Deep Brain Stimulation of the Subthalamic Nucleus: Patient-Specific Analysis of the Volume of Tissue Activated

Butson CR, Cooper SE, McIntyre CC

1 Cleveland Clinic Foundation, Department of Biomedical Engineering, Cleveland, OH, USA
2 Cleveland Clinic Foundation, Center for Neurological Restoration, Cleveland, OH, USA

E-mail: butsonc@ccf.org

Abstract

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has rapidly emerged as an effective treatment for Parkinson's disease (PD). However, our understanding of the neural response to DBS is limited, and the mechanisms by which DBS achieves its therapeutic effects remain a mystery. We have developed detailed computational tools to study the effects of DBS on a patient-specific basis. We combine diffusion tensor based finite element models of the electric field with 3D anatomical models of nuclei surrounding the electrode to predict the effects of electrode location and stimulation parameter adjustments on the volume of tissue activated (VTA). We compare the model results to clinical evaluations to establish correlations between the VTA and the therapeutic effects of DBS. Our results show that therapeutic STN DBS is characterized by a VTA that spreads well outside the borders of the STN; however, VTA spread into the internal capsule and thalamus is correlated with side effects including paresthesias and exacerbated bradykinesia. We are currently building a database of model and clinical results from a cohort of STN DBS PD patients. The goal of this research is to provide theoretical tools to augment pre-operative targeting and post-operative stimulation parameter selection strategies.

1. INTRODUCTION

The fundamental purpose of DBS is to modulate neural activity with extracellular electric fields, but the technology necessary to accurately predict and visualize the neural response to DBS has not been previously available. In turn, the current state-of-the-art in pre-operative targeting strategies and post-operative parameter selection processes do not take into account the influence of the electric field generated by the DBS electrode on the surrounding neural structures. DBS systems provide thousands of possible stimulation configurations, resulting in great flexibility in customization of therapy for individual patients, but at the expense of time-consuming clinical evaluation to determine therapeutic stimulation settings [1]. As a result, DBS patient management is primarily based on trial-and-error as opposed to quantitative understanding. To address these limitations, we have developed techniques to accurately model the electric field and its effects on the nervous system utilizing a combination of diffusion tensor based finite element models of the electric field and 3D magnetic resonance (MR) based brain atlases (Fig. 1). This paper presents the application of our technology to the study of a PD patient treated with STN DBS.

Figure 1: Model of STN DBS. A) DBS systems are permanently implanted with a pulse generator in the chest and a four contact electrode stereotactically placed in the brain. Post-operative MR is used to identify STN and local structures, as well as electrode location. B) Axial slice of the diffusion tensors co-registered with the anatomical volumes. The red to blue color coding of the diffusion tensor data represent high to low degrees of anisotropy, respectively. C) VTA (red volume) predicted by the integrated model for specific stimulation settings.
2. METHODS

Our models of DBS consist of three co-registered components: Anatomical Model, Electrical Model, and Stimulation Prediction (Fig. 1). A 3D brain atlas is used to localize the STN and thalamus relative to the electrode from magnetic resonance images to define the Anatomical Model. 3D tissue anisotropy and inhomogeneity are incorporated into the Electrical Model using conductivity tensors derived from diffusion tensor images [2,3]. VTAs are calculated with integrated stimulation prediction techniques that combine finite element based electric field solutions with multi-compartment cable models of myelinated axons [2,3,4] (Fig. 2). The Poisson equation is solved with a Fourier FEM solver [5] to determine voltage as a function of time and space within the tissue medium. The voltage solution is subsequently interpolated onto the model neurons to determine stimulation thresholds for action potential generation. Activating function values are then defined from the second difference of the voltage solution ($\frac{\partial^2 V_e}{\partial x^2}$) and used to provide a spatial map for VTA prediction.

Our hypothesis is that therapeutic effects of STN DBS are correlated with activation of the dorsomedial aspect of STN; side effects are correlated with activation of thalamus and internal capsule. Side effects (muscle contractions) as well as bradykinesia and rigidity are measured using a Prochazka device on the dominant hand of PD patients under a range of stimulation settings, and the corresponding VTAs are generated in the model to evaluate the validity of our hypothesis.

3. RESULTS

Clinical evaluation of an example subject showed monotonic improvement in rigidity with increasing voltage up to -4V (Fig. 3). In contrast, bradykinesia showed an inverted U-shaped curve, with an optimal voltage around -1V to -2V at the therapeutic electrode contact. At higher voltages bradykinesia was exacerbated, eventually reaching levels worse than with no stimulation. These effects are
consistent with the VTAs observed for this patient (Fig. 4). At -1V to -2V the VTAs show activation primarily of the dorsomedial aspect of the STN (including zona incerta). At -3V to -4V stimulation we observed substantial spillover into internal capsule and thalamus.

4. DISCUSSION AND CONCLUSIONS

The results of this study provide direct correlations between model stimulation predictions and clinical results for DBS. We believe coupling our modelling framework to clinical analysis represents an exciting new direction to improve the scientific understanding of the effects of DBS in humans. In addition, we are currently evaluating the potential for our theoretical tools to augment standard clinical implementation of DBS technology by providing visual aid and predictive power to pre-operative targeting and post-operative stimulation parameter selection strategies.

Stimulation of the dorsomedial aspect of STN has previously been associated with therapeutic effects of DBS [6]. The monotonic improvement of rigidity with increasing voltage corresponds with increasing VTA coverage of the sensorimotor region (dorsal) of the STN (Fig. 4). The inverted U-shaped result for bradykinesia can be associated with spillover into internal capsule resulting in competing activation of a large subset of muscles hindering control of the arm. However, conclusions based on a single patient are of limited value. Therefore, we are currently evaluating results from a cohort of 10 STN DBS PD patients to provide statistical analysis of the VTA (size, shape, location) and corresponding clinical measurements.

References

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