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Improving Postural Stability via Computational Modeling Approach to Deep Brain Stimulation Programming

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***Abstract*— Bilateral subthalamic (STN) deep brain stimulation (DBS) is generally effective in improving the cardinal motor signs of advanced Parkinson's disease (PD). However, in many cases postural instability is refractory to STN DBS. The goal of this project was to determine if postural instability could be improved with STN DBS by avoiding current spread to the non-motor territories of the STN. Stimulation parameters that maximized activation of a theoretically defined target region were determined via patient-specific computer models created in Cicerone. Postural stability was assessed under three conditions: Off DBS, Clinical DBS, and Model DBS. Clinical settings were the patients' DBS settings determined via traditional clinical practice and were considered optimized and stable for at least 6 months prior to study enrollment. Blinded and randomized evaluations were performed in five patients. Postural sway was significantly less during Model DBS compared to Clinical DBS. These results support the hypothesis that minimizing spread of current to non-motor territories of the STN can improve PD related instability with DBS.**

I. Introduction

Deep brain stimulation (DBS) in the subthalamic nucleus (STN) improves rigidity, bradykinesia and tremor for advanced Parkinson's disease (PD) patients [1]. However, data indicate a progressive decline in gait and postural instability scores following DBS that do not appear to be due to progression of the disease. Given the limitation of current therapies to adequately manage postural instability in patients with PD, a new surgical target, the pedunculopontine nucleus (PPN), has emerged. Currently, only limited and, in some cases, controversial data concerning the beneficial effects of PPN DBS on parkinsonian motor symptoms exist [2].

Recently, we have shown that DBS related cognitive declines can be reduced by avoiding spread of current to non-motor portions of the STN [3]. By minimizing cognitive declines, upper extremity motor function was improved under dual-task conditions (e.g. simultaneous performance of a cognitive and motor task). Maintaining a steady posture requires cognitive processing and is a cognitive-motor dual-task. Therefore, we hypothesized that DBS related cognitive declines may be interfering with the effectiveness of STN DBS in the treatment of PD postural instability. The aim of this study was to examine whether STN DBS could improve postural stability using a neurocomputational modeling approach to DBS parameter selection. It was predicted that minimizing the spread of current to the non-motor territories of the STN would free up cognitive resources that could be allocated to maintaining a steady posture.

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II. Methods

Five participants with advanced PD between the ages of 51 and 67 years (mean 57.6) with bilateral STN DBS participated in this study. Despite improvements in motor symptoms with their clinically defined DBS parameter settings, patients continued to experience postural instability. Clinical stimulation parameters had been determined through traditional clinical methods and were being used and were stable at least six months prior to study participation. Model parameters were determined using Cicerone DBS software [4], as described previously [3]. A representative patient-specific DBS model and the volume of tissue activated (VTA) in the subthalamic region with Clinical DBS and Model DBS parameters is provided in Figure 1.

Biomechanical data and blinded UPDRS-III evaluations were completed on three separate experimental sessions: Off, Clinical DBS, and Model DBS. Working memory was assessed with the n-back task. The n-back was administered at the 2-back level of difficulty. The percentage of letters responded correctly for each trial was the primary cognitive outcome.

Participants stood barefoot on the force platform (Kistler Instruments Corp., Winterthur, Switzerland) and were instructed to maintain an upright standing position while fixating on a static target 3.8 meters away from them. Ground reaction forces were recorded during three 60 second trials of quiet standing while completing the working memory task (i.e. dual-task). Quantitative analysis of the posturographic signal was performed by calculating the elliptical area of displacement, averaging three trials for each condition, known as the mean center of pressure (COP).

Three dual-task blocks were performed at random for each DBS condition in which the n-back task and postural stability task were completed simultaneously. The postural stability task was performed with three repetitions of the 2-back task. The participants were instructed to give equal importance to both tasks.

Repeated measures ANOVA was used to assess the main group effect. Paired sample t-tests were used to assess differences between the DBS conditions for clinical ratings (UPDRS-III), postural stability (COP area) and cognitive performance (percentage of correctly repeated letters).

III. Results

For all patients, the blinded UPDRS-III scores decreased with Clinical DBS and Model DBS compared with Off stimulation. Results from the repeated measures ANOVA revealed that both Clinical DBS and Model DBS resulted in a significant improvement, 30% reduction, in UPDRS-III ratings compared to Off DBS [P = 0.003].

During the n-back sequence for the dual-task, Model DBS yielded the best performance with 89 percent of correct repeated letters as compared to 88 percent for Clinical DBS and 87 percent Off DBS.

The average COP area was the significantly better under Model DBS ($3.78 cm^2$) compared to $4.54 cm^2$ under Clinical DBS [P = 0.022] and $5.96 cm^2$ Off DBS. Representative trials of the average COP area under each condition as well as the elliptical area of displacements are given in Fig 1.

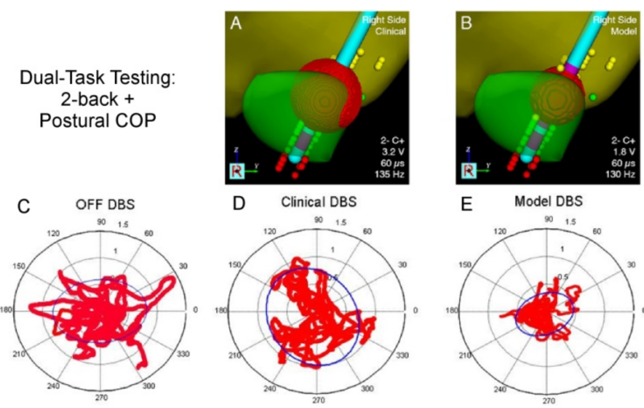

Fig. 1. Patient-specific model and dual-task performance. Representative example from one subject. A, B) 3D brain atlas was fit to match the patient's neuroanatomy (yellow volume – thalamus; green volume – subthalamic nucleus). Stereotactic locations of intra-operative microelectrode recordings (thalamic cells – yellow dots; subthalamic cells – green dots; substantia nigra cells – red dots). The DBS electrodes were positioned based on stereotactic coordinates and their anatomical locations were verified by post-operative imaging data. A) Right side clinical settings: contact 2, 3.2 V, 0.06 ms, 135 Hz. B) Right side model settings: contact 2, 1.8 V, 0.06 ms, 130 Hz. The red volume depicts the volume of tissue activated. C,D,E) Movement of the total body center of mass (red line) and center of pressure excursion (blue oval) is shown for each of the DBS conditions.

IV. Discussion

The current data indicate that under conditions that resemble those in the "real world" in which multi-tasking must be completed, postural stability was better with Model stimulation parameters compared to Clinical DBS parameters in patients with DBS refractory postural instability. Additionally, cognitive performance (working memory) was similar but slightly better under this type of dual-task condition with Model DBS compared to Clinical DBS. The clinical assessments of the patients indicated both methods of programming are effective in improving motor symptoms.

Activities of daily living generally require both cognitive and motor components be performed simultaneously, maintaining a steady posture and gait are no exception. Because of the cognitive declines resulting from STN DBS in advanced PD patients, routine daily activities that are comprised of a motor and cognitive component may be challenging. It is possible that the cognitive side effects of STN DBS require the patient to allocate greater attentional resources to cognition which compromises motor functioning or in many cases postural stability.

This study has presented the possibility that patients were allocating more attention to the cognitive part of the task, hence cognitive performance was similar across all DBS conditions. However, the postural stability measures were worse with Clinical DBS and while Off DBS compared to Model DBS parameters. The current data suggest that minimizing the spread of current to the non-motor areas of the STN, thereby diminishing cognitive declines, may allow the patients to more effectively divide attentional resources to both motor and cognitive portions of a task. No change of cognitive function across conditions may indicate that patients were more focused on the cognitive task as the risk of falling was essentially zero since they were secured in an overhead harness

The PPN has emerged as a potential new target in the treatment of postural instability associated with PD. However, the current data suggest that STN DBS has not fully been exploited for the treatment of postural instability of advanced PD patients. A computational modeling approach to improve STN DBS programming may offer a solution for optimizing currently used techniques rather than attempting to stimulate a difficult target such as the PPN.

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