WEARABLE SENSOR DRIVEN CLOSED-LOOP DEEP BRAIN STIMULATION

NCT03051178

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Background: The clinical value of a smarter deep brain stimulation (DBS) system that responsively stimulates when pathologic symptoms are present, or adaptively modifies stimulation parameters to match the degree of pathology has been long recognized within the neuromodulation community[1]. Continuous, or open-loop DBS may not be necessary for disorders that are paroxysmal. Hence, intermittent DBS delivered only when pathological activity is present might be equally effective and decrease adverse events. Compared to intermittent stimulation on demand, continuous DBS results in unnecessary disruption of normal brain function and has been linked to serious side effects including dysarthric speech and dysphasia[2], [3]. Open-loop DBS also results in rapid battery depletion necessitating frequent surgery for pulse generator replacements. Hence, closed-loop DBS has been hypothesized to have the following potential advantages compared to open-loop DBS: i) the provision of a better and tailored approach for individual patients, ii) the ability to address the paroxysmal symptoms, iii) reduced adverse side effects, and iv) prolonged battery life (fewer number of battery replacement surgeries). The proof-of-concept of these hypotheses, however, has been lacking and the clinical efficacy of closed-loop DBS remains to be demonstrated in movement disorders.

The overall purpose of this application is to capture pathological activity related to essential tremor using external wearable sensors to responsively initiate or terminate DBS. To this end, we propose to use the Nexus-D system, which can communicate with an Activa implantable neurostimulator (INS), and it will, in a smart way, turn DBS on/off in patients. We will recruit subjects with Activa SC, PC, or RC implants during 6 post-operative programming visits. We will ask patients to perform a baseline visit, where they will be asked to perform tasks (detailed below) the day before their surgery. They will also have the option to participate after the initial six post-operative programming visits. Our research group is already familiar with and is in possession of the Nexus-D system, and we have successfully performed responsive DBS in two patients with Tourette syndrome (TS) and in four patients with Parkinson's disease (PD) in acute settings. Our lab is also equipped with wireless wearable sensor and amplifier systems, such as a 16-unit wireless EMG+ acceleration+inertia Trigno Wireless Bioacquisition System (Delsys Inc, Natick, MA). We aim to combine these signal modalities to capture pathological symptoms and generate commands to initiate or terminate DBS (also record adverse side effects, if any). Our goal is to characterize the clinical efficacy, side effect profile, and battery life of closed-loop DBS in acute settings using wearable sensors in essential tremor patients.

We received an educational grant from Medtronic in 2015 to support a senior design project entitled "Integration of Wearable Sensors to Medtronic Nexus-D for Closed-Loop Deep Brain Stimulation" this past academic year, and the senior design team successfully developed a graphics user interface and platform for our sensors to communicate with Medtronic Nexus-D. Their final design review was approved by Medtronic Liaison Engineers: Benjamin Isaacson[1] and Duane Bourget[2]. We are now seeking approval to conduct a clinical feasibility and safety study in 20 patients with intention or kinetic tremor in essential tremor (i.e., patients with essential tremor who do not tremor at rest). To adequately capture the side effect profile, we will be recruiting 10 in-clinic ET-DBS patients along with the 20 pre-DBS ET patients to undergo speech testing between open-loop, closed-loop, intermittent, and sham stimulation. Closed-loop DBS is hypothesized to decrease adverse side effects associated with continuous DBS, and ET patients, speech impairments such as dysarthria, are prevalent after DBS[4]–[6]. However, there has been only one study that quantified speech side effects between open-

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loop and closed-loop, but this was conducted in PD patients with externalized leads in the acute setting[7]. Thus, the need to quantify these effects both in ET patients and across clinical populations is imperative.

Summary of Methodology: This is a preliminary pilot investigation that will utilize a within subject study design and will enroll 20 DBS patients with ET, who will receive DBS implants as part of standard care for ET. The implantation surgery is not part of the study. We will compare the effectiveness and safety of the standard chronic continuous stimulation mode to the novel acute closed-loop stimulation mode. We will assess both effectiveness and safety of closed-loop stimulation. We will employ blinded video reviews of a validated motor outcome scales, but will also employ objective physiological measures of motor dysfunction in all areas. Additionally, we will enroll 10 in-clinic (i.e. already had a lead placed) DBS patients with ET along with the 20 undergoing to quantify the effects of different stimulation paradigms on speech, namely open-loop, closed-loop, sham, and intermittent stimulation. Sham stimulation will be delivered within clinician limits.

Sample size: This will be a pilot study designed to assess the feasibility, safety and potential effectiveness of novel stimulation patterns. We will enroll 20 ET patients with kinetic or intention tremor scheduled for DBS implants (Activa SC, PC or RC) in the Vim over the course of 3 years. The study was designed to utilize each patient as their own control, and to compare results against the performance of motor symptoms versus open-loop DBS. UF has implanted 27 ET patients with Activa SC in 2014 alone. The feasibility of recruiting 20 subjects in 3 years therefore is very high. These patients will all receive these implants as standard of care and the only difference will be the trial of responsive DBS. Additionally, we will enroll 10 DBS patients with ET in- clinic along with the 20 closed-loop patients to quantify the effects of different stimulation paradigms on speech, namely open-loop, closed-loop, no stimulation, and intermittent stimulation. There are on average 2-8 ET-DBS patients in clinic every week. Therefore, the feasibility of recruiting 10 patients for a one-day study is high.

Research Plan:
For the first 6 months post-DBS surgery, subjects will participate in the research after their monthly clinical programming visit. Subjects may still be recruited several months after they have received DBS and still participate in the 6-month outcomes, however, these subjects will not have a research visit after a monthly programming visit. Their visits will be scheduled with the researcher. Additionally, if an already recruited subject undergoes surgery for the contralateral side, these subjects may provide consent again and closed-loop DBS will be tested on the contralateral side. Their research visits will happen after their monthly clinical programming visits or scheduled with the researcher. Subjects who provide consent again will participate in 12 research visits altogether. Stimulation parameters will be empirically derived for each research subject by a movement disorder specialist. These optimized parameters will be used for open- and closed-loop stimulation trials. Baseline tremor severity will be assessed using the following assessments:

- Fahn, Tolosa, Marin Tremor Rating Scale (TRS): This 5-point scale rates tremor severity based on tremor amplitude, from 0 (no tremor) to 4 (severe tremor) in each part of the body and includes assessments of specific abilities and functional disabilities
- Quality of Life in Essential Tremor (QUEST): This is a 30-item assessment that has 5 options for the patient including Never/No, Rarely, Sometimes, Frequently, and Always/Yes. The questionnaire also contains additional items including the sexual function, current work status and satisfaction with medications for tremor control and any side effects from the medication.

The recordings from the first and second research visits will be used to delineate rest from tremor. This will serve as the control feature for stimulation and detector validation. During visits 3-6, the output of the tremor detector will be used to provide acute responsive stimulation.

Subjects will complete all tasks in the protocol from a comfortably seated position. The study

will be videotaped in its entirety, and rated by a blinded movement disorders neurologist.

The following clinical data will be gathered from the patient and/or medical record:

- name,
- age,
- gender,
- race,
- phone number,
- diagnosis,
- stage,
- age at onset,
- past neurological medical history
- imaging performed as part of your DBS surgery (MRI, CT, etc)
- Records of past physical exams, treatments, evaluations, and any other procedures you may have done for ET
- Responses to ET questionnaires
- neurological assessments performed during the Fast Track appointment as part of your DBS surgery assessment,
- records about study devices
- pre-DBS off-medication ET scales, and current DBS settings.
- Programming visit dates

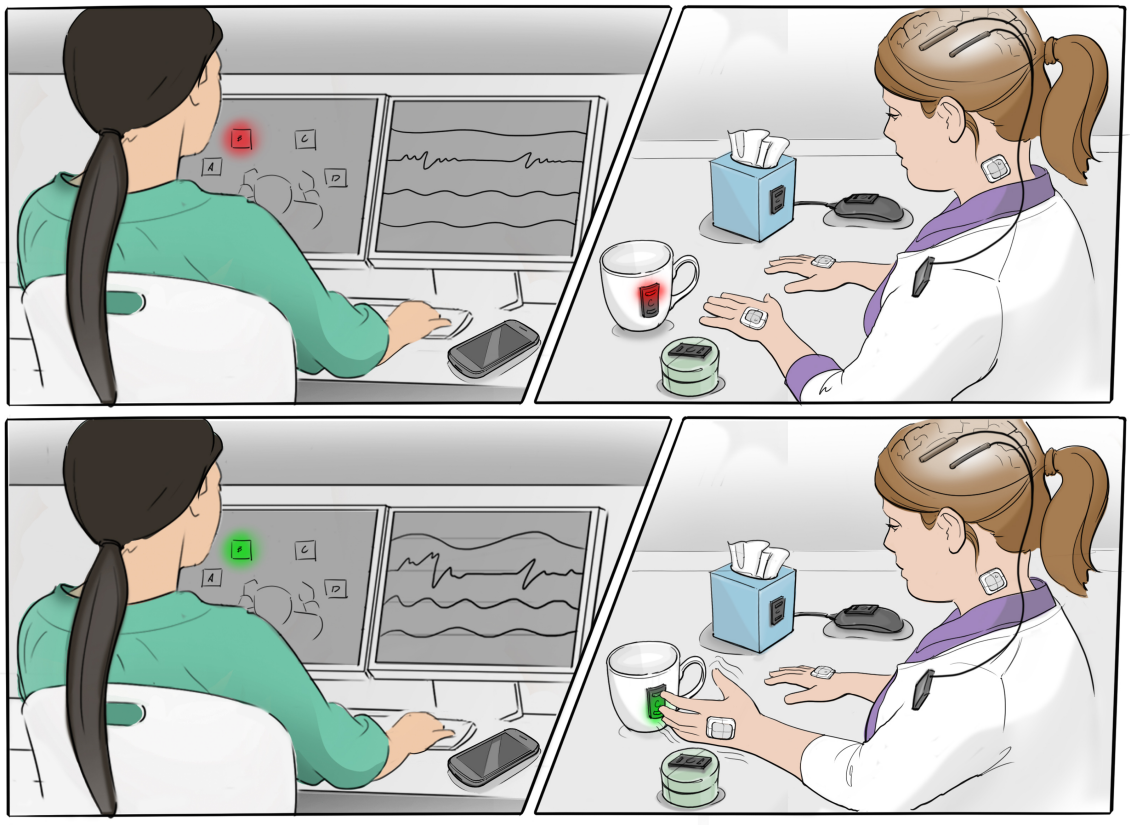

Figure 1. Experiment setup for recording EMG and inertia data during movement intention and tremor. Patient will be cued to pick up an object with the flashing of a red LED light (top). They will reach and grasp the object once the green LED on the same object lights up (bottom). In this setup, the patient will use the hand closer to the object (contra- or ipsilateral to the implant). During the next stage of experiments, they will perform volitional reach and grasp movements (i.e., without LED cues).

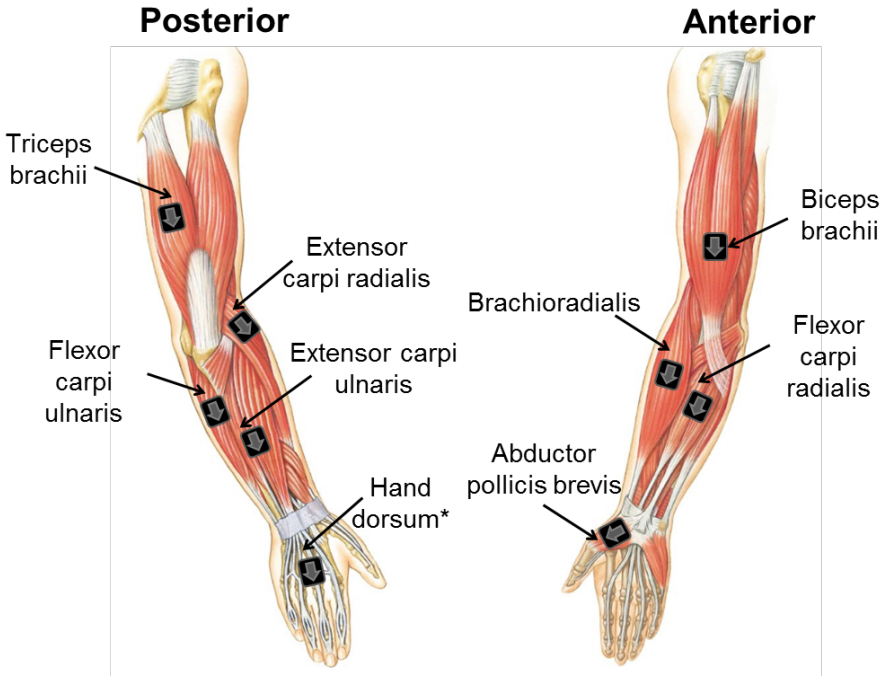

Figure 2. Example of the placement for the EMGs on the patient's arm

We will utilize the Direct Instrumented Measurements of Tremor Severity developed by our team to study the relationship between EMG, inertia data and tremor. A summary of this system includes the Activa SC or PC neurostimulator, the Nexus-D wand to stream data onto a computer, wireless sensors for EMG and inertia (Delsys, Inc., Natick, MA), a camera to capture behavioral activity, and 4-6 objects, each object with a red and green LED and accelerometers (Figure 1). The subject will sit in front of a table with the various objects distributed equally to the two halves of the table. The patient will wear wireless EMG and acceleration sensors on several muscles within the upper extremity (Figure 2). A red LED will light up on one of the objects, identifying it as the target object. The patient will be instructed to wait until the green LED on the target object lights up, signaling them to reach and grab the object. The time between the cue (red LED) and go signal (green LED) will be between 1-2 secs. The patient will be instructed to reach out with the hand closest to the target object. The end of each trial will be determined from inertial sensor on the target object. Subjects will repeat this task 5 times with rest periods of 1-2 mins in between. This first experiment and placing the sensors will last about 1.5-2 hours.

The time between the cue and go instructions will be labeled as the "intention" period. We will use these periods to extract EMG features of movement intention. We will do so by comparing the spectral content of intention periods to inter-trial intervals (i.e., rest condition), and statistically verify the significance of modulations using randomization tests. We will further utilize this biomarker of movement intention in offline linear discriminant analysis (LDA) on the external computer to develop detector weight coefficients that will be used to control the Activa neurostimulator through Nexus-D. We will first investigate the performance of the event detector, without using the output of the detector for responsive stimulation. We will use the metric measure *sensitivity* to optimize the weights. *Sensitivity* is the ratio of true positives detected (correct detections) over the sum of true positives and false negatives (missed events). This metric penalizes failures to detect intention to move, but does not penalize false positives, as the latter would merely lead to an unnecessary responsive stimulation. Since these patients would otherwise be receiving continuous stimulation, a few falsely initiated stimulations should be tolerable. The weights will be optimized until a satisfactory sensitivity measure that would lead to a tolerable and therapeutic number of stimulations in a responsive stimulation scenario is reached.

To test the system in a more natural setting, we will conduct a second set of experiments where

subjects will volitionally pick any object of their choice. All LEDs will turn red to cue the patient and then green to instruct them to reach and grab the object of their choice. Patients will repeat this task 5 times with rest periods of 1-2 mins in between. Additionally, patients will perform tasks of their choosing to mimic daily life activity (eating, reading a book, or putting on a jacket). The experiment will also include tasks pertinent to TRS. These experiments include tasks like finger to nose touching, posture holding with intervals of arms outstretched with wrists extended and arms retracted towards the patient's chest, and drawing an Archimedean spiral. In a final set of experiments, we will ask the patient to walk. This will test the robustness of detection in situ, where DBS should remain inactive in the absence of tremor. This portion of experiments should last between 2-2.5 hours.

These experiments will be repeated in DBS OFF and ON conditions at each study visit (post-operative months 1-6). In responsive DBS, the stimulator will responsively switch to the HIGH setting upon detection of intention to move, or detection of tremor; and will switch to the LOW setting when the signals for intention to move and for tremor are both absent (visits 3-6). To test the tolerability of intermittent stimulation, we will test a duty cycle as follows: active stimulation (HIGH setting) for 4 seconds then switching to the LOW setting for 30 seconds. We will optimize the HIGH and LOW amplitude settings, along with rise and fall times to find a therapeutic setting that is tolerable.

After the visit, battery consumption will be calculated and compared between the open- and closed-loop stimulation conditions. The Medtronic battery estimator helpline will be used to calculate battery life.

Since this is a pilot study, the trial will not be powered as a clinical trial, but instead will be exploratory and the results will be used for a larger clinical trial (efficacy rather than effectiveness).

For patients enrolled in the closed-loop DBS portion of this study, at one of their monthly postoperative research visits, we will test the effects of stimulation on speech. Specifically, we will test open-loop, closed-loop, intermittent, and sham stimulation. Sham stimulation will be delivered within clinician limits. For patients enrolled within the in-clinic speech assessment portion, we will approach them in clinic and perform a one-day assessment of the aforementioned stimulation paradigms on speech. Altogether, 30 individuals will undergo speech testing. We have added intermittent stimulation because we do not believe that closed-loop will be triggered during speech, since the patient is not moving. Speech will be assessed using the following paradigm:

1. Participants will be asked to produce a sustained vowel 'ah,' and complete repetition tasks including diadochokinesis (DDK; /p/, /t/, /k/) and 4 sentences:

    a. In the summer they sell vegetables.
    b. The shipwreck washed up on the shore.
    c. Please put the groceries in the refridgerator.
    d. The valuable watch was missing.

    Speech samples will be digitally recorded using a hand-held microphone for offline analysis. Analysis will be completed using PRAAT software (http://www.fon.hum.uva.nl/praat/) to determine duration of sustained vowel phonation, fundamental frequency, jitter, shimmer, DDK rate, sentence rate, and spectrogram metrics.

Regulatory approvals: We will write and obtain approval from the Institutional Review Board (IRB). Informed consent will be obtained from all subjects. Patients will be recruited during routine DBS programming sessions. DBS patients can also be recruited through the INFORM database (IRB approved) and approached over the phone to be informed of the study. The INFORM database is a database in which patients who present to the Movement Disorder clinic agree to be contacted for future research opportunities and have their data stored. These include patients who have undergone DBS. We will recruit 20 Vim DBS patients with

essential tremor for closed-loop testing. An additional 10 will be recruited to quantify the effects of stimulation on speech along with the 20 for closed-loop testing. This is non-significant risk study, as the amount of stimulation delivered will be shortened to times only when the patient is moving.

Privacy and Confidentiality: This entire visit will be videotaped for a blinded reviewer to assess the efficacy of the new treatment by rating the severity of your tremor. It is a requirement of the study to be videotaped. We will store this video on a secure network only accessible to research personnel associated with this study. After the study is over, the video will be destroyed.

Possible Discomforts and Risks: Participation in the study can cause exhaustion. During stimulation optimization, patients might be exposed to short duration stimulation parameters that are not comfortable. These settings will be noted down and will not be repeated. To minimize the risk of such discomfort during R-DBS, the tolerability of setting parameters will be tested by a clinical programmer through duty cycle stimulation. Usually, it is possible to achieve equivalent clinical benefit by lowering stimulation amplitude and increasing pulse width. The EMG and inertia sensors may cause skin irritability and discomfort.

Possible Benefits: This study also has the potential to guide in the development of responsive DBS therapy.

Compensation: Subjects will be compensated $25 for each 6-month post-operative visit or each in-clinic speech assessment and will be offered a one-night hotel stay if needed

Conflict of Interest: None.

Inclusion criteria:

- Patient provides informed consent.
- Patient is over 21 years of age.
- Patient has had a significant disabling, medication-refractory upper extremity tremor with no evidence of non-ET central nervous system disease or injury for at least three (3) months prior to implantation of Activa SC PC, or RC device.
- Patient receives Vim electrode and Activa SC, PC, or RC device implants, and recovers fully after surgery.
- Patient is available for study participation after their clinical programming appointments for six months.

Exclusion Criteria:

- Medication related movement disorders.
- Any suspicion of Parkinsonian tremor, including presence of Parkinsonian features such as bradykinesia, rigidity, or postural instability.
- Severe medical co-morbidity including cardiovascular disorder, lung disorder, kidney disease, continuous neurological disease, hematological disease, or frailty that impact tolerability of the surgery as judged by the screening physicians.
- Patient is undergoing a lead revision surgery.

Timeline: Figure 3 depicts the proposal timeline of the project until the study ends. Currently, there are 13/20 patients recruited for the closed-loop study. We will finish recruiting for this study in December 2020 with the last subject visit in June 2021. Between now and project end (July 2021), we will recruit 10 ET-DBS patients for a one-day speech assessment. This is highly feasible since 2-8 ET-DBS patients are seen in clinic weekly. Throughout the closed-loop study, these patients will also undergo the same speech testing.

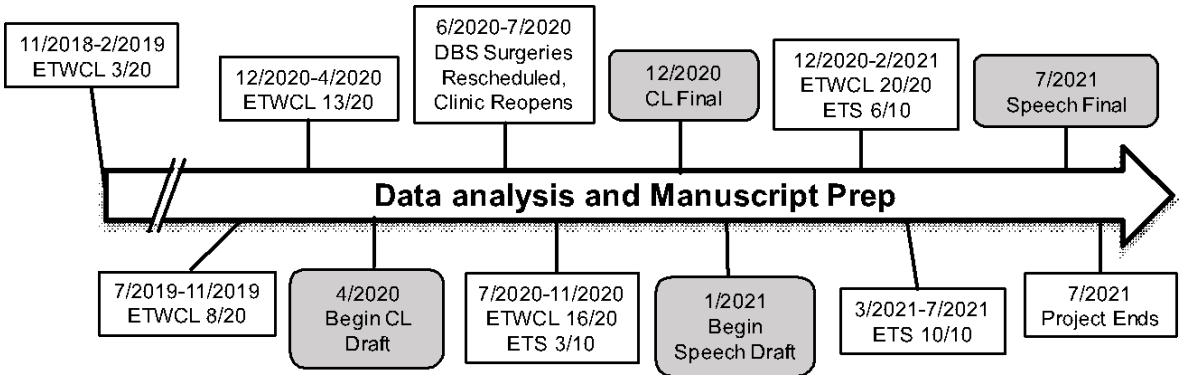

Figure 3. Proposed timeline until project ends

Data Safety Monitoring Board (DSMB): This study will have a designated DSMB composed of three members (A neurologist, a non-clinician scientist, and a non-neurological physician) without ties to the current study or any conflicts of interest. The DSMB will be charged with the duty of meeting every 6 months to discuss all of the AE's for the study. The safety experience will be frequently reviewed by the Data Safety Monitoring Board (DSMB). The DSMB will be informed of all serious adverse events and all mild adverse events which are potentially device related in the opinion of the investigator. The DSMB will designate each AE as mild or severe; as device related, uncertain to be device related or not device related; and as anticipated or unanticipated. Once the first subject is enrolled, the DSMB will meet by teleconference every 6 months until all subjects have completed the 6-month postoperative primary outcome assessment. The DSMB has the authority to suspend further enrollment pending investigation of safety concerns raised by SAEs occurring in the trial. The DSMB has a stopping rule for more than one death or more than 1 suicide deemed to be device related.

Adverse Event Reporting: Once a subject is enrolled into the study, continuous close monitoring will be conducted by the Principal Investigator (PI) in conjunction with the Co-PI and other investigators as well as the University of Florida's Institutional Review Board (IRB), through annual reports of progress and by immediate notification of serious and unanticipated adverse events by the PI to the IRB.

Stopping rules for the study have been established: This study will be suspended by the DSMB only if an unexpected and severe neurological complication occurs and they deem suspending or stopping the study appropriate. Specific examples that would warrant suspending the study include the following, only in the event that they do not reverse with adjustment or discontinuation of the therapy:

- worsening of symptoms
- neurological events such as changes in memory, cognition, and motoric or sensory modalities (the exception to this would be persistent dysarthria, which has been reported with PD and may be an acceptable side effect if symptoms are diminished.

Statistical Analysis: All statistical analyses will be performed in R 3.5.2. TRS scores and hand acceleration measures across different stimulation conditions (off, cDBS, rDBS) were assessed using a mixed model ANOVA with the participant as a random effect. All post-hoc comparisons were Bonferroni corrected. Equivalence testing was performed using two one-sided tests. Epsilon, or the region of similarity, for total TRS, contralateral TRS, or hand acceleration were 2 points, 1 point, and 0.1 m/s^2, respectively.

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