PUR Research Proposal for Summer 2021

Effect of white matter stimulation on clinical outcomes in thalamic deep brain stimulation for essential tremor

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Research Duration: 10 weeks (May-Aug 2021)

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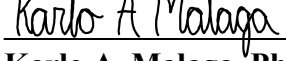

Karlo A. Malaga, Ph.D.

I. Background

Essential tremor (ET) is one of the most prevalent movement disorders, where individuals suffer from action or postural tremors of the hands. Many ET patients, therefore, are not able to engage in basic daily routines, such as eating, drinking, and writing. [1] Moreover, approximately 5% of adults 60 years of age or older suffer from ET.[1] While there are lines of pharmacological treatments and thalamotomy procedures that are used to treat ET patients, only 50% of them observe improvement in their condition.[1] Deep brain stimulation is a surgical therapy that involves implanting small electrodes deep within specific regions of the brain that correspond to certain motor functions and then stimulating those regions with continuous pulses of electricity that are controlled by a programmed brain pacemaker.[1] Thus, ET treatment-resistant patients undergo deep brain stimulation (DBS) of the ventral intermediate (VIM) nucleus of the thalamus, which is the traditional target structure.[1]

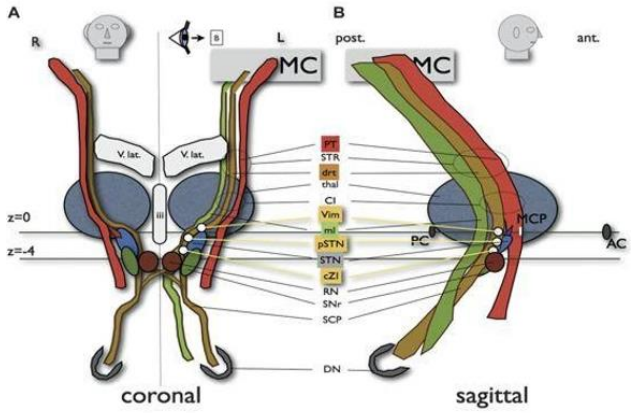

Figure 1. Coronal and sagittal view of the DRT (orange tract) and VIM topography. [2]

The dentato-rubro-thalamic tract (DRT) is a white matter tract near the VIM (Fig 1). The DRT interconnects the three conventional target sites: VIM, posterior subthalamic nucleus (pSTN), and caudal zona incerta (cZI) for treating various motor disorders. Hence, the electric field from VIM stimulation likely spreads to DRT fibers. Previous research suggests that the DRT is a better DBS target than the VIM for essential tremor.[2] However, results are typically reported on a case-by-case basis. [2] Therefore, more clinical data is necessary to validate this claim.

II. Research Value

Previous studies on VIM-DBS yielded relatively successful clinical outcomes with minor side effects. However, VIM-DBS has been found to lose efficacy over 10 years, ultimately leading to rebound of ET symptoms. [3] Thus, there is active research on targeting other gray matter (GM) sites in the brain such as the posterior subthalamic area and the subthalamic nucleus, to treat ET.[4] Since the DRT connects these GM structures, it has been identified as a potentially superior surgical target for treating essential tremor with DBS. Since the DRT is a subset of the Internal Capsule (IC), there are multiple fiber tract types near the DRT (Fig. 1). Hence, creating an anatomically accurate model of the DRT using fiber tractography is challenging. For the scope of this research project, I will focus on the IC in its entirety as the target of interest rather than the DRT specifically.

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[1] Lyons, K. E., & Pahwa, R. (2008). Thalamic Deep Brain Stimulation and Essential Tremor. *Deep Brain Stimulation in Neurological and Psychiatric Disorders*, 205–214. doi: 10.1007/978-1-59745-360-8_10

[2] Coenen, V. A., Allert, N., Paus, S., Kronenbu¨rger, M., Urbach, H., &Ma¨dler, B. (2014). Modulation of the Cerebello-Thalamo-Cortical Network in Thalamic Deep Brain Stimulation for Tremor. *Neurosurgery*, *75*(6), 657–670. doi:10.1227/neu.0000000000000540

[3] Paschen, S., Forstenpointner, J., Becktepe, J., Heinzel, S., Hellriegel, H., Witt, K., Deuschl, G. (2019). Long-term efficacy of deep brain stimulation for essential tremor. *Neurology*, *92*(12).doi:10.1212/wnl.0000000000007134

[4] Nazzaro JM, Lyons KE, Pahwa R. Deep brain stimulation for essential tremor. Handb Clin Neurol. 2013;116:155-66. doi: 10.1016/B978-0-444-53497-2.00013-9. PMID: 24112892.

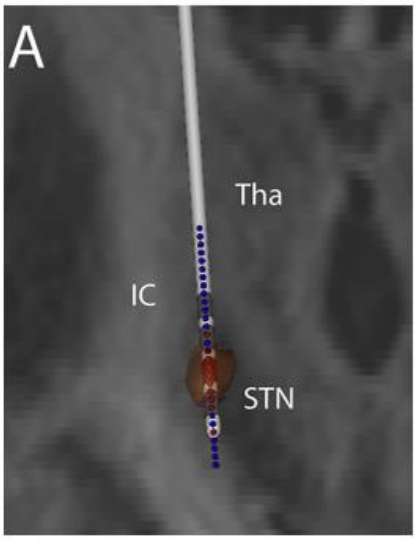

Figure 2. Clinically effective volume of tissue activation (VTA) estimated using DBS modeling. [5]

One way to study the location of stimulation within the brain is through the creation of volume of tissue activation (VTA) models.[5] These models use anatomical and tissue conductivity information to calculate a patient's stimulation profile. One of the limitations of VTA modeling is the common assumption that the conductivity is homogenous and isotropic (direction independent) throughout the target site.[2]

Dr. Malaga's work uses finite element analysis to model patient-specific VTAs, whereby patients' own medical imaging is used to model the VTA by STN-DBS (Fig. 2).[6] In my proposed research, I will use the same technique to investigate the VTA in VIM-DBS. The electrical conductivity of the brain tissue will be anisotropic and patient-specific.[6] The patient-specific modeling is assumed to produce more accurate results and the VTAs can be validated against the clinical outcomes of each patient. Hence, the assumption of the brain conductivity being an established uniform throughout the brain can be eliminated.

DBS is surgical therapy for movement disorders such as Parkinson disease and dystonia. However, DBS also has the potential to treat other cognitive disorders such as major depression and obsessive-compulsive disorder. Therefore, the white matter (WM) modeling technique from this research can be applied to modeling the fiber tracts involved in DBS for other cognitive disorders. Ultimately, this research will contribute to determining the optimal amount of WM and GM stimulation for treating ET patients with DBS.

III. Proposed Research

I received the PUR award in Fall 2020, but the funding was rescinded due to COVID-19. Despite summer research being cancelled, I still worked on my project over the summer and during the fall semester. The goal of my Summer 2021 research is to analyze how the spread of stimulation to WM during VIM-DBS relates to therapeutic and non-therapeutic outcomes of the ET patients. This research project will be a retrospective study using the de-identified data from ET patients that received DBS at the University of Michigan (i.e., all the clinical data that I need has been acquired).

Phase One: Develop algorithm to extract relevant clinical data and differentiate WM and GM (1 week)

I have designed a preliminary algorithm in MATLAB that can extract the Diffusion Tensor Imaging (DTI) data of the target structures from that of the whole brain. The algorithm uses three features to differentiate WM and GM based on anisotropy (Fig. 3). I have analyzed the features using two-sample t tests to ensure that they are robust enough for WM/GM classification. For the Summer 2021, I will be training and testing the algorithm with ET patient datasets (n=22).

[5] Lu, C. W., Malaga, K. A., Chou, K. L., Chestek, C. A., & Patil, P. G. (2020). High density microelectrode recording predicts span of therapeutic tissue activation volumes in subthalamic deep brain stimulation for Parkinson disease. *Brain Stimulation*, *13*(2), 412–419. doi: 10.1016/j.brs.2019.11.013

[6] Malaga, K. A., Costello, J. T., Chou, K. L., & Patil, P. G. (2021). Atlas-independent, n-of-1 tissue activation modeling to map optimal regions of SUBTHALAMIC deep brain stimulation for Parkinson disease. *NeuroImage: Clinical, 29*, 102518. doi:10.1016/j.nicl.2020.102518

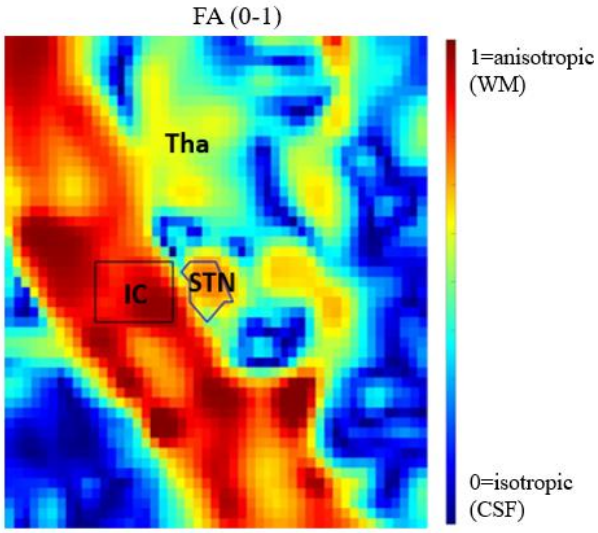

Figure 3. Color map of Fractional Anisotropy (FA) values in region of interest. WM is highly anisotropic and Cerebrospinal fluid (CSF) is highly isotropic. WM (internal capsule, IC) and GM (thalamus, Tha; subthalamic nucleus, STN) structures are labeled.

Phase Two: Generate the ET patient-specific WM model (2 weeks)

High-resolution magnetic resonance imaging (MRI) and DTI data from patients with ET will be used to model the patient-specific WM. Since DTI images have already been processed, the WM can be modeled for each patient (n = 22).

Phase Three: Create 3D finite element modeling of both therapeutic and non-therapeutic DBS (3 weeks)

3D finite element models of therapeutic and non-therapeutic DBS will be constructed for each patient in COMSOL by incorporating the DBS lead and clinically determined stimulation parameters. These models will allow me to determine the spatial distribution of the electric field surrounding the active electrode during DBS.

Phase Four: Calculate and analyze tissue activation volumes (3 weeks)

VTAs will be generated for each patient in COMSOL using the technique from Dr. Malaga's previous work.[5] VTAs will be used to calculate the amount of WM and VIM activation. I will analyze the percentage overlap between VTAs from DBS with the volume of WM stimulation for all patients. By analyzing the results of the percentage overlap, I will be able to determine the optimal amount of WM and GM stimulation to achieve therapeutic outcomes.

Phase Five: Conclude and prepare for presentation (1 week)

I will compile all the data, code, and results to complete a final report and an abstract for upcoming conferences and symposiums.

IV. Research Presentation

The project will be presented at the Kalman Research Symposium. I will also submit my abstract to the Biomedical Engineering Society (BMES) to potentially be able to present my research at the 2021 BMES National Conference.

V. Faculty Mentoring Relationship

Both Dr. Malaga and I will be in Lewisburg for the 10-week duration of the research. Dr. Malaga and I will meet weekly to monitor the progress and plan accordingly. All the required data will be obtained from Dr. Malaga. The software programs, such as COMSOL and MATLAB, are available in Dr. Malaga's medical computational modeling lab and on my personal computer for possible remote work. By undertaking this neuromodulation research, I will gain deeper insight into the intersection of the biomedical engineering and neuropsychology fields. The PUR experience will allow me to apply the knowledge I have gained in my engineering and neuropsychology classes. Upon completion of my undergraduate degree, I plan to pursue graduate school with a concentration in neural engineering. I am confident that this research experience will serve as an extraordinary step towards realizing my goal.