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Dual threshold neural closed loop deep brain stimulation in Parkinson disease patients

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ABSTRACT

Background: Closed loop deep brain stimulation (clDBS) in Parkinson's disease (PD) using subthalamic (STN) neural feedback has been shown to be efficacious only in the acute post-operative setting, using externalized leads and stimulators.
Objective: To determine feasibility of neural (N)clDBS using the clinical implanted neurostimulator (Activa™ PC + S, FDA IDE approved) and a novel beta dual threshold algorithm in tremor and bradykinesia dominant PD patients on chronic DBS.
Methods: 13 PD subjects (20 STNs), on open loop (ol)DBS for 22 ± 7.8 months, consented to NclDBS driven by beta (13–30 Hz) power using a dual threshold algorithm, based on patient specific therapeutic voltage windows. Tremor was assessed continuously, and bradykinesia was evaluated after 20 min of NclDBS using a repetitive wrist flexion-extension task (rWFE). Total electrical energy delivered (TEED) on NclDBS was compared to olDBS using the same active electrode.
Results: NclDBS was tolerated for 21.67 [21.10–26.15] minutes; no subject stopped early. Resting beta band power was measurable and similar between tremor and bradykinesia dominant patients. NclDBS improved bradykinesia and tremor while delivering only 56.86% of the TEED of olDBS; rWFE velocity ($p = 0.003$) and frequency ($p < 0.001$) increased; tremor was below 0.15 rad/sec for 95.4% of the trial and averaged 0.26 rad/sec when present.
Conclusion: This is the first study to demonstrate that STN NclDBS is feasible, efficacious and more efficient than olDBS in tremor and bradykinesia dominant PD patients, on long-term DBS, using an implanted clinical neurostimulator and driven by beta power with a novel dual threshold algorithm, based on customized therapeutic voltage windows.

Introduction

Deep brain stimulation (DBS) is an established therapy for cardinal motor signs and medication-related complications in Parkinson's disease (PD). Clinical DBS therapy is limited to "open loop" neurostimulation: the neurostimulator does not sense the brain signals nor the behavior it is modulating. It applies continuous pulse trains of fixed frequency, amplitude, pulse width, and pattern, and cannot adjust such parameters in response to neural activity, or the patient's state of activity or behavior. Emerging evidence suggests non-continuous, phase-shifted, irregular and/or adaptive neurostimulation may be more efficacious and efficient with fewer adverse effects than open loop (ol)DBS [1–4].

Adaptive or closed loop (cl)DBS uses real time physiological signals to inform the neurostimulator when and how to change

Abbreviations: PD, Parkinson's disease; LFP, local field potentials; DBS, deep brain stimulation; STN, subthalamic nucleus; NclDBS, neural closed-loop DBS; olDBS, open-loop DBS; TD, tremor dominant; UPDRS, Unified Parkinson's disease Rating Scale; TEED, total electrical energy delivered; rWFE, repetitive wrist flexion extension.

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stimulation, to provide optimal therapy and minimize adverse effects. Successful subthalamic (STN) clDBS in PD will require discovery of patient specific neural and behavioral features (control variables) that reflect the disease, state of activity and/or dominant symptom, along with control policy algorithms that will change stimulation parameters in a manner that modulates the variable and improves motor function. Different neurological symptoms may require different clDBS strategies. Intermittent symptoms such as tremor may require demand based clDBS [5], similar to demand cardiac pacemakers for bradycardia. Bradykinesia, rigidity and gait impairment may require 'thermostat' algorithms, where clDBS varies based on patient specific therapeutic windows. The ideal clDBS system will be able to concurrently sense and stimulate using a fully embedded sensing neurostimulator, which will automatically adapt stimulation based on a freely moving patient's state of activity, dominant symptom and level of dopaminergic medication.

The initial neural (N)clDBS studies for PD used the resting state STN local field potential (LFP) beta band power as a control variable, recorded via externalized leads several days after DBS lead implantation, and used external customized neurostimulators [1,6–9]. Control policy algorithms turned DBS on or off based on whether the recorded STN peak beta band power fluctuated above or below a single threshold. The single threshold was chosen as that which resulted in aDBS being on for ~50% of the time olDBS would have been on. Another set of studies using externalized leads and customized neurostimulators demonstrated that adaptive STN DBS could successfully vary its intensity in response to dopaminergic medication induced attenuation of beta band power [4,10,11]. These studies provide initial evidence that clDBS based on a single threshold can be therapeutic in the acute, post-operative setting. A recent pilot study in two subjects with an implanted sensing neurostimulator explored the use of cortical gamma band power to drive STN clDBS [12].

This study advances the field of closed loop DBS for PD by demonstrating the safety, tolerability and efficacy of NclDBS using a fully implanted neurostimulator (Activa™ PC + S, Medtronic Inc.), capable of concurrent neural sensing and stimulation, in freely moving PD subjects, who had been on long-term STN DBS. A novel dual threshold algorithm was chosen based on the patient specific therapeutic window, determined from the improvement of their dominant symptom of tremor or bradykinesia. The primary outcome of the study was whether the subjects could tolerate 20 minutes of NclDBS using a customized dual threshold algorithm. Secondary outcomes tested several hypotheses that will be important for the future of embedded NclDBS: a) that resting state beta band power would be measurable in bradykinesia and tremor dominant PD [13]; b) that NclDBS would be feasible and efficacious in tremor dominant PD subjects; c) that resting state beta band power would be attenuated during STN DBS in a voltage dependent manner [14,15]; d) that there would be an improvement in bradykinesia from STN DBS and that the improvement in bradykinesia would be associated with an attenuation of resting state beta power [16]; e) that NclDBS using a customized dual threshold algorithm would be efficacious for the subject's dominant symptom of bradykinesia or tremor; f) that NclDBS delivered less energy than olDBS using the same electrode.

Methods

Human subjects

Thirteen subjects with Parkinson's disease (20 STNs), with bilateral STN DBS leads connected to an implanted investigational sensing neurostimulator (lead model 3389, Activa™ PC + S, Medtronic Inc.) consented to the study, which was FDA IDE and Stanford School of Medicine IRB-approved. Preoperative selection criteria, surgical technique, and the assessment of subjects have been described previously [13,17–19]. The experiments were conducted off medication: long-acting dopaminergic medication was withdrawn over 24 h (72 h for extended release dopamine agonists), and short-acting medication was withdrawn over 12 h before all study visits. Six patients (8 STNs) had no tremor and seven patients (12 STNs) exhibited tremor as the dominant symptom, off medication/OFF DBS, at the time of the experiment.

The implanted closed loop DBS system

The Activa™ PC + S-NexusD3 system allows for bi-directional transmission of information between the implanted neurostimulator and an external portable computing device (PC). The PC received uncompressed LFP signals from the neurostimulator via Bluetooth and commanded the neurostimulator to change the stimulation voltage based on a set of rules defined in the dual threshold control policy algorithm hosted on the PC.

NclDBS dual threshold control policy algorithm

The control variable was the STN LFP beta band [13–30Hz] power, β_S (Supplementary Information). The NclDBS control algorithm changed stimulation voltage in relation to the STN LFP beta band power using a dual threshold policy. The control objective was to keep the beta power in a range, between an upper (β_{INC}) and lower (β_{DEC}) value, Fig. 1A. The controller had the following rule: if β_S increased above the upper threshold, β_{INC} ($\beta_S > \beta_{INC}$), the DBS voltage was increased towards an upper limit (V_U); if β_S decreased below the lower threshold, β_{DEC} ($\beta_S < \beta_{DEC}$), then DBS voltage was decreased; if β_S was between the beta thresholds the DBS voltage was kept constant. No lower voltage limit was set, such that if β_S was $< \beta_{DEC}$ for a long time, the stimulation voltage could reach 0 V.

Enforcing safe stimulation

The upper stimulation limit, (V_U), was determined by the clinician to be the maximum 'safe' voltage above which adverse effects such as paresthesias or muscle twitching appeared and was set in the controller such that the neurostimulator could not stimulate above it. A rate of increase in DBS voltage of 0.25 V/s was tested and found to be safe and tolerable by all subjects.

During NclDBS, a fixed rate lower than above was implemented for all changes in stimulation voltage. Activa™ PC + S streams uncompressed sampled LFP signals in data packets of 400 ms. For a robust power estimation of the LFP signal in the beta band during streaming when data packets may be lost, an estimation of beta power was made in real time for each data packet successfully received, which limited the window length to 400 ms, with a resultant frequency resolution of 1.65 Hz/bin. To reduce the variability in real time beta power and improve estimation, the summation of real time beta power of the last 50 - during calibration/10 - during NclDBS successfully received data packets was used by the controller to determine beta thresholds during calibration or in the decision process during NclDBS.

The NclDBS controller was designed to change stimulation voltage in relation to beta band power using a dual threshold policy. During NclDBS, a decision was made every 400 ms after receiving an LFP data packet, and the voltage was increased or decreased by one step of 0.1 V size, if a change was to be made. To eliminate the effect of the transient charge imbalance at the tissue electrode interface after each voltage step change, information from the two LFP data packets following a voltage change was ignored, resulting in a fixed rate of change in DBS voltage three times lower than

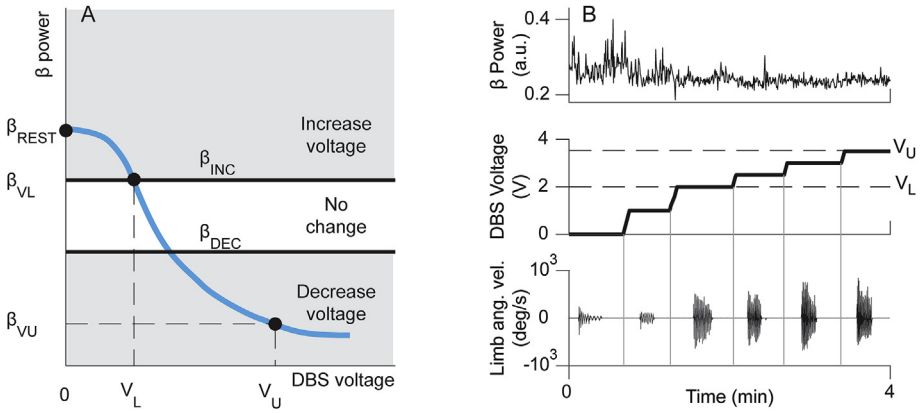

Fig. 1. A) The dual threshold NclDBS control algorithm. The blue line represents the relation between the stimulation voltage delivered by a commercial neurostimulator (140 Hz, 60 μs; Activa™ PC, Medtronic Inc.) and STN LFP beta band power as previously determined [14]. B) Identification of V_L from performance of rWFE at increasing DBS voltages in a representative case. The upper panel shows the online estimation of STN beta power as the (open loop) DBS voltage was increased stepwise up to V_U (middle panel); the corresponding angular velocity during rWFE at each voltage is shown in the lowest panel. V_L was chosen as 2 V for this case and V_U was 4 V. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

0.25 V/s. Additional processes such as transferring data packets, analyzing data, and transferring stimulation commands were performed during the 400 ms interval between receiving each LFP packet.

Thresholds determination

The controller design is based on previous determination that stimulation intensity attenuates STN resting state beta band power in a voltage dependent fashion [14]. By manipulating the stimulation voltage, the beta thresholds were determined as follows: the upper beta threshold (β_{INC}) was the STN beta band power recorded during constant olDBS at voltage V_L and the lower beta threshold (β_{DEC}) was the beta band power midway between that recorded at V_L and V_U, respectively, Fig. 1A.

Customized therapeutic window

The stimulation voltages used to determine the dual thresholds were chosen based on symptom improvement during olDBS. For each STN, the voltage was gradually increased to the upper limit, V_U, while motor symptoms were assessed. V_L was determined for each subject, as that which provided adequate improvement in the dominant symptom. For tremor subjects, V_L was the voltage below which tremor consistently recurred; for subjects lacking tremor, V_L was the voltage at which there was an acceptable improvement in bradykinesia (Fig. 1B).

A calibration period preceded the NclDBS trial, during which STN LFPs were recorded while the subject was sitting at rest, and during open loop DBS for 20 s at voltages V_L and V_U. The corresponding mean beta band power during DBS at V_L and V_U informed the determination of the control algorithm beta thresholds.

Experimental protocol

During experimental NclDBS in one STN, the contralateral STN DBS was kept ON, at the subject's clinical settings. During NclDBS, the subject was asked to sit still in a chair and avoid voluntary movements with the contralateral limbs. The contralateral hand was resting on the contralateral leg during NclDBS, and a real-time motion sensor placed on the dorsum of the hand recorded any contralateral leg/foot tremor [5]. The duration of NclDBS was set for at least 20 minutes, but if the subject indicated that the stimulation was intolerable, it could be stopped at any time.

Kinematic testing of bradykinesia was performed OFF DBS and ON olDBS at V_U during the calibration period and after 20 minutes of NclDBS, while still on NclDBS. Kinematic testing consisted of a contralateral repetitive wrist flexion-extension (rWFE) task, with a wearable sensor attached to the dorsal surface of the hand (Supplementary Information). The rWFE task was not measured in two tremor dominant limbs (6R and 7L) and in three cases, the rWFE data during NclDBS (5R, 9L and 12R) was not used due to technical issues during kinematic recording.

Outcome measures

The primary outcomes of the study were whether NclDBS using a fully implanted neurostimulator successfully varied voltage in relation to STN beta band power in a safe and tolerable manner and whether the subjects could tolerate at least 20 minutes of NclDBS; this was assessed by measuring the duration of NclDBS, while monitoring the subject for objective or subjective adverse effects, such as paresthesias, muscle twitching, discomfort, stiffness, and return of resting tremor. Secondary outcomes included: comparison of the resting state beta band power OFF DBS in PD subjects with tremor to those without tremor; quantitative measures of bradykinesia (angular velocity and frequency of the rWFE task) and tremor, and the percentage of the trial in which tremor resolved; whether STN beta band power was attenuated during DBS in a voltage dependent manner; whether the width of the dual thresholds affected the range of DBS voltage during NclDBS; the total electrical energy delivered (TEED) during olDBS and NclDBS using the same singular active electrode (Supplementary Information). The offline analysis was performed using MATLAB software (Version 9, The MathWorks, Inc., Natick, MA).

Statistics

Descriptive statistics of demographic and clinical data were calculated in the form of mean and standard deviation and normality was tested with the Shapiro-Wilk test. Paired t-tests checked the effect of olDBS and NclDBS stimulation on bradykinesia metrics. A two-way repeated measures ANOVA tested the main effects of stimulation voltage level (three levels: OFF, at V_L, at V_U) and the PD dominant symptom (two types: TD, AR) on STN LFP beta

power at rest. Spearman Rank Order Correlation was used for correlation results and a P value < 0.05 was considered significant. Statistical analysis was performed in SigmaPlot 12.5 (Systat Software Inc.). Please see Supplementary Information for details about the statistical methods.

Results

Table 1 details the demographic data, clinical and NclDBS settings of the thirteen subjects (11 male). Their age was 61.9 ± 9.5 years (mean $\pm$ SD). At the time of the NclDBS experiment, the subjects' mean disease duration since diagnosis was 9.5 ± 3.5 years and they had been on chronic olDBS for 22 ± 7.8 months. Subjects 1–7 exhibited tremor as their dominant symptom and will be called the tremor dominant (TD) group; subjects 8–13 did not exhibit tremor and will be called the akinetic rigid group (AR).

Prior to the experiment, STN olDBS had been delivered in a monopolar mode (case positive) in all STNs, through a single electrode in 11 STNs, through two electrodes in 8 STNs and through three electrodes in one STN. The mean clinical stimulation voltage was 3.0 ± 0.5 V. The median voltage used for NclDBS using a single active electrode was lower than the voltage used in clinical open loop DBS for all cases.

The patients had a mean 51% improvement in the UPDRS III score from medication at the pre-operative evaluation and a mean 68% improvement from STN DBS alone (off medication) after six months of STN olDBS, Table 1. All subjects underwent NclDBS using a single active electrode, so that the control variable (STN LFP) could be recorded during neurostimulation [14,17]. As more than one active electrode had been used for clinical olDBS in 11 STNs, we confirmed that there was a significant improvement in bradykinesia from STN DBS using the single active electrode chosen for NclDBS ($N = 18$ STNs, Voltage $= V_U$; Vrms: $t(17) = -6.6$, $p < 0.001$, average cycle frequency: $t(17) = -3.6$, $p = 0.002$). The degree of attenuation in resting state beta band power produced by DBS at V_U correlated with the improvement in bradykinesia (Vrms: rho $= 0.57$, $p = 0.013$, $N = 18$).

STN NclDBS was successful and well tolerated

STN NclDBS was well tolerated for at least 20 minutes in all subjects; the duration of NclDBS ($N = 20$ STNs) was 21.67 [21.10–26.15] minutes (median [IQR]). The group stimulation voltage delivered during NclDBS was 2.025 ± 0.914 V (mean $\pm$ SD). No adverse events were reported during NclDBS and no subject had to terminate the trial early. All subjects tolerated a voltage increase rate of 0.25 V/s. The investigational Activa™ PC + S neurostimulator used the same incremental changes of voltage (50 or 100 mV) at discrete times as the FDA approved, non-sensing Activa™ PC neurostimulator (Medtronic Inc.).

NclDBS improved bradykinesia and tremor, Fig. 2A–E. The mean angular velocity and average cycle frequency of the WFE task improved, Fig. 2A–B (Vrms: $t(14) = -3.5$, $p = 0.003$; average cycle frequency: $t(14) = -5.0$, $p < 0.001$, $N = 15$ STNs). During NclDBS, resting tremor was below a threshold visually observed to be barely perceptible tremor (0.15 rad/sec), see Supplementary Information, for almost the full duration of the trial in eight out of twelve cases, Fig. 2D; the median [25, 75 quartiles] % time below the threshold was 95.4 [65.4, 100.0] %. When tremor occurred, the median intensity of tremor was 0.26 rad/sec [0.32, 0.54], Fig. 2E. Across the group, NclDBS delivered 56.86 [23.33, 71.72] % of the total energy (TEED) that olDBS at V_U stimulation level would have delivered during the same period.

Successful neural classifier and control policy algorithms for NclDBS in tremor dominant and akinetic rigid subjects

The neural classifier algorithm was based on the premise that STN beta band power would be a useful control variable to drive closed loop DBS in both akinetic rigid (AR) and tremor dominant

Table 1
Demographics, pre- and post- DBS UPDRS III scores, clinical open loop DBS and NclDBS parameters. Note: Age, disease duration and months on olDBS are calculated at the time of experiment. Experiments for each STN were performed at different times in subjects 4, 5, 6 and 7; * denotes the case in which the clinical stimulation frequency was 185 Hz.

SBJ #	STN	Age (years)	UPDRS III pre-op		UPDRS III 6 month post-op		Disease duration (years)	ON olDBS (months)	clinical DBS settings		NclDBS settings			NclDBS median voltage
									pulse width = 60 μs stimulation frequency = 140 Hz		pulse width = 60 μs stimulation frequency = 140 Hz			
			off meds	on meds	off/ OFF	off/ ON			active electrodes	voltage (V)	active electrode	V_L (V)	V_U (V)	(V)
1	R	64.9	35	26	22	9	5.4	18	1-	3.5	1-	1.8	3.5	1.8
2	R	67.8	29	16	28	6	8.1	35	1-	2.5	1-	1.8	3.5	1.1
	L								1-,2-	2.5	1-	1.5	2.5	0.6
3	R	44.9	58	12	34	9	7.3	33	1-,2-	2.1	1-	1	4	1.9
4	R	70.8	41	28	65	18	12.3	21	1-,2-	3.1	2-	1.8	3	2.6
	L	71.6					13.2	31	1-,2-	3.3*	2-	2	4	1.0
5	R	74.3	47	23	36	13	11.0	26	1-,2-	2.8	2-	0	4.5	0.9
	L	74.6					11.3	29	1-,2-	3.7	2-	0	4	0.1
6	R	62.8	42	24	25	4	15.3	12	1-	2.9	1-	1.5	2.9	2.2
	L	63.4					15.8	19	1-	3.5	1-	2.5	3.5	2.7
7	R	58.1	38	18	17	6	12.8	15	1-	3.2	1-	1.5	3.2	2.5
	L	57.6					12.3	9	1-	2.7	1-	1.8	2.7	2.4
8	R	55.3	24	8	27	7	7.4	30	0-,1-,2-	3.5	1-	3	4	2.9
9	R	60.1	39	23	38	7	5.3	23	1-	3.3	1-	2.5	3.5	2.9
	L								1-	3.5	1-	2	3.5	2.6
10	R	55.3	52	29	52	15	9.4	22	1-,2-	3.7	1-	2	3.3	1.3
11	R	36.3	59	22	57	47	3.9	23	1-	4	1-	2.5	4.4	3.2
12	R	58.5	62	23	43	17	7.3	16	1-,2-	3.7	2-	2.5	3.7	3.4
13	R	68.8	44	25	11	3	7.3	15	1-	2.4	1-	2	2.4	2.2
	L								1-	2.5	1-	2	2.5	2.2

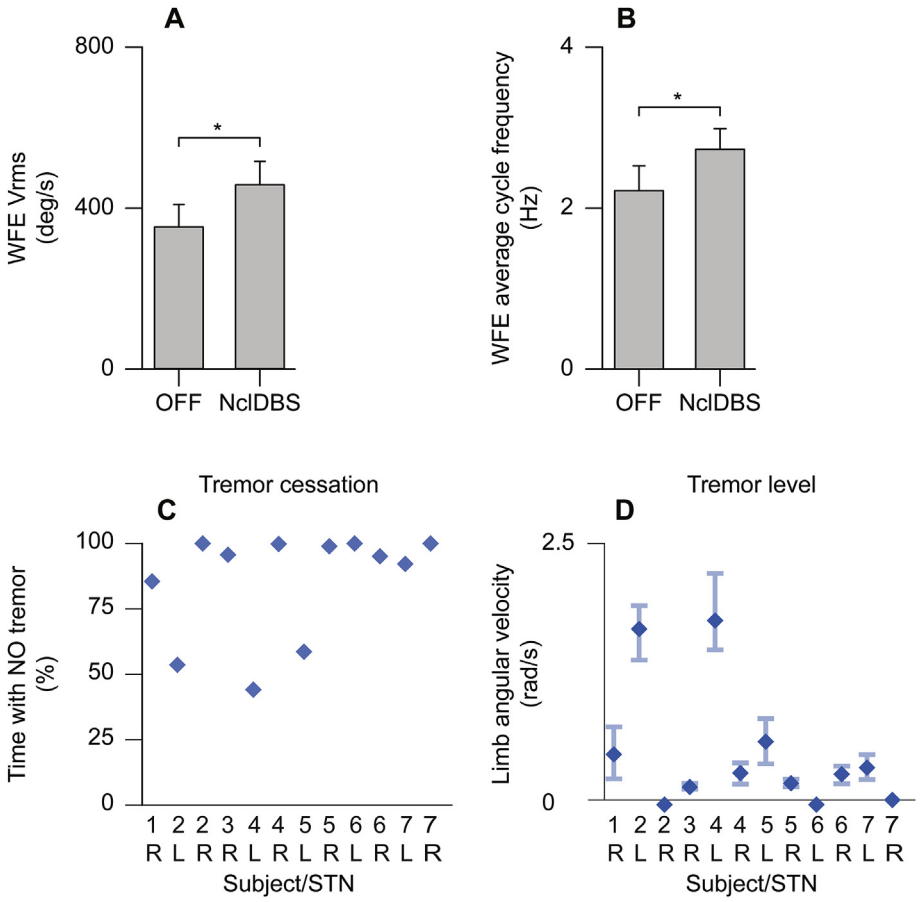

Fig. 2. NclDBS improved bradykinesia and tremor. The Vrms, A, and average cycle frequency, B, of rWFE improved on NclDBS (*Vrms: $p = 0.003$; average cycle frequency: $p < 0.001$). C, the percent of time with NO tremor in TD subjects; D, the median tremor level during periods of observable tremor in each subject.

(TD) PD subjects, even though it has been demonstrated that resting state STN beta band power is attenuated during periods of resting tremor [13,20]. The control policy algorithm was based on the premise that there would be an inverse relationship between STN resting state beta band power and STN DBS intensity (voltage) such that increasing STN DBS voltage would decrease STN beta band power, Fig. 1A [14,15].

Both premises were supported by the data: in the repeated measures analysis to test the effect of stimulation voltage on beta power within individuals, the dominant symptom had no effect ($p = 0.158$, all pairwise multiple comparison procedures, Holm-Sidak method), suggesting that there was no significant difference in resting state beta power between TD and AR groups. There was a significant voltage dependent attenuation of resting state beta band power, $F(2,36) = 42.2$, $p < 0.001$, Fig. 3A. The algorithm worked: the neurostimulator voltage adapted to fluctuations in beta power according to the dual threshold control policy algorithm. Fig. 3B demonstrates the fluctuations in resting state beta band power and corresponding variation in DBS voltage during the NclDBS trial, in a representative PD subject. The insert highlights the decision events over a one second period. When the neural control variable (beta power) was sensed, the stimulation voltage changed; red triangles indicate when beta power was above the upper threshold and voltage increased, no symbols indicate when beta power was within the thresholds and no change was made to the voltage, and blue triangles indicate when beta power was below the lower threshold and voltage decreased.

The range of voltage during the trial varied among both TD (#1–7) and AR (#8–13) subjects, Fig. 4A, and the median voltage during NclDBS was lower in the TD group ($t(18) = -2.552$, $p = 0.02$), Table 1. The voltage was allowed to vary freely in response to beta band power fluctuation over the trial; the control policy algorithm did not define an absolute lower limit of voltage. Across the group ($N = 20$) the median voltage during the NclDBS trial was 73.5 [39.5, 84.6] % of V_U which translated to 2.025 (± 0.914) V (mean ± std). However, the range of voltage (interquartile range of normalized stimulation voltage shown as blue shaded bars, Fig. 4A) varied among cases during the NclDBS trial, from less than 5% of V_U (0.4 V, case 5R) to over 50% of V_U (1.7 V, case 7R).

We hypothesized that the degree of variation in voltage would be smaller when there was a wider separation of beta thresholds (β_{INC} - β_{DEC}) as there would be a greater probability that resting state beta band power would lie in between the thresholds, for which the control policy would command 'no change' to the neurostimulator. This was confirmed: the difference between β_{INC} and β_{DEC} inversely correlated with the interquartile range of normalized stimulation voltage (rho = - 0.47, $p = 0.035$, $N = 20$ STNs). Among the AR subjects, the voltage range was within or close to the "therapeutic" voltage window in all but one of the cases. In this case (10L), Fig. 4B, the difference between the beta thresholds was so small that NclDBS essentially performed like a single threshold control policy algorithm and resulted in large fluctuations in NclDBS voltage.

Among subjects with tremor, the interquartile range of normalized stimulation voltage during NclDBS was below V_L in two cases, case 2L and case 4L, Fig. 4C and D. In case 2L, Fig. 4C, an early decrease in beta power resulted in a voltage decrease close to zero, after which the voltage responded appropriately to beta power

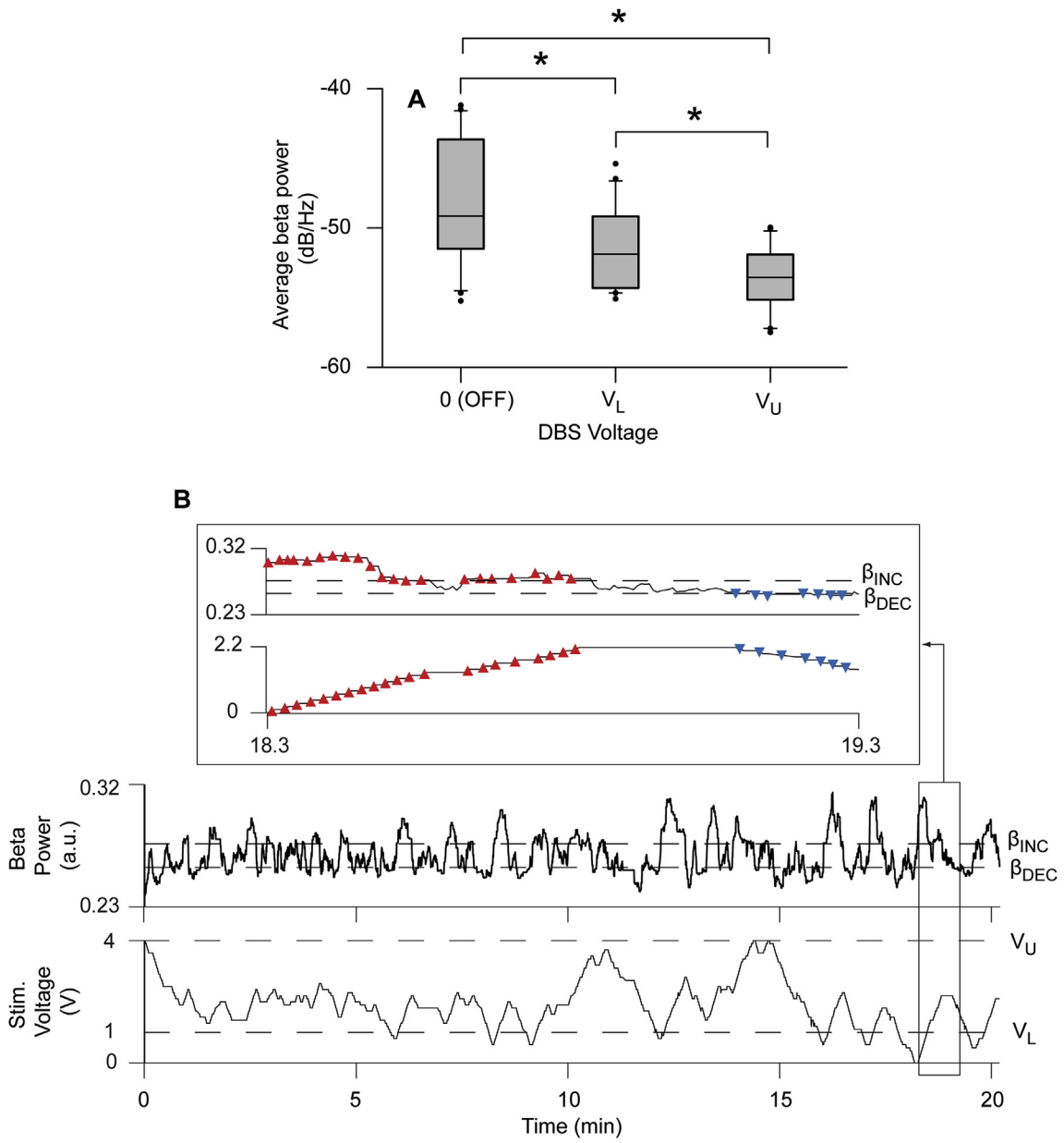

Fig. 3. A) Greater attenuation of STN DBS resting state β power at higher voltages. B) Example of a NclDBS trial: upper panel demonstrates fluctuation of STN beta power within, above and below the dual thresholds; lower panel demonstrates the DBS voltage response. The insert highlights the decision events over a one second period, whether DBS voltage increased (red triangles), stayed the same (no symbols), or decreased (blue triangles). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

fluctuations, but rarely rose above V_L. This was associated with episodic 'breakthrough' of tremor, as would be expected when the DBS voltage was below V_L. For case 4L, Fig. 4D, emergence of tremor ~13 min into the trial was associated with a progressive decrease in beta band power, which stayed at or below β_{DEC}; the voltage responded appropriately and decreased to zero resulting in sub-therapeutic treatment for tremor. Fig. 2D demonstrates that these were among the few cases where tremor resolution was not observed for close to 100% of the NclDBS trial.

Beta power varied over the trial as expected and in all but two STNs, the mean of the normalized range of beta power was below the upper beta threshold (β_{INC}), Supplementary Information Fig. S1. However, there was no correlation between the range of beta power during NclDBS and the improvement in bradykinesia.

Discussion

This study has demonstrated the safety, tolerability, and feasibility of STN neural closed loop (Ncl)DBS in bradykinesia and tremor dominant subjects with Parkinson's disease, using a fully implanted sensing neurostimulator, whose intensity was modulated by STN beta band power, using a dual threshold algorithm. There were no adverse effects reported and no subject stopped NclDBS before the end of the trial. Resting state STN beta band power was similar between bradykinesia and tremor dominant patients, and in both groups, NclDBS improved the angular velocity and frequency of a repetitive wrist flexion-extension task. In tremor dominant cases, there was resolution of tremor for a median of 95.4% of the trial and the median tremor intensity during NclDBS across the group was 0.26 rad/s. The improvement in bradykinesia

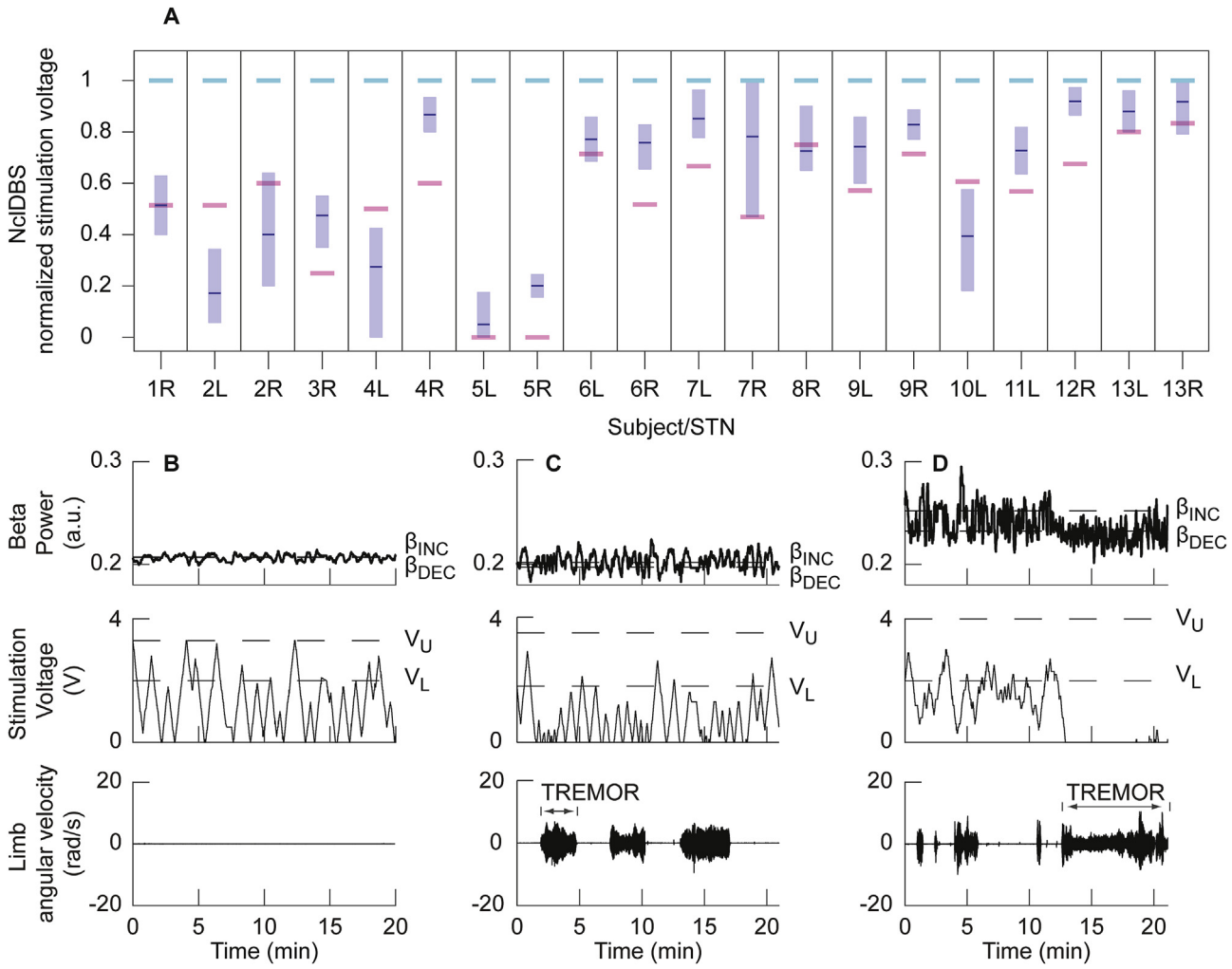

Fig. 4. A) Median (dark blue) and interquartile range of the stimulation voltage during NclDBS trial normalized to V_U. Pink and cyan lines represent V_L and V_U, respectively for each case; B, C, and D – details of NclDBS trials in cases where the voltage range was below V_L in an AR and two TD subjects respectively; B) case 10L, in which the control algorithm thresholds were so close that practically the control acted as a one threshold control algorithm, C) case 2L, that presents intermittent periods of tremor, D) case 4L, in which excessive tremor attenuates the beta power (neural control variable) and determines the voltage to decrease to 0 V for the last part of the trial. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and tremor was encouraging since the energy delivered during NclDBS was only 57% of that during olDBS at V_U, (single active electrode), and given that clinical olDBS used more than one active electrode in nine of the twenty STNs.

Neural closed loop DBS using a dual threshold algorithm

The implementation of NclDBS in this study was based on the premise that exaggerated beta band (13–30 Hz) power in STN LFPs reflects the abnormal state of cortico-subcortical networks that result in motor dysfunction in Parkinson's disease, and that STN beta band power is attenuated in a voltage dependent fashion during DBS [13–15,17,21,22]. Complete attenuation of the STN LFP beta band power however may not be optimal for motor performance: we demonstrated recently that attenuation of beta band power was greater and the movement performance was less consistent during 140 Hz DBS than during 60 Hz stimulation in PD subjects [18]. Consequently, we chose a dual threshold control strategy that constrained the beta band power in an optimal range, customized for each STN. The optimal range of beta band power was determined using a patient specific 'therapeutic window' of voltage for bradykinesia or tremor. By determining the stimulation voltage levels based on motor performance, the control strategy parameters used were clinically relevant. The upper beta threshold was chosen as that which corresponded to a (lower) voltage (V_L), which had to be lower than that chosen for optimal therapy (V_U). The control policy algorithm was designed to increase voltage if and when beta power increased above that corresponding to V_L, so that the therapy would not stay at V_L, and as it could not go above V_U, it was designed to stay within a therapeutic window. The choice of V_L was determined in a patient specific manner based on their symptom control at different DBS intensities, as demonstrated by a specific example in Fig. 1B. We did not think it prudent to take V_L so low that the clDBS therapy would be sub-therapeutic and therefore not tolerable. Hence, we chose V_L as the lower limit of the therapeutic range, at which there was some improvement in bradykinesia or tremor but not the optimal improvement. In clinical practice it is well known that optimal therapy, using medication and/or DBS, uses doses/intensity above the lowest therapeutic level. The advantage of developing closed loop and adaptive DBS is that it may not be necessary to always be at the upper level of DBS intensity and some fluctuation within a therapeutic range will reduce energy use and may reduce side effects.

In all cases the control policy algorithm worked: increases in beta band power triggered increased DBS voltage, and beta band power was attenuated during DBS in a voltage dependent manner. The dual threshold algorithm allowed the potential of 'no change' in NclDBS voltage if sensed beta power lay in between the thresholds; otherwise the voltage was allowed to vary in response to beta band power fluctuations with only an upper voltage limit as a restriction. The customized dual threshold control policy algorithm resulted in different ranges of voltage variation during NclDBS across the group. There was an inverse correlation between the separation of the beta thresholds and the range of voltage during NclDBS: beta thresholds that were very similar acted like a single threshold algorithm and resulted in a wide range of NclDBS voltage fluctuation.

We hypothesized that STN beta band power would be a useful control variable to treat both bradykinesia and tremor, and this was supported by the finding that the resting state beta band power was similar between bradykinesia and tremor dominant cases, demonstrating that there was a measurable control variable for the NclDBS algorithm in tremor dominant patients. However, arguments against NclDBS being useful for tremor include reports demonstrating that the degree of attenuation of resting state beta band power from medication and/or DBS was related to the improvement in bradykinesia and rigidity but not in tremor, and by demonstrations that STN beta band power may be attenuated during resting tremor [13,20,22–24]. The attenuation of beta band power during resting tremor impacted the efficacy of NclDBS for tremor in only one case, where the reappearance of tremor was associated with a progressive decrease in beta band power which triggered a decrease in DBS voltage. We have demonstrated successful closed loop DBS for tremor driven by tremor intensity measured with a Bluetooth enabled smart watch [5], which opens the possibility of dual neural and kinematic clDBS strategies for tremor in PD: if and when tremor reappears, the physiological classifier algorithm will override the neural algorithm to maintain DBS intensity in a therapeutic range.

Limitations

In two out of twelve cases there was breakthrough tremor, both associated with voltage decreases well below the determined lower limit of the therapeutic window (V_L). This suggests that placing a lower absolute limit of stimulation intensity in clDBS algorithms may be helpful for bradykinesia and to minimize tremor breakthrough. However, in certain TD cases when there was only intermittent tremor, it may be preferable to allow the clDBS voltage to go to zero to limit unnecessary use [5]. The clinical outcome of this feasibility study of NclDBS was not designed to be compared with open loop or random patterns of DBS; superiority of NclDBS to open loop DBS and to random patterns of DBS has been demonstrated [1]. The delays between sensing and stimulation encountered in the Activa™ PC + S NexusD3 system will be considerably shorter in the next generation Summit™ RC + S adaptive DBS system and will make it possible to use the duration of beta band power fluctuations, rather than only beta band power, as a control variable [25]. We have demonstrated that beta burst durations differentiate freezers from non-freezers during gait, making this advancement clinically relevant [26]. In addition, there will be fewer artifacts from subharmonics and more sophisticated control policy algorithms, which will allow variations for frequency as well as intensity, and which was another limitation of the Activa™ PC + S system.

Conclusions

This is the first study to demonstrate the safety, tolerability and efficacy of neural closed loop (Ncl)DBS, using a fully implanted sensing neurostimulator, Activa™ PC + S, and a novel dual beta threshold algorithm in both bradykinesia and tremor dominant PD subjects. The dual beta threshold algorithm was based on customized therapeutic windows of DBS intensity, and is the control policy algorithm employed by the next-generation investigative Summit™ RC + S system. This clinically relevant control strategy worked and resulted in improvement in progressive bradykinesia and/or tremor, despite delivering only 57% of the energy that would have been delivered during open loop DBS using a single active electrode. The median voltage used for NclDBS using a single active electrode was lower in every case than the voltage used in clinical open loop DBS, in which more than one active electrode had been used for nine STNs. The NclDBS voltage was constrained in its upper limit but was allowed to decrease below the lower therapeutic window (V_L), which was associated with breakthrough tremor in two cases. Narrower beta thresholds were associated with larger fluctuations in NclDBS voltage. Improvements in neural control policy algorithms might include a lower constraint in voltage and/or more sophisticated control strategies that employ additional physiological or behavioral sensing that overrides NclDBS when episodic symptoms such as tremor or freezing of gait emerge. Reduced energy consumption compared to current olDBS will extend battery life, may reduce adverse effects, and open possibilities for using smaller devices.

Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.02.020.

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