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SHORT COMMUNICATION

Subthalamic beta band suppression reflects effective neuromodulation in chronic recordings

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Abstract

Background and purpose: Biomarkers for future adaptive deep brain stimulation still need evaluation in clinical routine. Here, we aimed to assess stimulation-induced modulation of beta-band activity and clinical symptoms in a Parkinson's disease patient during chronic neuronal sensing using a novel implantable pulse generator.

Methods: Subthalamic activity was recorded OFF and ON medication during a stepwise increase of stimulation amplitude. Off-line fast fourier transfom -based analysis of beta-band activity was correlated with motor performance rated from blinded videos.

Results: The stepwise increase of stimulation amplitude resulted in decreased beta oscillatory activity and improvement of bradykinesia. Mean low beta-band (13–20 Hz) activity correlated significantly with bradykinesia ($\rho = 0.662$, $p < 0.01$).

Conclusions: Motor improvement is reflected in reduced subthalamic beta-band activity in Parkinson's disease, supporting beta activity as a reliable biomarker. The novel PERCEPT neurostimulator enables chronic neuronal sensing in clinical routine. Our findings pave the way for a personalized precision-medicine approach to neurostimulation.

KEYWORDS
biomarkers, chronic LFP recordings, deep brain stimulation, neuromodulation, Parkinson's disease

INTRODUCTION

For many years, research has focused on the identification of biomarkers that can be used to optimize deep brain stimulation (DBS) toward patient-tailored adaptive DBS (aDBS). Oscillatory biomarkers carry significant potential to serve as feedback signals for parameter selection of DBS settings and to modulate the stimulation amplitude in response to its real-time analysis for aDBS. Best known is the beta frequency activity in Parkinson's disease (PD), which was previously shown to correlate with symptom severity [1–3]. There

have been various investigations for aDBS in experimental settings in PD patients regarding stimulation strategy and underlying biomarkers [4–8]. Although these results are promising [9], clinical long-term application has not been feasible with current devices. The new Medtronic PERCEPT implantable pulse generator (IPG) has the capability for chronic sensing with real-time evaluation of power spectra at the bedside that makes guided electrophysiological contact selection and therapy steering for improved DBS parameter settings possible. Moreover, it has the potential for future aDBS therapy in the clinical routine. Here, we present a first case showing stimulation-induced, dose-dependent modulation of beta-band activity correlating with the respective motor state in routine clinical settings.

METHODS

The study was approved by the institutional ethics committee at the Charité Universitätsmedizin Berlin and conducted in accordance with the standards set by the Declaration of Helsinki. Written informed consent was obtained from the patient.

Patient data and surgical procedure

The 57-year-old patient, with disease onset at age 44 years, underwent subthalamic DBS for severe akinetic-rigid PD with on-off fluctuations and dyskinesia (Unified Parkinson's Disease Rating Scale [UPDRS] III 67/132 OFF medication, UPRDRS III 28/132 ON medication before surgery). Medtronic 3389 DBS leads and the PERCEPT IPG were implanted without surgery-related serious adverse events; the procedure is described elsewhere [2]. At 3 months follow-up, she presented with overall improvement of motor symptoms (UPDRS medication ON/stimulation ON: 23) with stimulation at contacts 1 (right subthalamic nucleus (STN)) at 2 mA and 9 (left STN) at 1.5 mA, 60 μs, 130 Hz.

Electrophysiological recordings

Recordings were performed at the 3-month follow-up visit after a period of 12 h of anti-parkinsonian medication withdrawal (OFF medication) and after administration of 100 mg/25 mg of levodopa/benserazide (ON medication) additional to her usual medication. Local field potentials (LFPs) were acquired with the PERCEPT IPG (Medtronic, Minneapolis, MN, USA). Raw LFP data were streamed at a 250-Hz sampling rate with a bipolar recording channel (from contacts 0 and 2) during stimulation (at contact 1). Stimulation was performed contralateral to the more affected side, at the right STN, with increasing stimulation amplitude at a 0.5-mA step size from 0 to 3.5 mA. LFPs were recorded continuously at rest and during repeated motor assessments (i.e., hand movements: making a tight fist and having the patient open the hand as fully and as quickly as possible [Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III, item 3.5] at each stimulation step.

All data were streamed to a Medtronic patient programmer, exported to the json-file format, and transferred to the lab's personal computer via Universal Serial Bus.

DBS effect on bradykinesia was rated off-line using item 3.5 (MDS-UPDRS-III, hand movements) by two movement disorder specialists (P.K., R.L.) for blinded evaluation from randomly mixed video clips.

Data analysis

Beta oscillatory peaks were identified during the recording session using the BrainSenseSurvey recording mode on the tablet. Mean peak beta values were extracted from the BrainSense data container, which included power averages from a 5-Hz window (14.65 ± 2.5 Hz) surrounding the peak frequency, which is derived from an on-line Fast Fouriet Transfomation implemented in the IPG.

All further analysis was performed off-line using MATLAB (MathWorks, Natick, MA, USA), the toolbox Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/) and a new openly shared code (https://github.com/neuromodulation/perceive/). Signals were high-pass filtered at 5 Hz to avoid movement artifacts and low-pass filtered at 80 Hz to avoid contamination with stimulation aliasing. All raw data were transformed to the time-frequency domain using Morlet wavelets with 10 cycles. Power spectra were averaged for resting segments (mean recording duration of 30.7 ± 2.12 s) at each stimulation amplitude, both OFF and ON medication. Because it is a single-case presentation, we present absolute power spectral density values for the different amplitude steps of stimulation, for total beta (13–35 Hz), low beta (13–20 Hz), and high beta frequency (20–35 Hz) bands.

Electrode localization was done by coregistration and normalization of preoperative magnetic resonance imaging and postoperative computed tomography using the open-access toolbox Lead-DBS (www.lead-dbs.org) [10]. Electrophysiological recordings were synchronized to the patient video by identifying the first frame associated with a change of recording time on the patient programmer and aligning that with the time stamps of LFP recordings. Correlation analysis of mean LFP beta power and UPDRS III motor scores for hand movement was performed using Spearman calculation. Videos (Video S1) were created using MATLAB (MathWorks) and Lightworks (LWKS Software, Swindon, UK)).

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

RESULTS

Beta-band activity is suppressed by medication and neurostimulation

Beta-band activity was suppressed by levodopa and neuromodulation (Figure 1a–d). Different values for beta-band activity are presented for each stimulation step and during medication OFF/ON in Table S1. Importantly, in the OFF-medication condition, we found

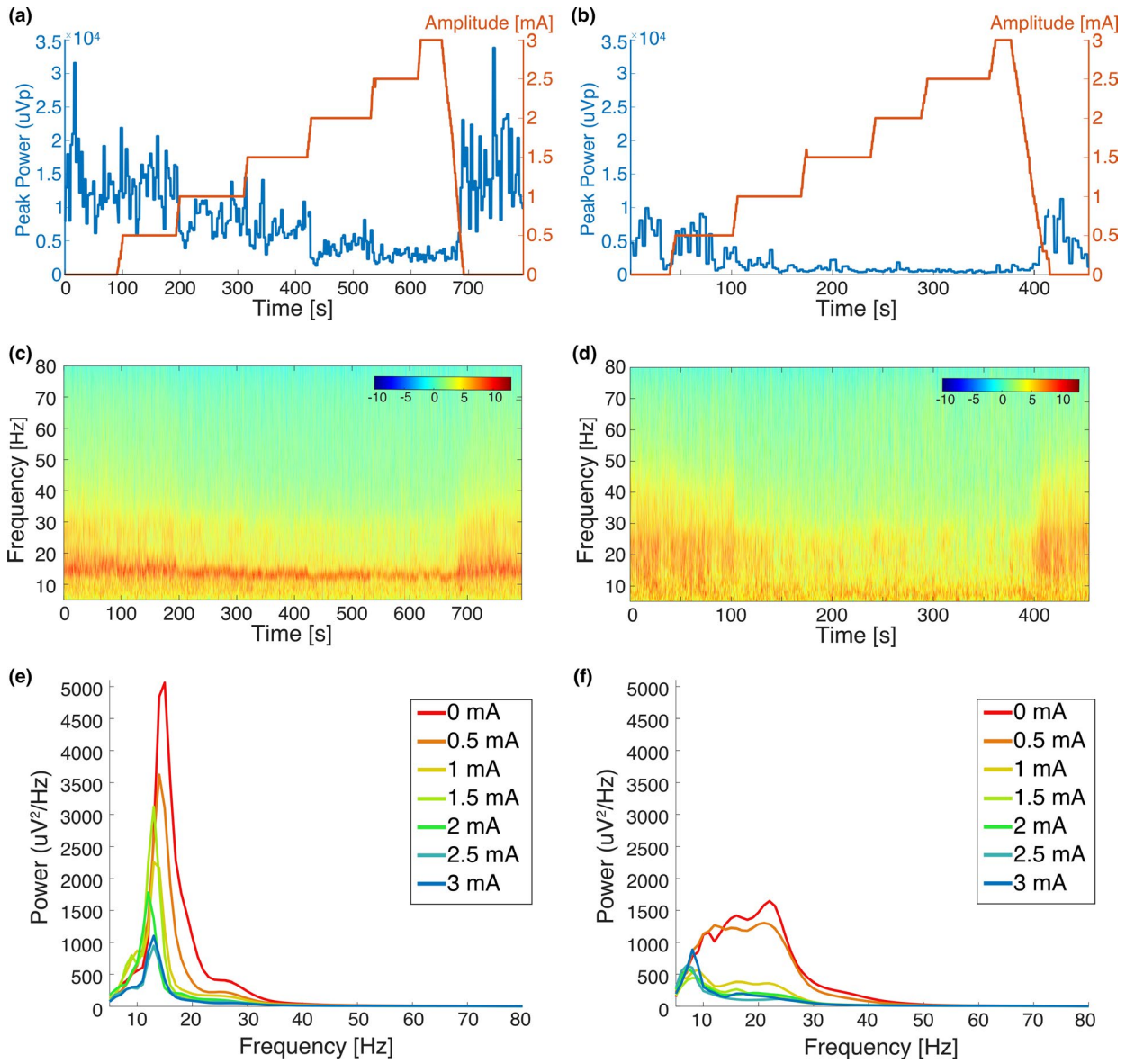

FIGURE 1 Stimulation-induced modulation of local subthalamic oscillatory activity during deep brain stimulation local field potential (LFP) recordings from the right subthalamic nucleus after 12-h medication withdrawal (OFF medication: a, c, e), and after administration of levodopa/benserazide (ON medication: b, d, f). Beta peak values (5-Hz analysis window around clinician-selected peak value, in this case 14.7 Hz) are provided in real time and show reduction of peak power with increasing stimulation amplitude (a, b). Full-spectra streamed LFP raw data of the same recordings were analyzed post hoc and transformed to the time frequency domain (c + d). This reveals excellent data quality with high signal-to-noise irrespective of stimulation and movement. Suppression of the beta frequency band (13–35 Hz) is shown for both OFF medication (c) and ON medication (d), with a predominant reduction in the low beta frequency band (13–20 Hz). Individual power spectra of rest periods on each stimulation step revealed a dose dependency of peak frequency suppression (e + f). While during OFF medication (e), there is a gradual suppression of beta frequency peak activity; during ON medication (f), there seems to be a more pronounced step-like reduction of beta around the clinical effect threshold (1–1.5 mA). UPDRS, Unified Parkinson's Disease Rating Scale. [Colour figure can be viewed at wileyonlinelibrary.com]

a stepwise suppression of local beta-band activity with increasing stimulation amplitude. Power spectra analysis of rest LFP signals revealed dose-dependent stimulation-induced suppression of the beta-band activity both with the OFF-medication peak value as well as mean beta-band activity (13–30 Hz) (Figure 1a,c,e). Although ON medication mean beta power level was already lower, stimulation further reduced beta power (Figure 1b,d,f) and improved motor symptoms. Suppression of beta-band activity was associated with improvement in motor symptoms as assessed by contralateral hand movements (Video S1). This correlation was significant for the total beta band (13–35 Hz, mean independent rating: Spearman $\rho = 0.49$, $p = 0.0453$; Figure 2a), and even more pronounced in the low beta band (13–20 Hz, mean independent rating: Spearman $\rho = 0.662$, $p < 0.01$; correlation significant for both independent raters), but not high beta band (20–35 Hz, mean independent rating: Spearman $\rho = 0.011$, $p > 0.05$). Beta peak values obtained from the PERCEPT

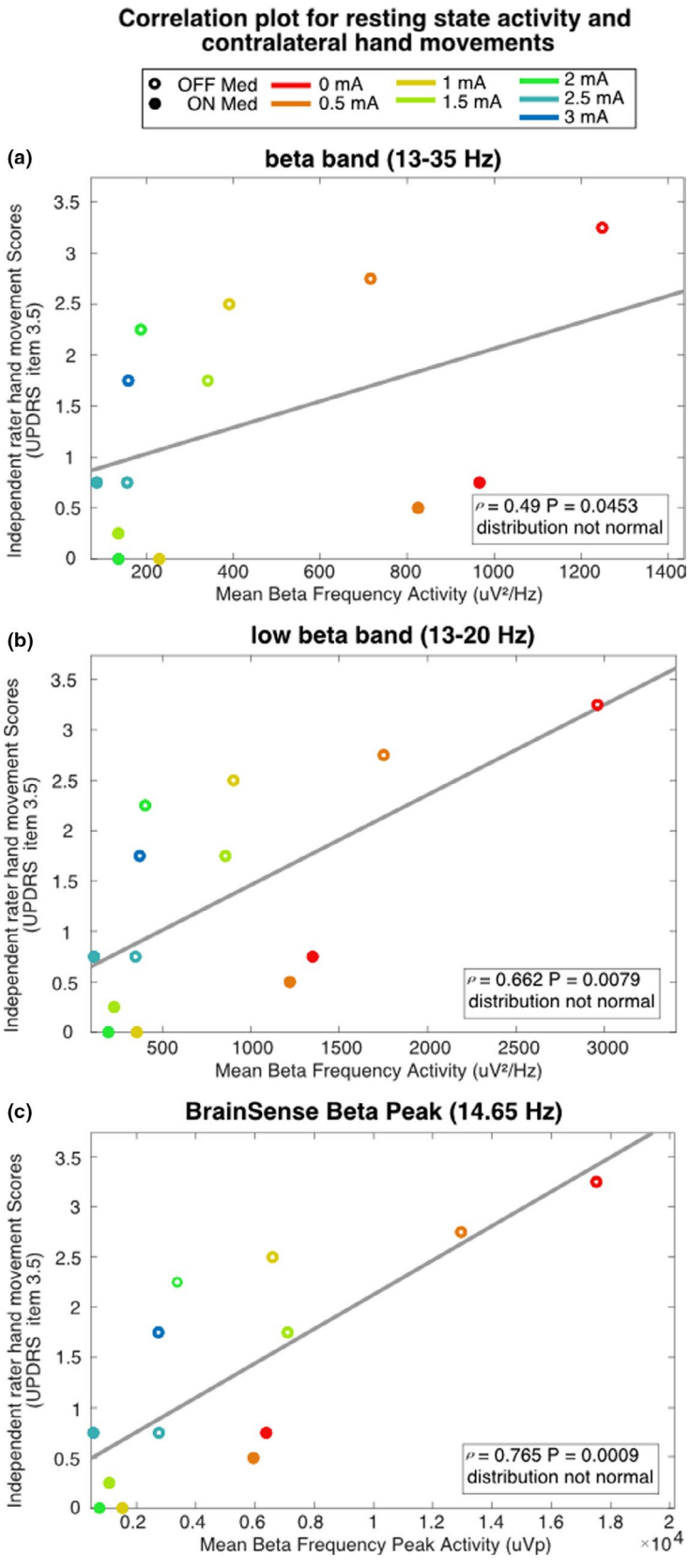

FIGURE 2 Correlation of motor performance with mean low beta frequency band activity. Correlation dot plot presenting a significant correlation of local right subthalamic nucleus (STN) resting-state beta (13–35 Hz) frequency band power (a), low beta (13–20 Hz) frequency band power (b), and BrainSense beta peak power (c), and motor performance as assessed in the UPDRS-III evaluation of left-hand movements (Item 3.5) by two blinded expert raters. Filled circles represent ON-medication recordings; empty circles represent OFF-medication recordings. The color coding represents the stimulation intensity steps as presented in Figure 1 UPDRS, Unified Parkinson's Disease Rating Scale. [Colour figure can be viewed at wileyonlinelibrary.com]

read-out also correlated significantly with motor performance (mean independent rating: Spearman $\rho = 0.765$, $p < 0.001$; correlation significant for both independent raters).

Beta-band power recovered promptly after reduction of stimulation amplitude to a level similar to the prestimulation baseline activity.

DISCUSSION

Here, we present that beta activity reliably reflects the current motor state in a PD patient with an implanted PERCEPT neurostimulator that allows chronic sensing during DBS. Beta-band activity correlated with the stimulation-induced improvement of motor performance in a dose-dependent manner. Our data suggest that this novel technology can be used to determine the therapeutic threshold for stimulation using beta-band activity as a biomarker. Moreover, the tight association of beta-band activity and motor performance further supports local STN beta-band activity as a reliable biomarker for future adaptive DBS. Our analysis of the different beta bands revealed robust correlation of motor performance with low beta-band activity, and even stronger correlation with the individual beta peak, which is reproducible across raters. This supports individual peak beta-band activity as a potential biomarker for aDBS algorithms with the PERCEPT IPG.

Our data show for the first time the technical feasibility of chronic sensing during DBS with the new PERCEPT device, which is now available for clinical routine at significantly improved signal-to-noise ratio as compared to the first-generation PC+S (primary cell plus sensing) with limited availability [11]. The routine assessment of an electrophysiological biomarker, which correlates with symptom severity and therapeutic effects, is of fundamental importance to transfer the concept of aDBS to the clinical routine. Another important detail for clinical application of aDBS is whether the biomarker is similarly suppressed when modulated through stimulation and medication, a question that should be investigated using more extensive motor assessments in larger patient cohorts.

Our findings here are in line with previous studies regarding correlation of beta oscillatory activity both acutely in postoperatively externalized patients [1, 3, 12] as well as in chronic recordings [13–15]. Hence, we demonstrate in a single case that the new technology allows stable, dose-dependent, and clinically meaningful biomarker analysis. One limitation in this study is that only unilateral recordings were performed, whereas independent fluctuations of beta-band activity in both STNs have been shown during bilateral aDBS [16]. On the other hand, the beta frequency band is coherent, and beta burst activity couples across STNs [17,18]; thus, the possibility of using unilateral biomarker assessment for bilateral aDBS should be explored further. Finally, we correlated resting-state beta activity with motor performance, and in light of clinical applicability of real-time aDBS, future studies should also take into account beta modulation during movement using objective measures of motor performance to further characterize beta activity as a useful biomarker for DBS parameter optimization, contact selection, and aDBS use.

CONCLUSIONS

This study demonstrates that beta oscillatory activity recorded with a novel implantable neurostimulator is a clinically meaningful biomarker to monitor therapeutic effects of DBS. This new approach should pave the way for real-time electrophysiological evaluations in clinical practice, and it offers for the first time the technical prerequisites of long-term biomarker analysis and closed-loop stimulation in chronically implanted DBS patients.

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CONFLICT OF INTERESTS

L.K.F., W.-J.N., R.L., and P.K. report no conflicts of interest. A.A.K. declares that she is on the advisory board of Boston Scientific and Medtronic, and has received honoraria from Boston Scientific, Medtronic, Abbott, Teva, and Ipsen. G.-H.S. received honoraria for talks for Medtronic, Abbot, and Boston Scientific.

AUTHOR CONTRIBUTIONS

Lucia K. Feldmann: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (lead); visualization (equal); writing–original draft (lead). **Wolf-Julian Neumann:** Conceptualization (equal); data curation (equal); investigation (equal); methodology (equal); software (lead); validation (equal); visualization (equal); writing–review & editing (equal). **Patricia Krause:** Investigation (supporting); writing–review & editing (supporting). **Roxanne Lofredi:** Investigation (supporting); writing–review & editing (supporting). **Gerd-Helge Schneider:** Investigation (equal); resources (equal); supervision (supporting); writing–review & editing (equal). **Andrea A. Kühn:** Conceptualization (lead); funding acquisition (lead); project administration (lead); resources (equal); supervision (lead); writing–review & editing (equal).

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 INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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