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Single threshold adaptive deep brain stimulation in Parkinson's disease depends on parameter selection, movement state and controllability of subthalamic beta activity

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ABSTRACT

Background: Deep brain stimulation (DBS) is an invasive treatment option for patients with Parkinson's disease. Recently, adaptive DBS (aDBS) systems have been developed, which adjust stimulation timing and amplitude in real-time. However, it is unknown how changes in parameters, movement states and the controllability of subthalamic beta activity affect aDBS performance.

Objective: To characterize how parameter choice, movement state and controllability interactively affect the electrophysiological and behavioral response to single threshold aDBS.

Methods: We recorded subthalamic local field potentials in 12 patients with Parkinson's disease receiving single threshold aDBS in the acute post-operative state. We investigated changes in two aDBS parameters: the onset time and the smoothing of real-time beta power. Electrophysiological patterns and motor performance were assessed while patients were at rest and during a simple motor task. We further studied the impact of controllability on aDBS performance by comparing patients with and without beta power modulation during continuous stimulation.

Results: Our findings reveal that changes in the onset time control the extent of beta power suppression achievable with single threshold adaptive stimulation during rest. Behavioral data indicate that only specific parameter combinations yield a beneficial effect of single threshold aDBS. During movement, action induced beta power suppression reduces the responsivity of the closed loop algorithm. We further demonstrate that controllability of beta power is a prerequisite for effective parameter dependent modulation of subthalamic beta activity.

Conclusion: Our results highlight the interaction between single threshold aDBS parameter selection, movement state and controllability in driving subthalamic beta activity and motor performance. By this means, we identify directions for the further development of closed-loop DBS algorithms.

1. Introduction

Deep brain stimulation (DBS) is an established treatment option for advanced Parkinson's disease (PD) [1–3]. While highly effective, conventional DBS (cDBS) is unresponsive to fluctuations and changes in the patient's symptoms, necessitating regular reprogramming visits and potentially leading to side effects mediated by over- or understimulation

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Abbreviations

aDBS	adaptive deep brain stimulation
cDBS	conventional deep brain stimulation
DBS	deep brain stimulation
FDR	false discovery rate
LFP	local field potential
LMEM	linear mixed effects model
MDS-UPDRS-III	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale Part III
PD	Parkinson's disease

[4,5]. To counter this limitation, adaptive DBS (aDBS) approaches have been investigated over recent years [6]. Adaptive DBS exploits biomarkers indicative of the patient's clinical state to adjust stimulation parameters in real-time. For PD, the most promising biomarker is spectral power in the beta frequency range (13–30 Hz) extracted from subthalamic local field potentials (LFPs) as it scales with the changes in motor performance induced by DBS [7–9]. Beta power based aDBS approaches encompass various types of feedback control such as single threshold [10–12], dual threshold [13,14] and proportional [15,16] algorithms with randomized controlled trials having commenced recently [17,18].

With the advent of adaptive DBS in clinical use [19], however, practical questions remain to be addressed to facilitate clinical translation: First, aDBS increases the parameter space of DBS programming [6]. So far, limited data is available on the effect of aDBS parameters like ramping rate, thresholds and others on clinical efficacy or patient safety [20–22]. Two parameters may be of particular importance to single threshold aDBS, which aims at suppressing pathologically prolonged bursts of beta power [23]: The onset time, which is the duration of supra-threshold power triggering stimulation ramp-up [24] and the amount of smoothing applied to real-time beta power. Beta burst duration may differentially contribute to motor performance, suggesting a rationale for selecting an onset time that specifically suppresses prolonged bursts while preserving physiological power fluctuations [23,25]. On the other hand, the extent of smoothing tunes the aDBS algorithm to different temporal scales of beta power fluctuations [26] and may therefore affect the sensitivity towards short-lived but clustered episodes of elevated beta power [27]. Second, most aDBS studies so far have investigated patients at rest. However, recent reports indicate that movement may interact with aDBS due to its suppressive effect on beta power [20,28]. Clinically, aDBS must be efficacious across a range of behavioral states, raising the question of how aDBS responsivity is affected by movement and whether this depends on parameter choice. Third, while the majority of PD patients exhibit an oscillatory peak in the beta frequency range, there are also cases where elevated beta power cannot be readily detected in subthalamic LFPs [29] or cannot be effectively suppressed by cDBS [30]. In these cases, controllability of subthalamic beta activity is impeded. However, controllability of the state of the biomarker has been stated as a prerequisite for closed-loop approaches [31,32]. Prior studies have circumvented this issue by pre-selecting patients (or hemispheres) featuring marked beta activity [11,15]. Thus, it is unclear how closed-loop algorithms operate in cases of reduced controllability of beta power and how aDBS parameter selection may affect adaptive stimulation performance in this context.

Here, we investigate how changes to aDBS parameters (onset time and smoothing), differential movement states and controllability of subthalamic beta power affect electrophysiological responses to adaptive stimulation and compare these to conventional DBS. Furthermore, we assess how these aspects interact with each other in contributing to closed-loop neuromodulation of subthalamic beta power in PD. To address these questions, we studied 12 PD patients featuring temporarily externalized DBS electrodes using a custom-made aDBS platform. Our results underpin that considering parameter selection, behavior and controllability are pivotal for future clinical adoption of adaptive deep brain stimulation.

2. Methods

2.1. Participants

Detailed Methods are available in the Supplementary Material. This study was approved by the institutional review board at Charité – Universitätsmedizin Berlin (study number EA2/129/17) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. 12 patients (4 female, 8 male; mean ± SD age 62 ± 7.4 years; pre-operative Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III) medication off 44.1 ± 15.6 points) diagnosed with PD underwent surgery for DBS targeting the subthalamic nucleus (STN) as previously described [33]. Permanent DBS electrodes were temporarily externalized (8-contact model B33005 "SenSight" (Medtronic, Minneapolis, MN, USA) in 11 patients and 16-contact model DB-2203 "Vercise Cartesia X" (Boston Scientific, Marlborough, MA, USA) in 1 patient). All recording sessions took place in the acute postoperative period (4 ± 1.7 days after electrode implantation) after overnight withdrawal of dopaminergic medication (except of patient 8, who was assessed in both the on and off medication state). Due to the long duration of the experiment, only one hemisphere was studied in most patients, whereas in patients 3 and 11, both hemispheres could be studied on two different days. Thus, 15 datasets were available in total. See Supplementary Table 1 for full clinical, demographic and recording details.

2.2. Adaptive deep brain stimulation setup

A setup for closed-loop stimulation was employed consisting of an alphaDBSext artifact-free recording device (Newronika, Milan, Italy) [34], custom-made software in Matlab 2021b (The MathWorks, MA, Natick, USA) and a NeuroOmega external neurostimulator (AlphaOmega, Nazareth, Israel). Subthalamic LFPs from one hemisphere were recorded bipolarly from levels 0–2 or 1–3 (with 0 being the lowermost level) and fed to a single theshold aDBS algorithm (Fig. 1A). Every 62.5 ms, real-time power was estimated in a pre-specified frequency band by a fast fourier transform over the latest 250 ms with a frequency resolution of 4 Hz. Smoothing was applied by averaging over successive estimates. Real-time beta power was then evaluated against a pre-specified threshold. Whenever real-time beta power exceeded/remained below this threshold for a given duration, stimulation amplitude was ramped up/down over a course of 500 ms. This way, stimulation amplitude was allowed to vary between 0 mA and an individually determined maximum stimulation amplitude. This amplitude was then fixed for 1 s to avoid real-time power distortion due to ramping artifacts. Stimulation was applied by the NeuroOmega neurostimulator on the contact between recording contacts (i.e., level 1 or 2) at 130 Hz with a pulse width of 60 μs.

2.3. Closed-loop parameters

In this study, two parameters of the single threshold aDBS algorithm were investigated.

a) The extent of smoothing of real-time power could be varied by averaging over consecutive power values (Fig. 1B).
b) The onset time triggering stimulation ramp-up could be customized by changing the minimum number of real-time power estimates exceeding the threshold (Fig. 1C).

Smoothing was either not performed or applied by averaging over 4

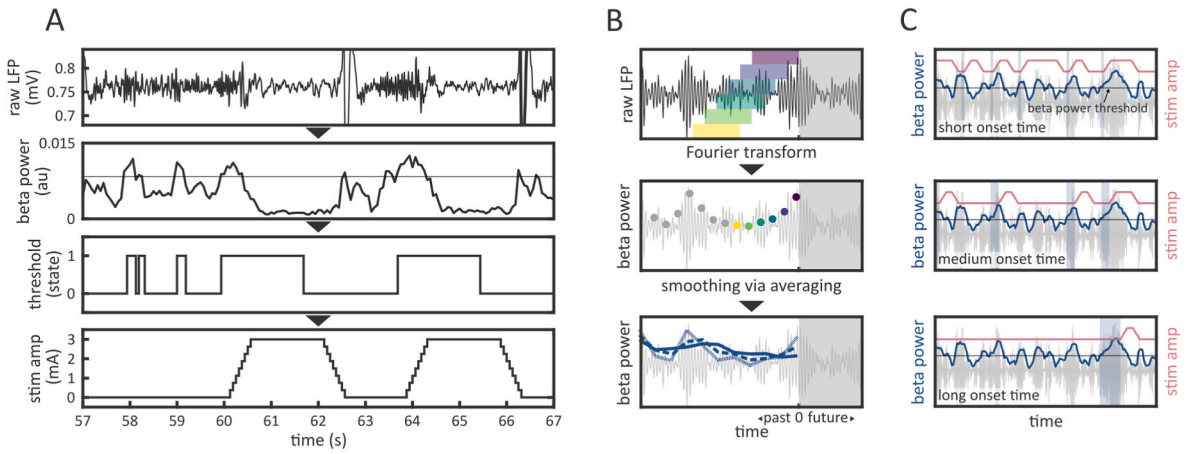

Fig. 1. Algorithm and parameters for adaptive deep brain stimulation. A) Single subject example showing raw LFPs (1st row) recorded from the STN. Spectral power in the beta frequency range was computed from this signal in real-time (2nd row). Once beta power surpassed a pre-defined threshold (2nd row, grey line), the threshold state changed from 0 to 1 and vice versa (3rd row). After crossing the threshold for a selected amount of time, stimulation was ramped up/down (4th row) and (together with the threshold state) kept fixed for 1s. Artifacts during ramp-up and ramp-down are visible in the raw data (e.g., at 64 s and 66.5 s). B) Smoothing was implemented by averaging over a specified number of successive power values obtained by Fourier transformation of the raw LFPs. Dash density in the 3rd row illustrates the extent of smoothing applied on beta power estimates. Zero indicates the point in time of the most recent sample. C) Onset time was changed by specifying the number of consecutive power values that must surpass the threshold in order to trigger stimulation ramp-up. Panels B & C show artificial data.

or 8 consecutive real-time power values, while the onset time was set to 250, 500 or 1000 ms (i.e., 4, 8 or 16 consecutive power estimates exceeding the threshold), yielding 9 aDBS conditions in total. For all conditions, real-time power had to fall below the threshold for a minimum of 500 ms to trigger stimulation ramp-down.

2.4. Procedure

Before each session the maximum stimulation amplitude was determined based on the side-effect threshold. After that, LFPs were recorded for 3 min at rest with DBS off. The channel with the most distinct peak in the beta frequency range (12–30 Hz) was selected by visual inspection. The distribution of real time power in the beta peak range was computed and the 60th percentile of the distribution was set as the threshold. Thereafter, 9 aDBS runs with one of the parameter combinations, one cDBS run and one run without stimulation were performed in randomized order. Each run consisted of a resting period of 3 min after which the patient was asked to perform finger tapping movements for 30 s with the hand contralateral to the STN that was being stimulated. A 3-axis accelerometer (TMSi, Oldenzaal, The Netherlands) attached to the distal phalanx of the index finger was used to track finger tapping. In between runs, stimulation was not applied for 2 min.

2.5. Signal processing

Beta power was extracted by applying a short time fourier transform on raw LFPs and by averaging over 13–30 Hz. This way, an offline estimate of beta power was obtained which was not affected by aDBS parameter choice [20]. The time periods from 0 s to 0.75 s relative to stimulation ramp-up and down were discarded from the transformed data due to potential artifacts. Average beta power during aDBS was obtained separately for rest and tapping periods by computing the mean over artifact free data. For normalization, power was expressed as percentage of average beta power during rest and DBS off if not stated differently. Average beta power was also calculated over all intervals with 0 mA during aDBS and in the time window of 0.75 s–2 s after stimulation ramp-up. To operationalize controllability, datasets were split into *controllable* and *non-controllable* groups based on the criterion of at least 20 % reduction in average beta power (13–30 Hz) during continuous stimulation in comparison to off stimulation. The reason for making this distinction is that beta power serves as the feedback signal for aDBS in this study. Thus, being able to modulate beta power to a certain extent is a requirement for controlling beta power in real-time with closed-loop stimulation. In an exploratory fashion, motor performance was assessed by calculating the root mean square of the signal vector magnitude of the accelerometer data using the first 10 s of the tapping period [20].

2.6. Stimulation patterns

For each aDBS condition, the ratio of total time spent on stimulation was computed by cumulating the duration of all stimulation blocks (including ramp-up and down) and dividing by the total duration of the respective rest or tapping period. Furthermore, the average stimulation block duration was computed alongside the number of stimulation blocks.

2.7. Statistics

Changes in beta power or stimulation patterns across aDBS conditions were assessed by means of linear mixed effects models (LMEMs). For this, fixed and random effects for the amount of smoothing, the onset time and their interaction were modelled with dataset as grouping variable. To investigate associations among outcomes, LMEMs with a single predictor variable as fixed and random effects grouped by dataset were established. Moreover, to compare differences between rest and movement periods or between *controllable* and *non-controllable* groups, LMEMs with fixed and random effects for behavioral state or controllability group were computed. All models were estimated by the maximum pseudo likelihood method. Estimates for predictor variables are reported as β-values and were tested against zero using a *t*-test. Comparisons between single DBS conditions were performed by paired t-tests. To assess time-resolved beta power modulation during ongoing stimulation, one-sample t-tests against 100 were conducted on beta power relative to off stimulation with false discovery rate (FDR) controlled by means of the Benjamini-Hochberg procedure [35]. All results were found to be statistically significant at a p-level of 0.05.

3. RESULTS

3.1. Rapid stimulation-induced beta power modulation is not dependent on parameter combination

Based on the criterion of at least 20 % suppression in beta power during cDBS, 9 out of 15 datasets were classified as *controllable* (Suppl. Fig. S1A). In the following, we first report results of the *controllable* dataset. We assessed the momentary impact of stimulation on beta power across parameter combinations. Stimulation ramp-up induced a rapid suppression of beta power during rest (Fig. 2A; one sample *t*-test, all $p < 0.05$, FDR corrected). Under ongoing stimulation, beta power remained suppressed at 31.3 ± 19.1 % relative to off stimulation when averaged over all parameters. There was no difference in the amount of beta power suppression across parameter combinations (Fig. 2B, onset time: $\beta = -0.17$, $t = -0.7$, $p = 0.48$; smoothing: $\beta = -0.41$, $t = -1.2$, $p = 0.24$, interaction: $\beta = -0.04$, $t = -1.1$, $p = 0.27$).

3.2. Parameter changes lead to systematic differences in stimulation patterns, affecting overall levels of beta power modulation

While momentary beta power suppression did not differ across parameter combinations, we investigated whether parameter choice affects beta power modulation when considering the entire resting period. Fig. 3A exemplifies that with shorter onset time stimulation was triggered more frequently than with longer onset time. This was corroborated on the group level as the total time spent on stimulation during aDBS was lower with higher onset time (Fig. 3B; $\beta = -3.8$, $t = -14.2$, $p < 0.001$) and with stronger smoothing ($\beta = -1.05$, $t = -2.8$, $p = 0.006$). Differential time on stimulation depended on how often stimulation was triggered (Suppl. Fig. S2A; $\beta = 0.16$, $t = 5.7$, $p < 0.001$), but not on the duration of stimulation blocks (Suppl. Fig. S2B; all $p \geq 0.42$). With higher smoothing the effect of onset time became less pronounced and stronger smoothing could either increase or decrease the total time spent on stimulation depending on onset time, respectively ($\beta = 0.25$, $t = 6.8$, $p < 0.001$). For beta power, we observed stronger suppression during rest for shorter onset time (Fig. 3C; $\beta = 1.93$, $t = 3.47$, $p < 0.001$), while neither the amount of smoothing ($\beta = -0.085$, $t = -0.1$, $p = 0.91$), nor the interaction between both parameters ($\beta = 0.02$, $t = 0.22$, $p = 0.83$) had an impact on beta power modulation. The strongest suppression with aDBS could be achieved with an onset time of 250 ms and smoothing of 4 pts (64.1 ± 17.6 % of beta power off stimulation), which did not reach the level achieved with cDBS, though (40.7 ± 21.6 % of beta power off stimulation, $p < 0.001$, paired *t*-test). Finally, spending more time on stimulation was associated with stronger suppression of beta power over the whole resting period (Fig. 3D; $\beta = -0.51$, $t = -3.6$, $p < 0.001$).

3.3. Movement related beta power suppression diminishes parameter-dependent aDBS responsivity

We proceeded by examining the effect of a behavioral change from rest to movement on adaptive stimulation. Fig. 4A depicts the transition phase from rest to performing a finger tapping task in an exemplary dataset. As soon as the patient started tapping, real-time beta power got suppressed leading to less stimulation. This finding could be confirmed on the group level: During movement, beta power was lower in periods without stimulation (Fig. 4B, $\beta = -28.4$, $t = -2.8$, $p = 0.006$) and exceeded the trigger threshold for shorter durations ($\beta = -0.046$, $t = -2$, $p = 0.043$). Consequently, less time was spent on stimulation (Fig. 4C, $\beta = -11.7$, $t = -2.1$, $p = 0.034$) during tapping than during rest. The time spent on stimulation during movement was solely dependent on the onset time (Suppl. Fig. S3, $\beta = -3.5$, $t = -3.9$, $p < 0.001$). With an onset time of 1000 ms and no smoothing, stimulation was totally absent during tapping in all datasets. Moreover, the extent of movement-related beta power suppression was strongly associated with the reduction in time spent on stimulation (Fig. 4D, $\beta = 0.41$, $t = 6.3$, $p < 0.001$). Albeit this drop in stimulation, average beta power under aDBS was still lower during tapping than during rest, however, differences across parameter combinations vanished (Fig. 4E, all $p \geq 0.059$). This reduction in beta power was due to joint modulatory effects of both movement and adaptive stimulation, as beta power was further suppressed when adaptive stimulation was triggered during movement (Suppl. Fig. S4). Exploratory analyses revealed no systematic differences in motor performance across parameters in the *controllable* group ($\beta = < 0.001$, $t = -0.42$, $p = 0.67$). However, when including all datasets we found that only the combinations of 250 ms onset time and 4 pts smoothing or 500 ms onset time and no smoothing were superior to DBS off ($p = 0.032$ and $p = 0.021$, respectively, paired *t*-test). These results need to be interpreted cautiously due to the low signal-to-noise ratio of a single tapping trial.

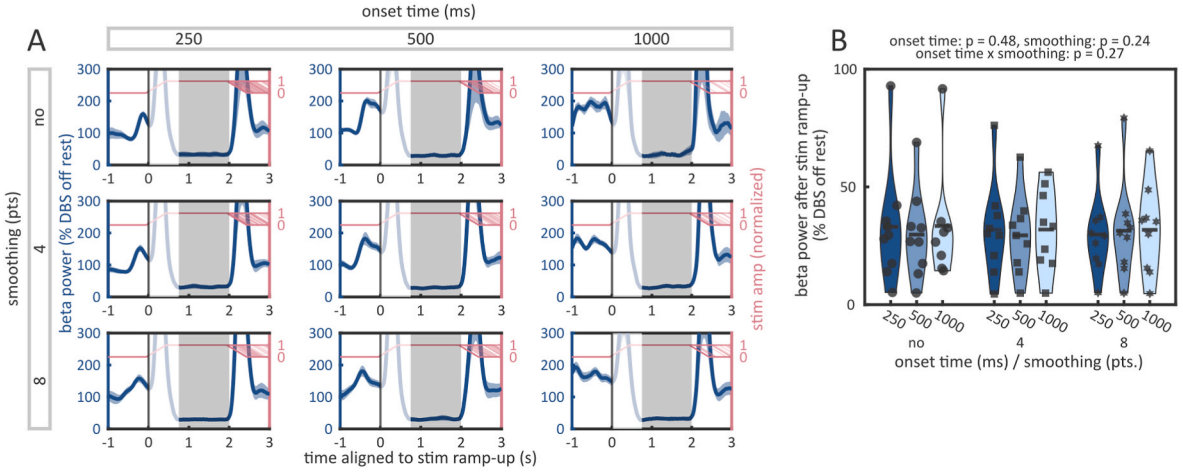

Fig. 2. Rapid momentary modulation of beta power in response to adaptive stimulation across parameter combinations. A) Beta power at rest during aDBS time-locked to the start of stimulation ramp-up indicates consistent beta power suppression across parameter combinations. Dark blue traces: beta power normalized to DBS off aligned to stimulation ramp-up averaged over all datasets. Grey vertical line: start of stimulation ramp-up. Light blue area: standard error of the mean of beta power. Pink traces: stimulation amplitude normalized to the upper stimulation amplitude within each dataset. Grey shaded area: periods with a significant beta modulation after FDR correction. The period from 0 s to 0.75 s relative to ramp-up was discarded due to ramping artifacts. B) On the group level, the extent of momentary beta power suppression in the time window of 0.75 s–2 s after stimulation ramp-up was independent of parameter combination.

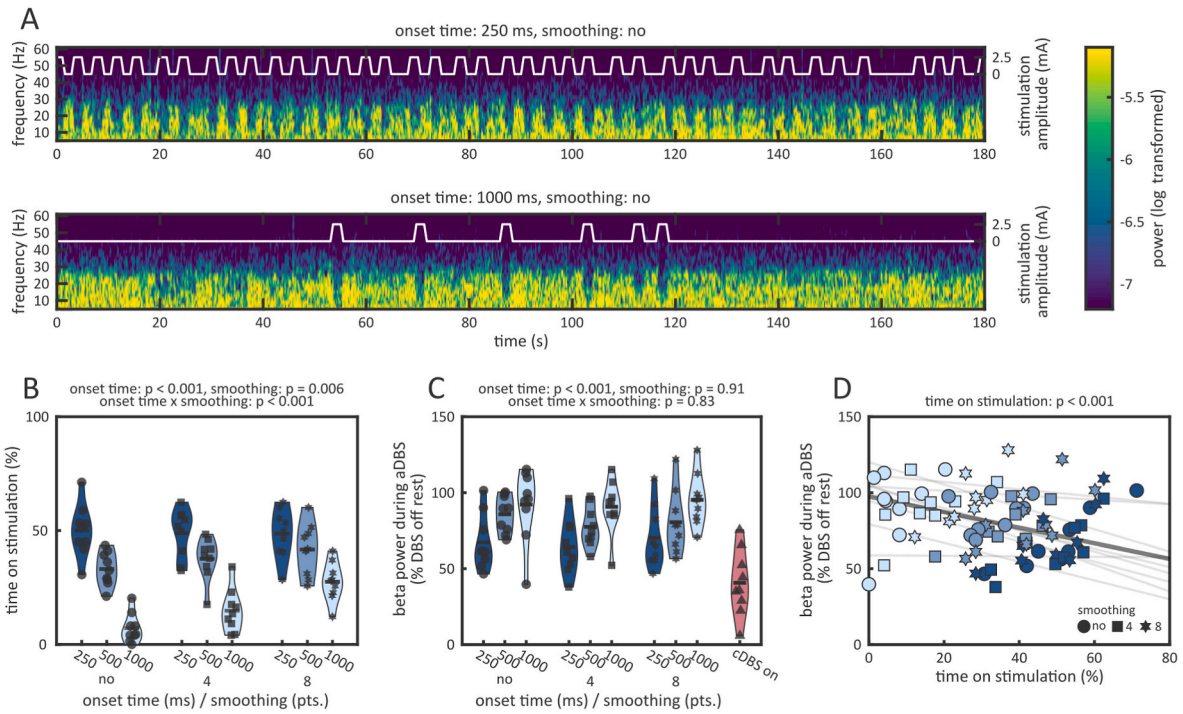

Fig. 3. Parameter combinations are associated with differential stimulation patterns mediating beta modulation over the whole recording period. A) Exemplary spectrograms from a single dataset for two different parameter combinations. Stimulation was triggered less frequently for an onset time of 1000 ms in comparison to 250 ms. White traces: stimulation amplitude. B) On the group level, the total time on stimulation decreased with higher onset time, however, this effect was less pronounced when stronger smoothing was applied. C) In contrast, beta power averaged over the whole recording period did only vary as a function of onset time. Still, continuous DBS (shown in red) was more effective in suppressing beta power than aDBS (paired *t*-test, $p < 0.001$). D) The total time spent on stimulation was associated with the extent of beta power modulation with more time on stimulation leading to stronger beta power suppression. Bold grey line: estimated beta power based on fixed effects. Thin grey lines: estimated beta power based on fixed and random effects for each dataset.

3.4. Parameter-dependent closed-loop modulation of subthalamic beta power requires controllability

The remaining 6 out of 15 datasets were classified as *non-controllable* according to the criteria set out above. There was no difference in electrode location between *controllable* and *non-controllable* groups (Suppl. Fig. S5). Likewise, both groups did not differ in the subject's age, pre-operative MDS-UPDRS-III on and off medication, post-operative MDS-UPDRS-III off medication, disease duration, stimulation amplitude and post-operative days until recording (all $p \geq 0.14$). With these datasets, we assessed whether *controllability* alters the sensitivity of aDBS to changes in parameters and behavioral state. In the *non-controllable* example illustrated in Fig. 5A, aDBS did not lead to stimulation related changes in beta power. On the group level, no momentary beta power modulation following adaptive stimulation could be observed (Suppl. Fig. 6, one sample *t*-test, all $p \geq 0.05$, FDR corrected), irrespective of parameter combination (Fig. 5B, all $p \geq 0.33$). The time spent on stimulation during aDBS still varied depending on parameter combination in the *non-controllable* group (onset time: $\beta = -4.61$, $t = -11.2$, $p < 0.001$; smoothing: $\beta = -1$, $t = -1.1$, $p = 0.26$; interaction: $\beta = 0.3$, $t = 3.4$, $p = 0.002$). However, this had no effect on average beta power during rest (Fig. 5C, $\beta = 0.19$, $t = 1.78$, $p = 0.08$). During movement, beta power suppression was preserved in the *non-controllable* cohort during periods off stimulation (Fig. 5D, $\beta = -17$, $t = -5.6$, $p < 0.001$), albeit being less pronounced than in the *controllable* cohort (*non-controllable:* 87.5 ± 24.9 %, *controllable*: 67.7 ± 28.1 % of resting state power). Accordingly, less time spent on stimulation was observed during aDBS in the *non-controllable* group, analogous to *controllable* datasets (Fig. 5E, $\beta = -11$, $t = -2.6$, $p = 0.01$). With ongoing aDBS, modulation of beta power was observed in the tapping period but was parameter-independent (Fig. 5F, all $p \geq 0.51$) and did not reduce average beta power below levels seen off stimulation (average beta power across parameters: 84.5 ± 21.1 %), thus mainly resulting from movement-related instead of stimulation-induced effects.

4. Discussion

In this study, we assessed the differential contribution of two aDBS parameters (onset time and smoothing), changes in the movement state and the controllability of beta power on the extent of beta power modulation by single threshold aDBS. We could show that changing parameter combinations did not affect momentary beta power suppression following adaptive stimulation. However, we observed that parameter choice was influencing stimulation patterns, which in turn determined the overall extent of beta power suppression at rest. During movement, aDBS responsivity was diminished leading to beta power being mainly modulated by movement instead of adaptive stimulation. Likewise, reduced controllability as defined by absent beta power suppression through cDBS lowered the sensitivity of aDBS to parameter changes. Our results provide electrophysiological evidence for guiding aDBS parameter choice and identify potential trajectories for the further development of closed-loop DBS.

4.1. Parameter choice affects the extent of beta power suppression in adaptive deep brain stimulation

The fact that changes to stimulation parameters can have an impact on the electrophysiological response to aDBS has been underappreciated so far. It has been stated that "through good fortune, rather than design […]" previous aDBS approaches were able to shorten beta burst duration in a way similar to dopaminergic medication [25]. Here, we report that parameter choice has a significant impact on the extent of beta power modulation through aDBS in the resting state. This effect was mediated by differential stimulation patterns, though, as momentary

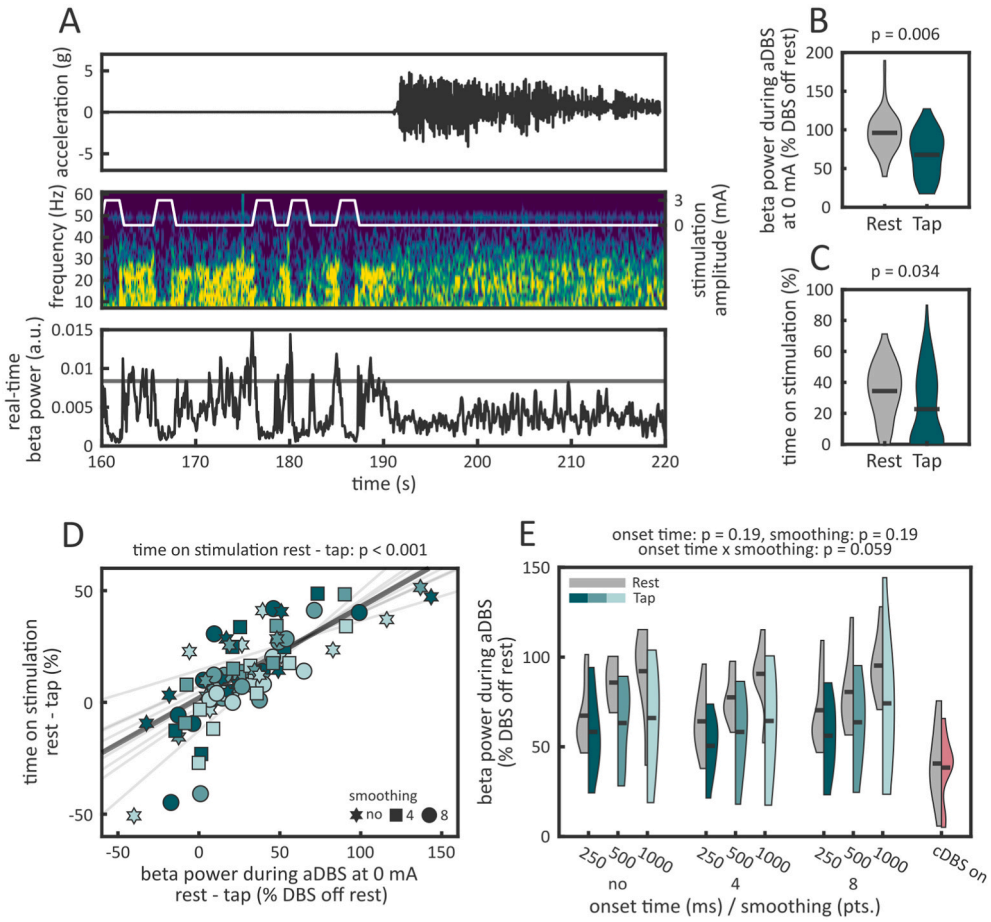

Fig. 4. Movement interferes with parameter-dependent adaptive stimulation. A) Transition from rest to movement in an exemplary dataset is indicated by tapping activity in the accelerometer trace (1st row) starting shortly after 190 s. The spectrogram (2nd row) computed from the LFP synchronized to the accelerometer signal shows suppression in the beta band and absent stimulation during movement. This is due to real-time beta power (3rd row) not surpassing the threshold throughout the movement period. B) On the group level, beta power in the periods without stimulation is lower during movement than during rest. C) Analogously, less time is spent on stimulation during movement than during rest. D) A larger difference in beta power without stimulation between rest and movement is reflected by a higher difference in time on stimulation. Bold grey line: estimated time on stimulation based on fixed effects. Thin grey lines: estimated time on stimulation based on fixed and random effects for each dataset. E) With ongoing adaptive stimulation, beta power is suppressed during movement but in contrast to rest (depicted in grey, same as Fig. 3C), no significant parameter dependency is observed anymore.

beta power suppression due to adaptive stimulation did not depend on parameter choice. These results are in line with previous findings on the time-scale of beta power modulation [36] and indicate that momentary effects on beta power are primarily driven by the amplitude of the applied electric current [7,8] instead of the intrinsic fluctuations in beta power preceding stimulation. However, aDBS parameter choice affected stimulation patterns: Higher onset time was associated with less time spent on stimulation, but this effect was less pronounced with increased smoothing. Whereas a recent report indicated that smoothing does not alter the time on stimulation [20], our data suggests that this effect depends on and interacts with onset time. In turn, differential time on stimulation was one factor to drive the total extent of beta power suppression. For example, an onset time of 1000 ms rarely triggered stimulation leading to a negligible effect on beta power modulation at all. On the other side, strongest beta power suppression was achieved with 250 ms onset time and 4 pts smoothing, which was also one of the two parameter combinations that achieved a behavioral benefit over DBS off in an exploratory analysis. Notably, although stronger smoothing increased the time on stimulation at longer onset times, this did not affect beta power modulation. This may be because consecutive short (and low amplitude) beta bursts will be detected as a single long burst when smoothing is stronger. Consequently, stimulation will be applied more frequently but these additional stimulation blocks may target rather low amplitude bursts, mirrored by minor effects on average beta power suppression. Thus, not only the total time on stimulation but also the beta power dynamics to which the closed-loop system is tuned to affect the extent of beta power modulation. Importantly, with all combinations of aDBS parameters investigated here, the extent of beta power suppression did not reach the level achieved with cDBS. However, full suppression of subthalamic beta power might interfere with the physiological role of beta oscillations in the STN, e.g., in response inhibition [37]. This is mirrored by proportional aDBS algorithms, which allow higher levels of average beta power than cDBS while maintaining clinical benefit [38]. As the electrophysiological target pattern that should be facilitated by aDBS is unknown, though, it remains unclear which closed-loop DBS approach shifts subthalamic LFP activity to the most physiological state. Nevertheless, our results provide guidance in how parameters for single threshold aDBS shape the electrophysiological response to adaptive stimulation.

4.2. *Movement state and controllability reduce the parameter dependency of adaptive deep brain stimulation*

The parameter dependency of aDBS algorithms may however be contingent on the patient's behavioral state [28] and the controllability of subthalamic beta activity [32]. Therefore, we also characterized the

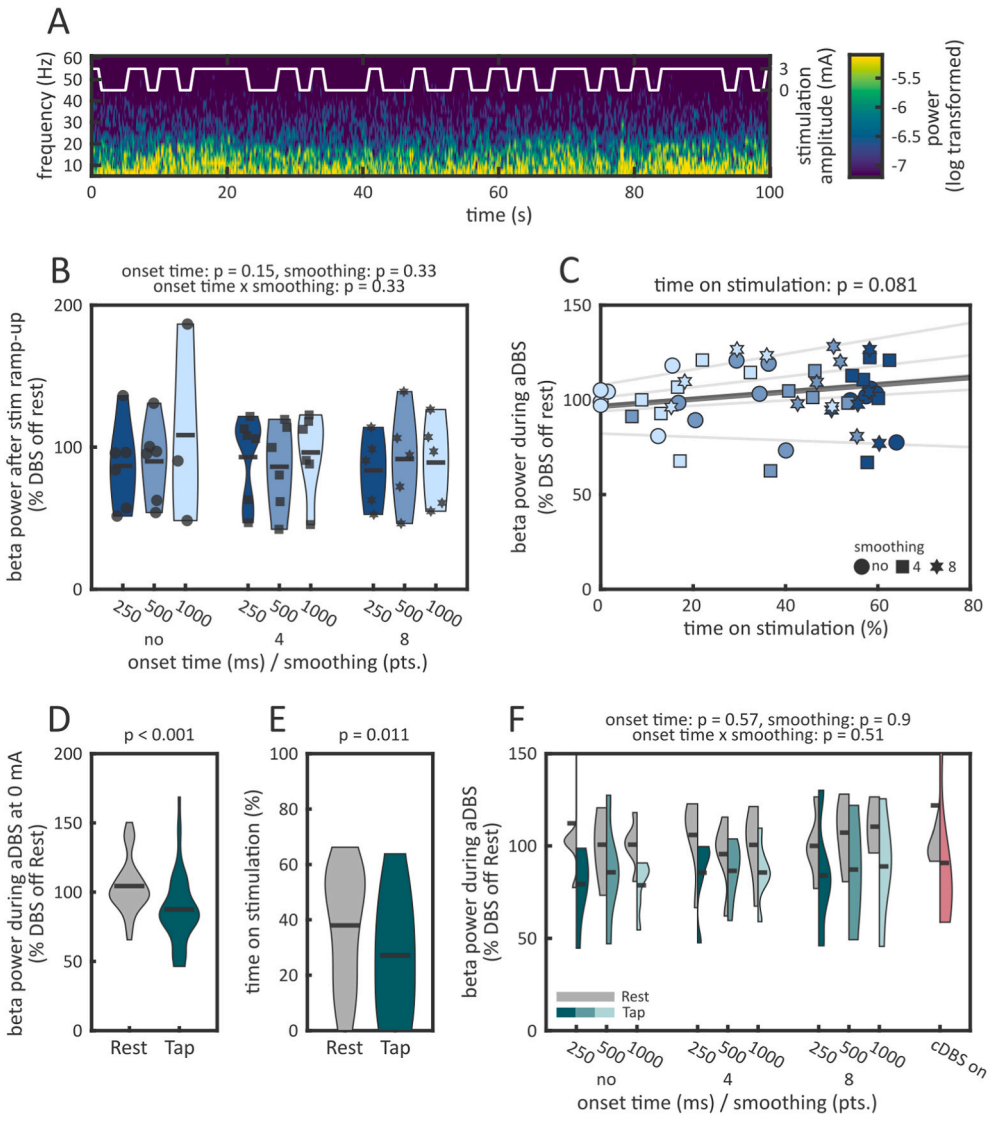

Fig. 5. Controllability of subthalamic beta power drives parameter dependency of aDBS. A) In an exemplar dataset of the *non-controllable* group, the spectrogram shows no modulatory effect of adaptive stimulation on subthalamic beta power. White trace: stimulation amplitude. B) Momentary beta power modulation following adaptive stimulation during rest was independent of parameter combination. C) While time on stimulation could be controlled by aDBS parameters, this did not result in differential effects on beta power during ongoing adaptive stimulation. Onset time is coded by brightness: dark blue: 250 ms, medium blue: 500 ms, light blue: 1000 ms. Bold grey line: estimated beta power based on fixed effects. Thin grey lines: estimated beta power based on fixed and random effects for each dataset. D) Beta power during aDBS but in periods without stimulation was lower during movement than during rest in the *non-controllable* group. E) As with the *controllable* group, less time was spent on stimulation in the *non-controllable* group during movement. F) Under aDBS and during tapping, beta power was suppressed but did not show any parameter-dependency.

response to parameter changes while patients were performing a simple motor task and in datasets showing reduced beta power suppression in response to cDBS.

We observed that aDBS responsiveness diminished when patients started to perform a finger-tapping task due to movement-induced beta power suppression. Setting the onset time to 1000 ms and not applying smoothing even led to total absence of stimulation during movement. Reduced adaptive stimulation has already been observed during a reaching task [20,28] and was to be expected given that movement leads to a reduction of subthalamic beta oscillations [39–41] and shortens beta bursts [23,42,43]. Moreover, the parameter dependency of beta power modulation observed at rest vanished during movement. This suggests that for parameter-dependent control over beta power modulation, a re-calibration of the threshold during ongoing movements may be required. This is supported by data showing that a higher rate of overall shortened beta bursts is associated with the magnitude of velocity decrement during continuous movements which therefore still need to be captured by the closed-loop system [43]. Accordingly, it may be reasonable to investigate whether incorporating information on the patient's behavior or other state variations improves aDBS responsivity across states [26,44,45]. In contrast, it has been suggested that aDBS with a rest based threshold may still perform adequately during movement by suppressing the remaining long bursts likely to induce motor slowing [46]. Interestingly, even in datasets where aDBS or cDBS did not modulate beta power, a movement-induced suppression could still be observed suggesting that the modulatory effects of focal electrical stimulation and movement might be mediated by partly incongruent neural processes and/or anatomical sites within the STN.

We further assessed controllability by splitting our data into two groups based on the extent of beta power suppression in response to cDBS. These two groups showed no apparent differences in electrode locations, demographic and clinical characteristics or recording details.

Furthermore, a beta peak was present in 2 of the 6 datasets in the *non-controllable* group. Thus, differences in pathophysiology or electrode placement are unlikely to account for reduced controllability which may be partly attributable to the micro-lesional effect of electrode insertion [30] or to the recording montage which may detect beta activity from a site that was not reached by the applied electric current [47]. Our data shows that controllability is a requirement for effective and parameter dependent closed-loop control of subthalamic beta activity: No beta power modulation in response to aDBS could be observed in the *non-controllable* group and effects of parameter changes were absent. Thus, with reduced controllability of beta power, a laborious search for aDBS parameters in the hope for marginal advantages favoring adaptive over continuous stimulation in modulating beta power is unlikely to provide any benefit. Hence, controllability of beta power may be assessed by continuous test stimulations to guide patient (or contact) selection for subsequent adaptive stimulation [8].

4.3. Towards automizing parameter optimization in adaptive deep brain stimulation

The full parameter space of single threshold aDBS is likely to feature more parameters than investigated here [6]. For example, the minimum duration below threshold required to trigger ramp-down or the method for defining the triggering threshold constitute other parameters that likely influence the responsivity of the closed-loop system. Moreover, other aDBS algorithms may feature different parameters that need to be explored separately. Short-duration in-clinic assessments as employed here only provide momentary outcomes, though, which may fail to capture long-term effects of parameter adjustments. This might especially apply to closed-loop algorithms that operate on time scales longer than ordinary clinical visits. Home-monitoring might therefore be necessary to trial different aDBS algorithms and parameter combinations [22,48]. However, this still poses a challenge for clinical translation, as limited resources for DBS programming render a thorough manual examination of parameter combinations unfeasible [49]. This calls for auto-updating aDBS algorithms, which optimize their parameters based on one or more observed outputs while the system is operating, e.g. by Bayesian optimization [50,51]. Future studies are required to assess the clinical applicability of such approaches.

4.4. Limitations

One limitation of this study is that recordings were conducted in the acute post-operative period during which subthalamic LFPs may differ from the chronically implanted state [52]. Future studies will need to corroborate our findings in chronically implanted patients using bi-directional neurostimulators [8,53]. Furthermore, although we designed our aDBS algorithm in a way as to resemble previous studies and available aDBS systems [11,24], generalizability is hindered due to the heterogeneity of available bi-directional DBS systems [54]. Finally, as it was necessary to discard data around stimulation ramp-up and ramp-down due to artifacts, we could not further investigate the effects of parameter changes, movement and controllability on beta burst dynamics in our offline analyses. Thus, it remains an open question how the distribution of beta bursts can be shaped by changing parameter combinations [23].

5. Conclusion

In conclusion, our investigation on the electrophysiological responses to aDBS parameter changes revealed that changing the onset time enables control over the extent of beta power modulation exerted by single threshold adaptive stimulation. We further provide evidence that using a threshold defined at rest diminishes aDBS responsiveness under movement and limits the control over beta power levels through changes to aDBS parameters. Finally, we underpin that controllability of subthalamic beta power by DBS is a pivotal factor for parameterizing aDBS algorithms. In sum, our results may guide parameter selection to effectively control subthalamic beta power with aDBS and emphasize that heterogeneous movement states and the controllability of beta must be considered in the future development of closed-loop DBS.

CRediT authorship contribution statement

Johannes L. Busch: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Jonathan Kaplan:** Data curation, Writing – review & editing. **Jeroen G.V. Habets:** Data curation, Formal analysis, Writing – review & editing. **Lucia K. Feldmann:** Data curation, Writing – review & editing. **Jan Roediger:** Methodology, Writing – review & editing. **Richard M. Köhler:** Software, Writing – review & editing. **Timon Merk:** Software, Writing – review & editing. **Katharina Faust:** Resources, Writing – review & editing. **Gerd-Helge Schneider:** Funding acquisition, Resources, Writing – review & editing. **Hagai Bergman:** Writing – review & editing. **Wolf-Julian Neumann:** Conceptualization, Writing – review & editing. **Andrea A. Kühn:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

JR has received speaker honoraria from Medtronic outside of this work.

GHS has received honoraria from Medtronic and Boston Scientific outside of this work.

WJN has received speaker honoraria from Medtronic outside of this work.

AAK has served on advisory boards of Medtronic and has received honoraria and travel support from Medtronic and Boston Scientific outside of this work.

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Appendix A. Supplementary data

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