Title: Physiology, Imaging and Modeling of Essential Tremor

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Physiology, Imaging and Modeling of Deep Brain Stimulation for Essential Tremor

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We aim to evaluate active-recharge biphasic deep brain stimulation (DBS) and to develop methods to study novel waveforms in patients with DBS refractory tremor. DBS is an effective surgical therapy for many medically refractory movement disorders such as essential tremor (ET), Parkinson's disease (PD), and dystonia. However, despite being highly efficacious, a portion of severe tremor patients will experience a suboptimal response or a progressive worsening of symptoms.

Patients with existing unilateral or bilateral ventralis intermedius nucleus (VIM) DBS with documented suboptimal tremor suppression on at least two successive clinic visits to a movement disorders neurologist will be recruited for this study. Patients will be scheduled for a research visit in which their DBS implantable pulse generator (IPG) will be flashed with a temporary custom firmware that will allow active biphasic pulse stimulation. The following random conditions will be applied: (1) home settings; (2) VIM biphasic; (3) stimulator off. A 30-minute washout period will be applied between each of the random conditions. During each random condition, tremor will be quantified by blinded rater using the Fahn–Tolosa–Marin Tremor Rating Scale (TRS) and by analysis of accelerometer using the Kinesia ONE® accelerometer system. Gait will be assessed by digital mat (GAITRite®).

We will study advanced physiology, imaging, field modeling and clinical outcomes to assess novel DBS waveforms and to construct a future NIH K award. We hypothesize that the use of novel waveforms such as active biphasic pulse stimulation will provide enhanced therapeutics compared to conventional DBS pulse stimulation and that by using advanced techniques we will better understand the circuitry and mechanism of action underpinning DBS. These methods, once developed, will be applied to expand the use of firmware updates across other neuromodulation targets and disorders as well as applied for the treatment of clinically relevant symptoms.

Research Plan

Background

Deep brain stimulation (DBS) is a neuromodulatory therapy that is effective in a subset of well selected essential tremor (ET) patients [1]. However, as many as 1/5 patients may initially improve and but then steadily worsen following the operation. For these patients, multiple strategies have been employed but success rates have been variable. Currently, the three primary approaches are 1) invoke high current density DBS programming parameters 2) surgically replace the DBS lead which is referred to as a "lead revision" or 3) surgically implant a second lead which is referred to as a "rescue lead". These options are limited by stimulation-induced side effects and by neurosurgical intervention. Thus, there are currently no solutions for the 1/5 post-ET

DBS patients with progressively worsening tremor.

Recent studies by our group have explored the use of non-conventional DBS stimulation for Parkinson's disease (PD) and ET in the clinic setting [2]. By utilizing our established protocol, we have developed a technique to study a variety of alternative stimulation methods without the use of an invasive repeat surgical intervention.

This study will build upon the parent R01 grant of Dr. Michael Okun (1R01NS096008-The Human Thalamocortical Network). The parent grant seeks to explore the underlying electrophysiology of the corticostriatal and thalamocortical circuits as related to Tourette Syndrome (TS). The Okun study utilizes intraoperative electrocorticography (ECoG) recording a well as local field potential (LFP) recording to characterize the aberrant network pathways in TS. The LFP recordings can also now be obtained in the outpatient setting.

The electrophysiological effects of non-conventional DBS differ from traditional DBS, however the physiological differences in the setting of human tremor remain largely unknown. Several studies have suggested potential clinical benefit with nontraditional programming and atypical DBS pulse shapes [3-7]. In this study, we plan to explore this gap in our knowledge of neuromodulation and we will collect and contribute essential information to the underlying mechanism of action of DBS. Our hypothesis is that active biphasic stimulation will provide a wider therapeutic window and a lower adverse event profile as compared to conventional DBS.

Study Design (n=50 total patients; n=25 in Aim 1 and n=25 for Aims 2-3):

Aim 1: Will be observational study of 25 ET patients undergoing initial DBS implantation. These patients will provide the preliminary physiology dataset for the future K23 grant. The K23 will allow more time for simultaneous study of the same cohort, but for this R25 the cohort for Aim 2 and 3 will be separate.

Aims 2+3: There will be a second group of 25 already implanted ET DBS patients utilized for these two aims. These patients will be enrolled in a randomized double-blind pilot study targeting patients with chronically implanted DBS devices for ET who experience progressive worsening of tremor symptoms over time.

Approach Specific Aim 1: Record and characterize the human cerebello-thalamo-cortical physiology in ET across multiple nodes of the cerebello-thalamo-cortical pathway.

We will intraoperatively record oscillatory activity in the thalamo-cortical pathway and model the neural network physiology. We will record post-operative LFPs and model the physiology in the tremor network. This will be an independent cohort of 25 patients separate from Aims 2+3.

Approach to Specific Aim 2: Image the thalamo-cortical circuitry during tremor suppression in DBS

This will be a separate cohort of 25 patients from Aim 1. We will image the network using DTI techniques and we will correlate to clinical outcomes (aim 3). We will

determine the feasibility of imaging to optimize the DBS targets.

Specific Aim 3: Model and test outcomes for novel stimulation patterns and waveforms in ET DBS.

This will be the same cohort as Aim 2. We will model multiple novel stimulation patterns (e.g. biphasic waveforms). We will calculate the volume of tissue activated (VTA) from the novel stimulation patterns. We will assess the feasibility of the patterns to address the worsening of ET that may occur in 20% or more of the ET population.

Brief summary of methodology

Sample size Aim 1:

N=25 de novo ET patients undergoing DBS. We will focus on this group of patients to develop a pre- and post-operative dataset on the network physiology. The Aim 1 participants will be patients with Essential Tremor who will be getting DBS regardless of their participation in this study. These subjects will be identified in the outpatient clinic, at their pre-operative visit. Dr. Wong will approach and discuss the protocol with the potential subjects, discuss the study with them and ask if they are interested in participation. Once all questions are addressed and the patient verbalizes interest and willingness to participate, the consent will be obtained.

Sample size Aim 2+3:

This will be a pilot feasibility trial. We will include n=25 ET DBS patients with at least 6 months of outcome data revealing optimization of tremor suppression. Because of the 2-year length of this grant we will not anticipate overlap in the 25 patients for aim 1 and the 25 needed for aims 2+3.

Inclusion criteria for aims 2+3:

Existing unilateral or bilateral VIM DBS for ET, non-demented (MMSE>24), and must have a documented suboptimal tremor suppression on two successive visits (compared to the baseline post-operative improvement at 6 months following ET DBS surgery). For bilateral cases, the most affected tremor side will be studied.

Existing unilateral or bilateral VIM DBS for ET, non-demented (MMSE>24), and must have a documented suboptimal tremor suppression on two successive visits to a movement disorders neurologist (compared to the baseline post-operative improvement at 6 months following ET DBS surgery). For bilateral cases, the most affected tremor side will be studied.

The patients meeting inclusion criteria will be consented and scheduled for a research visit. During this visit, the DBS implantable pulse generator (IPG) will be loaded with a temporary custom firmware to allow implementation of active biphasic pulse stimulation. Upon enrollment, patients will have programming thresholds for DBS side effects checked in conventional and active biphasic pulses for VIM DBS. The following random conditions will be applied: (1) home settings; (2) VIM biphasic; (3) stimulator off. A 30-minute washout period will be applied between each of the random conditions.

Therefore, each patient will serve as their own control.

Each of the conditions will be videotaped for blinded motor score assessment by an independent rater, and we will obtain objective measures of tremor with an accelerometer and gait with a digital mat.

Measurement and Outcomes

Safety and tolerability:

Patients will be monitored by a neurologist and side effects from stimulation will be documented in a standardized FDA style case report form as we use for the parent R01 DBS study (Okun).

Data collection:

Patient demographics, DBS system specifications, DBS programming parameters, and neurologic assessments as described above are collected and stored in the University of Florida's comprehensive UF INFORM database, under protocol #2015001166. We will query this database to obtain this data only. Data will only be accessible to researchers with IRB approval.

We will collect the MRI images, the DTI sequences and the intraoperative and post-operative physiology and assemble them into a dataset for advanced analysis/correlation and for VTA analysis.

Tremor and gait analyses:

Tremors will be quantified by using the Fahn–Tolosa–Marin Tremor Rating Scale (TRS) by a blinded rater, and by analysis of accelerometer using the Kinesia ONE® accelerometer system. Gait will be assessed by digital mat (GAITRite®) at each of the conditions applied to monitor their gait parameters.

Statistical analysis:

We will compare the standardized clinical scale at home settings versus biphasic pulse shape settings. We will set the criteria as 60% of the subjects must meet the responder criteria (a minimum of 25% improvement) for square biphasic pulses to qualify to proceed to a larger well-powered efficacy follow-up study. We will apply more objective measures (secondary outcomes) such as the tremor accelerometer, the kinesia accelerometer, and the GaitRite walking strip; and again compare baseline and each novel setting, and will utilize the responder criteria for each target.

Possible Discomforts and risks

The risks associated with this study will be explained to all participants, they will be shared in writing for the subject to review prior to participation.

Expected outcomes from neuromodulatory therapy (Aims 2 and 3) for this target include capsular side effects (e.g. feeling of tightness or, pulling on the contralateral hemibody to the stimulated side) or sensory changes (e.g. reported by patients as heaviness,

numbness or, tingling). These typically occur as part of standard outpatient clinic programming visits and are stimulation-induced, often transient, and can be stopped immediately by turning the device off or to a lower setting, as well as returning the device to its normal home settings. Those are defined for this study as expected neuromodulation outcomes, therefore not being considered/classified as an adverse event. Events associated with the intervention that are not expected from standard stimulation will be classified as adverse events and properly reported to the IRB and Medtronic Safety board according to FDA regulations.

A trained physician will be with the subjects throughout the study to assess side effects. Should the subject experience a side effect that is intolerable, the physician will immediately stop the novel stimulation pattern and return the subject to their original settings. Any adverse events will be reported to the local UF IRB-01 according to reporting requirements and FDA regulations.

Additionally, the programming strategy is within the safety range required by the FDA and should not pose any additional risk than the regular DBS programming we do in the Movement Disorder clinic.

Subjects will be asked to perform a gait and balance activity with this study. Trained personnel will accompany the subject during this task to ensure the subject's safety and prevent any falls.

We do not anticipate any additional risk with the additional OR time which will not last longer than a minute. The additional proposed testing will involve 3-4 additional pauses for roughly 5-10 seconds in duration during the entire targeting phase. This would prolong the surgical case for less than 1 minute.

All records and data will be kept confidential and in a secure/locked location. Access to data will be limited to key personnel and will be password protected. The study will be monitored directly by the Principal Investigator with oversight provided by the University of Florida Institutional Review Board (IRB). All investigators who interact with the subjects will closely monitor the safety of human subjects.

Possible Benefits

Enrolled subjects will not receive benefit from this study. Participants may receive benefit during a novel stimulation pattern; however, as subjects are returned to their original settings this benefit will not be permanent. Any additional benefit for the patient and future patients lies in the knowledge gained from this research.

Regulatory approvals and study feasibility

We will obtain approval from the Institutional Review Board (IRB) at the University of Florida. Informed consent will be obtained from all subjects. Patients will be recruited during routine DBS programming sessions from the University of Florida Fixel Center for Movement Disorders & Neurorestoration. Dr. Joshua Wong will approach patients during the routine clinic visit for potential participation. We will recruit 25 unilateral or bilateral VIM DBS patients with Essential Tremor.

Data Safety Monitoring Plan (DSMP)

The safety experience will be frequently reviewed (6 months) by the Principal and sub-investigators. Adverse events will be designated as mild or severe; as device related, uncertain to be device related or not device related; and as anticipated or unanticipated. Serious adverse events, possibly related to the study intervention, will be reported to the UF IRB-01 according to appropriate reporting requirements.

Once the first subject is enrolled, data will be reviewed every 6 months until all subjects have completed the 6-month primary outcome. If necessary, the research protocol will be suspended pending investigation of safety concerns raised by SAEs occurring in the trial.

Milestones

University of Florida already has a contract with Medtronic (DBS manufacturer) for use of investigational stimulation patterns in already implanted devices using and experimental software. We expect the following milestones

October to November 2018: Submission of amendment to Medtronic contract referring to current project

October 2018: Submission of project to University of Florida Institutional Review Board (IRB). A full board review takes 30-60 days to be approved depending on potential contingencies implied by the reviewers. Based on our records of previous similar research projects, we expect to have it approved by December 2018

January 2019 – January 2020: Screening and enrollment of patients. This will be a 2-day study per patient. We plan to enroll 1-2 patients per month.

February 2019 – April 2020: Data analysis and manuscript writing

May 2020 – June 2020: manuscript submission to a high-impact peer reviewed journal.

Potential pitfalls and solutions

Potential pitfalls include potential delays in the study approval by Medtronic and/or UF IRB. The allotted timeline described above can accommodate potential delays without compromising the final deadline of completion of data collection. As we have over 400 dystonia patients with implanted DBS, we will try to coordinate the research visit with their regular appointments in clinic for patient's convenience. It is very likely that we will have more than 1 patient per month fulfilling diagnostic criteria, shortening the time to complete data collection.

Other pitfalls include potential cancellations of clinic appointments, and therefore, the research study, and an active research of upcoming clinic visits should increase the number of patients screened and enrolled in a shorter period of time, to compensate for potential losses due to appointment cancellations.

Publications

This study will be also enrolled in clinicaltrials.gov and a summary of results will be available after completion of the study.

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Lay summary

This project aims to evaluate the benefits of a novel programming strategy in deep brain stimulation (DBS) devices that are already implanted in patients with Essential Tremor. Currently, DBS devices work by sending electrical currents to the brain in an active delivery stimulation phase followed by a passive recovery phase (where the device is waiting for the next stimulation cycle). With the appropriate computer software provided by the manufacturer, it is possible to temporarily re-program the device to allow custom stimulation where both the delivery phase and recovery phase are active processes. This is also called “square biphasic pulses”.

A recent study from University of Florida showed that these settings could be easily applied in the office setting, were well-tolerated by patients and that patients possibly experienced changes in symptoms in a 2-hour observation period while in clinic. This

current study aims to test patients in 2 different random conditions which will be applied blindly (without patient knowing which of the conditions is being applied to avoid bias): 1) home DBS settings in conventional DBS pulses; 2) home DBS settings in square biphasic pulses. This will be a 2-day study. On the first day, the patient will have one of the two conditions implemented in the morning, observed throughout the day for side effects. At the end of the day, the patient will have specific testing with motor scores, and specific motor tasks will be implemented. At the end of the testing, the patient will have the settings reverted back to their home settings. On the following day, the patient will have the remaining of the two conditions implemented, and undergo the same protocol of observation throughout the day and testing at the end of the day.

At the completion of the study the patient will be reverted to the baseline home settings. We expect no long term side effects as there will be no permanent change to the DBS devices. The evaluations will be videotaped by the clinician and the assessments will be scored by independent raters who will also be blinded to the conditions applied (the raters will not know if patients are in regular DBS or square biphasic DBS) to avoid potential source of bias.