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Customizing Deep Brain Stimulation to the Patient Using Computational Models

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Abstract

Bilateral subthalamic (STN) deep brain stimulation (DBS) is effective in improving the cardinal motor signs of advanced Parkinson's disease (PD); however declines in cognitive function have been associated with this procedure. The aim of this study was to assess cognitive-motor performance of 10 PD patients implanted with STN DBS systems during either clinically determined stimulation settings or settings derived from a computational model. Cicerone DBS software was used to define the model parameters such that current spread to non-motor areas of the STN was minimized. Clinically determined and model defined parameters were equally effective in improving motor scores on the traditional clinical rating scale (UPDRS-III). Under modest dual-task conditions, cognitive-motor performance was worse with clinically determined compared to model derived parameters. In addition, the model parameters provided a 33% reduction in power consumption. These results indicate that the cognitivemotor declines associated with bilateral STN can be mitigated, without compromising motor benefits, utilizing stimulation parameters that minimize current spread into non-motor regions of the STN.

I. Introduction

BIlateral subthalamic (STN) deep brain stimulation (DBS) provides significant symptom relief for the majority of well screened advanced Parkinson's disease (PD) patients [1]. However, bilateral STN DBS can also result in significant declines in the cognitive-motor performance of PD patients [2]. The spread of current to non-motor areas of the STN or adjacent structures has been implicated in cognitive and cognitive-motor declines.

While guidelines exist on stimulation parameter settings that are typically effective, it is not practical to clinically evaluate each of the thousands of possible stimulation parameter combinations. Therefore, the therapeutic benefit achieved with DBS is currently dependent on the intuitive skill and experience of the programming clinician. To assist the clinical programming process, we recently developed Windows-based software tools that enable 3D visualization of the volume of tissue activated (VTA) by DBS [3].

The goals of this study were: 1) assess cognitive-motor performance under clinically determined stimulation parameters in 10 STN DBS PD patients, 2) use computer models to define theoretically optimal stimulation parameters for each patient and 3) compare the effectiveness of the clinical and model derived parameters on cognitive-motor performance.

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Conflicts of Interest: CCM authored intellectual property related to the DBS software. CCM is a shareholder in and paid consultant to IntElect Medical Inc, and paid consultant to Boston Scientific Corp. AMN is a paid consultant to IntElect Medical Inc.

II. Methods and Results

Ten PD patients, implanted with bilateral STN DBS systems at least 1 year prior to study participation, were enrolled. Each patient's stimulation parameters were optimized by traditional clinical methods. With clinical parameter settings, the average improvement the in Unified Parkinson's Disease Rating Scale Motor Subscore (UPDRS-III) was 46%.

Patient-specific computational models were developed with Cicerone [3] and included coupled integration of magnetic resonance imaging data, intra-operative microelectrode recording data, 3D brain atlases, DBS electrode locations, and VTA predictions all co-registered into the neurosurgical stereotactic coordinate system [4] (Figure 1). The models were created without any a priori knowledge of the patient's clinical symptoms, drug regiment, clinical DBS programming notes, or clinically defined therapeutic stimulation parameter settings. The VTA predictions were used to define stimulation parameter settings for both sides of the brain to maximize current spread into the dorsal STN and white matter dorsal to this region of the STN, areas associated with optimized therapeutic benefit [4], while minimizing current spread into non-motor portions of the STN. The model derived parameters required on average 33% less power than the clinical settings, but also resulted in a 46% average improvement in the UPDRS-III.

Cognitive-motor performance was quantified using a dual-task paradigm [2], which consists of the simultaneous performance of a working memory task (n-back) and force-tracking (FT) task with the dominant limb. Each patient completed 15 dual-task trials while Off DBS and with their clinical and model parameter settings. The primary motor outcome variables for the force-tracking task were time within the target range (TWR) and relative root mean square error (RRMSE). Experimental testing with either the clinical or model settings was performed on separate days. For both sessions, participants reported to the laboratory off anti-parkinsonian medication (i.e. at least 12 hours since their last dose). The order of testing clinical or model DBS parameters was randomized across patients.

During simple dual-task conditions (FT + 0-back) there were no statistical differences between off, clinical, or model DBS. As task difficulty increased, working memory declined significantly while the patient was either off DBS or stimulated with clinically determined parameters. Model derived parameters resulted in significantly better ($P<0.001$) force-tracking during the 2-back dual-task conditions than clinical DBS.

III. Discussion

The aim of this study was to assess cognitive-motor performance during clinically determined stimulation settings and settings determined through computational modeling. Both methods of programming produced a significant improvement in clinical rating of PD symptoms. However, under modestly demanding dual-task conditions clinical parameters resulted in poorer cognitive (working memory) and motor (force-tracking) performance compared to model derived stimulation parameters. A possible explanation for the cognitive-motor declines observed with clinical parameters is unintentional spread of current to non-motor areas of the STN. Given its small size, stimulation within the STN can result in spread of current to limbic and associative areas as well as to surrounding structures and fiber systems that may affect cognitive function [4].

Disruption of information processing in the non-motor regions of STN may not produce a detectable deficit in cognitive function when patients are able to focus all of their attention on the performance of a single cognitive or motor task; as is the case during typical clinical examinations. However, as cognitive task and information processing demands increase, patients may attempt to draw on cognitive resources that are compromised as a result of the

stimulation induced disruption of non-motor pathways. This issue may be exacerbated by a loss of redundancy of these circuits with bilateral DBS. These preliminary data suggest that using visualization software to augment the stimulation parameter selection process can mitigate cognitive declines without compromising improvements in motor function.

Acknowledgments

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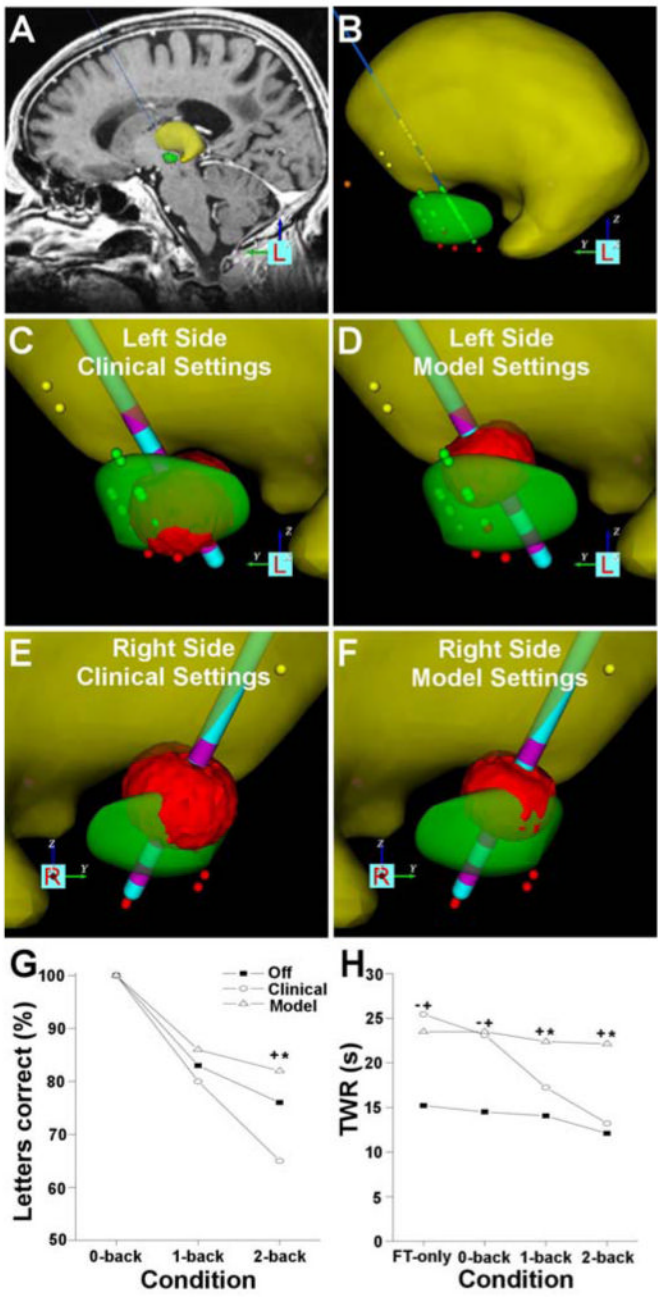

Fig. 1.

Patient-specific model and dual-task performance. Representative example from one subject. A) 3D brain atlas was fit to match the patient's neuroanatomy (yellow volume – thalamus; green volume – subthalamic nucleus). B) 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. C) Left side clinical settings: contact 1, 3.2 V, 0.06 ms, 185 Hz. D) Left side model settings: contact 2, 2.4 V, 0.06 ms, 130 Hz. E) Right side clinical settings: contact 2, 3.2 V, 0.06 ms, 185 Hz. F) Right side model settings: contact 2, 2 V, 0.06 ms, 130 Hz. G) Results of the n-back task during dual-task condition while off DBS (filled squares), clinical parameter

settings (open circles) and model defined parameter settings (open triangles). H) Results of the time within ±2 percent of the target force during single task force-tracking only (FT only) and dual-task (FT + n-back task) while off DBS, clinical parameters and model defined parameters. A cross designates a significant difference between model-derived and off DBS, an asterisk marks a significant difference between model and clinical DBS and a dash represents a significant difference between clinical DBS and off DBS.