

Beta-triggered adaptive deep brain stimulation during reaching movement in Parkinson's disease

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Abstract

Subthalamic nucleus (STN) beta-triggered adaptive deep brain stimulation (ADBS) has been shown to provide clinical improvement comparable to conventional continuous DBS (CDBS) with less energy delivered to the brain and less stimulation induced side-effects. However, several questions remain unanswered. First, there is a normal physiological reduction of STN beta band power just prior to and during voluntary movement. ADBS systems will therefore reduce or cease stimulation during movement in people with Parkinson's disease (PD) and could therefore compromise motor performance compared to CDBS. Second, beta power was smoothed and estimated over a time period of 400ms in most previous ADBS studies, but a shorter smoothing period could have the advantage of being more sensitive to changes in beta power which could enhance motor performance. In this study, we addressed these two questions by evaluating the effectiveness of STN beta-triggered ADBS using a standard 400ms and a shorter 200ms smoothing window during reaching movements. Results from 13 people with PD showed that reducing the smoothing window for quantifying beta did lead to shortened beta burst durations by increasing the number of beta bursts shorter than 200ms and more frequent switching on/off of the stimulator but had no behavioural effects. Both ADBS and CDBS improved motor performance to an equivalent extent compared to no DBS. Secondary analysis revealed that there were independent effects of a decrease in beta power and an increase in gamma power in predicting faster movement speed, while a decrease in beta event related desynchronization (ERD) predicted quicker movement initiation. CDBS suppressed both beta and gamma more than ADBS, whereas beta ERD was reduced to a similar level during CDBS and ADBS compared with no DBS, which together explained the achieved similar performance improvement in reaching movements during

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1 CDBS and ADBS. In addition, ADBS significantly improved tremor compared with no DBS but
2 was not as effective as CDBS. These results suggest that STN beta-triggered ADBS is effective in
3 improving motor performance during reaching movements in people with PD, and that shortening
4 of the smoothing window does not result in any additional behavioural benefit. When developing
5 ADBS systems for PD, it might not be necessary to track very fast beta dynamics; combining beta,
6 gamma, and information from motor decoding might be more beneficial with additional
7 biomarkers needed for optimal treatment of tremor.

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3 **Keywords:** adaptive deep brain stimulation (ADBS); Parkinson's disease (PD); reaching
4 movement; subthalamic nucleus; beta power; gamma power

5 **Abbreviations:** ADBS = Adaptive Deep Brain Stimulation; CDBS = Continuous Deep Brain
6 Stimulation; DBS = Deep Brain Stimulation; ERD = Event Related Desynchronization; GLME =
7 Generalized Linear Mixed Effect Modelling; LFP = Local Field Potential; MDS-UPDRS-III =
8 Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III; PD = Parkinson's
9 Disease; PSD = Power Spectral Density; STN = Subthalamic Nucleus

10

11 **Introduction**

12 Deep brain stimulation (DBS) targeting the subthalamic nucleus (STN) has been demonstrated to
13 be a successful treatment for patients with advanced Parkinson's disease (PD).¹ However,
14 continuous DBS (CDBS) can reduce in efficacy over time and may be accompanied by stimulation
15 related side-effects such as dyskinesia, postural instability, impairment of cognition and reduced
16 speech fluency.^{2,3}

17 Enhanced synchronisation of beta activity in the STN has been consistently observed in people
18 with PD, and is positively correlated with bradykinesia and rigidity. Conversely, improvement in
19 bradykinesia and rigidity with medication or DBS is positively correlated with suppression of beta
20 power.⁴⁻⁹ More recently, multiple studies have emphasized the importance of the temporal
21 dynamics of STN beta oscillations, where the occurrence of longer beta bursts are positively
22 correlated with motor impairment.¹⁰⁻¹³ Taken together, these findings suggest that STN beta
23 activity is a biomarker for parkinsonian motor symptoms, and has motivated the development of
24 beta-triggered adaptive DBS (ADBS, also called closed-loop DBS) algorithms, with the aim of
25 improving therapeutic efficacy while limiting side effects. The results of several pilot trials of
26 ADBS with temporarily externalized DBS electrodes,^{8,14-20} or chronically implanted DBS
27 devices²¹ suggest that beta-triggered ADBS in which the stimulation amplitude is adjusted based
28 on real time STN beta power estimation, is at least as effective as conventional CDBS in reducing

1 motor symptoms at rest as evaluated by Movement Disorders Society Unified Parkinson's Disease
2 Rating Scale part III (MDS-UPDRS-III).

3 However, several questions remain unanswered. First, does beta-triggered ADBS lead to worse
4 performance in reaching movements compared with CDBS in PD patients? There is a
5 physiological reduction of STN beta activity during voluntary movements, which is seen also in
6 people with PD.²²⁻²⁴ In the setting of beta-triggered ADBS, this will lead to reduction or cessation
7 of stimulation during movement. This could compromise motor performance compared with
8 CDBS if further beta suppression during movement is helpful for maximum therapeutic benefits
9 when patients attempt movements, which is arguably when they need it most.²⁵ Second, does
10 making the ADBS more responsive to the beta oscillation with shortened smoothing window to
11 quantify beta amplitude lead to improvement in motor performance? The smoothing window for
12 estimating beta is a key parameter that needs to be considered while developing ADBS, since
13 different smoothing windows alter the dynamics of the interactions between the stimulation and
14 the targeted oscillations. Most existing studies of beta-triggered ADBS have estimated beta
15 amplitude in real-time using an average moving window of 400-millisecond duration or longer,
16 aimed at capturing beta bursts of longer durations.^{10,14-16} Previous studies with single trial analysis
17 of LFPs recorded from striatum and motor-premotor cortex in healthy monkeys showed that brief
18 bursts of oscillation with the duration of 50-150 ms are responsible for virtually all beta-band
19 activity, and that most of the modulations in trial-averaged beta power primarily reflect
20 modulations of burst density.²⁶ This is consistent with results from healthy human participants
21 showing that high-power beta events from somatosensory and frontal cortex typically lasted
22 <150ms and had a stereotypical non-sinusoidal waveform shape.²⁷ Therefore, we hypothesized
23 that there might be extra benefits of an ADBS algorithm capable of truncating STN beta activities
24 into even shorter bursts, as observed in the healthy sensorimotor cortical-basal ganglia
25 network,^{26,27} via the use of a shorter smoothing time window (e.g., 200ms). To answer these
26 questions, we developed an experimental protocol combining a cued reaching task and a brain
27 computer interface allowing real-time estimation of STN beta and adjustment of stimulation
28 parameters (**Fig. 1**). We evaluated the motor performance of 13 people with PD in four different
29 stimulation conditions: no DBS, CDBS, ADBS-400 (ADBS with beta amplitude smoothed over
30 400ms), and ADBS-200 (ADBS with beta amplitude smoothed over 200ms).

1 **Materials and methods**

2 **Human subjects**

3 From Sep. 2021 to Aug. 2022, thirteen people with PD (six females) participated to the study after
4 being recruited at two different centres; King's College Hospital (KCH) and St George's Hospital
5 (SGH) (clinical details summarised in **Supplementary Table 1**). All underwent bilateral
6 implantation of DBS electrodes targeting the motor area of the STN. The implanted DBS leads
7 (manufacturer details in **Table 1** and supplementary methods) were temporarily externalized prior
8 to a second surgery to connect them to a neurostimulator. Lead placements were confirmed by
9 fusion of preoperative MRI and postoperative CT scans, which were further confirmed by
10 reconstructing the electrode trajectories and location of different contacts using the Lead-DBS
11 MATLAB toolbox (version 2.6.0).²⁹ As shown in **Fig. 1D**, most of the tested electrodes clustered
12 in a sweetspot that has been suggested to provide optimal overall motor improvement for PD with
13 DBS.³⁰ One electrode appears to be at the border of the STN (P1L in **Supplementary Fig. 1**), so
14 we applied volume-of-tissue activated (VTA) analysis using the stimulation parameters as used
15 during the recording for this electrode. This analysis confirmed that stimulation applied to this
16 electrode led to VTA that overlapped with the STN and the sweetspot for overall motor
17 improvement. The study was approved by the local ethics committees and all patients provided
18 their informed written consent according to the Declaration of Helsinki. Patients participated in
19 this study had an average age of 62.15 ± 1.58 (mean \pm SEM) and a disease duration of 10 ± 1.21
20 years and showed good response to dopaminergic medication with mean scores of the MDS-
21 UPDRS-III of 37.04 ± 2.95 and 12.42 ± 1.67 for medication OFF and ON, respectively. In this
22 study, all experiments were conducted with the patients off their dopaminergic medication for at
23 least six hours.

24 **Experimental protocol**

25 The protocol involved two tasks: a cued reaching task performed on a Tablet Drawing Monitor
26 (33 x 57 cm, Artist 22, XP-PEN, Japan) with a stylus pen, and a 20s finger-tapping task. The
27 reaching task was programmed in C# (Visual Studio 2013). As shown in **Fig. 1A**, each trial of the
28 reaching task started with presentation of a white-filled circle at the bottom of the monitor

1 indicating that the patient should bring the pen to the starting position when they were ready
2 (Ready Cue). Once the pen was in the starting position, the circle turned green to indicate that the
3 pen was detected. After a variable delay of 1-2 seconds, a red-filled circle (the Go-cue) appeared
4 on one of the three potential target positions (top-left, top-middle, or top-right of the monitor).
5 Following this Go-cue signal, the patient was instructed to reach the target and come back to the
6 start position as quickly as possible (see **Supplementary Video 1**). As shown in **Fig. 1B**, the whole
7 experimental session consisted of eight blocks of 15 trials, with an inter-trial interval of 4-5 s
8 (randomised). There were two blocks in each of the four tested stimulation conditions (no DBS,
9 CDBS, ADBS-200, ADBS-400; details in next section). After the reaching movement task, and at
10 the end of each block, the patient was asked to perform finger-tapping movements for 20 s, by
11 tapping their index fingers on their thumbs as wide and fast as possible. After changing each
12 condition, an average interval of 67.67 ± 9.20 s (mean \pm SEM) was included before starting a new
13 block for washing out the potential stimulation effect from the previous block. In total, the
14 recordings with each patient lasted up to 3 hours for two hemispheres or 2 hours for only one
15 hemisphere. The order of the experimental blocks was pseudo-randomised and counter-balanced
16 across patients. To achieve this, for each patient, the first four blocks included the four stimulation
17 conditions in randomised order, and the four conditions were repeated in reverse order in the
18 second four blocks (**Fig 1B**).

19 **Stimulation**

20 Stimulation was applied unilaterally to the hemisphere contralateral to the hand performing the
21 task. A highly configurable custom-built neurostimulator certified by the University of Oxford,
22 UK (an improved version based on what was used in *14, 15*) was used to deliver constant current
23 stimulation in monopolar mode. One of the two contacts in the middle was used as the stimulation
24 contact, and an electrode patch attached to the back of the patient was used for reference (**Fig. 1C**).
25 In cases of directional leads, the segmented contacts were used in ring mode. For those electrodes
26 with more than 4 levels, only the most inferior 4 levels which were supposed to locate in STN
27 based on imaging data were considered for stimulation/recording in this study. The stimulation
28 had a fixed frequency of 130 Hz, a biphasic pulse width of 60 microseconds, and an interphase gap
29 of 20 microseconds. Four different stimulation conditions were considered in this study, including
30 no DBS, continuous DBS (CDBS), adaptive DBS with the stimulator controlled by the beta

1 amplitude estimated in real-time using a 200-ms smoothing window (ADBS-200), and adaptive
2 DBS with a 400-ms smoothing window (ADBS-400). Before smoothing, the bipolar LFPs were
3 filtered at the selected beta frequency band and rectified.^{10,14,15} The implementation of ADBS was
4 the same as in previous studies,^{14,15} apart from using an advanced stimulator and adding a new
5 condition with shorter smoothing windows (ADBS-200) to capture faster beta dynamics. To
6 mitigate transient effects resulting in a re-entrant stimulation loop during ADBS,³¹ ramping was
7 applied at the start and end of each stimulation switching event, which forced the stimulation
8 amplitude to linearly increase to the desired value or decrease to zero within 250ms. In addition, a
9 refractory time window of 50ms was set after stimulation was switched off.

10 **Selecting stimulation contact and amplitude, and the beta frequency** 11 **band for feedback**

12 We followed a similar procedure used in a previous study¹⁴ to select the stimulation contact and
13 amplitude, and the beta frequency band as the feedback signal. Specifically, we delivered
14 continuous DBS to one of the middle two contacts initially at 0.5 mA. We then progressively
15 increased the amplitude in 0.5 mA increments, until clinical benefit was seen without side effects
16 such as paraesthesia, or until 3.5 mA was reached as the maximum amplitude. If no apparent
17 clinical effect was observed, we repeated this procedure for the other middle contact level. Once
18 the stimulation contact and amplitude were selected, a period of 2 minutes of rest recordings were
19 performed. LFPs were recorded from two contacts neighbouring the selected stimulating contact
20 in the differential bipolar mode. To select the individualized beta frequency band for feedback, the
21 recorded LFPs were first notch-filtered at 50 Hz and band-pass filtered between 1 and 95 Hz using
22 a second order zero-phase digital filter. The periodogram power spectral density (PSD) was then
23 estimated. The feedback beta frequency band was selected as ± 3 Hz around the largest beta peak
24 (13-30 Hz). In the ADBS conditions, the threshold for triggering the stimulation was set manually
25 for each hemisphere separately so that the DBS would be switched on for about 50 percent of the
26 time when the patient was at rest (**Fig. 1C**), as in the previous ADBS studies.^{8,10,14,15,18,32} For
27 patients who performed the tasks with both hands, the stimulation contact and amplitude, as well
28 as the beta frequency band and triggering threshold were selected separately for each hemisphere.
29 These stimulation parameters (summarized in **Table 1**) were kept constant for different stimulation
30 conditions for each hemisphere. Post-hoc comparisons confirmed that all contacts tested in this

1 study (100%) appeared to be at least at adjacent levels of the contacts used in chronic DBS, with
2 66.67% of them appeared to be from the same level.

3 **Data recording**

4 All recordings were carried out 3-6 days after the first surgery for DBS electrode implantation. A
5 TMSi Porti or Saga amplifier (TMS International, the Netherlands) was used to record bipolar
6 LFPs from the two contacts adjacent to the stimulating contact (**Fig. 1C**) at a sampling rate of 2048
7 Hz (cases 1-2, 4-8, Porti amplifier) or 4096 Hz (cases 3, 9-13, Saga amplifier). The acceleration
8 of the patient moving their hand was measured using a triaxial accelerometer taped to the back of
9 the index finger and simultaneously recorded with the same amplifier at the same sampling
10 frequency as the LFP signals. The precise timing of all cue signals of the reaching task (Start, Go,
11 Reached and Back, **Fig. 1A**) and the finger tapping task (Start/Stop) were captured using a
12 photodiode taped to the monitor, and recorded with the same amplifier. Furthermore, the
13 instantaneous stimulation amplitude applied during the real-time experiment was also
14 simultaneously recorded by a custom-developed C program. The ground electrode was placed on
15 the resting forearm of the patient. The X and Y coordinates of the stylus on the monitor and the
16 corresponding timestamps were recorded automatically at an irregular sampling rate of $84.3062 \pm$
17 3.3060 Hz (mean \pm SEM) by a custom-developed C# program (irregularity of sampling was due
18 to the imprecision of the timer in C#). In addition, videos of the finger-tapping movements were
19 recorded using a smartphone (iPhone 6s, Apple Inc., US) for further blinded assessment. Among
20 the 13 patients, seven (cases 2-3, 7, 10-13) performed the task with both hands separately, resulted
21 in 20 hemispheres in total. However, the left hemisphere for case 2 was excluded due to strong
22 stimulation artefact contaminating the estimated beta in all stimulation conditions, probably due
23 to the high amplitude of stimulation (3.5 mA) and/or high electrode impedance. Case 5 was
24 excluded due to obvious stimulation induced dyskinesia even at low stimulation amplitude (1.5
25 mA). The data from the remaining 12 patients (18 hemispheres) were analysed. Due to limited
26 time for conducting the experiment, case 10 did not perform the task in the ADBS-200 condition.

27 **Kinematic data analysis**

28 *Reaching movements:* The trajectories of the reaching movements were re-constructed for each
29 trial, based on the recorded XY coordinates and timestamps, as shown in **Fig. 3A** and **Fig. 4A**.

1 The mean velocities of the reach and return movements were calculated separately for each trial
2 by dividing the accumulated distances against the durations of the movements. Instantaneous
3 velocity was quantified using two adjacent coordinates and their timestamps. In addition, the
4 reaction time was defined as the time from the Go-cue to the first timestamp when the pen moved
5 out of the target button.

6 *Finger-tapping:* For each finger-tapping movement, we quantified the root-mean-square
7 acceleration based on the recorded three-axes accelerometer signals, and acquired the mean
8 blinded ratings from two experienced movement disorder specialists (F.B. and A.M. in the author
9 list) based on the recorded video, as overall evaluations of the tapping performance (detailed in
10 supplementary methods).^{33,34}

11 *Resting tremor* was quantified based on accelerometer measurements with details in
12 supplementary methods.

13 **Stimulation and LFP data analysis**

14 During ADBS-200 and ADBS-400, the average percentage of time when the stimulation was on
15 and stimulation switching rate (number of stimulation events per second) were quantified based
16 on the recorded stimulation amplitude.

17 The effects of the two different ADBS algorithms on the dynamics of the beta oscillations were
18 also analysed. The bipolar LFPs recorded from the feedback channel for each task were processed
19 off-line in the same way as used for real-time beta estimation, with the only difference that a 200-
20 ms smoothing window was used for all conditions, so that we could compare dynamics of beta
21 oscillations across stimulation conditions. Then the 75th percentile of the beta amplitude with the
22 patient at rest and stimulation off was used to define beta bursts. Next, average burst duration and
23 burst rate (events per second) were quantified as described before.^{10,35} To investigate the
24 movement related modulation in the STN, LFPs were first epoched starting 5 seconds before the
25 Go-cue to 2 seconds after the pen returned to the start button. Then the signals were pre-processed,
26 decomposed into time-frequency domain using continuous wavelet transformation, and the
27 relative changes in different frequency bands were quantified (more details in supplementary
28 methods). To investigate the associations between STN beta/gamma power and motor
29 performance, for each individual trial, we first quantified beta power at different time windows,

1 including average beta power in the 1 to 0.5 s window (W1 in **Fig. 5D**) before movement initiation
2 (β_{w1}) as baseline, average beta power in the 0.2 s window (W2 in **Fig. 5D**) around movement
3 initiation (β_{w2}) where beta was minimal, and beta event-related desynchronization (ERD) as the
4 difference between β_{w1} and β_{w2} . Then, we used each of these beta power windows, together with
5 stimulation condition index as independent variables to predict the reaction time of the reaching
6 movements in separate generalized linear mixed effect (GLME) models. In addition, the average
7 beta power during movement (from reach/return movement onset to target reached), average
8 gamma power during movement, stimulation condition index, and reach or return index were also
9 used as independent variables in GLME models to predict mean velocities of the reaching
10 movements.

11 **Statistical analysis**

12 Statistical analyses were conducted using custom-written scripts in MATLAB R2021-b (The
13 MathWorks Inc, Nantucket, Massachusetts).

14 For those metrics quantified on *per* condition basis (including stimulation switching rate, average
15 percentage of time when the stimulation was on, average burst duration, and burst rate), paired *t*-
16 tests were used to evaluate the effect of the stimulation condition. The normal distribution
17 assumption was tested using Anderson-Darling test. Multiple comparisons applied to different
18 measurements were corrected using Bonferroni correction. For each comparison, the number of
19 cases, *t*-values, and pre-corrected *p*-values were reported.

20 For those metrics quantified on individual trial/block basis (including reaction time, mean velocity,
21 rest tremor power, root-mean-square acceleration, and blinded video rating), GLME modelling
22 was used to investigate the effect of different stimulation conditions.³⁶ Due to the naturally skewed
23 characteristic of reaction time, normal distribution with log link function was used in the models
24 using reaction time as the dependent variable. Otherwise, normal distribution with identity link
25 function was used. We also used GLME to further investigate the effects of STN beta/gamma
26 power on performance of the reaching movement measured by reaction time and mean velocity on
27 a trial-by-trial basis. In each model, the slope(s) between the predictor(s) and the dependent
28 variable were set to be fixed across all hemispheres while a random intercept was set to vary by
29 hemisphere. Multiple comparisons applied to different measurements were corrected using

1 Bonferroni correction. For each GLME model, the parameters were estimated based on maximum
2 likelihood using Laplace approximation, the Akaike information criterion (AIC), estimate value
3 with standard error of the coefficient ($k \pm SE$), pre-corrected p -value (p), and proportion of
4 variability in the response explained by the fitted model (R^2) were reported.

5 A chi-squared reference distribution based likelihood ratio test was conducted for the comparison
6 of two fitted GLME models, and the likelihood ratio test statistic (LRStat), difference in degrees
7 of freedom between two models (deltaDF), and p -value for the likelihood ratio test were reported
8 for each pair of models comparison. The modelling is further detailed below together with the
9 results.

10 To compare the group averaged beta/gamma power at different time points relative to movement,
11 a nonparametric cluster-based permutation procedure (repeated 1000 times) was applied and
12 multiple comparisons were controlled.³⁷

13 **Data availability**

14 The data and codes will be shared on the data sharing platform of the MRC Brain Network
15 Dynamics Unit: <https://data.mrc.ox.ac.uk/mrcbndu/data-sets/search>.

17 **Results**

18 **1. No difference in motor performance between ADBS-200 and** 19 **ADBS-400**

20 As expected, the stimulation was overall switched on and off more frequently during ADBS-200
21 compared with ADBS-400 ($t_{15} = 16.5321$, $p = 4.8823e-11$, paired t -test, **Fig. 2A**), with a trend
22 towards a higher average percentage of stimulation on time during ADBS-400 but was not
23 statistically significant ($t_{15} = -2.1327$, $p = 0.050$, paired t -test, **Fig. 2B**).

24 Despite the clear difference in the stimulator switching rate between ADBS-200 and ADBS-400
25 as expected from a shorter beta smoothing window, there was no significant difference in motor
26 performance of the reaching task, including reaction time ($k = -0.0225 \pm 0.0181$, $p = 0.2155$, **Fig.**

1 **3B**) or mean velocity (Reach: $k = 0.0065 \pm 0.0062$, $p = 0.2977$, **Fig. 3C**; Return: $k = 0.0025 \pm$
2 0.0053 , $p = 0.6330$, **Fig. 3D**). Similarly, the two ADBS conditions led to similar performance in
3 the finger-tapping task as evaluated by the root-mean-square acceleration ($k = 0.0189 \pm 0.0310$, p
4 $= 0.5416$, **Fig. 3E**) and blinded video ratings ($k = 0.0047 \pm 0.1265$, $p = 0.9703$, **Fig. 3F**). There
5 was no difference in resting tremor either ($k = -0.1683 \pm 0.2336$, $p = 0.4714$, **Fig. 3G**) between the
6 two ADBS conditions.

7 Then we compared how these two ADBS conditions modulated the temporal dynamics of beta
8 oscillations. The average beta burst duration was shorter during ADBS-200 compared with ADBS-
9 400 ($t_{15} = -2.9817$, $p = 0.0093$, paired t -test, **Fig. 2C**). This was mainly due to more bursts with
10 shorter durations during ADBS-200 (<0.2 s, $t_{15} = 3.0478$, $p = 0.0081$, paired t -test, **Fig. 2D**), and
11 there was no significant difference for bursts with longer durations (>0.2 s) between these two
12 conditions. Please note that here beta bursts were re-quantified offline using the same method
13 based on the recorded bipolar LFPs using a 200-ms smoothing window for both ADBS conditions.
14 Even though the fast ADBS-200 cut the beta burst even shorter than the ADBS-400, this faster
15 algorithm did not further improve motor performance. These results confirm the findings of
16 previous studies showing that only long beta bursts are pathological.

17 **2. ADBS and CDBS equally improved motor performance compared** 18 **with no DBS, but not resting tremor**

19 Since we did not see any behavioural difference between ADBS-200 and ADBS-400, we
20 combined these two conditions into one ADBS condition and compared them against CDBS and
21 no DBS for further analysis. Compared with no DBS, both CDBS and ADBS significantly
22 improved motor performance of the cued reaching movements with reduced reaction time (CDBS
23 vs. no DBS: $k = -0.0557 \pm 0.0217$, $p = 0.0103$; ADBS vs. no DBS: $k = -0.0253 \pm 0.0094$, $p =$
24 0.0072 , **Fig. 4B**) and increased mean velocity (CDBS vs. no DBS: $k = 0.0144 \pm 0.0058$, $p = 0.0139$;
25 ADBS vs. no DBS: $k = 0.0128 \pm 0.0045$, $p = 0.0041$, **Fig. 4D**) during backward movements. The
26 effects on the mean velocity during reaching movements were smaller and only significant in
27 ADBS ($k = 0.0072 \pm 0.0028$, $p = 0.0106$, **Fig. 4C**) but not in CDBS ($k = 0.0076 \pm 0.0072$, $p =$
28 0.291 , **Fig. 4C**) conditions. Both CDBS and ADBS improved the finger-tapping movements with
29 increased root-mean-square acceleration (CDBS vs. no DBS: $k = 0.0875 \pm 0.0372$, $p = 0.0214$;

1 ADBS vs. no DBS: $k = 0.0339 \pm 0.0149$, $p = 0.0253$, **Fig. 4E**) and reduced blinded bradykinesia
2 ratings (CDBS vs. no DBS: $k = -0.3088 \pm 0.1345$, $p = 0.0249$; ADBS vs. no DBS: $k = -0.1738 \pm$
3 0.0593 , $p = 0.0042$, **Fig. 4F and Supplementary Video 2**), although some of them were only
4 nominally/marginally significant and did not survive Bonferroni correction for multiple
5 comparisons. When comparing between CDBS and ADBS conditions, no significant behavioural
6 difference was found in any of the evaluated metrics (**Fig. 4B-F**) for the reaching or finger-tapping
7 movements, suggesting that ADBS improved motor performance to a similar extent as CDBS.
8 However, there was more resting tremor during ADBS compared with CDBS ($k = 0.7605 \pm 0.2179$,
9 $p = 0.0005$, **Fig. 4G**), even though tremor was significantly reduced in both DBS conditions
10 compared with no DBS (CDBS vs. no DBS: $k = -2.152 \pm 0.3265$, $p = 6.8335e-11$; ADBS vs. no
11 DBS: $k = -0.5726 \pm 0.1256$, $p = 5.5933e-06$, **Fig. 4G**). The mean duration on stimulation was only
12 $39.39 \pm 3.14\%$ of time during ADBS, which was significantly less than CDBS where the
13 stimulation was continuously on ($t_{17} = 18.1342$, $p = 1.4736e-12$, paired t -test, **Fig. 4H**).

14 **3. Stimulation probability during ADBS followed a similar pattern as** 15 **movement-related beta modulation**

16 During all DBS conditions, a clear ERD in the beta frequency band (13-30Hz) was observed
17 around onset of the reaching movement (**Fig. 5A-C**), as well as around the time when the target
18 was reached, before the initiation of return movements (**Fig. 5E-G**). In fact, the beta power reached
19 its minimum around both reaching and return movement initiations, then resynchronized to or
20 above baseline level at the end of the movements (**Fig. 5D and H**). During ADBS, the averaged
21 stimulation probability followed a similar pattern as the modulation of beta, but with a constant
22 shift in time that was caused by real-time filtering and smoothing (**Fig. 5D and H**). In general, the
23 stimulation probability dropped from around 40% before the movement to $32.55 \pm 4.80\%$ in the
24 1-s time window after the initiation of the reaching movement in this paradigm.

25 **4. Reaction time and mean velocity during the reaching movement** 26 **were predicted by STN beta and gamma power**

27 The spectrograms averaged across trials and time locked to the movement initiation also revealed
28 clear gamma power increase during the execution of reaching movements (**Fig. 5 A-C and E-G**).

1 Here we further explored the potential associations between beta/gamma oscillations and motor
2 performance, as well as the effect of different DBS protocols. Here CDBS and ADBS were
3 combined since there was no behavioural difference between them. As shown in **Table 2**, the
4 GLME modelling results suggested that although there was a positive estimation effect for β_{w1}
5 (baseline beta) and a negative estimation effect for β_{w2} (beta around movement initiation) in
6 predicting reaction time, neither of the effects was significant. However, there was a significant
7 positive estimation effect on beta ERD ($k = 0.0301 \pm 0.0150$, $p = 0.0453$) in predicting reaction
8 time, together with a significant negative estimation effect on stimulation condition ($k = -0.0742$
9 ± 0.0363 , $p = 0.0409$), suggesting stimulation and smaller beta ERDs independently predicted
10 shorter reaction times. Non-significant interaction between stimulation condition and beta ERD
11 suggests that the association between beta ERD and reaction time was not altered by different
12 stimulation conditions. In addition, likelihood ratio test revealed that the GLME model using beta
13 ERD significantly outperformed the model using β_{w1} (LRStat: 6.748; $p < 0.001$, chi-squared test)
14 or β_{w2} (LRStat: 1.8418; $p < 0.001$, chi-squared test) in predicting reaction time.

15 While predicting movement velocity, GLME modelling (Model 6 in **Table 2**) revealed significant
16 negative effect of beta power ($k = -0.0042 \pm 0.0008$, $p = 6.7338e-07$) and positive effect of gamma
17 power ($k = 0.0049 \pm 0.0009$, $p = 7.7075e-09$), suggesting less beta and more gamma during
18 movement together predicted bigger velocities. Apart from this, the modelling also revealed that
19 the mean velocities were bigger during DBS compared with no DBS conditions ($k = 0.0142 \pm$
20 0.0039 , $p = 0.0003$), and during reach movements compared with return movements ($k = -0.0689$
21 ± 0.0034 , $p < 0.001$), which were consistent with the results shown in **Fig. 4**. The GLME model
22 combining both beta and gamma performed significantly better than the model only considered
23 beta (LRStat: 33.35; $p = 7.6987e-09$, chi-squared test) or gamma (LRStat: 24.685; $p = 6.7514e-$
24 07 , chi-squared test) in predicting mean velocities, further confirming that beta and gamma
25 simultaneously associated with the mean velocity during the reaching movement.

26 **5. DBS suppressed both STN beta and gamma, with a stronger** 27 **suppression during CDBS compared with ADBS**

28 As shown in **Fig. 6 A and D**, on top of the movement related modulation, STN beta and gamma
29 power were overall suppressed by DBS, which has been reported in previous studies,³⁸ and the

1 suppression was stronger during CDBS compared with ADBS conditions. Specifically, compared
 2 with no DBS, the suppression of beta and gamma during CDBS was significant along the whole-
 3 time course, while the suppression of beta and gamma during ADBS was only significant at certain
 4 time windows. We then compared the averaged beta power in the different time windows used in
 5 **Table 2** among different stimulation conditions. The results further confirmed that both ADBS
 6 (β_{w1} : $k = -0.5508 \pm 0.0696$, $p = 4.8748e-15$, **Fig. 6B**; β_{w2} : $k = -0.3061 \pm 0.0839$, $p = 0.0003$, **Fig.**
 7 **6C**) and CDBS (β_{w1} : $k = -2.3452 \pm 0.1816$, $p = 1.5153e-35$, **Fig. 6B**; β_{w2} : $k = -1.4809 \pm 0.1961$,
 8 $p = 9.157e-14$, **Fig. 6C**) significantly suppressed beta, and the suppression of beta was stronger
 9 during CDBS compared with ADBS (β_{w1} : $k = -1.1832 \pm 0.1135$, $p = 1.2901e-24$, **Fig. 6B**; β_{w2} : k
 10 $= -0.8398 \pm 0.1613$, $p = 2.1741e-07$, **Fig. 6C**). In addition, we found beta ERD was also
 11 significantly reduced during DBS condition compared with No DBS (CDBS vs. no DBS: $k = -$
 12 0.8642 ± 0.2082 , $p = 3.5655e-05$; ADBS vs. no DBS: $k = -0.2439 \pm 0.0990$, $p = 0.0138$). However,
 13 the difference between CDBS and ADBS was not statistically significant ($k = 0.3476 \pm 0.1932$, p
 14 $= 0.0723$). Results in the previous section showed that reaction time was more related to beta ERD.
 15 The results here may explain why CDBS and ADBS lead to similar changes in reaction time.

16 Similarly, beta (ADBS: $k = -0.2756 \pm 0.0749$, $p = 0.0002$, **Fig. 6E**; CDBS: $k = -1.5111 \pm 0.1910$,
 17 $p = 6.2992e-15$, **Fig. 6E**) and gamma (ADBS: $k = -0.3937 \pm 0.0767$, $p = 3.2493e-07$, **Fig. 6F**;
 18 CDBS: $k = -2.6497 \pm 0.2023$, $p = 1.8303e-36$, **Fig. 6F**) power during movement were significantly
 19 suppressed by DBS, and the suppression was stronger during CDBS compared with ADBS (Beta:
 20 $k = -0.9337 \pm 0.1189$, $p = 7.6942e-15$, **Fig. 6E**; Gamma: $k = -1.8405 \pm 0.1074$, $p = 2.3989e-60$,
 21 **Fig. 6F**). The results here may explain why CDBS and ADBS lead to similar changes in movement
 22 speed: even though CDBS suppressed beta more than ADBS, it also suppressed gamma more,
 23 whereas both reduction of beta and increase of gamma contributed to invigorating movements.

24

25 Discussion

26 There were three main findings from this study. First, we showed that shortening the smoothing
 27 window to 200ms did make the ADBS more responsive. Further, it shortened the average duration
 28 of beta bursts by increasing the number of bursts shorter than 200ms. However, this did not bring
 29 any behavioural benefit compared with ADBS with a 400-ms smoothing window for estimating

1 beta, supporting the argument that only long STN beta bursts are pathological in PD. Second, we
2 showed that although beta-triggered ADBS reduced the average time on stimulation during
3 reaching movements, it did not compromise motor performance in terms of reaction time and
4 movement speed compared with CDBS. Both ADBS and CDBS improved the performance of
5 reaching and finger-tapping movements to a similar extent compared with no DBS. Third, our
6 results indicated that although ADBS achieved similar effect as CDBS in reducing bradykinesia
7 and improving reaction time and movement speed, it was not as effective as CDBS in suppressing
8 resting tremor.

9 **Why was there no behavioural difference between ADBS-200 and** 10 **ADBS-400?**

11 Previous studies showed that STN beta bursts with different durations might have different roles
12 in PD. In particular, the occurrence of longer beta bursts with large amplitude positively correlates
13 with motor impairment,^{10-13,39} which has also been confirmed in animal models of PD.⁴⁰ Here, in
14 addition to the commonly used 400-ms smoothing time window (ADBS-400),^{10,14-16} we also tested
15 a faster ADBS algorithm in which a 200-ms smoothing time window was used (ADBS-200), to
16 test whether this might further improve the efficacy of ADBS. Our results showed no difference
17 between these two ADBS conditions in any of the evaluated motor performance metrics, including
18 reaction time, movement velocity, resting tremor, root-mean-square acceleration and blinded video
19 ratings of finger-tapping (**Fig. 3**). Please note that here the blinded video ratings were conducted
20 by two movement disorder specialists under the guidance of MDS-UPDRS-III (finger tapping
21 instruction), which we believe is somewhat representative of clinical assessment of bradykinesia.
22 As shown in **Fig. 3** (group level) and in **Supplementary Fig. 2** (individual level), blinded video
23 ratings did not differ between ADBS-200 and ADBS-400, but improved significantly during
24 ADBS compared to no DBS. These results were unlikely due to errors in implementation of these
25 two algorithms, as post-hoc analysis confirmed that ADBS-200 was more responsive to the beta
26 oscillations leading to more frequent switching on/off of the stimulator (**Fig. 2A**) despite a similar
27 total stimulation on time (**Fig. 2B**) compared with ADBS-400. We further compared how the two
28 ADBS strategies modulated beta burst characteristics and found that ADBS-200 reduced the
29 average beta burst duration compared with ADBS-400 (**Fig. 2C**), by increasing the number of
30 shorter bursts with durations less than 200ms while keeping a similar number of longer bursts (**Fig.**

1 **2D**). These results further support the hypothesis that only long beta bursts ($> 400\text{ms}$) have a
2 pathological effect in PD.¹⁰⁻¹³ Therefore, being more responsive to those short bursts with
3 durations less than 400ms appears unnecessary.

4 **Why did ADBS provide comparable improvement in motor** 5 **performance to CDBS?**

6 STN beta-triggered adaptive DBS has been shown to be at least as effective as conventional
7 continuous DBS as evaluated by MDS-UPDRS-III in multiple studies,^{8,14-21} but it is still unclear
8 whether beta-triggered ADBS is as effective when patients are engaged in a motor task, since STN
9 beta is suppressed during movement initiation and execution.²²⁻²⁴ A recent study of three people
10 with PD showed that ADBS might negatively affect the returning part of a reaching movement
11 and delay movement termination,¹⁷ although motor improvement as measured by MDS-UPDRS-
12 III was comparable to CDBS. In this study, we found that ADBS achieved similar effects as CDBS
13 in improving motor performance in a reaching task in terms of reaction time, movement velocity,
14 and in improving bradykinesia measured by root-mean-square acceleration and blinded video
15 ratings of finger-tapping movements (**Fig. 4**). Therefore ADBS, despite reduced stimulation during
16 ballistic reaching movements (**Fig. 5C-D**), did not appear to compromise movement initiation or
17 execution compared with CDBS.

18 There are two explanations for this finding. First, even though beta power is reduced during
19 movements when averaged across trials, transient episodes of long beta bursts can still be observed
20 in individual trials.⁴¹ This explains why in this study, some stimulation (~30% of the time) was
21 still delivered during movement in the ADBS conditions (**Fig. 5D, H**). We hypothesize that long
22 pathological beta bursts can still occur during movements, which can be curtailed by ADBS,
23 leading to improvement in motor performance. Second, our analysis revealed that during reaching
24 movement, the reaction time was not predicted by beta power *per se*, but was predicted by beta
25 ERD (**Table 2**), which was significantly reduced during DBS compared with no DBS with no
26 difference between CDBS and ADBS. Previous studies have suggested that beta ERD represents
27 cortical activation, while beta event related synchronization (ERS) represents an inactive, idling
28 state with reduced excitability of the cortex.⁴² Chen et al. found that during self-paced movements,
29 corticospinal excitability increases and reaches a maximal level during movement initiation, then

1 reduces after movement initiation,⁴³ which is a very similar pattern to beta ERD during movement
2 initiation. In a separate study from the same group, a negative correlation was found between
3 single-trial STN beta power and corticospinal excitability during successful stopping movement
4 in patients with PD.⁴⁴ Thus, quicker movement initiation could be associated with a quicker de-
5 activation of the corticospinal excitability as well as a quicker completion of beta
6 desynchronization, resulting in a smaller STN beta ERD. On the other hand, a positive correlation
7 was reported between the latency of STN beta ERD and RT in patients with PD using a go/nogo
8 task, with shorter RTs associated with earlier ERD onsets.^{45,46} Here we quantified beta ERD as the
9 difference in beta power between two fixed time windows relative to movement initiation, thus, a
10 smaller ERD could be due to an earlier ERD onset. However, these are still speculations, further
11 exploration on this would require new data and is outside the scope of this work. Furthermore, our
12 results revealed that reduced beta power and increased gamma power during movement together
13 predicted faster movement speed (**Table 2**). Previous studies showed that gamma power in the
14 human basal ganglia is positively correlated with movement speed in patients with either PD or
15 dystonia.⁴⁷⁻⁵⁰ Here we show that both STN beta and STN gamma power during movement help
16 predict movement speed, with significant negative and positive estimation effects for beta and
17 gamma, respectively. However, both beta and gamma power were more strongly suppressed
18 during CDBS compared with ADBS (**Fig. 6**). To better investigate the stimulation induced beta
19 and gamma suppression on individual hemispheres, we further compared the resting (5-s before
20 the Go-cue) beta and gamma power between no DBS and CDBS. As shown in **Supplementary**
21 **Fig. 3**, the suppression of beta (in 77.78% of recorded hemispheres) and gamma (in 83.33% of
22 recorded hemispheres) power was consistent for most of the tested hemispheres. The stimulation
23 induced power suppression in beta and gamma frequency bands shared similar spatial distributions
24 relative to the STN, and positively correlated with each other ($r = 0.8073$, $p = 5.1252e-05$, Pearson
25 correlation). This suggests that although beta was better suppressed during CDBS, ADBS
26 preserved gamma better which help invigorate movements, so that the overall movement speeds
27 were similar during CDBS and ADBS conditions.

28 **Why was ADBS not as effective as CDBS in suppressing resting**
29 **tremor?**

1 Previous studies have demonstrated that STN beta oscillations positively correlate with the
2 severity of bradykinesia and rigidity, but not with resting tremor.^{4-8,32,51-53} Several existing trials
3 testing the performance of STN beta-triggered ADBS in chronically implanted patients showed
4 re-emergence of tremor during ADBS in some tremor-dominant people with PD, although its
5 effectiveness with bradykinetic phenotypes has been consistently demonstrated.^{18,54} Indeed, a
6 decrease of beta activity during parkinsonian tremor has been reported in several studies.^{55,56} In
7 the presence of tremor, neuronal oscillations at tremor frequency (3–7 Hz) tend to increase in the
8 cortical-basal ganglia-thalamic circuit,⁵⁷ whereas beta power (13–30 Hz) and beta band coupling
9 in the motor network are reduced.⁵⁵ Our previous study also showed that in people with PD with
10 pre-existing symptoms of tremor, successful volitional beta suppression through neurofeedback
11 training was associated with an amplification of tremor, which correlated with increased theta band
12 activity in STN LFPs.³⁵ These results suggest that the underlying pathophysiology for tremor is
13 different from that for bradykinesia and rigidity in PD. Both CDBS and ADBS significantly
14 improved motor performance and resting tremor compared with no DBS. However, resting tremor
15 was better suppressed during CDBS than ADBS (**Fig. 4**). These results suggest that apart from
16 STN beta, an additional biomarker for resting tremor might be required while developing ADBS
17 strategies for simultaneous control of bradykinesia/rigidity and tremor in PD.

18 **Remaining challenges for the development of ADBS systems for PD**

19 The results of this study have implications for the further development of ADBS systems for PD.
20 First, we confirmed that tracking the fast beta dynamics using a short smoothing time window does
21 not bring any additional advantage compared to the 400ms windows used in previous trials. This
22 may inform future studies on the design of more sophisticated controllers (e.g., proportional-
23 integral-derivative, PID), in which the temporal dynamics of the beta oscillations are taken into
24 account, and the interactions between the controller and the targeted brain oscillations will be more
25 complicated. On the other hand, more research effort should be invested in addressing the
26 remaining issues of stimulation artefacts and self-triggering related to the fast termination of
27 stimulus trains.³¹ In our study, a 250-ms ramping up/down during each switching on/off plus a 50-
28 ms refractory time after each switching off were utilized to minimize this issue. However, this
29 could be improved at a hardware level.⁵⁸ Alternatively, continuous modulation of the stimulation
30 intensity using proportional control could also remove the self-triggering problem. Second, it

1 might be more beneficial to combine STN beta, gamma, and real-time detection of the patient's
2 movement status in creating an enhanced adaptive stimulation algorithm. Several previous studies
3 have demonstrated the feasibility of detecting movement state based on bioelectrical signals
4 recorded from the cortical-basal ganglia-thalamic circuit in people with PD or essential tremor.^{21,59-}
5 ⁶² Suppressing beta while minimizing the suppression of gamma during movement might result in
6 improved motor performance. However, extracting gamma power in real-time using currently
7 available chronically implanted devices is very challenging for several reasons including: 1)
8 stimulation artefact, which has a bigger impact on gamma than beta since it is closer to the
9 stimulation frequency; 2) Lower signal to noise ratio in the gamma band, since gamma activity has
10 a smaller amplitude than beta; 3) A higher sampling rate, larger cutting frequency of the anti-
11 aliasing filtering, and higher resolution of the analogue to digital conversion (ADC) are required
12 to record physiological gamma band activities. Despite this, with the currently available
13 implantable, miniaturised systems such as the Aactiva PC + S (Medtronic), it has been possible to
14 'sense' cortical gamma band activities which has been related to treatment induced dyskinesia.⁶³
15 The Summit RC + S (Medtronic) has also been used to simultaneously track two biomarkers, i.e.,
16 subcortical beta and cortical gamma, for distinguishing mobile and immobile states for ADBS,²¹
17 or gamma and theta-alpha oscillations for independent PD and sleep state detection, respectively.⁶⁴
18 Recently, Vaou et al. also used Percept (Medtronic) to monitor STN beta and gamma oscillations
19 for akinetic-rigid and dyskinetic symptoms, respectively, in patients with PD.⁶⁵ Therefore,
20 although some of the functions are not implemented in the currently existing commercialised
21 device, it should still be possible to estimate beta and gamma at the same time and to utilise both
22 biomarkers for ADBS in implantable device. Alternatively, STN DBS at a lower frequency than
23 the standard 130 Hz (e.g., 60 Hz) may be a workaround as it has been suggested to be of benefit
24 for axial features (freezing of gait, postural instability, speech, swallowing function, etc.) in
25 patients with PD.⁶⁶⁻⁶⁹ This could potentially be due to a better preservation of gamma whilst
26 suppressing beta with lower stimulation frequency, although this is yet to be established. In
27 addition, when gamma oscillation is to be used as a feedback signal, movement-related gamma
28 increase, which tends to correlate with movement speed, needs to be differentiated from finely-
29 tuned gamma which might be an indicator of dyskinesia.⁷⁰ Third, additional feedback signal(s)
30 apart from STN beta might be required to develop an ADBS systems for tremor-dominant people
31 with PD. Although ADBS does not necessarily mean less energy consumption by the implantable

1 pulse generator (IPG), since in general less energy will be delivered to the brain, it may still be
2 beneficial in reducing stimulation induced side-effects. With improved strategies for applying
3 ADBS, it is possible that ADBS will provide better clinical improvement than CDBS for people
4 with PD in the future.

5 **Limitations**

6 All experiments for this study were conducted 3-6 days after the first surgery for DBS electrode
7 implantation, when the postoperative stun effect was appreciable. In addition, the stimulation
8 configurations used in this study, such as ring-mode construction for directional DBS leads,
9 selection of the stimulation contact, amplitude, etc. could be suboptimal and different from what
10 are used in clinical practice. Therefore, the effect of DBS in general could be further improved.
11 However, the same stimulation parameters were used in all tested DBS conditions within each
12 patient, allowing for a fair comparison between the different conditions. Although we did not see
13 significant difference in any of the assessed discrete upper limb fine motor tasks between ADBS-
14 200 and ADBS-400, other parkinsonian symptoms, such as rigidity, balance and other axial
15 functions were not assessed in this study. Therefore, the effects of beta triggered ADBS using
16 different smoothing windows on those parkinsonian symptoms require further investigation. Here
17 only a relatively simple form of ADBS based on thresholding and the effects of different
18 smoothing windows was tested. It would also be interesting to test the effects of varying other
19 aspects such as different thresholds and/or using a more sophisticated controller such as PID for
20 continuous modification of different stimulation parameters beyond stimulation intensity for
21 ADBS. However, regardless of the control algorithms to be used, the smoothing window for
22 quantifying the beta amplitude as the feedback signal is a key parameter that needs to be
23 considered. The modelling results in this study showed that reaction time was predicted by STN
24 beta ERD while mean velocity during reaching movement were predicted by STN beta and gamma
25 power, but whether the relationships are causal is unanswered by the current study. Another
26 limitation is that only short-term effects of DBS were considered during two specific motor tasks,
27 i.e., ballistic reaching and finger-tapping movements. It is unclear to what degree the achieved
28 results could be generalised to longer experimental periods, especially when patients are engaging
29 in normal activities of daily living.

1 **Conclusion**

2 This study evaluated the effectiveness of STN beta-triggered ADBS during a reaching task
3 involving upper-limb movements in thirteen people with PD. We showed that beta-triggered
4 ADBS did not compromise the motor performance of cued reaching movements in terms of
5 reaction time and movement speed compared with CDBS. ADBS and CDBS significantly
6 improved motor performance by similar amounts compared with no DBS. In addition, we
7 demonstrated that using a shorter smoothing window to estimate beta did make ADBS more
8 responsive. It shortened beta burst durations by increasing the number of beta bursts shorter than
9 200ms, but this did not bring any additional benefit in motor performance. We also showed that
10 both STN beta reduction and gamma power increase during movement helped in predicting
11 movement speed, suggesting that combining beta, gamma and movement status might confer
12 added benefit in ADBS. In addition, beta-triggered ADBS was not as effective as CDBS in
13 suppressing parkinsonian resting tremor, suggesting that additional feedback signals might be
14 required for tremor-dominant patients. These findings have significant implications for the further
15 development of ADBS algorithms to improve the treatment for PD.

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25 26 **Competing interests**

1 The authors report no competing interests.

2

3 **Supplementary material**

4 Supplementary material is available at *Brain* online.

5

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9 10 **Figure legends**

11 **Figure 1 Experimental protocol.** (A) Timeline of one individual trial of the reaching task
12 performed on a tactile monitor with a pen. In each trial, patient is instructed to point at the start
13 button to initiate the trial, reach to the red target when the Go-cue is shown, and back to the start
14 button when the target disappears, as quickly as possible. (B) Timeline for the whole experimental
15 session which consists of eight counterbalanced blocks in four different stimulation conditions,
16 with two blocks in each condition. Each block contains 15 trials of reach-return movements
17 followed by 20 second of finger-tapping movements. (C) Schematic of the adaptive DBS system
18 which consists of bipolar measurement of subthalamic nucleus (STN) local field potentials (LFPs),
19 real time estimation of beta amplitude, and monopolar stimulation delivered to one of the middle
20 contacts while the patient is comfortably seated on a chair and performs the tasks. (D) Three-
21 dimensional reconstruction in coronal (left), axial (middle), and sagittal (right) views of all
22 analysed DBS leads localized in standard MNI-152_2009b space using Lead-DBS.^{28,29} Electrodes
23 in the left hemisphere were mirrored to the right hemisphere. The result confirmed that most of
24 the tested electrodes clustered in a sweepspot that has been suggested to provide optimal overall
25 motor improvement for PD with DBS (shown in green).³⁰

26
27 **Figure 2 Comparison of the stimulation events and beta bursts between ADBS-200 and**
28 **ADBS-400 conditions.** (A)-(D) Averaged stimulation switching rate (A), percentage of time when
29 the stimulation was on (B), averaged duration of beta bursts (C), and averaged rate of beta bursts

1 with different durations (D) in ADBS-200 (purple) and ADBS-400 (green) conditions. The error
 2 bar plots show the mean and SEM across all tested hemispheres in different conditions; * $p < 0.05$,
 3 ** $p < 0.01$; *** $p < 0.001$; p -values were quantified based on paired t-test on individual hemisphere
 4 basis (N=16) and corrected for multiple comparisons using Bonferroni correction.

5
 6 **Figure 3 No significant difference in motor performance between ADBS-200 and ADBS-400**

7 **conditions.** (A) Movement trajectories colour coded by the instantaneous velocities of the reaching
 8 movement in ADBS-200 (upper) and ADBS-400 (lower) conditions. The velocities were
 9 normalized to the individual maximum of each patient. White and red filled circles at the bottom
 10 and top indicate the start and target buttons, respectively. (B) Reaction time during the reaching
 11 movement in different stimulation conditions. (C)-(D) Mean velocities during the reaching
 12 movement while reach (C) and return (D) periods in different stimulation conditions. (E)-(F)
 13 Normalized root-mean-square acceleration (E) and blinded video ratings by two experts (F) during
 14 finger-tapping movement in different stimulation conditions. (G) Average power in tremor
 15 frequency band during rest in different stimulation conditions. The error bar plots show the mean
 16 and SEM across all tested hemispheres in different conditions. p -values were quantified using
 17 generalized linear mixed effect modelling on an individual trial (B, C, D, and G) or block (E and
 18 F) basis; n.s.: not significant.

19
 20 **Figure 4 ADBS and CDBS equally improved motor performance compared with no DBS,**

21 **but resting tremor was better suppressed during CDBS.** (A) Movement trajectories are colour
 22 coded by the normalized instantaneous velocities of the reaching movements with no DBS (left),
 23 CDBS (middle), and ADBS (right). White and red filled circles at the bottom and top indicate the
 24 start and target buttons, respectively. (B) Reaction time during the reaching movement in different
 25 stimulation conditions. (C)-(D) Mean velocities during the reaching movement while reach (C)
 26 and return (D) periods in different stimulation conditions. (E)-(F) Normalized root-mean-square
 27 acceleration (E) and blinded video ratings (F) during finger-tapping movement in different
 28 stimulation conditions. (G) Average power in tremor frequency band during rest in different
 29 stimulation conditions. (H) Time on stimulation in CDBS and ADBS conditions. The error bar
 30 plots show the mean and SEM across all tested hemispheres; * $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$; p -

1 values were quantified using generalized linear mixed effect modelling on an individual trial (B,
 2 C, D, and G) or block (E and F) basis or using paired t-test on an individual hemisphere basis (H)
 3 and corrected for multiple comparisons using Bonferroni correction. Grey * indicates
 4 nominally/marginally significant which did not survive Bonferroni correction; n.s.: not significant.

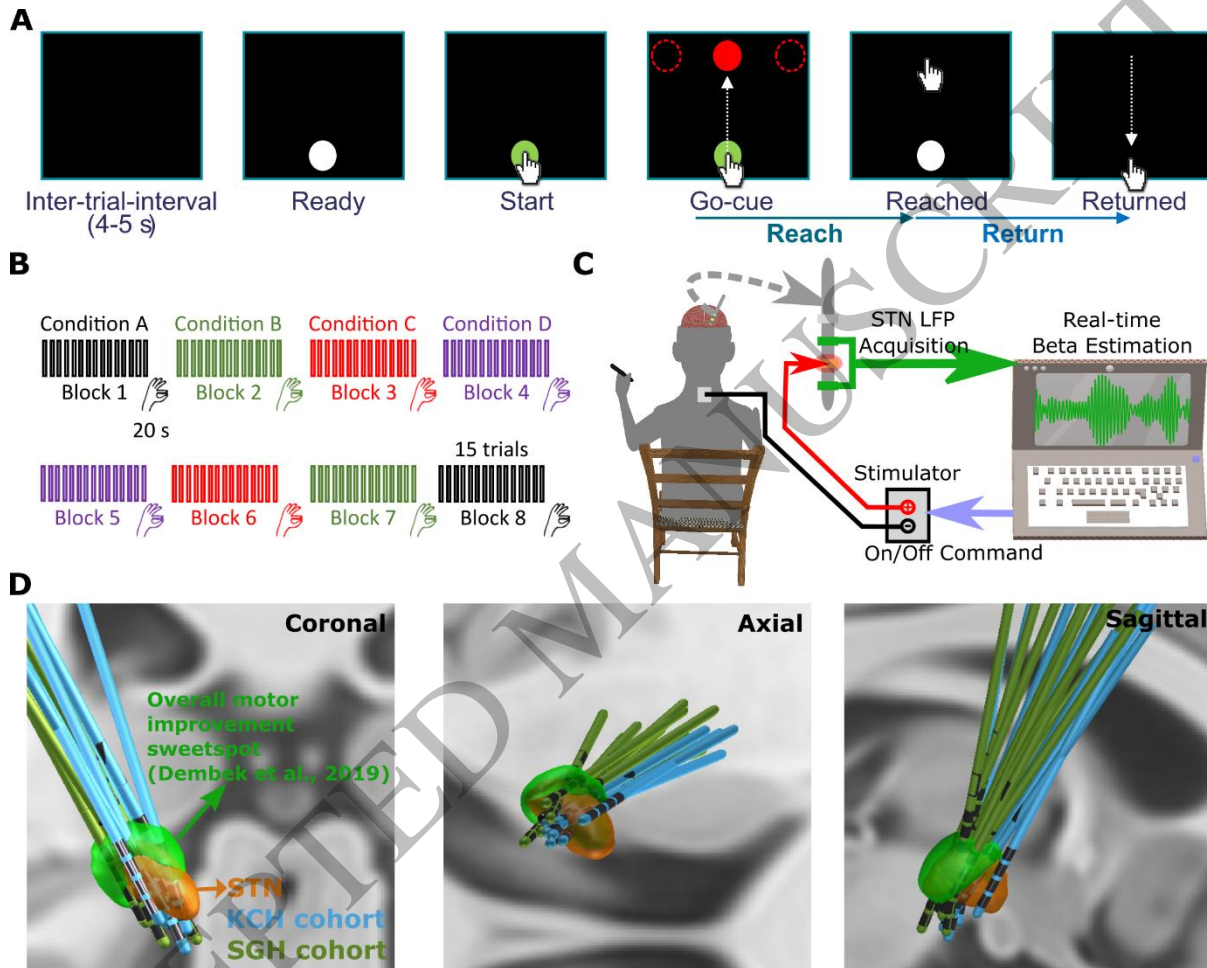
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 6 **Figure 5 Modulation of beta/gamma power and stimulation probability during reaching**

7 **movement. (A)-(C)** Group averaged time-frequency power-spectra of the targeted STN LFPs
 8 aligned to movement onset during reaching movement in no DBS (A), CDDBS (B), and ADDBS (C)
 9 conditions. The power spectra were normalized against a 1-s pre-Go cue resting period in each
 10 individual trial. Beta was suppressed around movement initiation and gamma was increased during
 11 movement. Lower panel in each subplot indicates the group averaged velocity during the reaching
 12 movement. **(D)** Group averaged beta power in different conditions (upper) and stimulation
 13 probability during ADDBS (lower) aligned to movement onset during reaching movement. Different
 14 colors indicate different conditions. Solid line and shade indicate the mean and SEM of the
 15 velocity, beta power, or stimulation probability averaged across all hemispheres, respectively. W1
 16 and W2 indicate two time-windows where the average beta power was used for predicting reaction
 17 time in **Table 2. (E)-(H)** The same as (A-D) but aligned to the time when the target was reached.

18
 19 **Figure 6 Beta and gamma power were both suppressed during DBS compared with no DBS,**
 20 **and the suppression was stronger during CDDBS compared with ADDBS. (A)** Group averaged

21 beta power aligned to movement onset during reaching movement in different conditions. The
 22 power was normalized against the average beta power during the 1-s pre-Go cue resting period in
 23 no DBS condition. Solid line and shade indicate the mean and SEM of the beta power, respectively.
 24 Gray and pink bars on the bottom indicate significant difference between no DBS and CDDBS, and
 25 between no DBS and ADDBS based on a cluster-based permutation procedure, respectively. **(B)-**
 26 **(C)** Averaged beta power without baseline normalization in a baseline time window (W1, 1-0.5 s
 27 pre-Onset) (B) and a 0.2-s time window around movement initiation (W2) (C) in different
 28 conditions. **(D)** The same as (A) but for gamma power. **(E)-(F)** Averaged beta (E) and gamma (F)
 29 power without baseline normalization during movement in different conditions. The error bar plots
 30 show the mean and SEM across all tested hemispheres in different conditions; * $p < 0.05$, ** $p < 0.01$;

1 *** $p < 0.001$; p -values were quantified using generalized linear mixed effect modelling on an
 2 individual trial basis and corrected for multiple comparisons using Bonferroni correction; n.s.: not
 3 significant.



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Figure 1
 159x127 mm (x DPI)

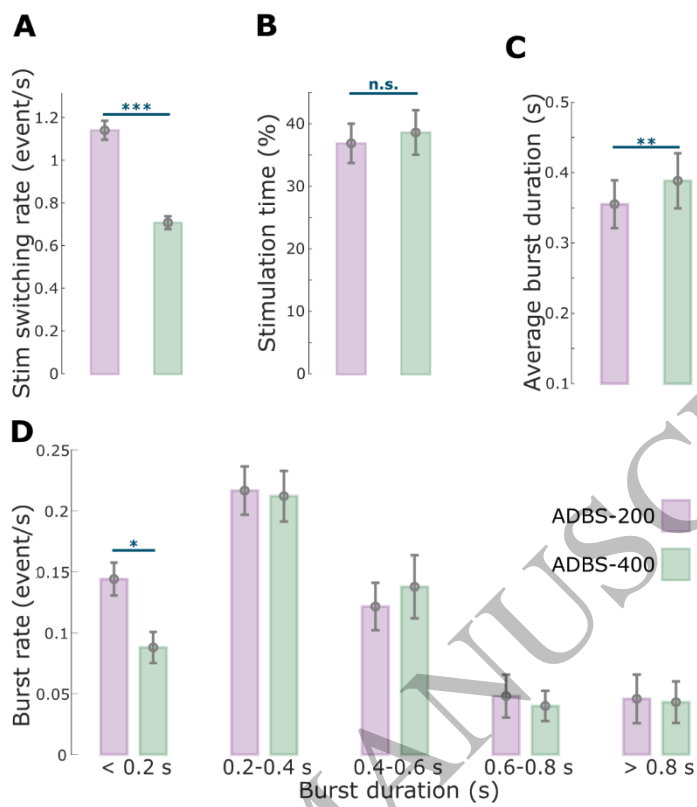


Figure 2
92x105 mm (x DPI)

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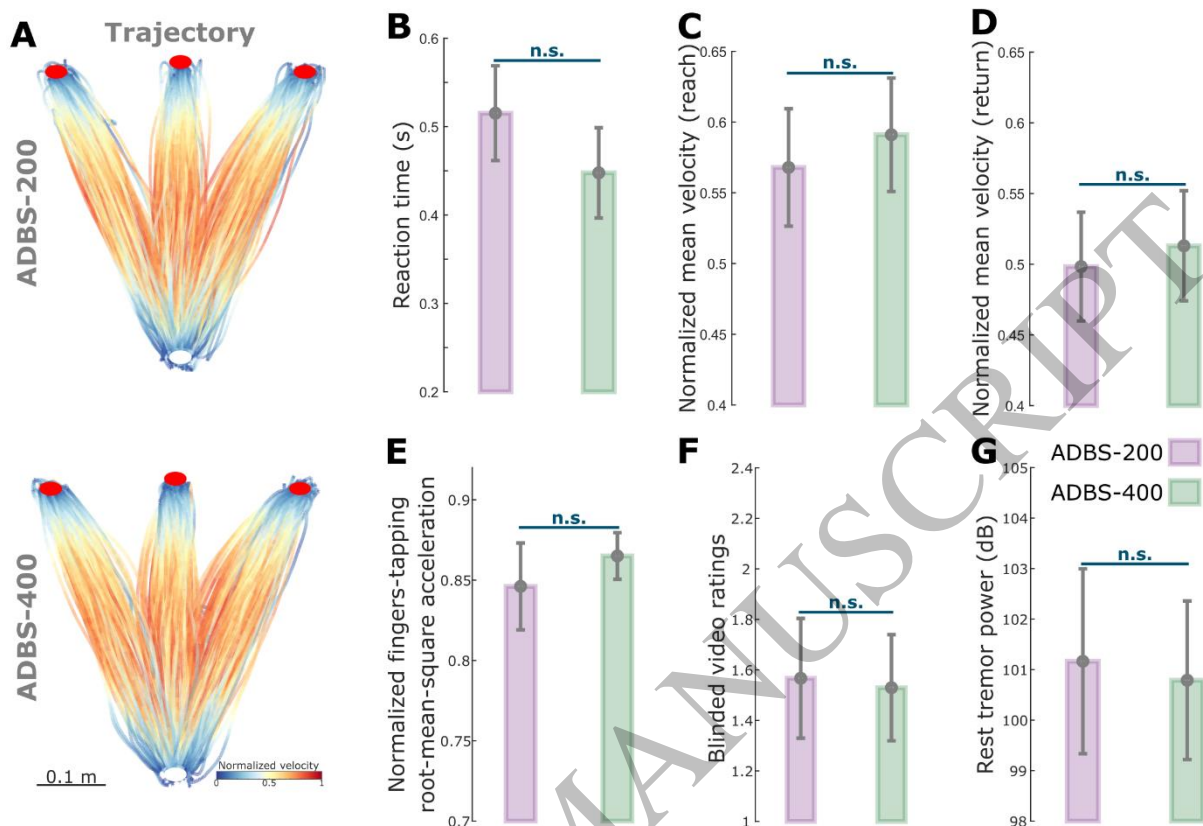


Figure 3
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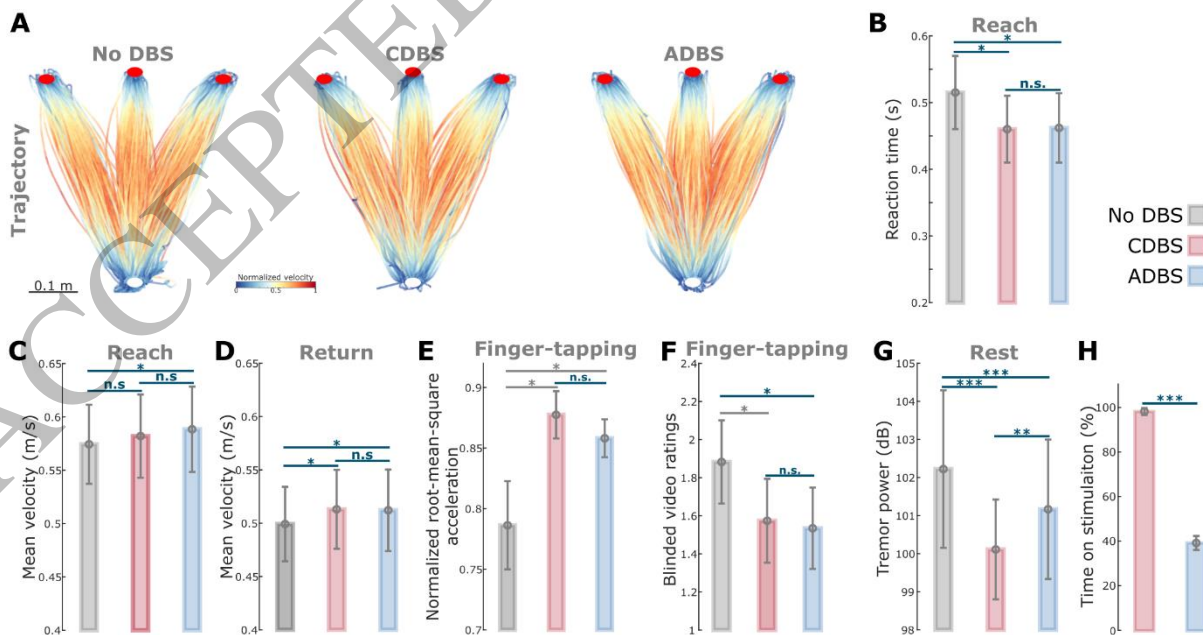


Figure 4
 159x83 mm (x DPI)

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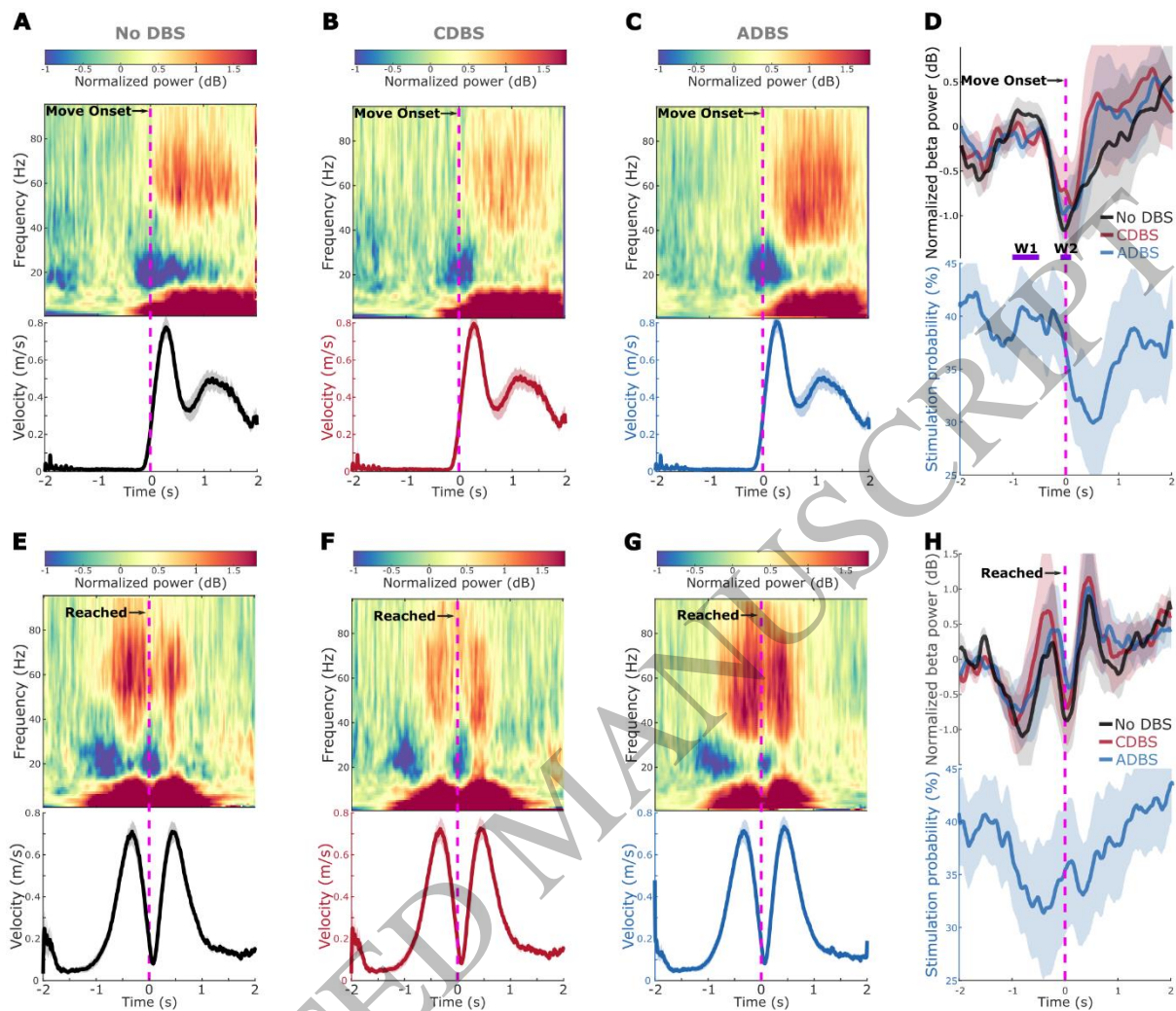


Figure 5
159x136 mm (x DPI)

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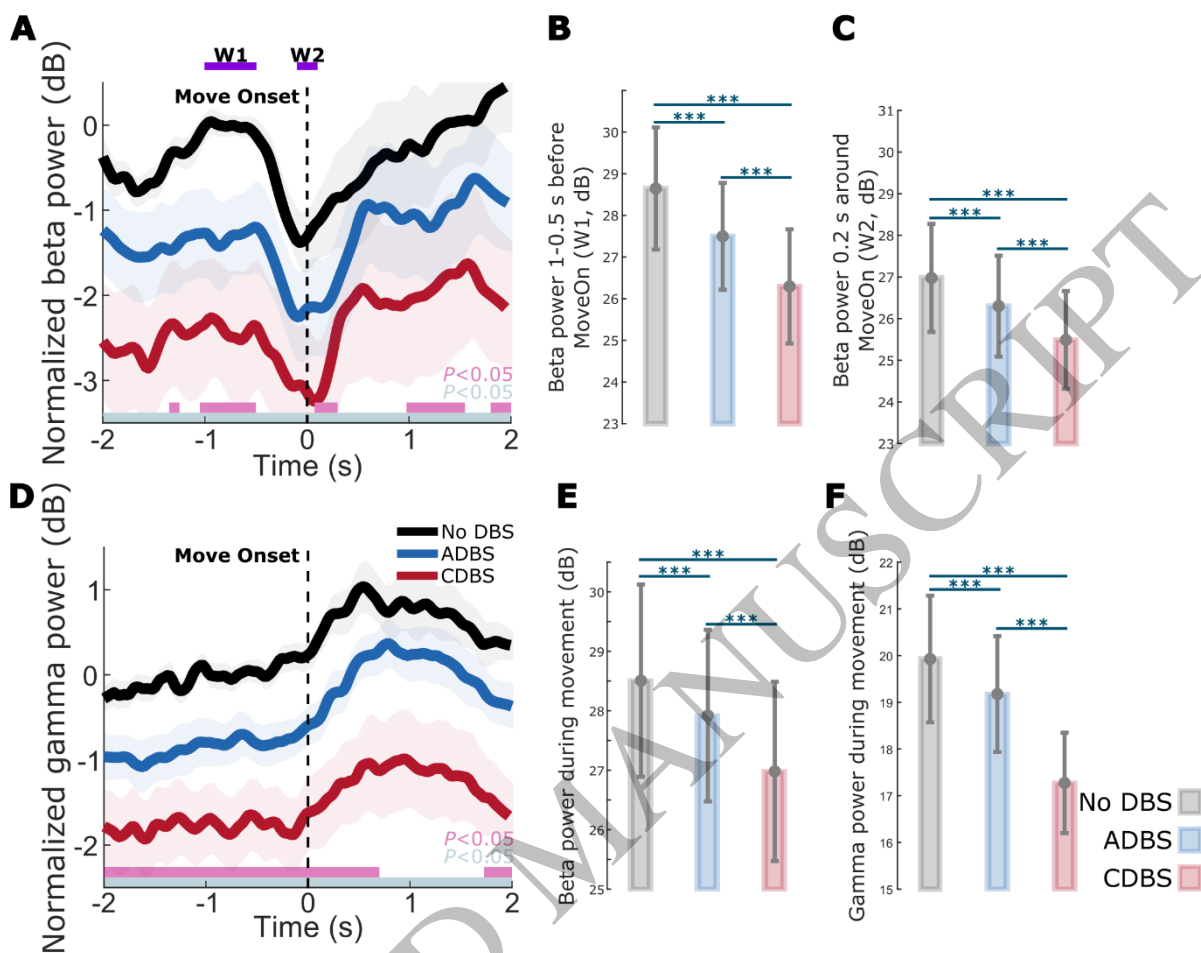


Figure 6
159x125 mm (x DPI)

Table I Details of the stimulation used during the recording of this study and in clinical

Case	DBS lead	Experimental DBS				Chronic DBS	
		Stim contact (L/R)	Stim Amp (L/R, mA)	Bipolar feedback channel (L/R)	Online filter range (L/R Hz)	Stim Contact (L/R)	Stim Amp (L/R)
1	Medt1	L3 ^a	3	L24	19–25	L2	3.3 V
2	Medt1	L3 ^b / R2 ^c	3.5 / 1.5	L24 / R13	14–20 / 15–21	L1 / R2	2.9 / 2.7 mA
3	Bost1	L2 ^c / R3 ^c	3 / 2	L13 / R24	15–21 / 14–20	L2-L3 / R2-R3	4.0 / 3.5 mA
4	Bost2	L3 ^c	1	L24	16–22	L2-L3	4.2 mA
5	Abbo	R3 ^{a,b}	1.5	R24	17–23	R2	3.2 mA
6	Medt2	R2 ^a	1.5	R13	19–25	R1	2.6 mA
7	Bost3	L2 ^c / R2 ^c	2.5 / 2.5	L13 / R13	16–22 / 22–28	L2-L4 / R2	2.8 / 2.3 mA
8	Medt2	R2 ^c	3	R13	15–21	R2	3.6 mA
9	Medt2	L3 ^a	1.5	L24	14–20	L4	2.5 mA
10	Medt2	L2 ^c / R2 ^c	1 / 3	L13 / R13	22–28 / 22–28	L2 / R2	2.4 / 3.5 mA
11	Medt2	L3 ^a / R2 ^c	3.5 / 3.5	L24 / R13	18–24 / 17–23	L2 / R2	1.9 / 1.7 mA
12	Medt2	L2 ^c / R2 ^c	3 / 3	L13 / R13	12–18 / 21–27	L2 / R2	1.0 / 1.0 mA

I3	Bost1	L2 ^c / R2 ^c	2 / 2	L13 / R13	18–24 / 20–26	L2-L3 / R2-R3	4.5 / 1.7 mA
Mean			2.38		17.3–23.3		2.77
SEM			0.18		0.66		0.22

DBS = deep brain stimulation; Stim = stimulation; L = left; R = right; Amp = amplitude; Medt1 = Quadripolar non-directional Macroelectrode, Model 3389, Medtronic; Bost1 = Vercise™ directional lead with 1-3-3-1 configuration, Boston Scientific; Bost2 = Cartesia™ X leads with 3-3-3-3-3-1 configuration, Boston Scientific; Bost3 = Cartesia™ HX leads with 3-3-3-3-1-1-1-1-1-1 configuration, Boston Scientific; Abbo = St. Jude Medical Infinity 0.5mm spaced directional DBS leads with 1-3-3-1 configuration, Abbott; Medt2 = SenSight™ 0.5mm spaced directional lead with 1-3-3-1 configuration, Medtronic; SEM = standard error of the mean.

^aThe contacts in experimental and chronic DBS appeared at adjacent levels.

^bHemispheres excluded from analysis (see text for detailed reasons).

^cThe contacts in experimental and chronic DBS appeared at the same level.

Table 2 Effects of beta/gamma power in predicting motor performance during reaching movement revealed by generalized linear mixed effect (GLME) modelling

Predicting RT									
Model 1: $RT \sim I + k_1 condID + k_2 \beta_{w1} + I HemID$									
AIC	k_1	p_1	k_2	p_2	k_{inter}	p_{inter}			R^2
1438.9	0.0349 ± 0.1337	0.7943	0.0097 ± 0.0087	0.2616	-0.0049 ± 0.0048	0.3128			0.2456
Model 2: $RT \sim I + k_1 condID + k_2 \beta_{w2} + I HemID$									
AIC	k_1	p_1	k_2	p_2	k_{inter}	p_{inter}			R^2
1434.7	-0.0238 ± 0.1385	0.8637	-0.0054 ± 0.0099	0.5877	-0.0035 ± 0.0054	0.5166			0.2462
Model 3: $RT \sim I + k_1 condID + k_2 \beta_{erd} + I HemID$									
AIC	k_1	p_1	k_2	p_2	k_{inter}	p_{inter}			R^2
1432.9	-0.0742 ± 0.0363	0.0409	0.0301 ± 0.0150	0.0453	-0.0118 ± 0.0085	0.1636			0.2478
Compare (Model 1, Model 3)					Compare (Model 2, Model 3)				
LRStat	deltaDF	P	LRStat	deltaDF	P				
6.0748	0	<0.001	1.8418	0	<0.001				
Predicting MV									
Model 4: $MV \sim I + k_1 condID + k_2 rrrID + k_3 \beta_{mov} + I HemID$									
AIC	k_1	p_1	k_2	p_2	k_3	p_3			R^2
-6481.9	0.0112 ± 0.0039	0.0041	-0.0710 ± 0.0034	<0.001	-0.0006 ± 0.0006	0.3147			0.6746
Model 5: $MV \sim I + k_1 condID + k_2 rrrID + k_3 \gamma_{mov} + I HemID$									
AIC	k_1	p_1	k_2	p_2	k_3	p_3			R^2
-6490.6	0.0139 ± 0.0039	0.0004	-0.0714 ± 0.0034	<0.001	0.0018 ± 0.0006	0.0019			0.6752
Model 6: $MV \sim I + k_1 condID + k_2 rrrID + k_3 \beta_{mov} + k_4 \gamma_{mov} + I HemID$									
AIC	k_1	p_1	k_2	p_2	k_3	p_3	k_4	p_4	R^2
-6513.3	0.0142 ± 0.0039	0.0003	-0.0689 ± 0.0034	<0.001	-0.0042 ± 0.0008	6.7338 × 10⁻⁷	0.0049 ± 0.0009	7.7075 × 10⁻⁹	0.6773
Compare (Model 4, Model 6)					Compare (Model 5, Model 6)				
LRStat	deltaDF	P	LRStat	deltaDF	P				
33.35	1	7.6987 × 10⁻⁹	24.685	1	6.7514 × 10⁻⁷				

RT=reaction time; condID=stimulation condition index; β_{w1} =average beta power during 1 to 0.5 second before movement initiation (W1 in Fig. 6A); β_{w2} =average beta power during 0.2 second around movement initiation (W2 in Fig. 6A); $\beta_{erd} = \beta_{w1} - \beta_{w2}$; HemID=hemisphere index; AIC=Akaike information criterion; inter=interaction; LRStat=likelihood ratio test statistic for comparing two models; deltaDF=difference in degrees of freedom between two models; MV=mean velocity; rrrID=reach or return index; β_{mov} =average beta power during movement (from reach/return movement onset to target reached); γ_{mov} =average gamma power during movement. Models 1–3 only considered reach movements since RT and β_{erd} were only quantified for reach movements. Model 4–6 considered all reach and return movements.