Short Communication

Low Beta-Band Suppression as a Tool for DBS Contact Selection for Akinetic-rigid Symptoms in Parkinson's Disease

Joshua N. Strelow MSc[1,2], Till A. Dembek MD[1], Juan C. Baldermann MD[1,3], Pablo Andrade MD, PhD[2], Gereon R. Fink MD[1,4], Veerle Visser-Vandewalle MD, PhD[2], Michael T. Barbe MD[1]

[1] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Neurology, Cologne, Germany

[2] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Stereotactic and Functional Neurosurgery, Cologne, Germany

[3] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Psychiatry and Psychotherapy, Cologne, Germany

[4] Cognitive Neuroscience, Institute for Neuroscience and Medicine (INM-3), Jülich Research Center, Jülich, Germany

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Correspondence author:

M.Sc. Joshua Niklas Strelow

Department of Neurology
University Hospital Cologne
Kerpenerstr. 62
50937 Cologne, Germany
E-Mail: joshua.strelow@uk-koeln.de

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ABSTRACT

Background: Suppression of pathologically altered activity in the beta-band has previously been suggested as a biomarker for feedback-based neurostimulation in subthalamic deep brain stimulation (STN-DBS) for Parkinson's Disease (PD).

Objective: To assess the utility of beta-band suppression as a tool for contact selection in STN-DBS for PD.

Methods: A sample of seven PD patients (13 hemispheres) with newly implanted directional DBS leads of the STN were recorded during a standardized monopolar contact review (MPR). Recordings were received from contact pairs adjacent to the stimulation contact. The degree of beta-band suppression for each investigated contact was then correlated to the respective clinical results. Additionally, we have implemented a cumulative ROC analysis, to test the predictive value of beta-band suppression on the clinical efficacy of the respective contacts.

Results: Stimulation ramping led to frequency-specific changes in the beta-band, while lower frequencies remained unaffected. Most importantly, our results showed that the degree of low beta-band suppression from baseline activity (stimulation off) served as a predictor for clinical efficacy of the respective stimulation contact. In contrast suppression of high beta-band activity yielded no predictive power.

Conclusion: The degree of low beta-band suppression can serve as a time-saving, objective tool for contact selection in STN-DBS.

Introduction

Elevated activity in the beta-band is widely accepted as an electrophysiological biomarker in PD [1–8]. Most recently, the suppression of activity within the beta-band has been evaluated as a valuable biomarker for feedback-based neurostimulation [9].

Apart from adaptive stimulation algorithms, programming stimulation parameters remains one of the most challenging factors in the postoperative management of patients undergoing deep brain stimulation (DBS) for Parkinson's Disease (PD). Up to date, however, the optimization of stimulation parameters remains time- and resource-consuming [10,11] and relies on the careful neurological examination of the patient. Although the current gold standard, this process could benefit from additional objective control.

This brief investigation aims to reveal the potential of sensing capacities in chronically implanted DBS devices apart from its use for feedback-based neurostimulation paradigms. In more detail, we aim to predict clinically efficient contacts based on the suppression of beta-band activity during active stimulation. Therefore, we recorded local field potential (LFP) activity during a standardized monopolar contact review and correlated these results with the clinical examination. Additionally, we have implemented a cumulative ROC analysis, to test the predictive value of beta-band suppression on the clinical efficacy of the respective contacts.

METHODS

Patients

We included seven PD patients (13 hemispheres) from the University Hospital Cologne DBS center in this analysis (more details in supplementary table 1). All patients underwent bilateral DBS of the subthalamic nucleus (STN) as per clinical routine and received a Medtronic Percept^{TM} PC neurostimulator with directional SenSight^{TM} leads (Medtronic, USA; Electrode reconstructions are shown in supplementary figure 1). The study was approved by the institutional review board of the University of Cologne (Protocol-Number 21-1162) and carried out following the Declaration of Helsinki. All patients gave written informed consent.

Monopolar Review (MPR)

Stimulation parameters were optimized during hospitalization three months (± six weeks) after surgery. After an overnight withdrawal of medication (12 hours for short-, 24 hours for long-lasting dopaminergic medication), the clinical effect of each directional level (directional level in ring mode e.g. contact 9A/B/C, n = 2 per hemisphere; and directional contacts separately, e.g. contact 9A; n = 6 per hemisphere) was tested at a fixed (delivered) amplitude of 2.0 mA, a frequency of 125 Hz and a pulse width of 60 µs. Contacts (n = 8 per hemisphere in total) were selected in a randomized order. The patients were blinded to the selected contact level and stimulation amplitude. The rater was unaware of the results from the electrophysiological examination. Between contacts, a period of 1 minute and 30 seconds was implemented to assure cessation of stimulation. This was confirmed by reassessment of the parkinsonian symptoms in StimOFF-MedOFF condition. We assessed overall tremor according to the sum of item 20 (resting tremor) and item 21 (action tremor) of the Unified Parkinson's Disease Rating Scale

(UPDRS) Part III. Akinetic-rigid symptoms were assessed as the sum of item 22 (rigidity), item 23 (finger tapping) and item 25 (hand rotation). Half-point steps increased the resolution of the rating. We defined clinical efficacy as the total difference between the sum of baseline scores (StimOFF-MedOFF) prior to testing and the sum of scores at the above-mentioned stimulation parameters (StimON-MedOFF).

Electrophysiological recordings and signal processing

Recordings for each contact were performed simultaneously with clinical MPR. LFPs from adjacent contact pairs were recorded in a bipolar configuration while increasing the stimulation amplitude (in increments of 0.5 mA) up to 2.0 mA. Raw LFP data were recorded at a sampling rate of 250 Hz using the standardized Brainsense™ Streaming feature of the Medtronic Percept™ PC neurostimulator (Medtronic, USA). LFPs were recorded after a stimulation wash-out period of two minutes and patients were instructed to sit comfortably without moving for the first (approx.) 30 seconds of the increments followed by a neurological examination at 2.0 mA. Further (approx.) 30 seconds were recorded after stimulation cessation. No movement, nor electrocardiographic (ECG) artifacts were detected upon visual inspection. Offline raw data were bandpass-filtered from 4 Hz to 98 Hz. Additionally, we applied a bandstop-filter from 48 to 52 Hz to eliminate line noise. We used a short-time Fourier transform with a hamming window lasting 1 second, an overlap between segments of 50% and frequency bins with a resolution of 1 Hz/bin to calculate the time-frequency distribution of each recording. Recordings were analyzed using in-house MATLAB scripts (version 2022b, MathWorks, USA).

Statistical analysis

For each recording, the first ten seconds after stimulation ramping were discarded to avoid contamination stimulation artifacts. Subsequently power spectra were averaged over the ensuing 10 seconds. Recordings were next normalized to the total power across the sum of frequencies (from 4 to 98 Hz) and represented as the percentage (%) of the total sum [5,9]. The degree of suppression was calculated as the percentage change from baseline activity (StimOFF) to the activity at 2.0 mA.

To test whether stimulation affects different frequency sub-bands (theta: 4-7 Hz; alpha: 8-12 Hz; lowbeta: 13-20 Hz; highbeta: 21-35 Hz) in a dose-dependent manner, we calculated a general linear model that describes the relationship of activity within the respective band as variable of interest and the stimulation amplitude as fixed effect. For each sub-band investigated (n = 4) we applied a Bonferroni post-hoc correction for multiple comparisons. Only Bonferroni corrected p-values are reported.

Similarly, to evaluate whether the degree of suppression is an appropriate biomarker for clinical efficacy of the respective contact, we calculated a general linear model using the clinical outcome as variable of interest and the degree of either low or high beta-band suppression as fixed effect. This was performed for all contacts investigated across the cohort (n = 100).

As suggested by recent publications [8,12], we employed a cumulative ROC analysis to study the predictive value of beta-band suppression for clinical efficacy of the respective contact in comparison to the MPR as the gold standard (= prediction by chance). This was done by calculating the cumulative probability of choosing the best stimulation contact based on the highest ranked beta-band suppression (for both, high and low beta-band) of all contacts per hemisphere investigated, starting with the contact that exhibits highest ranked beta-band suppression and consequently adding contacts with the next ranked beta-band suppression. To test whether clinical efficacy of contacts chosen by these approaches statistically differ from

one another, we performed a parametric one-way ANOVA that compares the mean clinical efficacy of the best ranked contacts chosen by either highest rank in the MPR, low, or high beta-band suppression per patient and per hemisphere (n = 13). Consequently, we applied a post-hoc Bonferroni test that corrected for multiple comparisons to determine which groups significantly differ from another if p was < 0.05. Again, only Bonferroni corrected p-values are reported. All statistical analyses were performed using MATLAB (version 2022b, MathWorks, Natick, MA, USA).

Results

Frequency-specific changes after stimulation ramping

A representative example of stimulation ramping is shown in figure 1A/B. Across all investigated contacts we could identify a dose-dependent suppression of mean activity within the low beta-band, explaining $R^2 = 8\%$ of variance within the model ($p < 0.001$) and within the high beta-band, explaining $R^2 = 11\%$ of variance ($p < 0.001$), while activity in the theta- ($R^2 < 0.001\%$; $p > 0.999$) and alpha-band ($R^2 = 0.002\%$, $p = 0.648$) are almost unaffected by stimulation ramping (n = 100; figure 1C). This signifies that activity in the beta-band is suppressed in a dose-dependent manner from pre-stimulation baseline, revealing a maximum suppression at 2.0 mA. After cessation of stimulation, a low and high beta-band recovery to baseline can be observed, approaching baseline activity values.

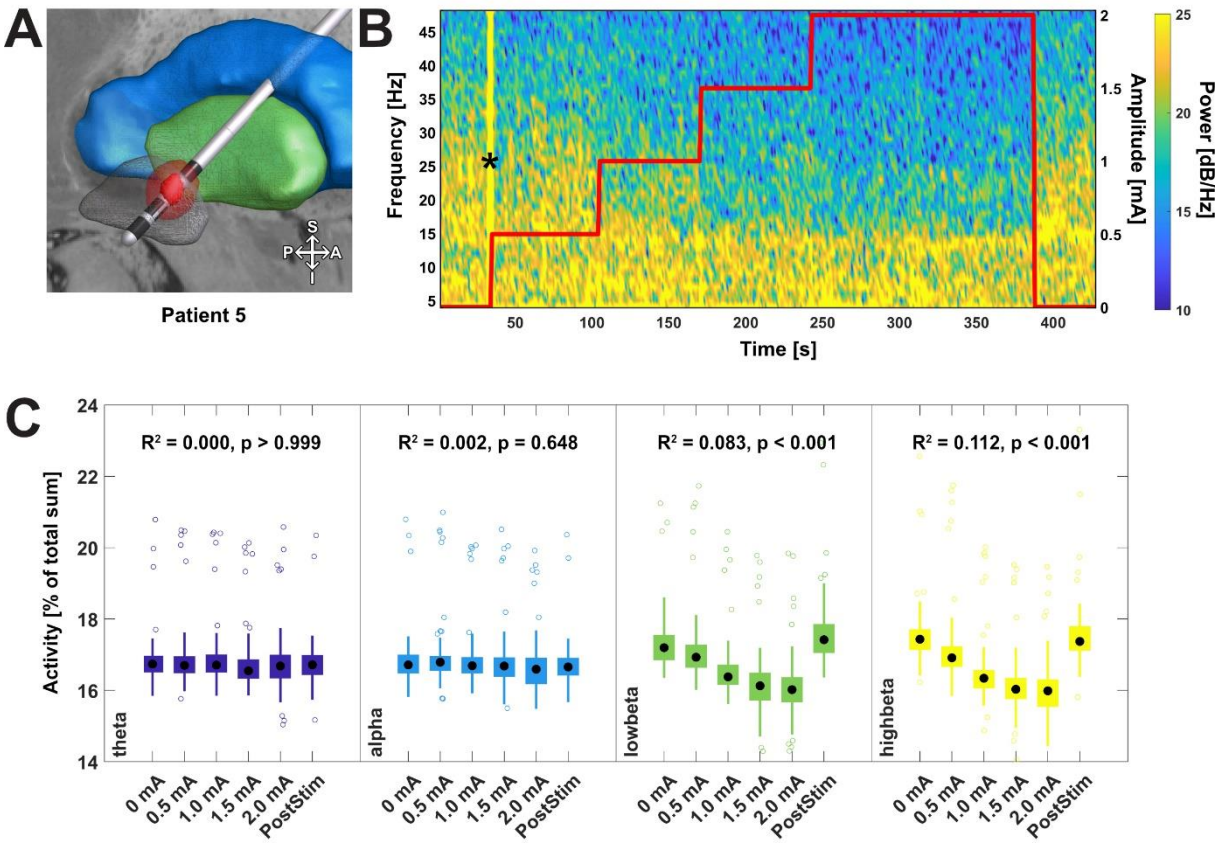

Figure 1: Representative example of stimulation ramping. (A) Reconstruction of the DBS lead in common MNI space (see supplementary material for more information on visualization processes). Two VTAs (red/transparent) with an amplitude of 0.5 and 2.0 mA are shown. Globus pallidus externus (GPe): blue; Globus pallidus internus (GPi): green, STN: grey grid; S = superior; P = posterior; I = inferior; A = anterior. **(B)** Time-frequency plot during stimulation ramping of the respective contact (2A/B/C in ring mode) is shown. Note a dose-dependent suppression of low (13-20 Hz) and high (21-35 Hz) beta-band activity during stimulation ramping. The delivered stimulation amplitude is layered as a red line. * depicts the stimulation artifact at the 0.5 mA increment. The illustrated raw data serves only for visualization purposes. Data were further processed as reported in the methods section. **(C)** Averaged activity during stimulation ramping for frequency sub-bands across all investigated contacts is shown as boxplots (n = 100). Dose-dependent suppression of low and high beta- and gamma-band activity followed stimulation ramping, while activity in the theta- and alpha-band remained unaffected.

Beta-band suppression as a biomarker for contact selection

To investigate whether the degree of suppression is a valuable biomarker for the efficacy of the tested stimulation contacts, we calculated a general linear regression using the clinical efficacy at 2.0 mA as variable of interest and the degree of either low or high beta-band suppression at 2.0 mA of the respective contacts as a fixed effect (n = 100). As beta-band activity evolved as a biomarker for exclusively akinetic-rigid PD symptoms, we investigated improvement of akinetic-rigid symptoms and tremor separately. Notably, the degree of low beta-band suppression displays as a statistically significant relationship for the improvement of akinetic-rigid symptoms, explaining R^2 = 7% (Coefficient estimate (ß) = 0.091; p = 0.004; figure 2A) of the variance, whereas high beta-band suppression could not be correlated with improvement of akinetic-rigid symptoms (Coefficient estimate (ß) = -0.016; R^2 = 0%; p = 0.608; figure 2B). In contrast the improvement of resting tremor could not be explained by either, degree of low (coefficient estimate (ß) > 0.004; R^2 = 0%; p = 0.754) or high (coefficient estimate (ß) = -0.013; R^2 = 0%; p = 0. 413) beta-band suppression (Supplementary figure 2A/B).

To validate whether beta-band suppression can be used as a predictor for contact selection, we employed a model that calculates the cumulative probability of choosing the best clinical stimulation contact based on either low or high beta-band suppression. Prediction of the best clinical contacts by the MPR serves as the gold standard. In our cumulative ROC analysis, this was implemented as prediction by chance (Figure 2C). Subsequently, using low beta-band suppression as predictor model, prediction accuracy reaches a probability of 75% when only considering half of the tested contacts (4 out of 8 contacts per hemisphere) and outperforms prediction by chance, yielding an acceptable prediction accuracy with an AUC of 0.74. However, using high beta-band suppression as predictor, prediction accuracy worsened to 66% when considering half of the tested contacts, therefore yielding an insufficient prediction accuracy with an AUC of 0.64. Next, we determined the best ranked contact per patient and hemisphere, based on either highest low and high beta-band suppression and the best clinical contact as determined by MPR as gold standard. When comparing the mean clinical efficacy of contacts chosen by these three approaches, we could identify statistically significant differences between groups using a parametric one-way ANOVA ($p = 0.036$, $F = 3.61$, $df = 2$, figure 2D). A Bonferroni post-hoc test that corrects for multiple comparisons revealed that the mean clinical improvement of contacts chosen by the MPR was higher (mean = 4.8) than for contacts that were chosen by highest ranked high beta-band suppression (mean = 3.3, $p = 0.044$), but not higher as the mean clinical efficacy of contacts chosen by highest ranked low beta-band suppression (mean = 3.8, $p = 0.276$). Further, no significant differences between low and high beta-band suppression was determined ($p = 1.0$).

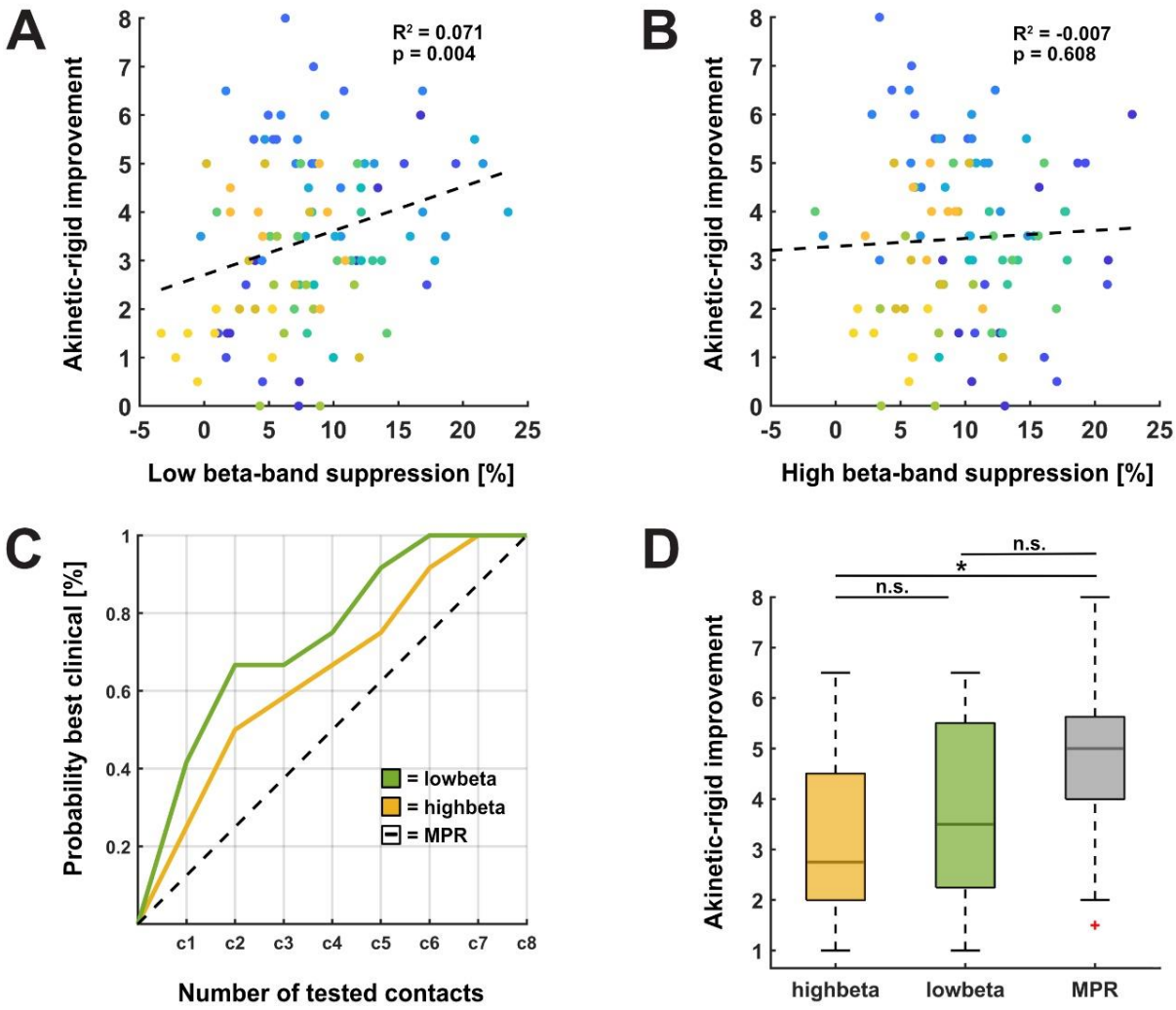

Figure 2: Frequency-specific suppression during active stimulation. (A-B) Linear regression (dashed lines) between the clinical improvement of akinetic-rigid symptoms (according to UPDRS-III item 22, 23 and 25) and the degree of suppression in the low **(B)** and high **(C)** beta-band (n = 100). Suppression of low beta-band activity statistically significant explained 7% of the variance, whereas suppression of high beta-band activity did not explain an improvement in akinetic-rigid symptoms. Individual patients are color-coded. **(C)** Cumulative ROC analysis that tests the predictive value of activity suppression by stimulation at 2.0 mA for clinical effectivity of the respective contact. The dashed black line illustrates prediction of the best contact by the monopolar contact review (MPR), the green line represents prediction by low (AUC_{low}: 0.74) and the yellow line prediction by high beta-band suppression (AUC_{high}: 0.64). Using high beta-band suppression as predictor model, the best clinical contact could be identified with a probability of 66%, whereas low beta-band suppression increased the prediction accuracy to 75% after considering half (n = 4) of the possible stimulation contacts. **(D)** Boxplots show the mean clinical improvement (akinetic-rigid symptoms) of contacts determined by the three strategies (prediction by highest low and high beta-band suppression, or best clinical contact according to the MPR per patient and per

hemisphere, n = 13). One-way ANOVA indicated a statistical significant difference among groups ($p = 0.036$, $F = 3.61$, $df = 2$). This was Bonferroni corrected for multiple comparisons if p was < 0.05. Black line indicate medians. Red cross indicates outliers. $*p < 0.05$.

Discussion

In this study, we investigated the potential value of beta-band suppression as a predictor for the clinical efficacy of stimulation contacts investigated during prospective monopolar contact review. While lower frequency bands remained unaffected by stimulation ramping, low and high beta-band activity were suppressed in a dose-dependent manner. Notably, although both were suppressed by active stimulation, only suppression of low beta-band activity could serve as a predictor for contact efficacy.

Low beta-band suppression as a biomarker for PD

Overall, we could evaluate the therapeutic use of beta-band suppression as a tool to guide contact selection in STN-DBS for PD. As hypothesized, we could identify a linear relationship between the degree of beta-band suppression and clinical improvement of the stimulated contact. This observation holds true for akinetic-rigid PD symptoms, whereas the improvement of tremor was unrelated to the degree of beta-band suppression. Notably, we observed a dose-dependent suppression for both, low and high-beta activity, however, only low beta-band suppression was predictive of stimulation contact efficacy. Interestingly, the amount of activity (regardless of low or high beta-band activity) has been used to localize functional zones of the STN and consequently effective stimulation contacts [8]. Consistently, recent insights have shown that low and high beta-band activity reveal similar spatial patterns across the STN boundaries and both, suppression of low and high beta-band activity was correlated with symptom severity [9]. Contrary, it has been reported that exclusively low beta-band activity is more sensitive to treated and untreated symptoms of PD [5,13]. Although, this proof-of-concept has been already shown in two pilot studies [14,15], we here provide more evidence that especially low beta-band activity, or suppression of its activity respectively, might serve as a valuable tool for contact selection in the future.

Anatomically informed contact selection

A growing body of evidence supports the utility of pathologically increased beta-band activity as a biomarker for contact selection in PD. However, especially anatomically-informed contact selection achieved through postoperative lead reconstruction and approximations of the stimulated tissue targeting the posterodorsal region of the STN, can achieve motor outcomes that are non-inferior to those obtained through contact selection by clinical MPR [16–19]. However, there is inconsistency in the definition of the optimal target area for DBS among these studies, and the establishment of a widely accepted guideline remains a topic for future investigation. While both grey and white matter structures adjacent to the STN have been considered part of the optimal target in these studies, the therapeutic success of DBS contacts has been also attributed to the spatial localization of pathologically increased beta-band activity [20–22]. Therefore, future studies should prospectively compare these two approaches or explore the implementation of a combined imaging and electrophysiological methodology to define the optimal DBS target for PD.

Limitations

Firstly, this analysis is limited by its small sample size (n = 7), consequently results shown in this study might be underpowered. However, previous studies showed robust results with similar sample sizes, additionally the number of investigated contacts across the cohort was higher (n = 100) and the analysis was corrected for multiple comparisons using a Bonferroni correction. Therefore, we believe that our results present a novel and significant finding. Secondly, low beta-band suppression was a reasonably good predictor of the stimulation contact that was chosen by the monopolar review, but a trial comparing the best contact chosen by low beta-band suppression with the best contact chosen by monopolar review will be needed to investigate which of the two approaches provides better clinical outcomes with chronic

stimulation. It was shown that the effect of chronic DBS is time-dependent and major parkinsonian symptoms improve, or reappear differently after activation, or withdrawal of chronic stimulation respectively, ranging from seconds to hours [23,24]. Although the MPR has been widely accepted as the first programming step after implantation [25,26], it must be stated, that the short-term assessment of stimulation efficacy is prone to the time-dependent effects of chronic stimulation and must be validated by studies investigating long-term outcomes of these varying stimulation settings. Therefore, the results of our study might be comprised as there are differences between acute, short-term testing's and long-term outcomes. Additionally, it is important to emphasize that our results specifically show the predictive value of beta-band suppression on bradykinetic-rigid symptoms of PD, while the improvement of tremor could not be attributed to any of the frequency bands. Whether this discrepancy arises from time-dependent effects of STN-DBS on tremor or necessitates the identification of an additional biomarker for parkinsonian tremor remains unaddressed in this study. However, it was also shown that beta band spectra did not significantly profit from longer withdrawal durations [27], therefore we advocate that suppression of beta-band activity might serve as a valuable time-saving and objective biomarker for akinetic-rigid symptoms in the future. Thirdly, recording capacities of the Medtronic Percept™ are limited to directional levels, or directional contacts respectively. Therefore, the most distal (ring) contacts cannot be accounted for, although they might yield good clinical efficacy. Further, baseline activity between recordings varied due to the usage of different bipolar montages for the two directional levels investigated per hemisphere. We have partly overcome this problem by calculating the degree of suppression per single contact. Nevertheless, influences of varying baseline activities might impact the data. Additionally, we only investigated effects on general frequency bands, while individual peaks (of beta activity) were neglected. While this might come with a loss of information, this also increases the generalizability of our results. Lastly, we used sub-scores of the UPDRS-III, with additional half-point steps to assess the clinical efficacy of the respective contacts. Note that

this approach has not been validated and might be prone to additional errors. Thus, we advocate replicating our findings in independent, larger samples using a strongly confounder-controlled design with an *a priori* power analysis.

Conclusion

This pilot study provides first evidence that exclusively suppression of low beta-band activity serves as a valuable, time-saving and objective biomarker to guide parameter setting in STN-DBS for PD. Although these results stem from a small sample size, they underline the clinical utility of electrophysiological examinations in STN-DBS.

Author Roles

J.N.S.: Conception, design, acquisition of data, analysis and interpretation of data. Drafting article and figures. **T.A.D.:** Statistical analysis, revision of the manuscript and final approval of the version to be submitted. **J.C.B.:** Statistical analysis, revision of the manuscript and final approval of the version to be submitted. **P.A.:** Acquisition of data, revision of the manuscript and final approval of the version to be submitted. **G.R.F.:** Revision of the manuscript and final approval of the version to be submitted. **V.V.V.:** Acquisition of data, revision of the manuscript and final approval of the version to be submitted. **M.T.B.:** Conception, revision of the manuscript and final approval of the version to be submitted.

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Conflicts of interests

J.N.S. has received funding for an investigator-initiated trial (IIT; Reference number: ERP-2021-12740) and received speaker honoraria from Medtronic GmbH. **T.A.D.** received speaker honoraria from Medtronic GmbH. **P.A.** has received honoraria for lecturing fees and educational activities from Medtronic GmbH. **V.V.V.** received support für contributions to congresses from Boston Scientific and Medtronic GmbH. The authors declare that there are no additional disclosures to report.

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Ethics compliance statement

The study was carried out following the Declaration of Helsinki (2008) and Good Clinical Practice guidelines. All patients gave written informed consent and before taking part in this study. The study was approved by the institutional review board of the University of Cologne (Protocol-Number 21-1162). We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Data availability statement

All in-house MATLAB scripts are made freely available within the Open Science Framework (DOI: 10.17605/OSF.IO/94YFW). Raw data is available upon reasonable request to the corresponding author.

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Legends

Figure 1: Representative example of stimulation ramping. (A) Reconstruction of the DBS lead in common MNI space (see supplementary material for more information on visualization processes). Two VTAs (red/transparent) with an amplitude of 0.5 and 2.0 mA are shown. Globus pallidus externus (GPe): blue; Globus pallidus internus (GPi): green, STN: grey grid; S = superior; P = posterior; I = inferior; A = anterior. **(B)** Time-frequency plot during stimulation ramping of the respective contact (2A/B/C in ring mode) is shown. Note a dose-dependent suppression of low (13-20 Hz) and high (21-35 Hz) beta-band activity during stimulation ramping. The delivered stimulation amplitude is layered as a red line. * depicts the stimulation artifact at the 0.5 mA increment. The illustrated raw data serves only for visualization purposes. Data were further processed as reported in the methods section. **(C)** Averaged activity during stimulation ramping for frequency sub-bands across all investigated contacts is shown as boxplots (n = 100). Dose-dependent suppression of low and high beta- and gamma-band activity followed stimulation ramping, while activity in the theta- and alpha-band remained unaffected.

Figure 2: Frequency-specific suppression during active stimulation. (A-B) Linear regression (dashed lines) between the clinical improvement of akinetic-rigid symptoms (according to UPDRS-III item 22, 23 and 25) and the degree of suppression in the low **(B)** and high **(C)** beta-band (n = 100). Suppression of low beta-band activity statistically significant explained 7% of the variance, whereas suppression of high beta-band activity did not explain an improvement in akinetic-rigid symptoms. Individual patients are color-coded. **(C)** Cumulative ROC analysis that tests the predictive value of activity suppression by stimulation at 2.0 mA for clinical effectivity of the respective contact. The dashed black line illustrates prediction of the best contact by the monopolar contact review (MPR), the green line represents prediction by low (AUC_{low}: 0.74) and the yellow line prediction by high beta-band suppression (AUC_{high}: 0.64). Using high beta-band suppression as predictor model, the best clinical contact could be identified with a probability of 66%, whereas low beta-band suppression increased the prediction accuracy to 75% after considering half (n = 4) of the possible stimulation contacts. **(D)** Boxplots show the mean clinical improvement (akinetic-rigid symptoms) of contacts determined by the three strategies (prediction by highest low and high beta-band suppression, or best clinical contact according to the MPR per patient and per hemisphere, n = 13). One-way ANOVA indicated a statistical significant difference among groups ($p = 0.036$, $F = 3.61$, $df = 2$). This was Bonferroni corrected for multiple comparisons if p was < 0.05. Black line indicate medians. Red cross indicates outliers. *$p < 0.05$.