Adaptive Deep Brain Stimulation as an Advanced Parkinson's disease Treatment (ADAPT): a pseudorandomised clinical trial

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Running title: ADAPT study

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Word count
Abstract: 185
Full text: 2369
Number of figures/tables: 4
Number of references: 25

Keywords:
Parkinson's disease, adaptive deep brain stimulation, subthalamic nucleus, local field potentials, beta oscillations, closed-loop, dysarthria.

Abstract

Beta-based adaptive Deep Brain Stimulation (aDBS) is effective in Parkinson's disease (PD), when assessed in the immediate post-operative phase. However, potential benefits of aDBS on stimulation-induced side effects in chronically implanted patients are yet to be assessed. To determine the effectiveness and side-effect profile of aDBS in PD we compared to conventional DBS (cDBS) and no stimulation (NoStim) in the chronically implanted state. 13 PD patients undergoing battery replacement were pseudo-randomised in a crossover fashion, into three conditions (NoStim, aDBS or cDBS). Patient videos were blindly evaluated using a short version of the Unified Parkinson's Disease Rating Scale (subUPDRS) and the Speech Intelligibility Test (SIT). subUPDRS scores were significantly lower both in aDBS (p=<.001), and cDBS (p=.001), when compared to NoStim. Bradykinesia subscores were significantly lower in aDBS (p=.002), but not in cDBS (p=.08), when compared to NoStim. SIT scores of patients with stimulation-induced dysarthria significantly worsened in cDBS (p=.009), but not in aDBS (p=.407), when compared to NoStim. Beta-based aDBS is effective for PD in chronically implanted patients, especially in controlling bradykinesia symptoms. Furthermore, aDBS has a more favourable speech side-effect profile than cDBS.

Introduction

Parkinson's disease (PD) patients in advanced stages of the disease usually present with motor symptoms which are not sufficiently suppressed by dopaminergic medication, together with intolerable medication-related side-effects. Deep brain stimulation (DBS) is a successful treatment option as the disease progresses (Deuschl *et al.*, 2006). Although DBS is highly effective, both in terms of motor improvement and improvement in quality of life, there are still limitations. These include incomplete symptom suppression and side effects, such as stimulation-induced dysarthria (SID), and dyskinesias. Recent developments in adaptive DBS (aDBS) systems may help overcome these drawbacks. In aDBS, the amount of stimulation is modulated according to variations in clinical state. Here the aim is to only deliver stimulation as necessary to improve motor impairment, thereby avoiding side-effects when stimulation can be spared or lowered. Up to now, the majority of clinical studies investigating aDBS in PD have applied stimulation based on the amount of beta activity (13-35 Hz) in the subthalamic nucleus (STN) local field potential (LFP), as this biomarker is correlated with contralateral bradykinesia and rigidity (Neumann *et al.*, 2016*a*; Beudel *et al.*, 2017), and is suppressed by DBS (Eusebio *et al.*, 2011; Quinn *et al.*, 2015).

Although studies have confirmed the efficacy of 'beta-based' aDBS (Little *et al.*, 2013, 2016*a*; Rosa *et al.*, 2015; Arlotti *et al.*, 2018), and suggested a superior side effect profile compared to continuous, conventional, DBS (cDBS) (Little *et al.*, 2016*b*; Rosa *et al.*, 2017), these have been mostly performed in newly implanted patients. Such studies are potentially compromised by the microle-

sion effect (Chen *et al.*, 2006), as this confounding factor provides temporary symptom relief, which can mask the true effects of stimulation. For example, tremor may be suppressed by the microlesion effect, and the effect, or lack of effect, of stimulation on this symptom thereby masked. However, it is feasible to investigate the utility of aDBS in chronically implanted patients using externalised electrodes (Piña-Fuentes *et al.*, 2017), and in patients implanted with bidirectional devices (Velisar *et al.*, 2019). Nevertheless, whether there is additional benefit over cDBS, particularly with respect to side-effects, remains unclear. One such side-effect is SID, and another is motor impulsivity, as measured by tests of response inhibition (Witt *et al.*, 2004). Here, we compare the clinical effect, efficiency and side-effect profile of aDBS with both cDBS and no stimulation in PD patients with chronically implanted electrodes in the STN.

Materials and Methods

Patients

We tested 13 patients with advanced idiopathic PD who were chronically treated with bilateral DBS of the STN and needed battery replacement surgery (Table 1). All patients gave written informed consent to the study protocol, which was approved by the local ethics committee. The study was registered in the Dutch Trial Register (trialregister.nl, trial # 5456) and the study protocol was published (Pina-Fuentes *et al.*, 2019*a*). All patients stopped prolonged-release dopaminergic medication at least 24h prior to the measurements, and skipped at least one dose of regular antiparkinsonian medication before the surgery, in order to achieve an off-medication state at the moment of the recordings.

Recording procedure

In brief, the old battery was removed and a custom-made external stimulator-amplifier device (for details see Little *et al.*, 2013) was connected to the chronically implanted DBS electrodes (Figure 1). From this point the protocol took about 25-30 minutes to be completed. Bipolar STN local field potentials (LFPs) were recorded in the resting state for 30-60 seconds, using contact pairs 02 and 13. Power spectral density estimates in the beta band range and their peak frequency were calculated. The contact (either 1 or 2) in the middle of the contact pair with the greatest beta activity on each side was selected for stimulation, and the beta activity in this bipolar channel used for the feedback control of aDBS. A common frequency range (±3Hz) that included beta-peak frequencies of both hemispheres, was used in each patient to filter bilateral LFPs. Stimulation voltage was titrated before the experimental conditions until either optimal symptom reduction was achieved or side-effects occurred. Bilateral aDBS, cDBS and no stimulation (NoStim) were applied in a pseudo-randomised order, with a short washout period (1-2 min) between them (Figure 2). aDBS was trig-

gered on and off when rectified beta power crossed a median power threshold up and then down, respectively.

Tests and data processing

During each of the three conditions, the following four tests were performed (See Pina-Fuentes *et al*., 2019 for a more detailed description of the tests):

-A short version of the motor Movement Disorders Society version of the Unified Parkinson's Disease Rating Scale (subUPDRS) (Goetz *et al.*, 2008) was assessed and video recorded for subsequent blinded rating. Items included were finger tapping, hand movements, hand pronation-supination, rest tremor and postural tremor. Videos were evaluated by three clinicians with expertise in movement disorders. Total scores were calculated for each rater/patient combination. Subgroup scores were calculated for bradykinesia and tremor items.

-The speech intelligibility test (SIT) (Little *et al.*, 2016*b*), in which each participant had to read out approximately 110 words divided into 18 sentences. Sentences were recorded, and the number of intelligible words of each SIT was blindly evaluated by a speech therapist. The total amount of intelligible words of each trial was determined. This score was normalised between 0 and 1, with 0 representing completely unintelligible speech.

-Response inhibition was assessed with a tablet-based version of the reverse Stroop effect (RST) (Blais and Besner, 2006), with 5 congruent words and 15 incongruent words randomly presented on each trial. Reaction times were determined for each word, and the amount of correct words for congruent and incongruent conditions were calculated. Reaction times with duration ≤200 or ≥5000 ms were discarded. The RST was chosen over the Stroop test as the former arguably is less attention demanding. It has been postulated that any impaired Stroop-test responses in PD patients might be a consequence of deficits in attentional resources, rather than impairments in impulse control (Woodward *et al.*, 2002).

-A bradykinesia test was performed using a tabled-based version of previously validated tapping test (Bronte-Stewart *et al.*, 2000; Noyce *et al.*, 2012), in which patients had to press two separate squares in an alternating pattern (20 iterations). The first iteration of each trial was discarded, as it systematically differed from the rest, leaving 19 iterations for further analysis. Incorrect iterations were defined as each time a patient pressed the same square twice.

Statistical analysis

All items were assessed for normality using Q-Q plots. Iteration times of the tapping test, and RST reaction times were log-transformed prior to further analysis. subUPDRS scores, transformed iteration times, SIT scores and transformed RST reaction times were compared using a lin-

ear mixed-effects model. Condition was treated as a fixed effect in all tests and subject as a random effect. In addition, in the subUPDRS model, randomisation order was included as a fixed effect. Additionally, bradykinesia and tremor subscores were analysed using independent models. The intra-rater absolute agreement of UPDRS-subscores was analysed using 2-way random-effect intra-class correlation coefficient (ICC). In the SIT model, the presence of SID was included a fixed effect, with SID defined as a decrement on the SIT score during cDBS, aDBS or both. In the RST analysis, congruency (congruent/incongruent) and accuracy (correct/incorrect) were added as fixed effects. In the tapping test, errors and their interaction with condition were added as fixed effects. Additionally, error counts of the tapping test and RST were analysed using a generalised linear mixed-effects model with a log-linear Poisson distribution model and an offset of 19 for each tapping-test trial, 5 for congruent words and 15 for incongruent words. In the RST error analysis, congruency was initially included as a fixed effect to test the presence of a reverse Stroop effect, and afterwards, its interaction with condition was added to the model, to test the selectivity of this effect to each condition. Models were compared using the Bayesian information criterion (BIC). The percentage time on stimulation was calculated for the aDBS condition. All results are expressed as mean ± standard error.

Data availability statement

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

Results

Of the 13 patients included in this study, all patients completed the bradykinesia test. Due to time and technical constrains, the rest of the tests were completed only by 11 patients each. All patients tolerated the test procedure, and stimulation-induced transient paresthesias were present only at stimulation voltages above those used for the experiment.

subUPDRS: independent raters showed an excellent degree of agreement in the scores, (ICC=0.939, $F(35,70)=16.312$, p=<.001). The linear mixed-effect model was significant for condition, ($F(2,88)=8.144$, p=<.001) (Fig 3). subUPDRS scores were significantly lower in aDBS (12.30±0.85) when compared to NoStim (15.81±0.75), ($t(88)=-3.731$, p=<.001), and in cDBS (12.57±0.74) when compared to NoStim, ($t(88)=-3.252$, p=.001), but not between aDBS and cDBS, ($t(88)=-0.443$, p=.659). There was no significant effect of randomisation order, ($F(2,88)=2.62$, p=.07). When bradykinesia subscores were analysed, aDBS scores (11.09±0.58) were significantly less than NoStim scores (12.90±1.27, $t(88)=-3.096$, p=.002), but cDBS scores (11.87±0.58) only showed a trend to be less than NoStim ($t(88)=-1.754$, p=.08). There was no difference in bradyki-

nesia subscores between aDBS and cDBS (t(88)=1.341, p=.18). Tremor subscores were reduced with both interventions (cDBS scores, 1.33±0.73 vs NoStim 6.13±0.92, t(40)=-6.572, p=<.001 and aDBS, 2.47±0.73 vs No Stim, t(40)=-5.02, p=<.001). There was no difference in tremor subscores between aDBS and cDBS (t(88)=1.189, p=.237).

SIT: the linear mixed-effect model showed a significant effect for the interaction of condition and SID (F(2,22)= 4.231, p=.027). SIT scores of patients with SID significantly worsened only in cDBS (0.74±0.08) when compared to NoStim (0.85±0.08, t(22)=-2.833, p=.009), but not in aDBS (0.84±0.08) when compared to NoStim (t(22)=-0.845, p=.407).

RST: the simpler model revealed a significant effect of congruency, (Chi^2(1)=4.576, p=0.032), where incongruent words had a significantly increased error rate, (z=2.139, p=0.032). No significant effect of condition was found, (Chi^2(2)= 1.772, p=0.41). A model with an interaction factor was not a better fit (BIC 146.09 vs 138.34 for the simpler model), and interaction was not significant, (Chi^2(2)= 0.586, p=0.745). No significant effect was found in reaction times for congruency, (F(2,626.03)=0.266, p=0.766, condition, F(1, 625.99)=0.310, p=0.577), or their interaction, (F(1, 626.02)=0.723, p=0.485).

Tapping test: correct iteration times were reduced in cDBS (571.29±9.83ms) and aDBS (612.31±10.14ms) compared to NoStim (619.53±10.35ms). However, this reduction was only significant for cDBS, (t(1412.29)=-2.388, p=0.017), and not for aDBS, (t(1412.24)=-0.776, p=0.438). There was no significant difference between the two interventions, (t(1412.04)=-1.620, p=0.105). No differences in errors were found between conditions, (Chi2(2)= 1.512, p=0.469).

Overall, stimulation was applied 48.8% (SEM 3.8) of the time during aDBS.

Discussion

Our study provides the first pseudorandomised and blinded comparison of UPDRS scores and side-effects in aDBS versus cDBS in the chronically implanted state. The results confirm previous findings that aDBS is well tolerated (Little *et al.*, 2013; Arlotti *et al.*, 2018), performs equally well as cDBS, and does not compromise speech (Little *et al.*, 2016*b*) in patients studied within days of electrode implantation. The effects in the chronically implanted state were seen despite stimulation being delivered about 50% of the time.

While the analysis of the total UPDRS scores showed similar results between cDBS and aDBS, the subanalysis of the bradykinesia subscores suggested that aDBS has the potential to be more effective than cDBS in controlling bradykinesia symptoms, although the difference was not significant in our study. The opposite was true for tremor subscores, where cDBS tended to suppress tremor scores more than aDBS, although again the difference was again not significant. During our study, most patients showed tremor suppression; even when stimulation was triggered off during aDBS

(Supplementary video 1). However, two patients demonstrated re-emerging tremor lapses when stimulation triggered off (Supplementary video 2). This phenomenon was previously described in a similar proportion (2/12) of cases undergoing aDBS (Velisar *et al.*, 2019), and might be related to the fact that beta oscillations are only correlated with bradykinesia symptoms, but not tremor (Neumann *et al.*, 2016*a*; Beudel *et al.*, 2017). This raises the possibility of a potential trade-off between bradykinesia and tremor suppression with beta-based aDBS in a minority of patients.

The potential benefits of aDBS regarding dysarthria are promising. SID is one of the most common side effects of cDBS, with a prevalence of around 10% in treated patients (Kleiner-Fisman *et al.*, 2006). This usually adds to speech problems which are already present as consequence of the disease (Ho *et al.*, 1999). Adaptive DBS may therefore particularly provide a useful alternative to cDBS in patients with SID.

We found non-significant differences between cDBS and aDBS in the tapping test. Iteration times were shorter with cDBS, even though bradykinesia UPDRS subscores were lower with aDBS. The contrast might be explained by the effects of break-through tremor in some patients on aDBS. In the RST, an interference effect was found, but this was not affected by stimulation (either continuous or adaptive).

Limitations

Because of its intra-operative nature of this study, the time available to complete the protocol was limited. Therefore, the results may potentially be affected by incomplete washouts between stimulation conditions. Pseudo-randomisation should have helped limit the impact of incomplete washout and condition order was not found to be a significant factor upon analysis. Another possible confound in the present methodology is that both aDBS and cDBS were limited to monopolar stimulation at either contact 1 or 2. The resultant choice may therefore differ from the chronically optimised contact selection prior to battery change (see Table 1). Nevertheless, voltages, pulse width and stimulation frequency were identical between cDBS and aDBS conditions.

Conclusion

Beta-based aDBS is as effective as conventional DBS in chronically implanted patients, just as it is immediately after electrode implantation (Little et al. 2013). This is in line with the evidence that beta oscillations remain present and informative over time (Neumann *et al.*, 2016*b*). This is important, as the assessments in chronically implanted patients are not confounded by microlesion effects. Furthermore, comparisons were performed with cDBS, using stimulation parameters that were optimised, with the exception of stimulation contacts. We found that SID was reduced with aDBS, most likely because stimulation was applied only as necessary. However, it remains to be

seen whether aDBS remains effective with prolonged use, and whether stimulation algorithms have to be adjusted in some patients with tremor.

Acknowledgements:

We would like to thank Renske de Vries for the evaluation of the voice recordings, and Jasper Peeters for his assistance during the measurements.

Conflict of interest:

All the authors declare no conflict of interest.

Funding:

This study is publicly funded by grants received from the Dutch Brain Foundation ('Hersenstichting Nederland', grant F2015(1)-04), the National Mexican Council of Science and Technology (CONACYT) grant number CVU 652927, and the University of Groningen/University Medical Centre Groningen (RuG/UMCG). SL is personally supported by a Wellcome trust post-doctoral clinical research training grant (105804/Z/14/Z)

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Table 1. Clinical characteristics of the PD patients included in the study. Pt=patient, S=sex, A=age at the moment of the experiment, y=years, PD=Parkinson's disease, M=male, F=female, LEDD=levodopa equivalent daily dose, L=left, R=right, C=case (used for monopolar stimulation).

[a]Peaks reported here were calculated offline. Therefore, they might slightly differ with the frequencies used to filter the signal intraoperatively.

[b]Due to a technical failure in one of the LFP channels, this patient was measured unilaterally in both hemispheres.

[c]This patient had the right electrode implanted in the GPi. Therefore, only results from the right hand (left electrode) were included in the analysis.

[d]This patient had the right electrode off as their standard clinical setting, as only the right hemibody required both stimulation and medication to supress clinical symptoms. However, both electrodes were tested and included in the analysis.

Figure 1. Schematic representation of aDBS

During the operation, and after the old battery is exposed, the battery is detached from the DBS electrodes and explanted. At this moment, two temporary wires are attached to the DBS electrode extension cables at the level of the chest incision, and connected to a combined stimulator and amplifier (represented here). On the right side, an aDBS recording is depicted. From top to bottom:

-Original signal from left (blue) and right (red) electrodes, using a bandpass filter from 3 to 37 Hz. At this stage it is possible to appreciate artifacts caused by stimulation.

-Left and right LFPs filtered around the beta peak. Here it is possible to observe the individual beta bursts.

-Left and right envelopes of the beta-filtered and rectified LFPs. The dotted lines represent the thresholds selected to trigger stimulation.

-Stimulation bursts, with a ramping period when stimulation is switched on and off.

Figure 2. Flowchart of the inclusion algorithm and pseudorandomisation order.

[1]The protocol and tests were modified after the inclusion of this patient, who was therefore excluded. Findings have been reported in (Piña-Fuentes *et al.*, 2017).

[2]This patient was operated in the GPi, and therefore the results were reported separately in (Pina-Fuentes *et al.*, 2019*b*)

[3,4]These randomisation orders belong to the same patient (PD01). As this patient had to be measured unilaterally in both hemispheres, due to a defect in one of the aDBS box channels, each hemisphere was assigned to a different randomisation order.

[5]During patient surveillance, one patient presented a superficial infection on the surgical site, which was resolved completely after antibiotic treatment.

Figure 3. Results of the subUPDRS and SIT scores.

Left: total subUPDRS scores.

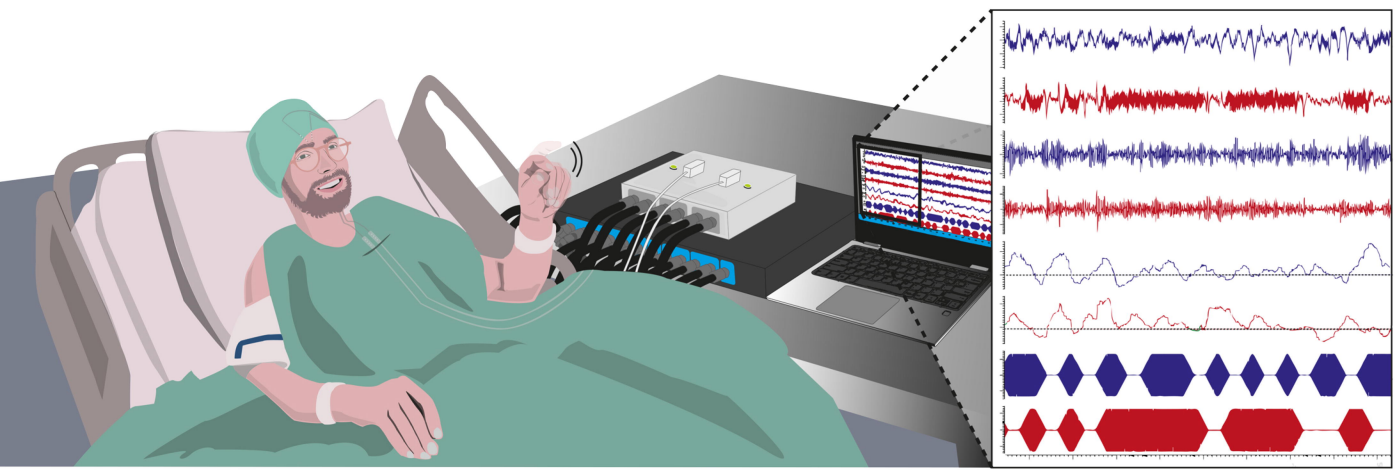
Upper center: subscores of bradykinesia items of the UPDRS III.

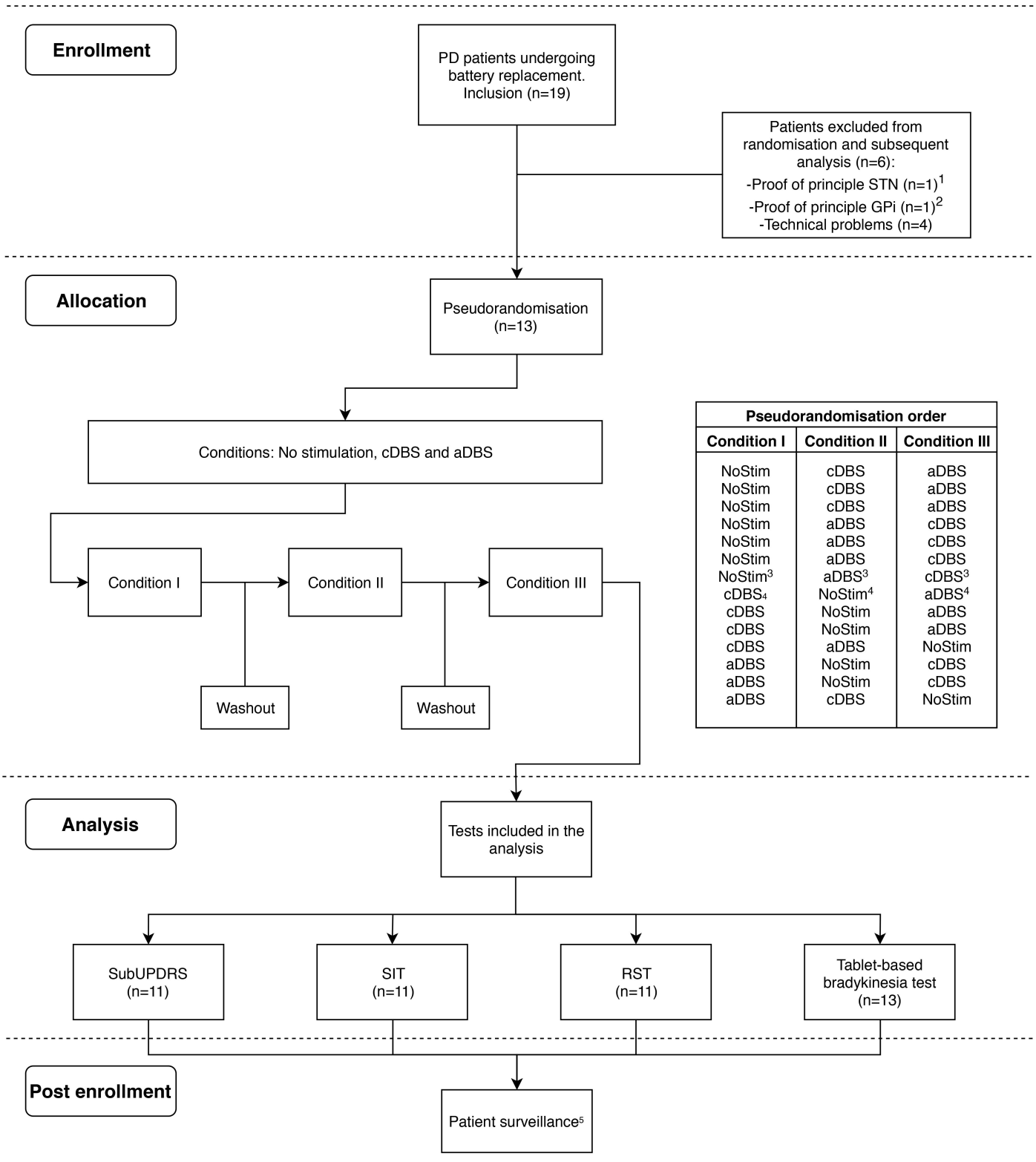
Lower center: subscores of tremor items of the UPDRS III.

Right: SIT scores of patients with SID.

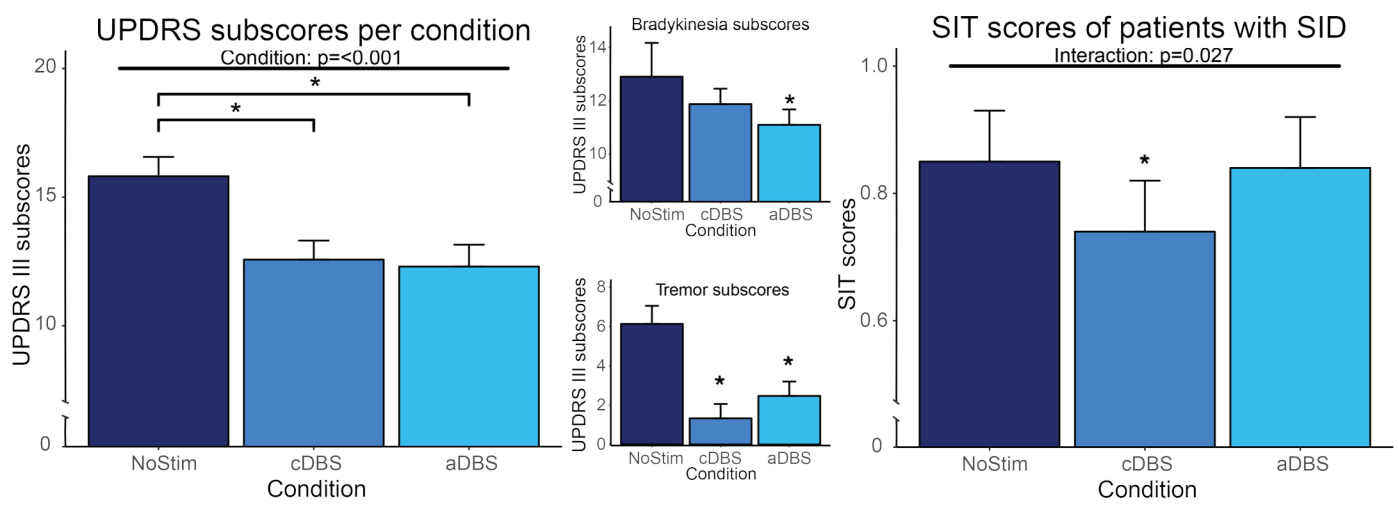
Supplementary video 1. Clinical examination of a PD patient, in whom tremor is suppressed during aDBS

Supplementary video 2. Clinical examination of a PD patient with breakthrough tremor during aDBS.





Pseudorandomisation order		
Condition I	**Condition II**	**Condition III**
NoStim	cDBS	aDBS
NoStim	cDBS	aDBS
NoStim	cDBS	aDBS
NoStim	aDBS	cDBS
NoStim	aDBS	cDBS
NoStim	aDBS	cDBS
NoStim[3]	aDBS[3]	cDBS[3]
cDBS[4]	NoStim[4]	aDBS[4]
cDBS	NoStim	aDBS
cDBS	NoStim	aDBS
cDBS	aDBS	NoStim
aDBS	NoStim	cDBS
aDBS	NoStim	cDBS
aDBS	cDBS	NoStim


UPDRS subscores per condition
Condition: p=<0.001
UPDRS III subscores
20
15
10
0
*
*
NoStim
cDBS
aDBS
Condition
Bradykinesia subscores
UPDRS III subscores
14
12
10
0
*
NoStim
cDBS
aDBS
Condition
Tremor subscores
UPDRS III subscores
8
6
4
2
0
*
*
NoStim
cDBS
aDBS
Condition
SIT scores of patients with SID
Interaction: p=0.027
SIT scores
1.0
0.8
0.6
0
*
NoStim
cDBS
aDBS
Condition

Pt	S	A (y)	Time since PD start (y)	DBS use (y)	Most affected side	PD type	Medication	Clinical setting		Experimental setting		Freq used for filtering (±3Hz)	OFF Beta peak (Hz)[a]
								Contacts used	Parameters	Contacts used	Parameters		
PD01[b]	M	58	24	9	Left	Tremor	Levodopa, pramipexole amantadine 1738 mg LEDD	L: -3/2+ R: -10/C+	2.9V 60µs 185Hz 0.8V 60µs 185Hz	L: -2/C+ R: -10/C+	1.8V 60µs 130Hz 1.8V 60µs 130Hz	15	L: 15 R: 15
PD02	M	47	16	12	Right	Tremor	Levodopa pramipexole 1538 mg LEDD	L: -3/2+ R: -11/C+	3.5V 60µs 135Hz 2.2V 60µs 135Hz	L: -2/C+ R: -10/C+	2V 60µs 130Hz 2.2V 60µs 130Hz	15	L: 15 R: 13
PD03	M	46	8	5	Left	Tremor	Levodopa duodopa 1582 mg LEDD	L: -1/2+ R: -11/10+	2.2V 90µs 180Hz 1.5V 90µs 180Hz	L: -2/C+ R: -10/C+	1.86V 60µs 130Hz 1.86V 60µs 130Hz	20	L: 21 R: 21
PD04	F	49	9	6	Left	Tremor	Levodopa rotigotine 1558 mg LEDD	L: -1/2+ R: -9/10+	2.8V 60µs 180Hz 1.2V 60µs 180Hz	L: 1-/C+ R: -9/C+	2.8V 60µs 130Hz 1.2V 60µs 130Hz	17	L: 17 R: 19
PD05	M	67	10	5	Left	Tremor	Levodopa 1500 mg LEDD	L: -2/C+ R: -11/C+	1.7V 60µs 180Hz 2.2V 60µs 180Hz	L: -2/C+ R: -10/C+	1V 60µs 130Hz 1.3V 60µs 130Hz	20	L: 22 R: 21
PD06[c]	F	64	23	9	Left	Rigid-bradykinetic	Duodopa amantadine 1759 mg LEDD	L: -2/3+	3V 60µs 130Hz	L: -1/C+	2.54V 60µs 130Hz	22	L: 21
PD07[d]	M	59	19	9	Right	Tremor	Duodopa 2540 mg LEDD	L: -0/1+	2V 60µs 1.85Hz	L: -1/C+ R: -9/C+	2V 60µs 130Hz 2V 60µs 130Hz	23	L: 21 R: 21
PD08	M	54	7	3	Right	Tremor	Levodopa pramipexole 725 mg LEDD	L: -0/-1/-2/3+ R: -9/10+	4.5V 90µs 190Hz 0.6V 60µs 190Hz	L: -1/C+ R: -10/C+	2.5V 60µs 130Hz 1.5V 60µs 130Hz	15	L: 16 R: 16
PD09	M	66	32	8	Left	Rigid-bradykinetic	Levodopa, pramipexole amantadine 1125 mg LEDD	L: -1/2+ R: -10/11+	4.5V 90µs 135Hz 4.8V 90µs 135Hz	L: -1/C+ R: -9/C+	2.05V 60µs 130Hz 2.05V 60µs 130Hz	18	L: 16 R: 15
PD10	M	48	12	4	Left	Tremor	Levodopa, pramipexole amantadine 1081 mg LEDD	L: -1/C+ R: -9/C+	3.2V 120µs 130Hz 2.4V 120µs 130Hz	L: -1/C+ R: -9/C+	3.2V 60µs 130Hz 2.4V 60µs 130Hz	29	L: 29 R: 27
PD11	M	81	15	6	Left	Tremor	Levodopa, pramipexole amantadine 900 mg LEDD	L: -1/2+ R: -10/9+	2.1V 60µs 135Hz 2.5V 60µs 135Hz	L: -1/C+ R: -10/C+	2.5V 60µs 130Hz 2.5V 60µs 130Hz	17	L: 17 R: 17
PD12	M	71	12	7	Right	Rigid-bradykinetic	0 mg LEDD	L: -2/C+ R: -11/C+	3.5V 80µs 90Hz 3.6V 80µs 90Hz	L: -2/C+ R: -10/C+	3V 60µs 130Hz 3V 60µs 130Hz	18	L: 18 R: 18
PD13	M	72	21	7	Right	Rigid-bradykinetic	Levodopa amantadine 1098 mg LEDD	L: -2/C+ R: -8/C+	2.3V 70µs 185Hz 2.9V 90µs 185Hz	L: -2/C+ R: -10/C+	3V 60µs 130Hz 3V 60µs 130Hz	26	L: 26 R: 24
Mean (±SE)		60.1 (3.0)	16 (2.0)	6.9 (0.6)			1318.7 (169.4)					19.6 (1.2)	19.2 (1.2)