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# Closed-loop deep brain stimulation effects on parkinsonian motor symptoms in a non-human primate -- is beta enough?

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## Abstract

**Background—**Incorporating feedback controls based on real-time measures of pathological brain activity may improve deep brain stimulation (DBS) approaches for the treatment of Parkinson's disease (PD). Excessive beta oscillations in subthalamic nucleus (STN) local field potentials (LFP) have been proposed as a potential biomarker for closed-loop DBS (CL-DBS).

**Objective—**In a non-human primate PD model we compared CL-DBS, which delivered stimulation only when STN LFP beta activity was elevated, to traditional continuous DBS (tDBS).

**Methods—**Therapeutic effects of CL-DBS and tDBS relative to the Off-DBS condition were evaluated via a clinical rating scale and objective measures of movement speed during a cued reaching task.

**Results—**CL-DBS was comparable to tDBS at reducing rigidity, while reducing the amount of time DBS was on by ≈ 50%; however, only tDBS improved bradykinesia during the reaching behavior. This was likely due to reach-related reductions in beta amplitude that influence the timing and duration of stimulation in the CL-DBS condition.

**Conclusion—**These results illustrate the potential utility of closed-loop DBS devices for PD based on STN beta LFP levels. They also point to possible consequences in behavioral tasks when restricting real-time sensing to a single LFP frequency that itself is modulated during performance of such tasks. The present study provides data that suggest alternate algorithms or more than one physiological biomarker or may be required to optimize the performance of behavioral tasks and

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demonstrates the value of using multiple objective measures when evaluating the efficacy of closed-loop DBS systems.

### Keywords

deep brain stimulation; Parkinson's disease; subthalamic nucleus; local field potentials; closed-loop

## Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective surgical treatment for advanced Parkinson's disease (PD) [1]. While traditional DBS systems are always on, continually delivering pulsed stimulation at high rate (i.e., > 100 Hz) regardless of the clinical state, a promising approach to improve DBS therapy is to incorporate feedback control of the stimulation based on measures of pathological brain activity that reflect a patient's moment-by-moment fluctuations in symptoms [2]. Such a strategy would have the advantage of stimulating only when necessary, potentially reducing negative side effects of prolonged stimulation [3] and increasing device battery life.

Prominent synchronization of beta (~13–30Hz) oscillations in STN local field potentials (LFPs) has been identified in PD patients [4–6] and animal models of PD [7, 8]. Several groups report beta activity is markedly reduced following dopaminergic treatment [9–11] and during DBS [12–14]. In some cases this reduction has been correlated with clinical improvement of PD symptoms such as rigidity and bradykinesia [6], leading to the hypothesis that STN beta LFPs may be an effective programming biomarker for real-time, closed-loop control of DBS [2, 15–18].

In this study we implemented a closed-loop DBS (CL-DBS) strategy that delivers STN stimulation based on the level of beta activity in the LFP recorded directly from the STN DBS lead implanted in a parkinsonian non-human primate. We hypothesized that CL-DBS would be more effective than traditional DBS (tDBS) at improving rigidity and bradykinesia while operating at a reduced stimulation duty cycle.

## Materials and Methods

### Animal Preparation

All methods were approved by the Institutional Animal Care and Use Committee. Data were collected from one female rhesus macaque (25 yr.) rendered parkinsonian by two intra-carotid and two systemic injections of the neurotoxin 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) and implanted in the STN with a 4-contact scaled version of a human DBS lead (NuMed) using standard approaches described elsewhere [19]. The animal's overall severity was determined using a modified Unified Parkinson's Disease Rating Scale (UPDRS) that rated rigidity, bradykinesia, akinesia, and tremor in the arm and leg on the side opposite the STN implant, as well as food retrieval, on a scale of 0–3 (3 = severe). The mean (std) score was 8.2 (0.27) out of a total possible score of 27 (n = 6 observations).

### DBS Stimulation Conditions

Three experimental conditions were tested: Off-DBS, Traditional DBS (tDBS), and Closed-Loop (CL-DBS). tDBS consisted of a continuous biphasic pulse train (133Hz, 700μA, 80μs/phase, no interphase gap, monopolar C2 cathodic first). The pulse train for CL-DBS was similar but was triggered on only when a real-time measure of beta amplitude in the bipolar LFP activity from contacts 1–3 exceeded a pre-determined threshold level. LFP C1-3 was bandpass filtered (9–20Hz, chosen based on beta peak observed in LFP power spectral density, Fig. 1A), rectified and low-pass filtered (400ms moving average) to produce the beta amplitude signal (Fig. 1B). This signal is referred to as 'beta' for simplicity and because the bandpass filter peaked in the beta range, though the filter range does include much of the alpha (8–13Hz) band. CL-DBS included a 250ms ramp up/down when triggered on/off, respectively. This methodology is similar to Little et al. [15]. Recording, online processing and stimulation were programmed using a TDT workstation (Tucker Davis Technologies) operating at ~25kHz sampling rate. There was a 5 sample point delay (0.205 ms) delay between the detection of a beta threshold crossing and the change in stimulation output. The beta LFP and stimulus signals were saved for analysis (Fig. 1G)

### Clinical and Behavioral Assessments

An experimenter blinded to the experimental conditions assessed rigidity in the arm and leg joints contralateral to the DBS implant using a modified UPDRS scale ranging from 0–3 (0.5 point increments). Effects of DBS on bradykinesia were assessed based on movement times and speeds during a trained, cued reaching task (Fig. 1D). Trials initiated when the animal placed its hand on a start pad. After a variable delay (1–1.5s) a circle (8cm) appeared on a touchscreen. The animal was required to leave the start pad (reaction time <1s), touch the target (reach time <2s) to receive a liquid reward and return to the start pad to initiate the next trial. Trials in which return time exceeded 6s were excluded from analysis (3%). Movement position and speed was monitored using a reflective marker on the wrist and motion capture system (Motion Analysis Corp.) in both the normal and MPTP states for comparison. Statistical comparisons of rigidity scores and movement times/speeds were made as a function of experimental condition using one-way ANOVA with Bonferroni correction for multiple comparisons ($P<0.05$).

### Experiment Design

The experiment design is illustrated in Fig. 1C. The threshold level for the CL-DBS was set as the median beta amplitude calculated from a 3 minute baseline recording collected at the start of each experimental session, with the expectation that stimulation would be delivered ~50% of the time during CL-DBS. A block consisted of a control (Off-DBS) or stimulation (CL-DBS or tDBS) period (8 minutes); rigidity assessment was performed after stimulation was on for 2 minutes, while bradykinesia assessments were performed after stimulation was on for 5 minutes after which stimulation was discontinued. There was a 5 minute washout period following cessation of stimulation after which motor signs were reassessed. The block was repeated for each of the three conditions, and the order of blocks was randomized each day (six days).

## Results

Both CL-DBS and tDBS significantly reduced rigidity scores compared to Off-DBS (Fig. 1E). Elbow rigidity was lower during CL-DBS compared to tDBS, and mean total rigidity scores for CL-DBS trended lower than tDBS, though this difference did not reach significance. These results suggest that CL-DBS has similar if not better therapeutic effect on rigidity compared to tDBS, even though during rigidity assessment CL-DBS was found to be on only 52.6% of the time, compared to 100% during tDBS.

Relative to Off-DBS, performance on the reaching task improved only during tDBS, reflected by the significant reduction in total movement time (Fig. 1F). There was no difference between conditions in the peak reach speed. Peak return speed was significantly faster only during tDBS approaching the speeds observed before induction of the PD state. Surprisingly, peak return speed during CL-DBS was slower compared to Off-DBS.

In all conditions the envelope of beta LFP decreased after reach onset (Fig. 1G, top). Consistent with this, stimulation in the CL-DBS condition was least likely to occur during the reach and beginning of the return epoch (Fig. 1G, bottom).

## Discussion

We found that CL-DBS can operate at a reduced stimulation duty cycle and still be equally or more effective than tDBS at alleviating rigidity, one of the cardinal motor symptoms of PD. These results support the findings of Little and colleagues [15] who implemented a similar STN beta-triggered DBS paradigm in PD patients and found superior clinical effectiveness based on composite tremor, rigidity and finger tapping UPDRS scores. A recent case study by Rosa et al. [16] showed that a closed-loop strategy that adjusted the stimulation level of continuous DBS every second according to the measured STN beta LFP amplitude was comparable to traditional DBS when the patient was off levodopa medication, but superior to traditional DBS at improving UPDRS bradykinesia scores and controlling levodopa-induced dyskinesia when the patient was in the on state. All of these studies point to the promising utility of closed-loop DBS devices for improving the treatment of Parkinson’s disease.

In the current study we also compare the effectiveness of traditional and closed-loop DBS using objective, quantitative measures in a reaching task, which is different from clinical assessments used in other studies [15–17]. We quantified movement variables in distinct aspects of the motor behavior, revealing deficits that may be less apparent when using subjective clinical rating scales. Indeed, we found that CL-DBS did not improve total movement time, and whereas tDBS increased peak speed during the return epoch of the task, CL-DBS provided no comparable improvement. The utility of clinical assessments is not in question, however we posit that objectively measured kinematic data from behavioral tasks such as the one used here can offer new insights into the effects of DBS algorithms on motor behavior.

The lack of improvement in bradykinesia on the reaching task during CL-DBS may be explained by intrinsic task-related modulations in beta amplitude that influence the timing

and duration of stimulation. Previous studies in PD patients have shown that a reduction in LFP beta amplitude coincides with movement initiation [20, 21]. The reduction in beta we observed at reach onset led to stimulation turning off during the reach and start of the return epochs, compared to tDBS where stimulation was delivered continuously during all phases of the reaching task (Fig. 1G). Though evidence suggests that the level of beta activity is correlated with PD motor symptoms [6], it is evident that voluntary movement also dynamically modulates beta activity, which can be expected to influence how stimulation is delivered in beta-based closed-loop DBS systems. Our results highlight the possibility that such systems may not achieve superior benefit over traditional DBS in some contexts, and may actually compromise motor performance in movement-related activities. It is plausible that stimulation throughout periods of movement, or at specific time points relative to movement initiation and execution, is necessary to achieve maximal benefit of DBS. Alternatively, one may need to use a complementary biomarker to supplement beta activity as a CL trigger in certain movement contexts.

That peak reach speed did not significantly increase during tDBS is not entirely surprising given the cued nature of that task epoch. Majsak and colleagues [22] found that the maximal movement speed of PD patients was comparable to healthy controls when making visually cued movements, but impaired when making internally driven movements (e.g. reaching to a stationary object). In our experiment, the return epoch could be considered internally driven; the animal is well-trained and returns to the start pad to initiate the next trial, but this movement is not explicitly cued. It has been argued that the basal ganglia is more integral to the control of internally generated rather than externally cued movements [23]. This might explain why tDBS markedly improved performance in return, but not reach task components in our study. Similarly, Schenk et al. [24] found in PD patients that the effects of DBS in the globus pallidus internus on the speed of reaching were less pronounced when external cues were provided. The degree of improvement in peak return speed during tDBS observed here (~15%) is not dramatically different from what has been reported in patient studies. For example, Bastian et al. (2003) quantified peak velocity of the wrist during reaching movements to a stationary object in patients receiving STN DBS and found that unilateral stimulation improved peak movement speed by ~20% relative to the off-DBS condition [25]. Moreover, in our study a ceiling effect may have limited further improvement in speeds beyond what was achieved in the normal state (Fig. 1F).

Our results have important implications for how to implement feedback control of DBS using brain-based biomarkers. These results suggest that closed-loop algorithms using beta as a biomarker will need to be improved, perhaps by adaptively switching algorithms depending on the behavioral context. It may also be the case that a single biomarker is insufficient, and that algorithms using multiple biomarkers, for example beta and gamma band oscillations [21] or interactions between frequencies bands [26], or even different biomarkers in different locations of the same structure [27, 28], will be more effective for closed-loop control. In addition, closed-loop DBS may need to be phenotype specific, customized for each patient using biomarkers specific to a given patient's pathophysiology and symptom profile, i.e. patient specific CL-DBS. As we develop new technology to monitor physiological activity throughout the basal ganglia thalamo-cortical circuit [29, 30] it will be critically important that we understand how physiological activity drives the

altered movement in PD if we are to use this activity to develop new generation CL-DBS systems.

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## Abbreviations

| | |
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| **DBS** | deep brain stimulation |
| **PD** | Parkinson's disease |
| **STN** | subthalamic nucleus |
| **LFP** | local field potential |

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## Highlights

- Excessive beta oscillations in subthalamic nucleus (STN) local field potentials (LFP) have been proposed as a potential biomarker for closed-loop DBS (CL-DBS).
- We found that CL-DBS, which delivered stimulation only when STN LFP beta activity was elevated, was comparable and in some cases better than traditional DBS at reducing rigidity, while reducing the amount of time DBS was on by ~50%; however, only traditional DBS improved bradykinesia during a reaching task.
- Reach-related reductions in beta amplitude influenced the timing and duration of stimulation in the CL-DBS condition.
- Our results illustrate the promising utility of closed-loop DBS for PD based on STN beta LFP levels, but also suggest that researchers and device manufacturers may need to consider additional features in a closed-loop DBS device, beyond sensing of a single LFP frequency band or employing a single algorithm, in order for it to reach its full therapeutic potential.

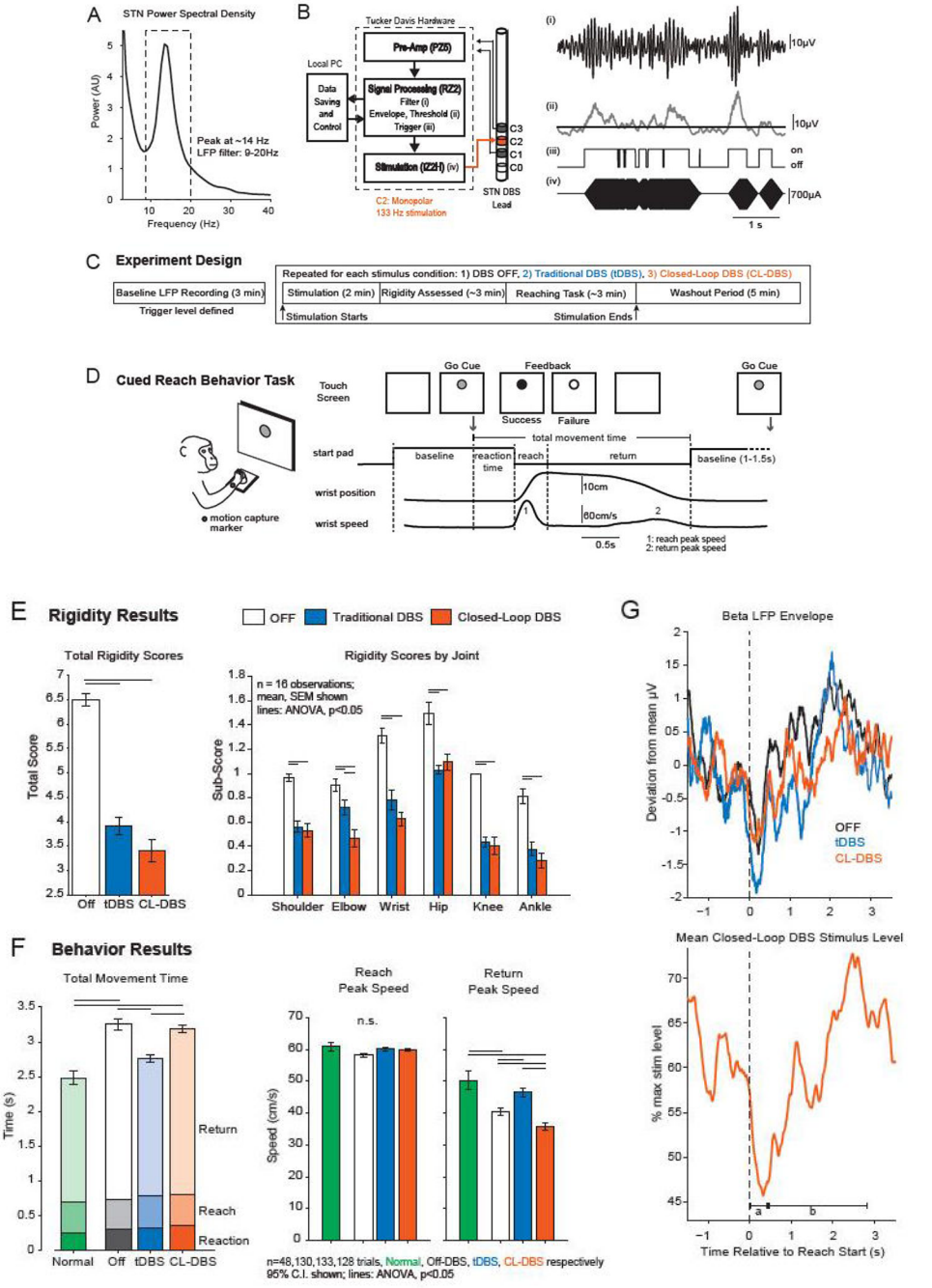


**Figure 1.**

Closed-loop DBS (CL-DBS) that delivers STN stimulation based on the level of beta activity in the STN has comparable therapeutic effect on rigidity compared to traditional DBS (tDBS) but does not improve performance on a cued reaching task. **A)** In the parkinsonian (MPTP) macaque used in this study, a peak (~14Hz) in the low beta range is present in the normalized power spectral density calculated from LFPs recorded from STN DBS electrode contacts 1–3. This plot was derived from LFPs recording during one of the 3 minute baseline recording sessions. **B)** Schematic of the system used to implement real-time CL-DBS, which

incorporates Tucker Davis Technologies (TDT) hardware. LFPs were recorded from DBS contacts 1 and 3, subtracted to achieve a bipolar LFP signal and bandpass filtered (9–20Hz) to extract what we are defining as beta LFP (*i*). The beta amplitude envelope was calculated by rectifying and low-pass filtering by means of a 400ms moving average filter (*ii*). The threshold level for stimulation was fixed at the median of the beta amplitude envelope calculated from the baseline LFP recording acquired at the start of each experimental session. During CL-DBS, a trigger that was switched on/off whenever the beta amplitude was greater/less than the threshold (*iii*) controlled stimulation (Monopolar C2, 133Hz, 700μA, 80μs/phase, (*iv*)). An on/off ramp time (250ms) was employed to reduce potential paresthesias induced by switching on stimulation. **C)** Experiment design. Following the 3 min. baseline recording session, from which the CL-DBS trigger level was defined, an experiment block consisting of a control or stimulation (CL-DBS or tDBS) period, clinical rigidity assessment, behavior assessment, and washout; experiment blocks were repeated for each experimental condition: Off-DBS, tDBS, CL-DBS. The order of blocks was randomized each day. **D)** Schematic showing the cued reach behavior task. **E)** Rigidity scores for arm and leg joints based on blinded assessment during each condition (mean ± SE; $P<0.05$). **F)** Total movement time (*left)* and peak speeds during reach and return task epochs (*middle,right)* for each condition (mean and 95% C.I.; $P<0.05$). The “normal” condition reflects data collected when the animal was in the normal state before MPTP administration. **G)** *Top:* beta amplitude envelope averaged over all trials in each condition, aligned to reach onset (Time = 0 s). *Bottom:* DBS stimulus level (as a percentage of the maximum level) averaged over all trials in the CL-DBS condition, aligned to reach onset (Time = 0 s). a: mean reach duration, b: mean return duration