CLOSED LOOP DEEP BRAIN STIMULATION FOR FREEZING OF GAIT

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1.1 Abstract

Freezing of gait (FOG), a devastating symptom of Parkinson’s disease (PD), can be refractory to current treatments such as medication and open-loop deep brain stimulation (oDBS). Recent evidence suggests that closed-loop DBS (cDBS), using beta local field potential power from the subthalamic nucleus (STN) as the control variable, can improve tremor and bradykinesia; however, no study has investigated the use of cDBS for the treatment of FOG. In this study, we provide preliminary evidence that cDBS was superior to oDBS in reducing percent time freezing and in reducing freezing behavior (gait arrhythmicity) in two people with PD and FOG, with less total energy delivered. These findings warrant further investigation into the use of cDBS to treat FOG while also minimizing the total energy delivered to maintain a therapeutic effect.
1.2 Introduction

Freezing of gait (FOG) is a devastating symptom of Parkinson’s disease (PD), affecting over half of the patient population [1] and drastically impacting mobility and patient quality of life. These symptoms have been difficult to treat with dopaminergic medications, and they can become refractory over time [2]. Moreover, it is debated how much deep brain stimulation (DBS) provided in an open-loop manner (olDBS) can mitigate FOG [3]–[5].

Closed-loop deep brain stimulation (clDBS) has been demonstrated to alleviate the signs and symptoms of PD by adjusting stimulation in response to elevations in local field potential (LFP) beta band power in the subthalamic nucleus (STN). Improvements in tremor and bradykinesia on clDBS have been observed using beta power as the control variable in both single and dual threshold algorithms [6]–[8]. To date, no study has used similar closed-loop paradigms to reduce FOG, although we have shown that STN olDBS attenuated pathological beta fluctuations while improving FOG [9]. In this paper, we demonstrate preliminary evidence that clDBS driven by STN beta band power was superior to conventional olDBS in reducing the percent time freezing during a stepping in place task on dual force plates.

1.3 Methods

Two male participants with PD and FOG symptoms participated in the study. Both participants were implanted with an investigative sensing neurostimulator (Medtronic Activa® PC+S, FDA IDE approved) and bilateral STN DBS leads (Medtronic model 3389). All procedures were approved
by the Stanford University Institutional Review Board and participants provided informed written consent.

Participants performed a stepping in place (SIP) task [10] during three stimulation conditions: off DBS (OFF), on open-loop DBS (olDBS), and on closed-loop DBS (clDBS). All testing was performed in the off medication state (refrained for 12 hours for short- and 24 and 48 hours for long-acting dopaminergic medication). The clDBS was modulated by the power of the local field potentials contained in beta frequency range (13-30 Hz) [6]. The dual threshold control algorithm parameters (beta thresholds) were determined from beta band power during movement as opposed to during the resting state. Movement band beta power was measured during voltage titration in 5 voltage increments performed between 0 and 100% of V_{Max} while stepping in place. The movement bandwidth was 3-4 Hz around the peak frequency of elevated beta band power during SIP [9], [11]. The maximum voltage that provided clinical improvement without side effects (V_{Max}) in each STN was determined for each participant. A single beta threshold was used for Participant 1 based on the movement band power measured at 0% and V_{Max} for the left and right STNs, respectively. The upper and lower values of the dual threshold controller for Participant 2 were set to the average beta measured during the stepping in place task at V_{Max} (upper threshold) and the minimum voltage (V_{Min}) that showed improvement in stepping and freezing behavior (lower threshold, 25% of V_{Max}). For Participant 1, the stimulation settings for olDBS were set to V_{Max} for each STN, while the settings of olDBS for Participant 2 were set to the average voltage observed in each STN during the clDBS condition.
Freezing events were detected offline using an automated algorithm [10]. FOG and freezing behavior were assessed using the percent time freezing during the task and SIP arrhythmicity (coefficient of variation (CV) of stride time), respectively. Total electrical energy delivered (TEED) was calculated for both oDBS and cDBS using the following equation:

\[
TEED = \frac{V^2 p f t}{Z}
\]

where \( V \) = stimulation voltage, \( p \) = stimulation pulse width, \( f \) = stimulation frequency, \( t \) = time, and \( Z \) = electrode impedance.

1.4 Results

Both participants experienced FOG in the off-stimulation (OFF) condition as their stepping behavior began to break down (i.e., loss of force modulation), Figure 1A and B.
Figure 1: Stepping in place vertical ground reaction force traces for Participant 1 (left) and Participant 2 (right) off simulation, on open loop stimulation, and on neural adaptive closed loop stimulation. FOG events detected by the algorithm [10] are indicated by the vertical green lines. % time freezing and arrhythmicity are presented above each condition.

During olDBS there was improvement in the duration of normal stepping but FOG episodes were still detected for both participants, Fig. 1C and D. During cDBS, no FOG was detected for Participant 1, Fig. 1E, and only a short start hesitation episode was detected for Participant 2, Fig. 1F. The percent time freezing was: 36.4% OFF DBS, 0.94% during olDBS, and 0% during cDBS for Participant 1, and: 68.7% OFF DBS, 23.5% during olDBS, and 1.5% during cDBS for Participant 2.

SIP arrhythmicity also improved during DBS, with Participant 1 having slightly more improvement.
during clDBS compared to olDBS (Participant 1: 30.4% OFF, 16.3% olDBS, 15.6% clDBS; Participant 2: 20.4% OFF, 10.4% olDBS, 13.1% clDBS). In addition to the improvements in behavior, TEED was lower in the clDBS conditions compared to olDBS, with a larger reduction being observed in Participant 2 (Participant 1: 5%, Participant 2: 46%).

1.5 Discussion

These findings, to the best of our knowledge, are the first to demonstrate that neural closed-loop stimulation (clDBS) was superior to open loop DBS (olDBS) and no stimulation (OFF) in reducing FOG in PD. Freezing behavior, manifesting as arrhythmic stepping and lack of maintaining a consistent rate of force/amplitude control during stepping (i.e., the “sequence effect”[12], [13]), also improved more during clDBS compared to olDBS and OFF DBS. Interestingly, similar improvements were observed using both a single (Participant 1) and dual-threshold (Participant 2) algorithm aside from a larger reduction in TEED using the dual threshold algorithm compared to the single threshold algorithm. Future investigations should evaluate how much the system needs to adapt to maintain a therapeutic effect while also minimizing the energy needed.

The most dramatic effects observed in this study were the decrease in FOG and improvement in sustained stepping by clDBS, especially compared to conventional olDBS. These findings suggest that allowing the stimulation to adapt during the trial may allow the motor system to sustain or regain movement control, whereas continuous stimulation cannot prevent the “sequence effect” [12] because it is not changing in response to the oscillations of neural activity in the STN. Overall,
these findings warrant further investigation into the use of cDBS for improving FOG as well as other Parkinsonian symptoms.

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1.7 References

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