Sixteen patients (31 hemispheres) with PD implanted with segmented electrodes in the subthalamic nucleus and a sensing-enabled neurostimulator were included in this study. Recordings were conducted 3 months after DBS surgery following overnight withdrawal of dopaminergic medication. LFPs were acquired while stimulation was turned OFF and during a monopolar review of both directional and ring contacts. Directional beta power and stimulation-induced beta power suppression were computed. Motor performance, as assessed by a pronation-supination task, clinical programming and electrode placement were correlated to directional beta power and stimulation-induced beta power suppression.

Results: Better motor performance was associated with stronger beta power suppression at higher stimulation amplitudes. Across directional contacts, differences in directional beta power and the extent of stimulation-induced beta power suppression predicted motor performance. However, within individual hemispheres, beta power suppression was superior to directional beta power in selecting the contact with the best motor performance. Contacts clinically activated for chronic stimulation were associated with stronger beta power suppression than non-activated contacts.

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Conclusions: Our results suggest that stimulation-induced β power suppression is superior to directional β power in selecting the clinically most effective contact. In sum, electrophysiological biomarkers may guide programming of directional DBS systems in PD patients.

Key Words: deep brain stimulation; Parkinson's disease; local field potentials

Introduction

Deep brain stimulation (DBS) is a highly effective treatment option for patients with Parkinson's disease.[1,2] Recently, two major innovations in DBS technology have been introduced. First, segmented electrodes which allow for steering of the electric field and second, sensing-enabled neurostimulators capable of recording local field potentials (LFPs).[3] While segmented electrodes promise to increase therapeutic flexibility through directional stimulation,[4] sensing-enabled neurostimulators provide a means to extract electrophysiological biomarkers that may aid clinical programming.[5]

Before segmented DBS electrodes were introduced, electric current could only be applied via ring contacts placed along the main axis of the DBS electrode.[3] However, deviations from the surgical target[6] may cause current spread to adjacent structures, potentially leading to therapy limiting side effects with ring stimulation. Several studies have shown that directional stimulation with segmented DBS electrodes offers a wider therapeutic window with directional DBS over ring stimulation.[4,7] However, additional segmented contacts impose greater programming burden on clinicians.[8] Therefore, the potential advantages of directional DBS systems are attenuated by a more time-consuming programming process, calling for biomarkers aiding contact selection. Beside imaging-based programming algorithms that have recently been explored in clinical studies,[9] a candidate for an even more direct biomarker is beta power recorded from the DBS target region. Resting subthalamic nucleus (STN) beta power has been related to bradykinesia and rigidity of Parkinson's disease (PD) patients in large cohorts[10,11] and its modulation by stimulation provides information on the clinical efficacy of DBS.[12-14] First evidence linking intraoperative LFP recordings with clinical outcomes has been established previously.[15-18] However, LFP recordings from DBS electrodes were only feasible in specialized research centers,[19] because directional DBS and sensing-enabled neurostimulators were not integrated within the same system until recently. Now, with the commercial availability of segmented electrodes compatible with sensing-enabled neurostimulators, the combination of both technological innovations may provide biomarkers aiding contact selection in clinical routine.

In this study, we investigate subthalamic LFPs from 16 patients with PD chronically implanted with segmented electrodes and sensing-enabled stimulators to assess the utility of beta power and its modulation by DBS for contact selection in directional DBS. Specifically, we first compare the effects of ring and directional stimulation on both subthalamic beta power and motor performance. We then assess whether stimulation-induced beta power suppression and directional beta power with stimulation turned OFF are associated with motor performance. This leads up to comparing the predictive value for contact selection and clinical stimulation settings between beta power suppression and directional beta power. Finally, we investigate the anatomical relationship of both electrophysiological biomarkers to the clinical "sweet spot". Our results provide evidence for the use of electrophysiological biomarkers acquired with sensing-enabled neurostimulators in guiding clinical programming of segmented DBS electrodes.

Methods

Participants

This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board at Charité-Universitätsmedizin Berlin (EA2/256/20) and at Universitätsklinikum Düsseldorf (2019-629_2). All patients provided written informed consent. Sixteen patients with PD who underwent DBS of the STN were included in this study (eight female; mean ± SD age 61 ± 9.87; pre-operative The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale part III [MDS-UPDRS-III] medication *off* 48 ± 18.68). Thirteen patients were included at Charité-Universitätsmedizin Berlin and three patients at Universitätsklinikum Düsseldorf. Surgery was conducted in a two-step procedure in Berlin as previously described,[20] whereas in Düsseldorf lead placement and neurostimulator implantation were performed in one session. All patients were implanted with B33005 "SenSight" directional leads (Fig. 1A and Supplementary Fig. S1) and sensing-enabled "Percept" implantable pulse generators (IPGs) (Medtronic, Minneapolis, MN). See Supplementary Table S1 for full clinical and demographic details.

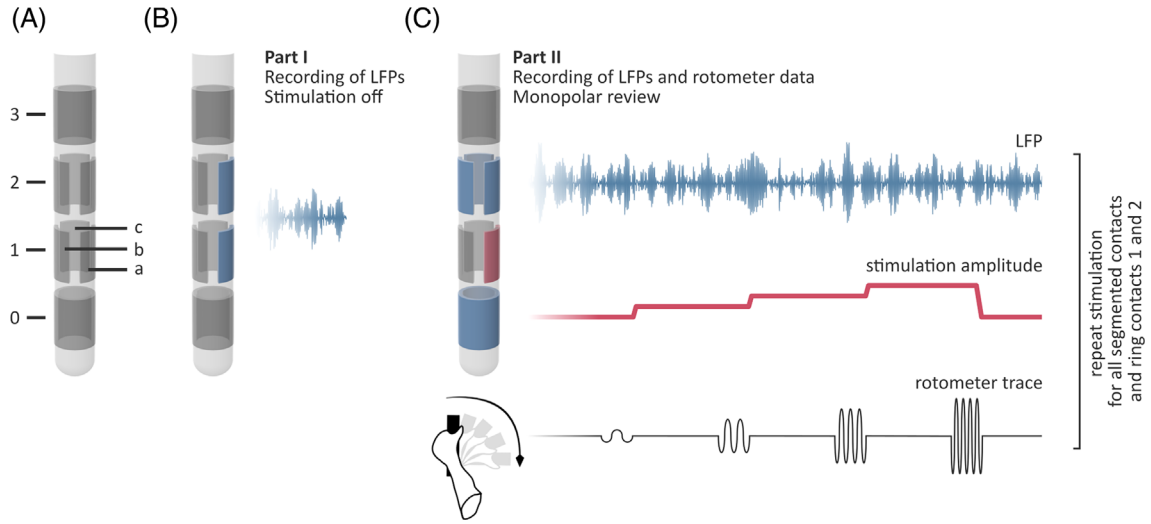

FIG. 1. Methods. (**A**) The "SenSight" directional lead's layout featuring four levels, with levels 1 and 2 comprising three segmented contacts each. (**B**) During the first part of the study, bipolar local field potentials (LFPs) were recorded using "BrainSense Survey" mode while stimulation was turned OFF and the patient resting. With this mode, LFPs were acquired from both directional contacts and ring contacts. (**C**) During the second part, "BrainSense Streaming" was used to record bipolar LFPs while stimulation was either applied over directional or ring contacts (red). LFPs were always acquired using the ring contacts adjacent to the stimulating contact (blue), irrespective of the direction of stimulation. A "rotometer" device (bottom) was used to track the handle's position during rotatory hand movements. For each tested contact, stimulation was ramped up in 1 mA steps. At every step, 2 minutes of rest were followed by 30 seconds of rotatory movements. For visualization, LFPs, stimulation amplitude, and rotometer traces are represented by artificial data. [Color figure can be viewed at wileyonlinelibrary.com]

Procedure

All recordings took place 3 months post-surgery during inpatient visits. Patients were withdrawn from dopaminergic medication for 12 hours before recordings. Stimulation was switched OFF 30 minutes before recordings.[21,22] Each recording session consisted of two parts. First, recordings were performed at rest using the "BrainSense Survey" (BSSU) mode (see below) with stimulation turned OFF (Fig. 1B). Second, a monopolar review was conducted while LFP data were acquired using the "BrainSense Streaming" (BSST) mode (see below; Fig. 1C). Here, current was applied at 125 Hz with 60 μs pulse width. Segmented contacts were tested in randomized order (directional stimulation) followed by stimulation of the whole level (ring stimulation). Monopolar reviews consisted of iterative blocks comprising a rest period of 2 minutes followed by rotatory movements[14] for 30 seconds with the hand contralateral to the side of stimulation at greatest speed and amplitude possible. After a baseline block OFF stimulation, amplitude was iteratively increased in steps of 1 mA until 3 mA were reached or patients reported side effects. In the latter case, the last block was conducted at the highest amplitude below the side-effect threshold. Before switching to the next contact, DBS was turned OFF for at least 3 minutes. All possible segments were tested in eight patients (two levels with segmented contacts per hemisphere, 96 segments) and a reduced number was tested in the remaining eight patients because of fatigue (>1 hour of recording per level). In total, 50 levels from 31 STNs (150 segments) were examined in 16 patients.

Data Acquisition

LFPs were recorded with the "Percept" IPG at a sampling rate of 250 Hz and exported for offline analysis. With BSSU, bipolar recordings were obtained from ring contacts 0 to 2 and 1 to 3, as well as from directional contacts 1a to 2a, 1b to 2b, and 1c to 2c in both hemispheres while stimulation was turned OFF (Fig. 1B). With BSST, bipolar recordings were retrieved from the ring contacts adjacent to the level on which stimulation was applied, irrespective of the direction of stimulation (eg, stimulation on contact 1a, recording from contacts 0–2) (Fig. 1C). In both modes, LFPs were analog lowpass filtered at 100 Hz and highpass filtered at 1 Hz. Rotometer data were acquired using a TMSi SAGA (sampling rate: 4000 Hz) or TMSi Porti (sampling rate: 2048 Hz; TMSi, Oldenzaal, The Netherlands) in Berlin and with the miscellaneous channels of an MEG system (sampling rate: 5000 Hz; Elekta Oy, Helsinki, Finland) in Düsseldorf. The output signal was linearly scaled from −1 to 1 and represented the handle's position.

LFP Processing

Raw LFPs were visually screened for electrocardiography and motion artifacts. For monopolar review recordings, 1 minute of motion artifact-free data was selected from each rest period. Signals were transformed to the time-frequency domain by a short time Fourier transform and averaged over time to obtain power spectra. As BSSU only allows to acquire bipolar signals, power values corresponding to each segmented

contact were generated by combining power spectra originating from both ring and segmented contacts. For example, to obtain directional power estimates for contact 1a, the spectrum of 0 to 2 was multiplied by the percentage spectrum of 1a to 2a:

$$P(f)_{1a} = P(f)_{02} \times \frac{P(f)_{1a2a}}{\frac{1}{3} \times \left(P(f)_{1a2a} + P(f)_{1b2b} + P(f)_{1c2c}\right)},$$

where P is power, f is frequency and subscripts denote recording contacts. For all recordings, beta power was extracted by averaging over the 13–35 Hz range. For BSST, beta power suppression at each stimulation amplitude was obtained by dividing by baseline beta power and multiplying by 100. Details of the processing pipeline are described in the Supporting Data.

Behavioral Data Processing

In two subjects (1 and 6), technical problems led to exclusion of behavioral data. Therefore, 27 STNs (44 levels) were available for motor performance analyses. Rotometer data were downsampled to 250 Hz. Motor performance was operationalized by rectifying the first derivate of the rotometer data (movement velocity) and the raw rotometer data (movement amplitude), respectively, followed by averaging over time. Modulation of movement velocity and movement amplitude was obtained by normalizing to baseline as described above.

Electrode Localization and Calculation of Distance to Sweet Spot

Electrodes were localized using Lead-DBS by linear co-registration of preoperative magnetic resonance imaging and postoperative computed tomography images.[23] Electrode rotation was corrected manually by the same rater for all electrodes using the orientation markers integrated in SenSight leads. The sweet spot coordinates used were established by Dembek et al.[24] First, sweet spot coordinates were transformed from montreal neurological institute (MNI) space to patient space. Subsequently, for each segmented contact, the distance to the transformed sweet spot was calculated.

Prediction of Motor Performance

To assess whether directional beta power or stimulation-induced beta power suppression may inform contact selection we first analyzed the interrelation between electrophysiological data and motor performance using Spearman's rank correlation within each STN. Next, the rank difference between the first-ranked contact for movement velocity and the corresponding electrophysiological rank was computed and normalized to the number of contacts tested within each STN. Furthermore, the cumulative probabilities of finding the best motor contact were calculated for each rank in descending order as previously described.[17] To investigate whether using both directional beta power and stimulation-induced beta power suppression may improve contact selection, a generalized linear mixed effects model (GLMM) was established to predict movement velocity based on both features in a leave-one-STN-out scheme. Model predictions were ranked and compared to the observed motor outcome as described above. Sixteen STNs with both levels tested and with at least two contacts reaching 2 mA were included.

Clinical Programming

Stimulation parameters were programmed based on blinded clinical evaluation during a 3-month and 12-month follow-up visit at both centers. To investigate a possible association between clinical programming and β activity, we compared directional beta power and stimulation-induced beta power suppression at 2 mA between stimulation contacts that were clinically selected for stimulation (used) versus inactive contacts (not used) on discharge. After the 3-month follow-up, stimulation was not active on any directional contact in one hemisphere. Therefore, 31 STNs were available for this analysis. Thirteen of 16 patients completed the 12-month follow-up, rendering 25 STNs available.

Statistics

GLMMs were used for statistical analysis to account for the non-independent data structure. *P*-values were calculated based on the t-statistic and reported alongside fixed effects estimates (β). First, we analyzed the effects of stimulation amplitude and stimulation type (ring or directional) on beta power. We further modeled the effects of stimulation amplitude and type on motor performance. These analyses focused on associations across stimulation amplitudes within each contact. We therefore tested whether beta power suppression and directional beta power were associated with motor performance across directional contacts within each STN. In a similar fashion, we analyzed the relationship between a contact's distance to sweet spot and directional beta power, beta power suppression, and motor performance. For this, we confined to data obtained at a stimulation amplitude of 2 mA. This served as a rationale for LFP-based outcome predictions, which were then established for directional beta power, beta power suppression, and for a model-based combination of both biomarkers as laid out above. Mixed models were used to assess the difference in Spearman's rank correlation coefficients and normalized rank difference between predictions. Differences in directional beta power and beta power suppression between "used" and "not used" contacts were also compared by means of mixed models. For the latter two analyses,

P-values were calculated based on the F-statistic. The log link function was used in case of exponential relationships between independent and dependent variables as revealed by data inspection. Further control analyses are outlined in the Supporting Data.

Results

Directional DBS Suppresses Beta Power and Improves Motor Performance

We first assessed how directional DBS modulates subthalamic beta power and motor performance in comparison to ring stimulation within contacts and across amplitudes. Higher stimulation amplitudes led to suppression of beta power ($\beta = -0.37$, $t = -9.76$, $P < 0.001$) (Fig. 2A) and improvement of movement velocity ($\beta = 0.21$, $t = 6.68$, $P < 0.001$) (Fig. 2B). These associations were non-linear: For example, the difference in predicted beta power for directional stimulation was 28.4% between 0 mA and 1 mA, but only 19.9% between 1 mA and 2 mA. Stimulation type (ring or directional) did not influence beta power ($\beta = -0.008$, $t = -0.45$, $P = 0.65$) irrespective of stimulation amplitude ($\beta = 0.047$, $t = 1.07$, $P = 0.28$). Likewise, there was no interaction between stimulation amplitude and stimulation type for movement velocity ($\beta = -0.043$ $t = -1.17$, $P = 0.24$), indicating that both ring and directional stimulation modulated beta power and motor performance similarly across stimulation amplitudes. We proceeded with investigating the association between beta power modulation and motor performance for both ring and directional stimulation. Movement velocity increased with stronger suppression of beta power ($\beta = -0.008$, $t = -4.69$, $P < 0.001$) (Fig. 2C). This association pertained for both ring and directional stimulation ($\beta = -0.18$, $t = -1.14$, $P = 0.26$), irrespective of the extent of beta power suppression ($\beta = 0.0025$, $t = 1.33$, $P = 0.18$). We obtained comparable results for movement amplitude, which are laid out in detail in the Supporting Data.

Directionality-Dependent Beta Power Suppression Is Associated with Motor Performance across Segmented Contacts

We could establish that beta power and motor performance were modulated by stimulation amplitude

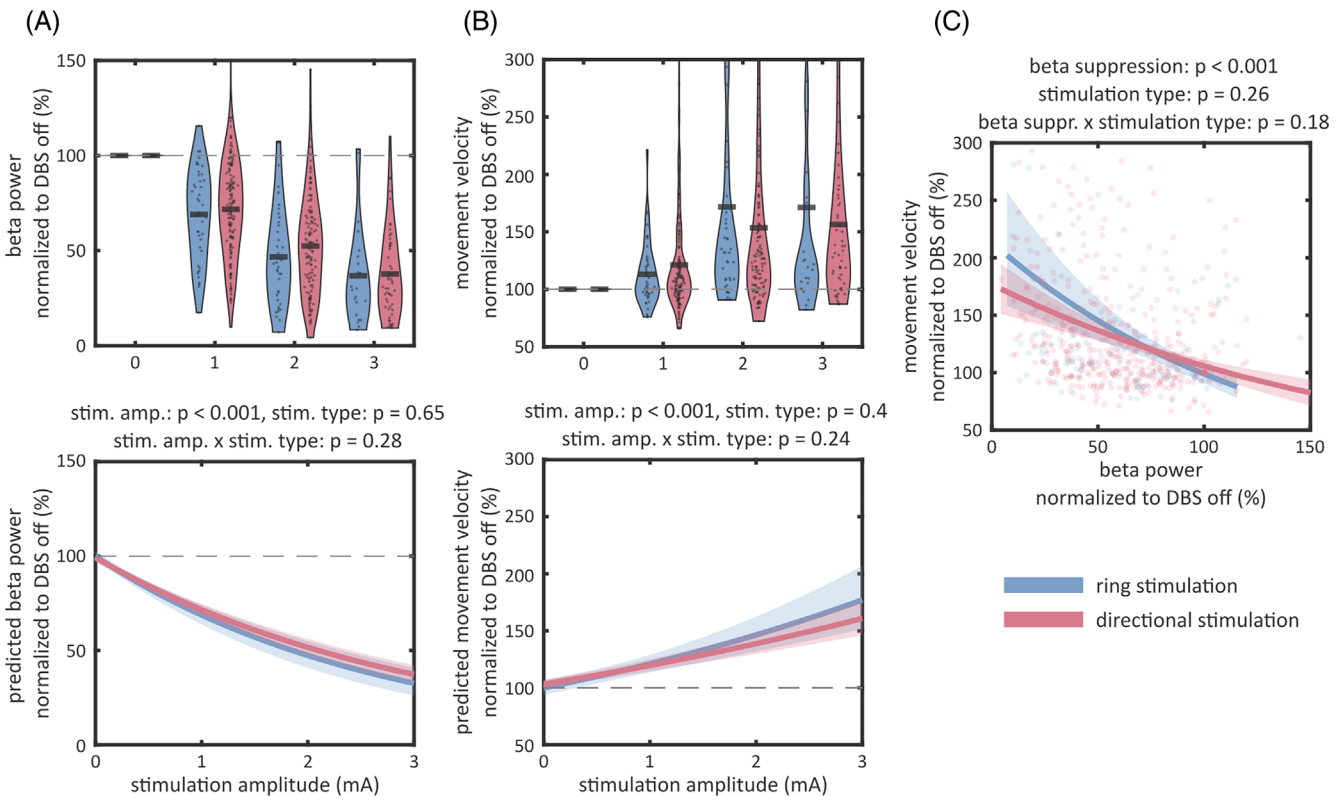

FIG. 2. Directional and ring stimulation lead to beta power suppression and improvement in motor performance. With higher stimulation amplitudes, beta power was suppressed (**A**) and movement velocity improved (**B**) for both ring and directional stimulation. Lower row: solid lines indicate the fixed effects estimates, shaded areas show the 95% confidence interval of the fixed effects estimates. (**C**) Movement velocity improved with stronger beta power suppression across all stimulation amplitudes investigated. Black solid lines indicate the mean. Colored solid lines indicate the fixed effects estimates, shaded areas show the 95% confidence interval of the fixed effects estimates. [Color figure can be viewed at wileyonlinelibrary.com]

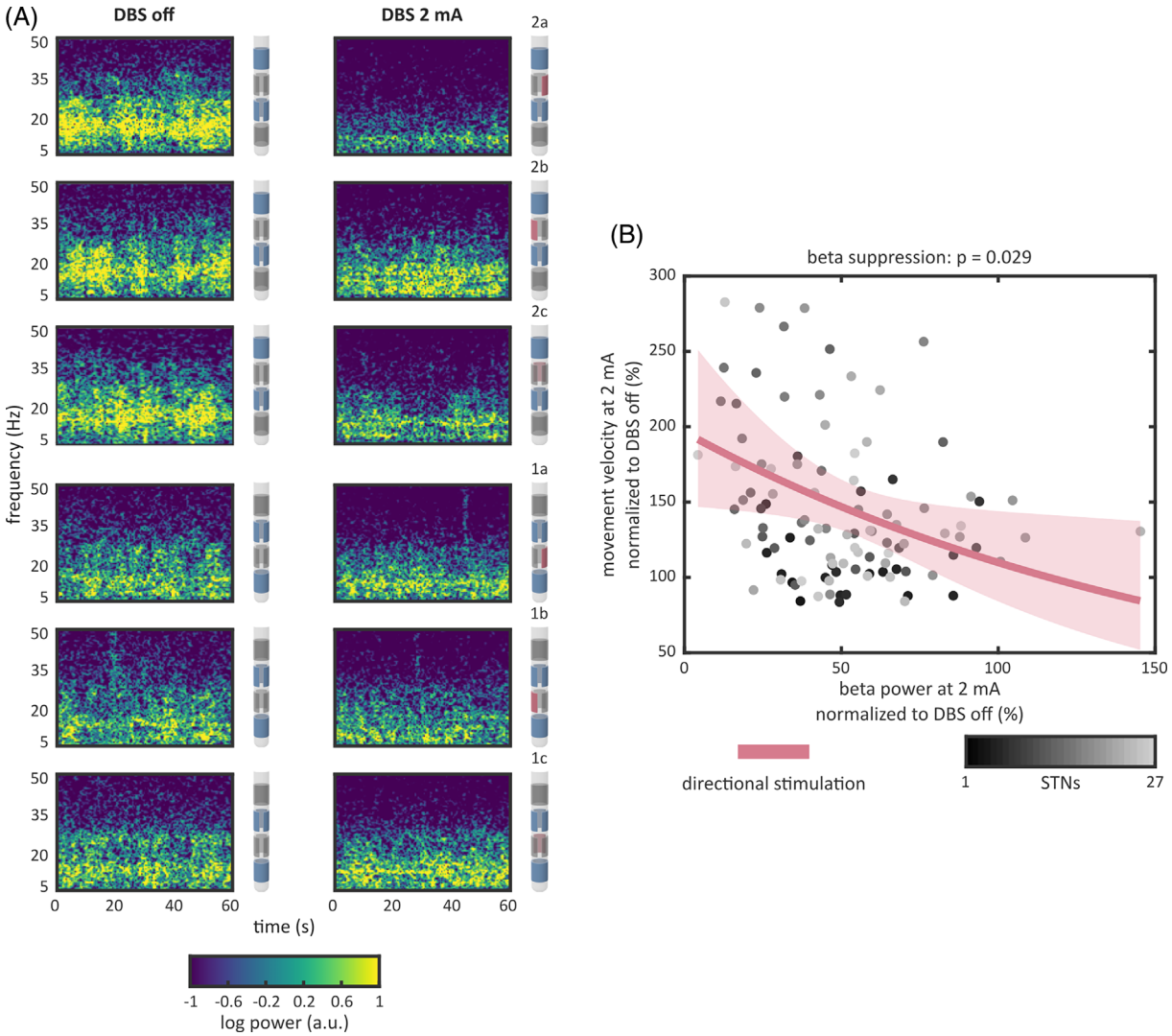

FIG. 3. Differential beta power suppression across segmented contacts informs motor performance. (**A**) Exemplar time-frequency representations for all six segmented contacts (rows) from a single subthalamic nucleus (STN) while stimulation was turned OFF (left column) and at a stimulation amplitude of 2 mA (right column). Note that within each electrode level (1 or 2), the recording contacts (blue) did not change across the different segmented contacts through which stimulation was applied (red). Therefore, differential beta power suppression was depending on the direction of stimulation: on level 2, the strongest suppression of beta power was observed when stimulating on contact 2a, whereas on contact 2b only slight changes in beta power were found. On level 1, baseline beta power was lower than on level 2 and directional stimulation did not exert a modulatory effect on β activity. (**B**) At a stimulation amplitude of 2 mA, faster movement velocity was present at contacts with stronger beta power suppression within each STN. Solid lines indicate the fixed effects estimates, shaded areas show the 95% confidence interval of the fixed effects estimates. [Color figure can be viewed at wileyonlinelibrary.com]

similarly for both ring and directional stimulation. In a next step, we investigated whether differential beta power suppression may be informative for differences in motor performance across segmented contacts. Figure 3A exemplifies differential beta power suppression across segmented contacts in an exemplary hemisphere. On the group level, differences in beta power suppression across segmented contacts were associated with motor performance: stronger beta power suppression was paralleled by faster movement velocity ($\beta = -0.006$, $t = -2.2$, $P = 0.029$) (Fig. 3B) at a stimulation amplitude of 2 mA.

Directional LFPs Are Informative for Contacts with Higher Motor Performance

As direction-dependent beta power suppression was indicative for differences in motor performance, we assessed whether this association also holds true for directional beta power with stimulation turned OFF. Figure 4A shows differential directional power spectra extracted from LFPs recorded with BSSU from an exemplar STN. On the group level, higher directional beta power across contacts interacted with stimulation amplitude in predicting stronger beta power suppression ($\beta = -0.12$, $t = -8.14$,

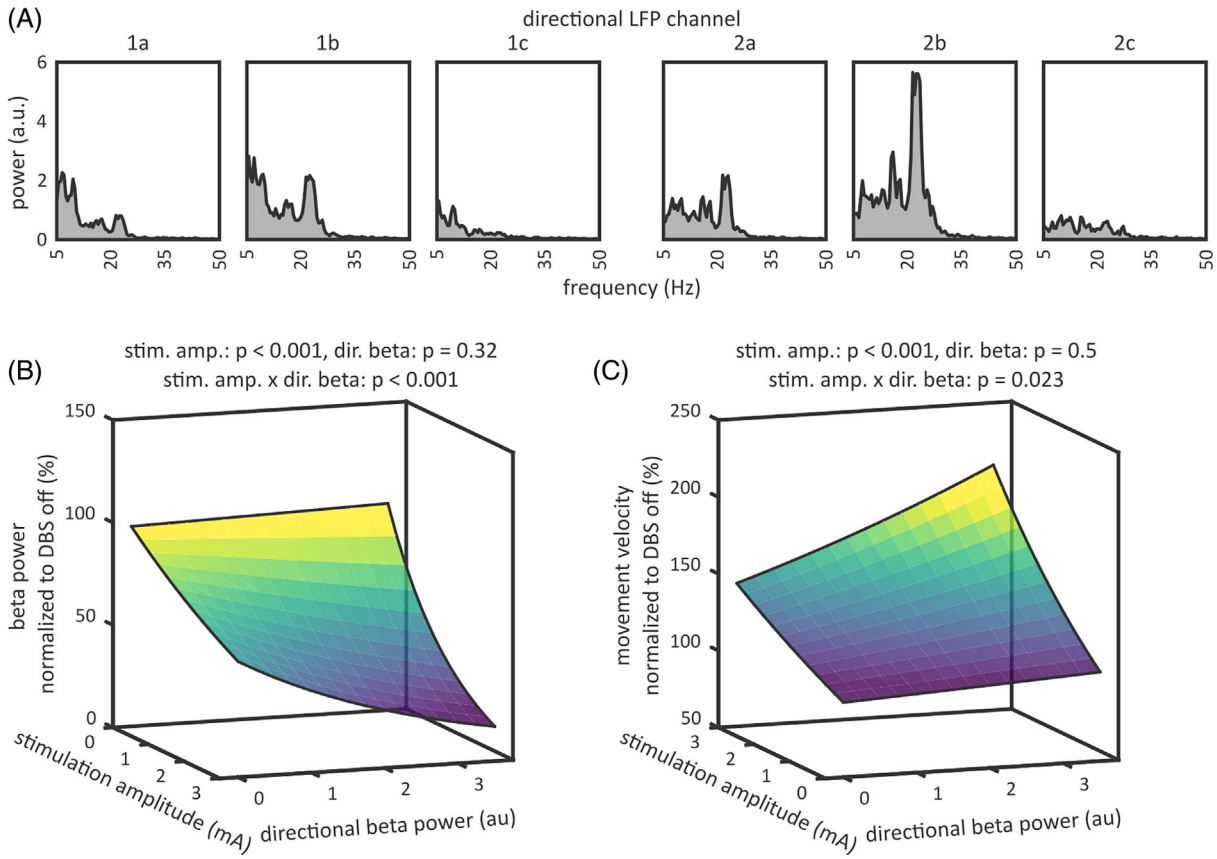

FIG. 4. Directional beta power interacts with stimulation amplitude in predicting beta power suppression and motor performance. (**A**) Exemplar power spectra of directional local field potentials (LFPs) from a single subthalamic nucleus (STN) recorded with "BrainSense Survey" while stimulation was turned OFF. Spectra associated with each segmented contact were computed by incorporating information from bipolar recordings from both ring contacts (0–2 and 1–3) and segmented contacts (1a–2a, 1b–2b, 1c–2c) into a single spectrum, respectively. In this STN, a spectral peak around 22 Hz was observed, which was more pronounced on level 2, especially in the direction of contact 2b. (**B**) beta power suppression because of directional stimulation was particularly strong on those contacts that were associated with high directional beta power. (**C**) Similarly, faster movement velocity at higher stimulation amplitudes was more evident on contacts with high directional beta power. The surface shows the fixed effects estimates, color-coded by the values of the z-axis. [Color figure can be viewed at wileyonlinelibrary.com]

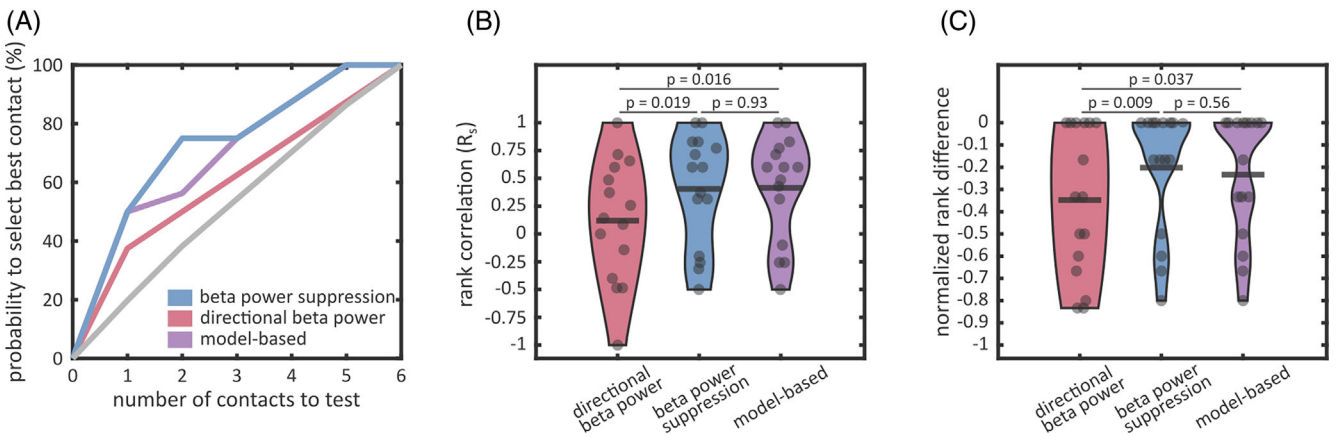

FIG. 5. Directional beta power is superior to beta power suppression in predicting motor outcomes. (**A**) Choosing contacts based on rankings of directional beta power, β suppression, or based on a model incorporating both features yielded a higher probability to select the contact with the highest movement velocity than chance level (grey line). For example, the probability to find the best contact is 75% when only considering the two contacts with highest beta power suppression. (**B**) The correlation coefficients between beta power suppression ranks and movement velocity ranks within each subthalamic nucleus were higher than those for directional beta power, whereas model-based ranks were not superior to beta power suppression. (**C**) The normalized difference between the contact ranked first on movement velocity and the corresponding rank for beta power suppression was smaller than for directional beta power. Model-based ranking did not yield an additional benefit. [Color figure can be viewed at wileyonlinelibrary.com]

$P < 0.001$) (Fig. 4B). Behaviorally, higher directional beta power with stimulation turned OFF was accompanied by stronger improvement in movement velocity with increasing stimulation amplitude ($\beta = 0.028$, $t = 2.28$, $P = 0.023$) (Fig. 4C).

Beta Power Suppression Is Superior to Directional Beta Power in Predicting Motor Performance and Clinically Activated Contacts

Having established that beta power suppression and directional beta power were associated with motor performance across contacts, we investigated whether beta power suppression and directional beta power were able to predict contact rankings based on motor performance within individual STNs and whether a model incorporating both features resulted in improved predictions. Ranking the contacts based on electrophysiological biomarkers increased the probability to choose the contact with the best motor performance above chance level (Fig. 5A). With the two contacts featuring strongest beta power suppression, there was a 75% chance to select the best contact in terms of movement velocity. There was a stronger correlation between movement velocity rankings and contact rankings based on beta power suppression than for directional beta power ($F = 5.9$, $P = 0.019$) (Fig. 5B) and there was no additional benefit of model-based rankings over beta power suppression alone ($F = 0.008$, $P = 0.93$). When only focusing on the best behavioral contact, there was a smaller difference in ranks between the contact ranked first on movement velocity and the corresponding rank for beta power suppression than for the respective directional beta power rank ($F = 7.51$, $P = 0.009$) (Fig. 5C) with no superiority of model-based rankings ($F = 0.34$, $P = 0.56$). These findings were reflected in clinical programming settings at the 3- and 12-months follow-up visits. Stronger beta power suppression at 2 mA was found in those contacts that were used clinically ($F = 9.91$, $P = 0.002$ at 3 months; $F = 14.32$, $P < 0.001$ at 12 months) (Supplementary Fig. S2A). The relation between stronger directional beta power and clinically chosen active contacts, however, did not reach statistical significance at 3- or 12-months follow-up ($F = 3.45$, $P = 0.065$ at 3 months; $F = 2.234$, $P = 0.14$ at 12 months) (Supplementary Fig. S2B).

Directional Beta Power and Beta Power Suppression Are Related to the Distance to Sweet Spot

Finally, we analyzed how a contact's distance to a predefined anatomical sweet spot influences the directional beta power at that contact and the extent of beta power suppression. Within STNs, contacts that are closer to the sweet spot featured higher directional beta power than more distant contacts ($\beta = -0.34$, $t = -2.6$, $P = 0.01$) (Supplementary Fig. S3A). Likewise, we found that a smaller distance to sweet spot was associated with stronger beta power suppression at higher stimulation amplitudes ($\beta = 0.1$, $t = 6.29$, $P < 0.001$) (Supplementary Fig. S3B). Importantly, the distance to sweet spot also interacted with stimulation amplitude in predicting movement velocity ($\beta = -0.05$, $t = -2.39$, $P = 0.017$) (Supplementary Fig. S3C).

Discussion

In this study, we investigated how subthalamic beta power and its modulation by DBS inform motor responses to directional stimulation in chronically implanted patients with PD. We could show that directional stimulation induces beta power suppression and motor improvement in a similar way to ring stimulation. Furthermore, we evaluated whether beta power suppression and resting state directional beta power with stimulation turned OFF are valuable biomarkers that can be used to guide clinical DBS programming. Here, we found that both stronger beta power suppression and higher directional beta power were associated with better motor performance across segmented DBS contacts. However, beta power suppression was superior to directional beta power in predicting the contact with the best motor performance within individual hemispheres. This was also reflected in blinded contact selection during long-term clinical programming, with activated contacts featuring stronger beta power suppression during DBS. Finally, we could show that both electrophysiological biomarkers are also related to the anatomical "sweet spot". Our results therefore provide a rationale for electrophysiology-guided DBS programming at the bedside.

Stimulation Amplitude Modulates Beta Power and Motor Performance in Directional DBS Similar to Ring Stimulation

Hitherto, investigations on the impact of DBS on subthalamic beta power primarily employed non-segmented ring electrodes using either external research amplifiers[25] or sensing-enabled neurostimulators.[12,13,26,27] Although it was shown that directional stimulation is able to suppress beta power in the intraoperative setting,[28] the exact relationships between stimulation amplitude, beta power modulation and motor performance were unclear for directional DBS. Our results show that the association between stimulation amplitude and beta power suppression is comparable to the dose–response pattern observed with ring stimulation: beta power is modulated by DBS in a non-linear way, with less additional modulation achieved at higher stimulation

amplitudes.[12,25] Moreover, motor performance was associated with the degree of beta power modulation, further reflecting previous data obtained with ring stimulation.[12-14] In sum, our findings implicate that local electrophysiological and behavioral responses to directional DBS do not qualitatively differ from conventional ring stimulation. Importantly, we show for the first time that directional stimulation allows for artifact-free recordings of local β band activity using a chronically implanted pulse generator and leads to direction-specific modulation of β band activity, which in turn is related to motor performance. These results imply that closed-loop DBS based on local beta power modulation may also be feasible with directional DBS.

Directional Beta Power and Stimulation-Induced Beta Power Suppression as Biomarkers for Contact Selection with Segmented Electrodes

A pertinent issue with directional DBS is the manifold degrees of freedom for contact selection[29] leading to substantially increased programming time over conventional ring stimulation.[8] Besides imaging-based approaches, electrophysiological profiling has been suggested as one way to reduce this complexity and to support clinical programming.[17] Generally, such electrophysiological features can be obtained under ongoing stimulation or with DBS turned OFF. With ongoing stimulation, differential electrophysiological responses due to changes in the direction of stimulation have been reported locally in the STN,[28] but also in the prefrontal and motor cortex as indicated by means of evoked cortical potentials.[30,31] However, subthalamic LFP recordings with simultaneous directional stimulation were not commonly available until recently because of the need for specialized intra- or perioperative recording setups. Using novel IPG technology in conjunction with directional DBS leads, our results demonstrate that direction dependent differences in beta power suppression are associated with the degree of motor improvement. However, to obtain electrophysiological responses to (directional) DBS, contacts still need to be activated for a reasonable amount of time, though, mitigating advantages over clinical testing in the time spent on DBS programming. To circumvent this limitation, differences in directional beta power in LFPs recorded from segmented electrodes with stimulation turned OFF were previously shown to be associated with motor improvement as well.[15-17,32,33] Segmented electrodes may help to obtain "more local" LFPs and therefore identify distinct oscillatory activity in smaller neuronal clusters compared to recordings from ring contacts.[34] However, previous studies were linking intraoperative directional beta power to the contact's therapeutic window and clinical efficiency, which comes with several limitations. For instance, DBS electrodes might rotate in the acute post-operative period and changes in contact impedances may accrue over time.[35] Furthermore, intraoperative directional LFP recordings are harder to obtain and require specialized personnel as opposed to LFP recordings acquired with sensing-enabled IPGs. Our results partly support previous data from the intra- and perioperative setting,[15,17,32] as directional beta power extracted from LFPs recorded in chronically implanted patients was informative for short-term improvement in motor performance. However, our data suggests that the extent of beta power suppression constitutes a biomarker that is more closely related to short- and long-term clinical improvement and programming settings, respectively, than directional beta power with stimulation turned OFF. This may be partly because of the processing steps needed to link biomarkers extracted from bipolarly acquired LFPs to single (directional) contacts, for which there is no gold standard.[5] Importantly, the strength of the association of both beta power suppression and directional beta power to motor performance will only allow to guide, but not to replace clinical programming. Combining image-guided algorithms[9] and other biomarkers such as β band activity will help to improve future programming algorithms.[33]

Electrophysiological and Imaging Biomarkers Are Anatomically Related

Previous work has identified functional sweet spots in the dorsolateral STN that can predict motor improvement with DBS in PD.[24] In our cohort, a contact's distance to sweet spot was related to both beta power suppression and directional beta power. Using segmented DBS electrodes, our results corroborate previous studies establishing that β oscillatory activity is highest in the dorsolateral STN.[36] This motivates further research investigating the utility of combining anatomical and electrophysiological biomarkers for contact prediction.[33]

Linking Electrophysiology and Directional Stimulation for Personalized and Automatized DBS

In this study, we could show that (1) beta power modulation through directional DBS is qualitatively similar to ring stimulation and (2) that both beta power modulation and directional beta power are informative for short-term motor response, with beta power suppression featuring higher predictive value. The implications of these results for future developments in DBS technology are twofold. First, our results suggest the feasibility of integrating adaptive DBS[37-39] with directional stimulation. Current DBS systems capable of adaptive stimulation feature restricted options for

contact selection, potentially reducing the number of patients suitable for closed-loop stimulation.[40] Directional adaptive stimulation could mitigate this limitation by increasing the number of available contacts, for example, in patients with suboptimal lead placement. Second, previous studies introduced automated programming algorithms that predict stimulation settings based on electrode positioning.[9,41-44] These imaging-based programming algorithms may be further improved by the integration of easily acquirable electrophysiological data.[33] This might especially hold true for longer follow-up periods, because changes at the electrode tissue interface,[45,46] impedance changes,[35] alterations of the spatial distribution and extent of oscillatory activity[47] or changes in clinical symptoms might warrant adaptation of stimulation settings. In this situation, LFPs obtained at the day of (re-)programming may provide spectral characteristics reflecting the current state, potentially improving the algorithm's performance in predicting optimal stimulation settings.

Limitations

Several limitations need to be addressed. First, our analyses were restricted by the IPG's technical capabilities. With a sampling rate of 250 Hz and a hardware lowpass filter at 100 Hz, other spectral features than beta power that were found to be associated with motor performance in PD could not be investigated.[48] Furthermore, recording modalities can influence the oscillatory activity measured. With BSSU, bipolar recordings of relatively short duration and restricted to adjacent ring or directional contacts are available. However, monopolar recordings from the contact of interest[17] and for longer durations[15] as conducted in intraoperative settings may yield more accurate and robust spectral estimates. Moreover, if both recording contacts lie within the oscillatory region, β-based contact predictions might be impaired because only minor potential differences will be captured,[34] but stimulation induced improvement will be pronounced. Predicting the contact with the best motor performance was done at a fixed stimulation amplitude of 2 mA to ensure comparability across contacts. However, at 2 mA maximum stimulation efficacy might not have been reached on some contacts, whereas on others, subtle motor deterioration near the clinical side effect threshold might have emerged. Both effects might bias contact predictions. Moreover, we focused on bradykinesia as the target symptom and results might not apply to patients with tremor-predominant disease. Finally, we conducted our study in a laboratory setting with patients performing a simple motor task to quantify motor performance. This setting does not allow drawing conclusions on the association between electrophysiological patterns and other motor symptoms such as tremor, gait or speech impairment, non-motor symptoms, or quality of life. For this, prospective clinical studies comparing clinical and LFP-based programming with fine-grained behavioral assessments are needed.

Conclusion

In this study, we could show that directional DBS modulates subthalamic beta power and motor performance in a similar way as conventional ring stimulation. Differential beta power suppression and directional beta power across contacts were both informative for motor performance in chronically implanted patients. Importantly, beta power suppression was superior in predicting the contact with the best motor performance over directional beta power. Although prospective clinical studies will be needed to assess the long-term efficacy of LFP guided DBS programming, our results underline the potential value of DBS electrophysiology in guiding clinical care of patients with PD and may pave the way for closed-loop directional DBS.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

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