Directional Local Field Potentials in the Subthalamic Nucleus during Deep Brain Implantation of Parkinson’s Disease Patients

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Abstract

Segmented deep brain stimulation leads feature directional electrodes, that allow for a finer spatial control of electrical stimulation compared to traditional ring-shaped electrodes. These segmented leads have demonstrated enlarged therapeutic windows and have thus the potential to improve the treatment of Parkinson’s disease patients. However, this is accompanied by complex and time-consuming device programming. Here, we investigated whether directional local field potentials can help identify the best stimulation direction to assist device programming.

Four Parkinson’s disease patients underwent routine implantation of the subthalamic nucleus. First, local field potentials were recorded in three directions for two conditions: In one condition the patient was at rest, in the other condition the patient moved their arm. Second, current thresholds for therapeutic and side effects were identified intraoperatively for directional stimulation. This determined the 1st, 2nd and 3rd best stimulation direction. The spectral power of the beta frequency band (13–35 Hz) and its sub-bands were analyzed in more detail post-hoc.

The direction with the highest spectral power in the total beta band was most indicative of the 1st best stimulation direction. The resting condition seemed to be slightly more informative about the best stimulation direction than the moving condition.

Directional local field potentials can therefore help identify the best stimulation direction. Further studies with larger sample sizes are needed to better distinguish the informative value of different conditions and the beta sub-bands.

# Introduction

Deep brain stimulation (DBS) is an effective treatment option for movement disorders such as advanced Parkinson’s disease, essential tremor or dystonia (Deuschl, 2006; Weaver, 2009). Stimulation leads are implanted into specific structures of the basal ganglia. In Parkinson’s disease, the subthalamic nucleus is a preferred target. Accurate and precise lead placement in the dorsolateral motor part of the nucleus is essential for beneficial outcome (Bot et al., 2018; Wodarg et al., 2012). Modern stereotactic surgery with image-guided navigation and intraoperative microelectrode recording can achieve sub-millimeter targeting accuracy (Nowacki et al., 2017), but deviations of about 2 mm or more were reported for other surgical approaches (Guo et al., 2007; Lee et al., 2018). These deviations increase the likelihood of stimulation-induced side effects and up to 50 percent of implanted patients can be affected (Volkmann et al., 2009).

To reduce the likelihood of side effects, segmented leads were introduced (Pollo et al., 2014). These have more and smaller electrodes that allow for directional stimulation, i.e., they can steer current into a specific direction of interest in contrast to classic omnidirectional stimulation. Put differently, they can steer the current *away* from certain regions to avoid side effects. Indeed, directional stimulation has demonstrated higher side effect thresholds than omnidirectional stimulation in chronically implanted patients (Contarino et al., 2014; Dembek et al., 2017).

Monopolar review is the standard programming approach to identify these therapeutic and side effect thresholds for each electrode. It was originally proposed for classic omnidirectional leads with four electrodes (Volkmann et al., 2006). But the larger number of electrodes on segmented leads (e.g., eight electrodes for Boston Scientific’s Vercise Directional or St. Jude Medical Infinity) has markedly increased programming time and complexity (ten Brinke et al., 2018). Therefore, additional tools are needed to support programming.

Electrophysiological information has been suggested as a programming tool to identify the best stimulation direction (Bour et al., 2015; Tinkhauser et al., 2017a). Local field potentials (LFP) recorded in the subthalamic nucleus are an established biomarker for Parkinson’s disease. Excessive oscillations in the beta frequency band (13–35 Hz) were found to be correlated with the severity of the disease (Chen et al., 2010; Hammond et al., 2007; Little et al., 2012) and their suppression by DBS was also found to be correlated with motor improvement (Kühn et al., 2008). With segmented leads, stimulation in the direction with the highest power in the beta frequency band was associated with better motor improvement (Bour et al., 2015) or a wider therapeutic window (Tinkhauser et al., 2017a) than stimulation in other directions with lower power in the beta frequency band. Both these studies recorded LFP intraoperatively with patients *at rest*. However, motor tasks have been shown to decrease the power in the beta frequency band (Kühn et al., 2004) or modulate specific spectral bands (Tinkhauser et al., 2019). This may therefore serve as supplementary information for programming. In the exploratory study here, we recorded LFPs therefore in two conditions: i) with patients at rest and ii) with patients moving their arm. By analyzing the spectral power in the total beta frequency band and its sub-bands, we investigated whether and how the resting and moving conditions are indicators of the best stimulation direction.

# Materials and Methods

## Patient Recruitment, Surgical Procedure and Intraoperative Assessment

Four patients with Parkinson’s disease were included in this study at the University Hospital of Bern. Two patients were female; ages ranged from 33 to 70 years with a median age of 62 years. The local ethics committee and the Swiss Competent Authority approved the study protocol, which conformed to the Good Clinical Practice guidelines and the International Organization for Standardization 14155 standard. All four patients provided written informed consent and represented a subset of our previous study (Pollo et al., 2014), who in addition agreed to LFP recordings. These were patients 9, 11, 12 and 13 in the previous study and relabeled here Patients 1 through 4 (Table 1).

The DBS surgery was performed as detailed previously (Pollo et al., 2014). For surgical planning, preoperative magnetic resonance images were coregistered with stereotactic computer tomography images. The patients were off medication and they were implanted under local anesthesia with a stereotactic frame (Leksell frame, Elekta, Stockholm, Sweden). The patients were implanted bilaterally, but testing with the segmented lead was performed only in the first hemisphere operated on.

First, microelectrode recording and macrostimulation were performed to confirm the location of the subthalamic nucleus and to identify the target trajectory and target depth for permanent implantation (systematically 2 mm after electrophysiologically determined entry into the nucleus).

Second, the segmented lead was inserted (directSTN Acute, Aleva Neurotherapeutics, Lausanne, Switzerland, Fig. 1A). It was placed in the same trajectory and at the same depth as intended for the permanent lead. The segmented lead’s first directional electrode at 0° was oriented towards medial, the second electrode at 120° towards antero-lateral and the third electrode at 240° towards postero-lateral. The surgeon used a marker line at 0° along the lead for orientation and inserted the lead without extra rotation. The depth of the segmented lead was intraoperatively confirmed with fluoroscopy. We did not verify the orientation of the lead at target depth with imaging, but relied on the marker line at 0°.

Third, the segmented lead was used for intraoperative LFP recording. The three directional electrodes on the distal level were used to record LFP simultaneously for twenty seconds. The electrical return was set to the cannula, 19 mm away from the recording contacts. The LFPs were recorded for a resting condition (i.e., patient at rest) and then a moving condition (i.e., patient moved their arm). However, the approved study protocol did not include instrumentation or experimental steps to synchronize movement and LFP recording. The LFPs were acquired with the Medtronic Leadpoint system (Medtronic, Fridley, MN, USA) with a sampling rate of 24 kHz for each direction. The Leadpoint system was additionally configured to apply a band-pass filter between 5 Hz and 5 kHz, and a notch filter at 50 Hz.

Fourth, the segmented lead was used for intraoperative clinical testing. It was connected to an external neurostimulator with multiple independent current-driven sources (Osiris Stimulators, Model 504196, Inomed GmbH, Emmendingen, Germany). Each of the three directional electrodes was tested with monopolar stimulation. The stimulation pulses were cathodic-first with a pulse width of 90 µs and frequency of 130 Hz. A metal plate was used as a distant current return and placed in the subclavicular area, similar to the area for the permanent implantable pulse generator. A separate operator configured the stimulation direction and current amplitude, thus the patient and the clinician assessing the clinical effects of stimulation were blinded to the stimulation configuration.

The clinical effects were assessed based on the rigidity of the patient’s hand. The assessment was performed by the same experienced neurologist for all four patients. The stimulation current was increased in 0.2 mA steps to determine the therapeutic current threshold, i.e., the lowest stimulation current that resulted in no rigidity. Then the stimulation current was further increased to determine the side effect current threshold, where a sustained side effect such as paresthesia, dysarthria or focal muscular contraction was observed. The difference between the two thresholds was defined as the *therapeutic window* and was used to rank the stimulation directions. The direction with the largest window was ranked as 1st best direction and so on. When directions had the same therapeutic window, the direction with the lower therapeutic current threshold was ranked higher. Therapeutic current thresholds, side effect current thresholds and therapeutic windows for all patients and directions are listed in Table 1.

Fifth, the segmented lead was removed after clinical testing and the permanent lead (Medtronic model 3389) was inserted using the same guide tube.

## Data Analysis

The LFP recordings were analyzed post-hoc with Matlab 2016b (MathWorks, Natick, MA, USA). First, the recordings were downsampled to 375 Hz and visually inspected for artifacts. Power spectral densities were then computed with the Welch method with 25 percent overlap and a spectral frequency resolution of 0.5 Hz. The spectral power of the beta frequency band was calculated as the area under the density curve between 13 and 35 Hz (Fig. 1B). Furthermore, we calculated the power in three sub-bands: low beta (13–20 Hz), high beta (20.5–35 Hz) and peak beta, i.e., 2 Hz around the beta peak (Tinkhauser et al., 2017a). The spectral power was normalized to the average power in the beta frequency band across the three recorded directions (Geng et al., 2018). This normalization was done separately for the resting and moving conditions. For the comparison of movement condition versus resting condition, the normalization factor from the moving condition was applied to both conditions. For the statistical analysis of patient averages, a one-way ANOVA was used with a significance threshold of 0.05. For the correlation of power in the beta band and the therapeutic window, we normalized the therapeutic windows for each patient and then used Spearman’s rank correlation.

# Results

## Power Spectral Densities

We recorded directional LFPs with a segmented lead in four Parkinson’s disease patients undergoing DBS implantation of the subthalamic nucleus. Filtered voltage traces and power spectral densities for the resting condition are illustrated for Patient 2 in Fig. 1B. The power spectral densities of the other patients and conditions are shown in Fig. 1C. Patient 1 had a spectral peak in the high beta band, Patients 2 and 4 in the low beta band, but Patient 3 had no clear spectral peak (27.5, 18.5 and 20 Hz, respectively).

## Power for Different Directions and Conditions

We observed power differences for the three directions in all patients (Figs. 2, 3). Generally, the directional differences were consistent across the resting and moving conditions as well as across the sub-bands. For instance for Patient 2 resting condition, the highest power in the total beta frequency band was recorded in the antero-lateral direction followed by the postero-lateral and medial directions. This directional ranking remained consistent across the sub-bands and was also observed in the moving condition. Only Patient 1 showed a change of directional ranking for the low beta and peak beta sub-bands compared to the other bands.

The most noticeable directional differences were observed for Patient 2. For the other patients, directional differences were less marked and no sub-band emphasized directional differences in particular.

Calculating the power ratio of moving-to-resting condition showed various changes in the beta band and its sub-bands (Fig. 4). The ratios for the total beta band indicated only minor changes between the conditions (i.e., ratio of 1). The ratios for the low beta band indicated a decrease in power in the movement condition (i.e., ratio less than 1). This decrease was most marked for Patients 1 and 3. The ratios for the high beta band, on the other hand, indicated an increase in power in the movement condition (i.e., ratio greater than 1). This was most noticeable in Patients 2 and 4. The power in the peak beta band indicated an increase in power in the movement condition for Patient 1, and only small changes for Patients 2 and 4. In terms of directions, the ratios did not show a tendency.

## Power and Best Stimulation Direction

Averaging across the four patients, we observed that the 1st best stimulation direction had the highest spectral power, the 2nd best stimulation direction had the second largest power and the 3rd best direction had the lowest power (Fig. 5). Importantly, this was valid for both the resting and moving conditions, for the total beta frequency band and all the three sub-bands. The directional differences were most noticeable for the total beta frequency band. A statistically significant difference was found for the resting condition in the total beta band between the 1st and 3rd best stimulation direction (p = 0.04). The power ratio of moving-to-resting did not show a trend across patients.

Finally, we observed a significant correlation between power in the total beta frequency band and normalized therapeutic window (Spearman’s rank correlation p = 0.004, rho = 0.77, resting condition, Fig. 6). The correlation was also significant for the power in the high beta band (p = 0.01, rho = 0.69, resting condition). No other significant correlations were found.

# Discussion

Classic omnidirectional DBS is often limited by stimulation-induced side effects caused by current spread to non-targeted brain regions. To overcome this limitation, directional DBS with segmented leads enable current steering to contain the current to targeted brain regions. It has demonstrated clinical potential (Contarino et al., 2014; Dembek et al., 2017; Pollo et al., 2014), but has also increased programming complexity (ten Brinke et al., 2018). Tools to assist programming are therefore needed. Local field potentials have been suggested to identify the best stimulation electrode (Bour et al., 2015; Tinkhauser et al., 2017a). Here, we investigated the relation between directional LFPs and best stimulation directions by recording intraoperative LFP in four patients during a resting and a moving condition.

First and most importantly, we found that ranking directions according to their power in the *total beta frequency band* mirrored the ranking of best stimulation directions. In other words, the direction with the highest power was also the 1st best stimulation direction (on average and in three out of four patients). Our finding is in agreement with previous studies that recorded directional LFPs with patients at rest. These reported better motor improvement or wider therapeutic window for stimulation in the direction of highest beta activity (Bour et al., 2015; Tinkhauser et al., 2017a). The direction with the highest beta activity may point towards a highly pathological cell cluster in the subthalamic nucleus that limits information coding in the motor network of the brain (Little and Brown, 2014). Stimulation in that direction may suppress beta activity as has been shown with omnidirectional leads (Kühn et al., 2008) and segmented leads (Bour et al., 2015). This in turn may release information flow in the motor network as demonstrated in computational simulations (Humphries et al., 2018; Müller and Robinson, 2018) and thus improve motor symptoms.

Second, our main finding was valid for both the resting and moving conditions. We would argue that the resting condition seemed more informative than the moving condition in our study given the slightly larger directional differences in power for the resting condition (i.e., the 1st and 3rd best stimulation directions were significantly different). We were additionally interested in a moving condition as it has been shown that movement decreases activity in the beta band, in particular directly after movement onset (Kühn et al., 2004). However, the protocol of this exploratory study did not include synchronization of LFP recording and movement onset of the arm. Thus we were not able to analyze temporal characteristics, which may have added directional information as has been recently suggested in non-human primates (Zhang et al., 2018) or patients (Tinkhauser et al., 2019).

Third, we analyzed three beta sub-bands, and these confirmed in general the directional information derived from the total beta band. We observed spectral peaks in the low and high beta band in three patients, whereas one patient did not have a clear peak. The beta band was divided into a low and a high beta band previously to discuss different influences (Priori et al., 2004). Spectral peaks in the low beta band were significantly reduced by acute antiparkinsonian medication (levodopa), while activity in the high beta band was affected by movement (Kühn et al., 2004; Tinkhauser et al., 2019).The divergence of peaks in our cohort may help explain why none of the sub-bands provided additional directional information. The divergence also seems to agree with a previous study suggesting that the beta band profile was a patient-specific ‘fingerprint’ (Bronte-Stewart et al., 2009). This view has been recently supported by a computational study of LFPs (Maling et al., 2018).

Several limitations of our study are noteworthy. Our recordings were performed at one depth only due to intraoperative constraints, but the beta band profile changes along the subthalamic nucleus (Bour et al., 2015; Geng et al., 2018; Horn et al., 2017). We only tested patients with rigidity dominant Parkinson’s disease, though LFPs were reported to be symptom-specific (Fernández-García et al., 2017; Telkes et al., 2018). Our exploratory study examined the averaged power in the beta band across 20-second recordings and did not analyze beta bursts that may reveal further information (Tinkhauser et al., 2017b, 2018). Future studies therefore need to shed more light on the beta band or beta burst profile of Parkinson’s disease. In the meantime, the total beta band may be the most robust indicator of best stimulation direction.

In summary, directional LFPs were indicative of the best stimulation direction. Specifically, the power in the total beta band in the resting condition was the best indicator. This preliminary finding needs to be confirmed in a future study with a larger patient cohort. This study should also have a refined protocol to better analyze the movement condition and help understand the patient-specific beta band profile.

Table . Patient details and best stimulation directions with therapeutic windows in mA.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Patient | Gender | Age | Main symptom | 1st best direction (mA) | 2nd best direction (mA) | 3rd best direction (mA) |
| 1 | female | 69 | rigidity | antero-lateral (2.7) | medial (2.7) | postero-lateral (2.1) |
| 2 | male | 55 | rigidity | antero-lateral (2.1) | postero-lateral (1.3) | medial (1.3) |
| 3 | female | 70 | rigidity | medial (2.4) | antero-lateral (1.6) | postero-lateral (0.7) |
| 4 | male | 33 | rigidity | medial (2.7) | antero-lateral (2.4) | postero-lateral (1.7) |

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# Author Contributions

TAKN: data analysis, visualization, manuscript original draft and editing.

MS: data curation and manuscript review.

AM: conceptualization, data curation.

AD: data curation.

CP: conceptualization, data curation, supervision, manuscript review and editing.

# Conflict of Interest

TAKN was previously an employee of Aleva Neurotherapeutics SA and has no financial stake with the company.

MS has received financial support from Boston Scientific, but not related to this study.

AM is a co-founder of Aleva Neurotherapeutics.

AD is an employee of Aleva Neurotherapeutics.

CP is a co-founder of Aleva Neurotherapeutics and did not receive any honorarium or consulting fees for this study from Aleva Neurotherapeutics. He has received consulting fees from Boston Scientific, but not related to this study.

# Contribution to the Field (max 200 words)

Directional deep brain stimulation with segmented leads can significantly improve the treatment of patients with movement disorders. However, segmented leads come with a higher programming complexity and tools are needed to assist programming. Our study adds evidence that directional local field potentials can help identify the best stimulation direction. Specifically, the direction with the highest spectral power in the total beta band (13–35 Hz) was also the best stimulation direction across four patients tested intraoperatively. Our study also highlights the need for a study with a larger cohort to better understand differences between resting and moving conditions, and to investigate the beta band profiles of Parkinson’s disease.

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# Data Availability

Raw voltage values for all four patients will be uploaded as comma-separated-value files to BORIS, the University Bern’s open repository. The files will be publicly accessible upon publication. For review purposes, the reviewers may request these files from the corresponding author at any time.

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**Figure 1.** Segmented lead and recording of directional local field potentials. (A) The segmented lead had two levels of directional electrodes and two levels of ring electrodes. Only the most distal level of directional electrodes towards the tip was used for recording and stimulation. (B) Example of filtered traces and power spectral densities (PSD) from Patient 2 for the three directions. (C) The PSDs for the resting and moving conditions in all four patients for the different directions.



Figure . Power for the different patients, directions and sub-bands in the resting condition. The bars are ordered by 1st, 2nd and 3rd best stimulation direction for each patient (Table 1). The error bars represent the 95% confidence interval. A – antero-lateral, M – medial, P – postero-lateral directions.



Figure . Power for the different patients, directions and sub-bands in the moving condition. The bars are ordered by 1st, 2nd and 3rd best stimulation direction for each patient (Table 1). The error bars represent the 95% confidence interval. A – antero-lateral, M – medial, P – postero-lateral directions.



Figure . Ratio of moving-to-resting power for the different patients, directions and sub-bands. The bars are ordered by 1st, 2nd and 3rd best stimulation direction for each patient (Table 1). The dashed horizontal line indicates no change between moving and resting. A – antero-lateral, M – medial, P – postero-lateral directions.



Figure . Patient averages of power for the different conditions and sub-bands sorted by best stimulation direction. The asterisk in the resting condition (top row) indicates significant difference between 1st and 3rd best stimulation direction (p = 0.04).



Figure . Correlation between total beta, high beta power and normalized therapeutic window. These two pairs were statistically significant correlations (Spearman’s rank correlation, p-values 0.004 and 0.01, rho values 0.77 and 0.69 for total beta band and high beta band, respectively).