PROTOCOL TITLE:

Direct measurement of motor cortical responses to transcranial direct current stimulation

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1.0 Objectives / Specific Aims

Parkinson's disease (PD) is a movement disorder characterized by resting tremor, slowness of movement (bradykinesia), muscle rigidity and postural imbalance. These motor symptoms arise predominantly from abnormal activity in the basal ganglia-thalamocortical circuit. Deep brain stimulation (DBS) of the basal ganglia was developed as a surgical treatment for PD patients who have become refractory to medical therapy. In a recent study (Rowland et al, 2015 – pdf uploaded in General Comments section), we compared movement dynamics in two types of patients undergoing DBS surgery – PD and essential tremor (ET) patients – performing the same motor task.[1] We found that motor cortical activation, i.e., reduction of beta oscillations, in PD patients preceded that of ET patients, beginning during motor preparation before movement had begun. This finding demonstrates a compensatory strategy that can be used by motor networks in the brain to augment voluntary movement and offers a potential biomarker that may be used in future forms of neuromodulation to improve PD symptoms.

Approximately 2-5% of patients undergoing DBS will experience a surgery-related complication.[2] The most serious of these is hemorrhage and stroke due to penetration of the brain parenchyma by the DBS electrode to reach the basal ganglia. One alternative form of stimulation that has been shown to have modest benefit in some patients with PD is transcranial direct current stimulation (tDCS), in which electrodes are placed on the scalp and deliver current noninvasively to the motor cortex. Although the results from tDCS are promising, our **central hypothesis** is that this form of stimulation produces inconsistent results in PD patients because a detailed understanding of motor cortical response to tDCS is lacking. To address this problem, we propose performing direct measurement of motor cortical oscillations in response to tDCS to determine how these signals might be used in improving this noninvasive therapy for treatment of PD-related motor symptoms. Progress in treating PD symptoms noninvasively might also lead to similar treatment strategies for all movement disorder patients undergoing DBS, including ET and dystonia patients.

In our previous study (Rowland et al, 2015), PD patients undergoing DBS surgery performed an arm-reaching task during subdural electrocorticography (sECOG) recording of beta (13-30 Hz) and broadband gamma (70-200 Hz) oscillations, showing modulation related to both movement preparation and execution. However, the exact frequency bands and phases of movement modulated by tDCS remain poorly understood. Patients undergoing DBS surgery for PD and ET are usually awake and, furthermore, the procedure provides access to primary motor cortex. Thus, during awake, frameless DBS surgery, responses in motor cortex can be measured safely in behaving subjects. Patients undergoing DBS surgery for dystonia are usually asleep, offering an opportunity to compare how tDCS affects motor cortical oscillations when patients are not engaged in a motor task. In some instances, PD and/or ET patients also request to be asleep during DBS surgery, allowing comparison between awake and asleep populations.

We will investigate the effect of tDCS on motor cortical oscillations in patients undergoing DBS surgery through the following specific aims:

Aim 1. Quantify the change in primary motor cortical (PriMC) oscillations during cued arm reaching in relation to tDCS activation. Question: Does tDCS differentially modulate movement preparation vs movement execution? In this aim, we will record beta and broadband gamma oscillations in PriMC in awake patients undergoing frameless DBS surgery using an

sECoG electrode while applying high-density tDCS focused on PriMC. Patients will be videotaped in order to correlate movement dynamics with ECoG signals. *We hypothesize that cortical beta and broadband gamma spectral power changes will be enhanced moreso during movement preparation than execution following anodal tDCS activation.*

Aim 2. Quantify the change in PriMC oscillations during framed DBS (either awake or under general anesthesia) in relation to tDCS activation. Question: Does tDCS modulate motor cortical oscillations in the absence of movement? In patients undergoing framed DBS (either awake or asleep), cortical oscillatory changes will be recorded during application of tDCS using different amplitudes, durations, polarities, lateralities, and stimulation patterns. *We hypothesize that cortical beta and broadband gamma spectral power will be modulated using different amplitudes, durations, polarities, lateralities, and stimulation patterns in the absence of movement.*

This project has been awarded grant funding through a South Carolina Clinical and Translational Research Institute (SCTR) K12 award (#UL1 TR001450).

2.0 Background

Understanding tDCS effect through synchronized cortical oscillations

Transcranial direct current stimulation (tDCS) has been shown to transiently improve deficits during physical rehabilitation sessions in small studies of patients with motor dysfunction, such as PD and chronic stroke.[3] Nevertheless, widespread clinical use of tDCS has not gained significant traction because several large multi-center, randomized, sham-controlled trials have not yet shown consistent effects across these populations.[4] One plausible explanation is incomplete understanding of tDCS effect on motor networks, in part due to lack of direct access to in vivo recordings to inform its mechanism. In other models with access to in vivo cortical recordings, such as epilepsy, cortical beta (13-30 Hz) and broadband gamma (70-200 Hz) oscillations have been shown to play critical roles during voluntary movement. In cued motor tasks, the spectral power of cortical beta decreases, termed event-related desynchronization (ERD, associated with release of movement inhibition), while broadband gamma power increases, or undergoes event-related synchronization (ERS, reflecting cortical population spiking).[5, 6] In both health and disease states these frequency bands are important neurophysiological correlates of movement and can be detected in functionally connected areas throughout the sensorimotor cortex, including premotor cortex (PreMC), primary motor cortex (PriMC) and primary sensory cortex (PSC).[7-9] Several authors have attempted to record oscillatory patterns with scalp EEG in relation to tDCS activation in healthy subjects, however no consistent theme has emerged and the results are often contradictory.[10-12] In the only study of its kind, Jang and colleagues used subdural electrocorticography (sECoG) in anesthetized beagles during tDCS and observed broad-spectrum but nonspecific oscillatory changes.[13] A recent systematic review underscored the lack of understanding of the physiological mechanism underlying motor cortical influence of tDCS in patients with motor dysfunction.[14]

In summary, motor cortical oscillatory changes related to movement can serve as a powerful cortical biomarker of intended or actual motor activity, as shown in our previous work. tDCS, which delivers current noninvasively to cortical targets, has the potential to expand the options for treatment of motor deficits in many clinical populations. Combining sECoG with tDCS will allow a detailed characterization of motor cortical oscillation changes during movement in

relation to tDCS activation. The clinical standard of care evaluation and treatment for movement disorders will not be modified by this research. The surgery for movement disorders will not be hampered by the research procedures (application of tDCS and the sECoG electrode) as explained in detail in section 3.0 below. Our previous data on PD provides an important proof of concept to demonstrate that tDCS might possibly work by modulating oscillations to improve motor symptoms.

3.0 Intervention to be studied

Overview

This study will perform the following research-specific procedures:

1) transcranial direct current stimulation (tDCS), the effect of which will be measured using
2) subdural electrocorticography (sECoG)

Definitions and nomenclature

tDCS **stimulation** as implemented in this protocol will be carried out through use of an array of five independently arranged electrodes (see Figure 1). sECoG **recording** will be carried out through use of an array of six electrode contacts arranged in a linear strip. The tDCS electrodes are separate devices placed on the scalp, while the sECoG contacts are encased in a single piece of silastic material, i.e., the sECoG electrode. Throughout the rest of this document, the tDCS electrodes and sECoG electrode will be referred to in the plural and singular forms, respectively. The terms 'electrode array' and 'electrodes' will be used interchangeably. Positioning the tDCS electrodes onto the scalp will be referred to as 'placement' of the electrodes, while positioning of the sECoG electrode inside the skull (but on top of the brain surface) will be referred to as 'insertion' of the electrode.

It is important to note that neither the tDCS nor sECoG electrodes will penetrate the brain at any time. Both electrodes will remain outside the brain itself. The tDCS electrodes will remain on top of the scalp; the sECoG electrode will remain underneath the skull and on top of the brain surface (see Figure 1, Step 3). Only the DBS electrode performed for standard of care treatment will penetrate the brain.

Procedure steps

In brief, standard of care DBS surgery involves drilling a 1.4 cm burr hole in the skull and implanting an electrode that penetrates the brain parenchyma into the basal ganglia or thalamus. For patients participating in this research, all surgical procedures will be the same, with the exception of the research-dedicated steps: 1) the sECOG electrode will be inserted using the same burr hole drilled previously but will remain on the surface of the brain and will not penetrate the brain, 2) the tDCS electrodes will be applied to the scalp (awake patients with frameless DBS will also be outfitted with virtual reality goggles), 3) the tDCS electrodes will be activated (awake, frameless DBS patients will perform up to two motor tasks before, during and/or after stimulation and videotaped during the task); the task will not be performed if the patient is awake but has a stereotactic headframe on or is asleep under general anesthesia, 4) in all patients the surgical site will be photographed to capture the tDCS montage as well as any other aspect of the setup relevant to offline reconstruction of behavioral and physiology data), 5)

all research-related equipment will be removed from the surgical field, 6) the subject will proceed to have the DBS surgery as per standard of care.

DBS surgery is reimbursed by insurers using a Diagnosis Related Group (DRG) model. This means that once a patient is preauthorized by an insurer to undergo DBS surgery, the surgery, hospital stay and all related procedures are bundled together and covered at a fixed cost. Costs related to research activity during this study (20 minutes total) will be charged to a research account and will not result in additional charges to the patient, hospital or the patient's insurer. In a recently published study documenting 200 cases of sECoG insertion during DBS surgery in movement disorder patients and in which all study related procedures took place in 20 minutes or less ('Intraoperative electrocorticography for physiological research in movement disorders: principles and experience in 200 cases', by Panov et al, 2017), **no infections related to the sECoG electrode occurred**.[15] In this study, we will allow 20 minutes total to include setup and breakdown of the study-related equipment.

Device use

The tDCS electrodes (Soterix Medical, NY, NY, model #s 2001tE and 4x1-C3A) will be used for their intended purpose – non-invasive electrical stimulation of the brain – however, according to the manufacturer's website this is strictly an investigative tool and will be used for research purposes only.

The sECoG electrode (Ad-Tech Medical Instrument Corporation, Racine, WI, model# MS06R-IP10X-0JH) is an FDA-approved, commercially available device for intraoperative monitoring. According to the manufacturer's website, these electrodes are 'ideal for brain mapping and intraoperative monitoring of the cortical surface'. The electrode as used for intraoperative monitoring does not specify a clinical indication/population, thus, the electrodes as implemented in this protocol will be used for their intended and marketed purpose.

4.0 Inclusion and Exclusion Criteria/ Study Population

Only patients considered an acceptable surgical candidate for DBS will be eligible for recruitment into this study. All diagnostic procedures, including imaging, will have taken place prior to recruitment as part of the routine diagnosis and care of movement disorder patients. In addition, patients are screened for cognitive impairment by a neuropsychologist to rule out those unlikely to benefit from DBS surgery due to cognitive impairment. No patient will receive a CT or MRI scan in order to be included in this study, and patients who did not have a CT or MRI as part of their clinical assessment will not be eligible for this study. Patient eligibility for this study will be based on the following inclusion/exclusion criteria:

Inclusion criteria:

- Patients consented and scheduled for DBS surgery with the PI
- Age 18-80

Exclusion criteria:

- Patients unable to actively participate in the consent process physically and/or cognitively

- Presence of scalp injury or disease

- Prior intracranial surgery with the exception of deep brain stimulation surgery

- Prior brain radiotherapy

- Prior history of intracranial tumor, intracranial infection or cerebrovascular malformation

- Prior history of seizures

The rationale for these criteria are as follows: The major risks to subjects in this study consist of #1) scalp irritation from the tDCS electrodes and #2) damage to the cortical surface or surrounding structures (such as cortical bridging veins) during insertion of the sECoG electrode. The subdural space between the skull and cortical surface can be compromised by scarring from intracranial surgery (at the site of sECoG insertion), brain radiation and/or infection of the brain. Furthermore, abnormalities of cortical vasculature, such as with an intracranial tumor or cerebrovascular malformation, may impede safe insertion of the sECoG electrode. Finally, history of seizure disorder may indicate underlying cortical abnormalities that might confound our data analysis.

5.0 Number of Subjects

A total of 25 subjects will be enrolled. Our group performs approximately 100 DBS surgeries per year, thus we are confident we will be able to meet our recruitment goal during the period of the award. In our previous study (Rowland et al, 2015) comparing PD (n=10) and essential tremor (n=8) patients we observed an absolute difference in cortical beta ERD during movement preparation of 0.24 with a standard deviation of 0.19 (PD -0.31 ± 0.06, ET -0.071 ± 0.05, $\log_{10}(\mu V)^2/Hz$, mean±SE, $p = 0.0061$).[1] Based on our experience, with an observed absolute difference in cortical beta ERD of 0.24 $\log_{10}(\mu V)^2/Hz$ and an assumed standard deviation to be as observed in our preliminary data for the PD group, we estimate a sample size of 20 subjects will be sufficient to yield a power of 91% assuming a moderate intra-class correlation of 0.7. We have allowed for 5 additional subjects in the event that any subjects are withdrawn from the study and not included in the final analysis.

6.0 Setting

The data for this study will be recorded in the operating room at MUSC. Coded and identifiable data will be stored electronically on a secure server in separate folders. Signed consent forms will be located in a locked cabinet in a locked laboratory in the Clinical Sciences Building at MUSC.

7.0 Recruitment Methods

An eligibility screening checklist will be used prior to completing the informed consent process. The screening will not require access to PHI and will be allowed under a waiver of signed consent for the prescreening. The screening checklist will contain only the inclusion and exclusion criteria for the study. The purpose of the screening is to ensure that patients meet ALL inclusion and exclusion criteria for the study prior to executing the informed consent. This process will work in the following manner: During a preoperative clinic visit with the PI, the PI will

ask the patient if they would like to learn more about the study. If so, the PI will then complete the screening checklist then sign and date the form. If the subject meets all inclusion and exclusion criteria, the PI will review the protocol and consent form with the patient and then leave the room in order to give the patient sufficient time to read the consent form.

The PI is the surgeon performing the surgery, so he will have the knowledge to carefully explain the research study. Careful attention will be placed on good communication. The PI will be sure to emphasize that participation in the study is not necessary for the standard of care surgery. He will also emphasize that the patient can withdraw from the study at any time prior to the surgery.

8.0 Consent Process

Once the patient has been given an opportunity to review the consent form in detail, the PI, along with another member of the IRB-approved personnel team for this study, will re-enter the room and go over the sections of the consent with the participant. They will answer any questions the patient may have. The voluntary nature of the study will again be emphasized. It will also be emphasized that the patient may exercise their right to take the consent form home to discuss with family and friends prior to signing. For patients that provide consent to the research study during their clinic visit, a copy of the signed and dated consent form will be provided to them before leaving the clinic. The PI will also review the HIPAA authorization form prior to the patient signing the form. The patient will be given a copy of this form. Original forms will be placed in a locked cabinet in a locked laboratory in the Clinical Sciences Building at MUSC. On the morning of surgery, IRB-approved study personnel will once again review the study procedures and study consent document – emphasizing the voluntary nature of the study and the ability of the patient to withdraw at any time. Patients who did not sign the consent and HIPAA authorization forms during their clinic visit and who still wish to participate in the study will be able to sign the forms on the morning of surgery, at which time a copy of the signed and dated forms will be provided to them.

Patients will be informed during the consent process that information about them (including identifiable private information) may have all of their identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from them.

9.0 Study Design / Methods

The study will begin with a medical chart review by the research staff, who will extract data elements from the patient's electronic medical record (EMR) to be stored in a database (see Data Management section).

Following this, the study will implement the steps described below (see Figure 1):

Step 1: Insertion of sECoG electrode

After the burr hole is made as part of the clinical DBS procedure, we will insert an ECoG electrode in the subdural space to cover primary motor cortex for research purposes. The flat, circular, platinum-iridium contacts within the ECoG strip are arranged in 1 row of 6 contacts separated by 1 cm center-to-center and suspended in a silastic finish. The ECoG electrode is 75 mm x 8 mm in dimensions and each contact is 4 mm in diameter with a 2.3 mm exposed

surface. These electrodes come prepackaged sterilely and will be handled using standard operating room procedures. The sECoG electrode is anchored by a cable that will extend outside the burr hole and connect to an amplifier (Cascade Pro, Cadwell, Kennewick, WA). ECoG data will be amplified one thousand times and sampled on all 6 channels at 3000 Hz with each channel recorded in monopolar configuration referenced to a grounding needle in the scalp. sECoG recording will last a total of approximately 20 minutes, after which the sECoG electrode will be removed. sECoG recording will be manually switched on and off by IRB-approved study personnel in the operating room to assist with the procedure.

Step 2: Placement of tDCS electrodes and virtual reality goggles

We will place the tDCS electrodes onto the patient's scalp which will be previously shaved of all hair (depending on laterality of procedure – either unilateral or bilateral) in accordance with the standard clinical DBS procedure. The electrode array consists of one central electrode and four surrounding electrodes (total of five ring electrodes, each 1 cm in outer diameter, 2 mm thickness). The central electrode will be placed at a location directly overlying primary motor cortex as determined by coordinates generated through neuronavigational software used for DBS electrode trajectory planning. For purposes of sterility, the patient's scalp will be covered with an iodine-impregnated adhesive film per standard of care procedures. The electrodes, which will be sterilized with ethylene oxide prior to the procedure, will be secured in place using additional sheets of this film, which will serve as an additional preventive measure against possible infection. Next, the tDCS electrodes will be connected to a low-current generator placed away from the surgical field and powered by alkaline batteries. The device will be manually controlled by IRB-approved study personnel in the operating room to assist with the procedure. For presentation of visual images for patients who are awake and undergoing frameless DBS, patients will be outfitted with virtual reality goggles (Oculus Rift, Menlo Park, CA). The Oculus system also comes with a hand controller that is held by the patient and tracked in three-dimensional space, serving as a marker of upper extremity movement. Presentation of visual images will be manually controlled by IRB-approved study personnel in the operating room to assist with the procedure.

It is important to note that neither the tDCS nor sECoG electrodes will penetrate the brain at any time. Both electrodes will remain outside the brain itself. The tDCS electrode will remain on top of the scalp; the sECoG electrode will remain underneath the skull and on top of the brain surface (see Figure 1, Step 3). Only the DBS electrode performed for standard of care treatment of PD will penetrate the brain.

Step 3: Motor task for awake, frameless DBS patients

After all electrodes and VR goggles have been set up, the goggles, which will be connected to a computer, will display an interactive task beginning with appearance of a red dot in the center of the screen for 3 seconds (Note that this task will be similar to the task used in the Rowland et al, 2015 study). This single red dot will be followed by a red and blue dot of the same size appearing together for a period of 3 seconds with the blue dot located 10 cm above the red dot. After 3 seconds, the red dot in the center of the screen will become green. When the blue dot located above the green dot is touched virtually (patient's outstretched finger approaches within 2 mm of the position of the dot), it will disappear and then reappear 10 cm below the green dot. When the blue dot is touched virtually at this location, it will reappear above the green dot again. Successive virtual touches will continue to cycle the blue dot a total of 5

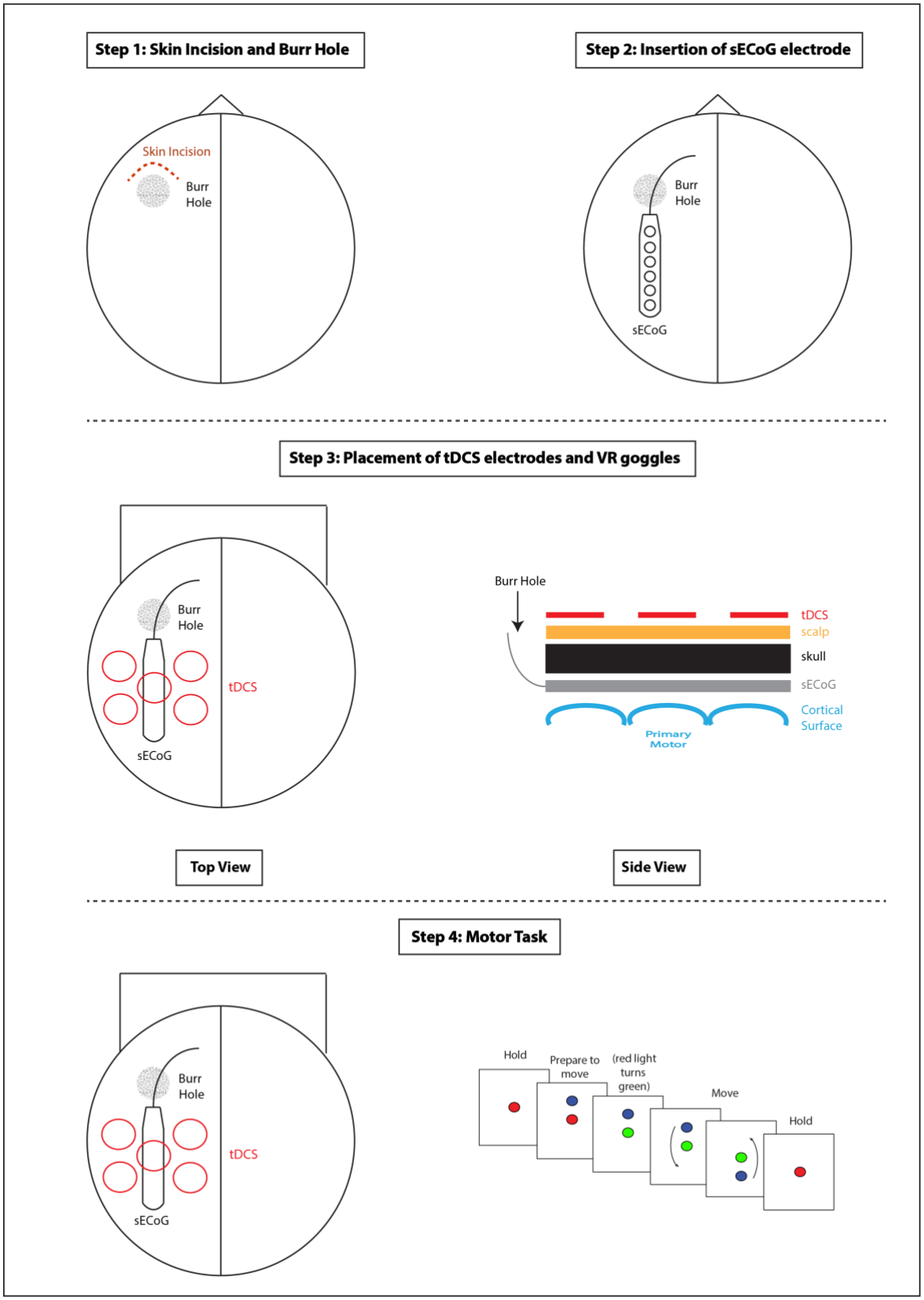

Figure. 1. Recording and stimulation schematic. Following skin incision and burr hole drilling, an ECoG electrode is inserted into the burr hole over the cortical surface. The source electrode (anode) of the hd-tDCS electrode array is shown centered over primary motor cortex.

times. If no virtual touch is made at a location for 2 seconds, the blue dot will cycle to the next location automatically. Once the blue dot has cycled 5 times, both the blue and green dots will disappear and the red dot will reappear in the center of the screen (accompanied by an auditory cue) to complete 1 trial. Patients will be instructed to rest quietly when the red dot appears (rest phase). Appearance of the blue dot will signal that the patient is to prepare to move once the green dot appears (movement preparation phase). Patients will be instructed to move at a natural speed. This is to avoid confounding changes in beta and broadband gamma oscillations due to movement speed and force. Patients will be given an introduction to the task and an opportunity to practice several trials in the preoperative area while waiting for surgery to begin. Rest, movement preparation and movement execution will be analyzed as separate epochs. Beta and broadband gamma spectral power during each movement phase (rest, prep and move) will be analyzed separately. In our previous work (Rowland et al, 2015), the entire task took 3 minutes to complete.[1] The entire task will be videotaped and repeated no more than twice. Videotaping will occur using a high-resolution web camera secured to a computer monitor facing the patient. The video signal is cotemporaneous with all other data streams. Patients who are asleep will not perform the task or be videotaped.

All patients – whether awake or asleep – will undergo photography of the surgical site as well as any other aspect of the research necessary to reconstruct the electrode configurations (all patients) and/or behavioral task (awake, frameless DBS patients only).

Step 4: Fluoroscopy

At the conclusion of the recording, several fluoroscopic images will be taken to capture the position of the tDCS and sECoG electrodes in situ. Fluoroscopy is already used in the standard of care DBS procedure to verify placement of the DBS lead. Finally, the tDCS electrodes, sECoG electrode and VR goggles will be removed.

Subject Followup

Following removal of electrodes (and the VR goggles for awake, frameless DBS patients), the DBS procedure will then be completed. Research staff will follow up with each participant by phone within a week of the procedure to make sure the participants are not having any problems. Additionally, research staff will review each participant's medical record at 30 days after the procedure to collect information on clinical outcomes and any additional treatments, tests or procedures the participant may have had in the postoperative period.

10.0 Data Management

Once a patient is screened, they will be assigned a participant ID. Participant IDs will be assigned consecutively. We will maintain a database that accurately reflects all the patients that were screened and the results of eligibility evaluation (screen failure vs enrolled). For enrolled subjects, the specific types of data that will be collected include: 1) analog local field potentials from the sECoG electrode, 2) digital and analog output signals from the tDCS and VR goggle devices, 3) photography and videography data, and 4) imaging data (dicom files). Raw data will remain on data acquisition machines with encrypted hard drives and stored behind a locked door when not directly supervised in the operating room. Data will be copied from all data acquisition machines to a password protected network server under the participant ID. This will constitute the master copy of all data for the lab and will consist of separately stored coded and identifiable folders. The purpose of keeping a copy of the raw data on the data acquisition

machines is in case the server is interrupted and it is necessary to reconstruct the data. Portions of data will be copied to end-user devices (e.g., desktop, laptop, etc) for data analysis, however only the portion needed for analysis will be copied. As with data acquisition machines, any end-user device such as a laptop that physically leaves the lab will be encrypted (while desktop machines that do not leave the lab will not be encrypted). All data on data acquisition and end-user devices will be deleted at the conclusion of the study. A linking database associating the participant ID and patient identifiers will be maintained on MUSC Box, separately from the research data. Patient identifiers to be collected include first and last name, medical record number, gender, and telephone numbers. Telephone and medical record numbers are required for the 7-day phone call and 30-day chart reviews. Findings from the phone call and chart review will be stored in the linking database. Additionally we will collect information pertaining to disease severity for each subject, including year of diagnosis, laterality of worst symptoms, laterality of surgery, and pre- and post-surgical scale ratings. These measures will assist in correlating our physiological data with severity of disease for each subject. Photography and videography data will be stored in the identifiable folder on the password protected network server as well. The purpose of this data is to correlate movement dynamics with the ECoG signal. Finally, radiographic imaging data is used to plan the DBS surgery for each patient. We will save this data on a password protected network server in order to analyze and correlate with our physiological data. Only IRB-approved personnel will have access to the linking database. Consent forms will be stored in a locked cabinet in a locked laboratory in the Clinical Sciences Building at MUSC.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Data and Safety Monitoring Plan

The proposed research involves use of a neural stimulation device and warrants oversight by a Data Safety Monitoring Board (DSMB). The primary purpose of the DSMB is to ensure the safety of participants and the validity and integrity of data collected during the study. The overall framework involves biannual review of the enrollment, safety and adverse event data, and quality control data by the DSMB throughout the period of the proposed research.

DSMB composition

The DSMB will be appointed by the PI and will be composed of individuals who are not on the study team and have the following qualifications: (1) a board-certified Movement Disorders neurologist who also is a movement disorders researcher and is experienced in care of movement disorders patients, (2) a biostatistician with expertise in design and analysis of clinical trials and (3) a clinical electrophysiologist with expertise in transcranial stimulation and intraoperative monitoring. These three individuals bring substantial expertise adequate to monitor data and safety for the proposed research.

DSMB responsibilities

The responsibilities of the DSMB are as follows. Prior to any enrollment, the DSMB will review the study design, protocol, recruitment/enrollment plan, statistical analysis plan, and data and safety monitoring plan. Once enrollment begins, the DSMB will convene every 6 months to review the enrollment data, the safety and adverse event data and quality control data (see below for detailed data description). The DSMB will review the aggregated summary data as well as the individual participants' data (de-identified). The DSMB may provide

recommendations for any safety concerns. The DSMB may recommend stopping the study early if the protocol has significant safety concerns. The DSMB will review the results and document their reviews in writing. In summary, the stopping rules are if the study has unanticipated safety concerns. The DSMB will also be able to make recommendations for appropriate action to maintain a reasonable safety profile for the study. The PI will provide a report for the IRB to review that summarizes oversight activities, DSMB recommendations and any concerns regarding participant safety.

Safety reporting to the DSMB

Subjects may report safety issues with the study directly to the PI, any member of the PI's clinical and/or research teams, the MUSC Family Care Liaison, the IRB and/or ORI Director. In the absence of any such reports, the PI will systematically attempt to uncover any safety issues experienced by a subject during the one week followup phone call and/or 30-day chart review. Any of the following will be reported to the DSMB if noted by the subject during the one week followup phone call: severe headache unresponsive to pain medication, repeated falls/imbalance, excessive bleeding from wounds, scalp irritation or bleeding, change in vision, seizure(s), and/or return to the hospital. Any of the following will be reported to the DSMB if noted during the 30-day chart review: return to hospital, evaluation by another provider for findings related to deep brain stimulation surgery, imaging, lab values and/or other reports indicating complications from deep brain stimulation surgery. All the above-mentioned issues are outside of what would be reasonably expected for a normal postoperative course following deep brain stimulation. In accordance with HRPP Section 4.7, all the above-mentioned issues constitute adverse events and will be submitted to the DSMB for review (at 6 month intervals) in addition to being recorded in the adverse events log. Events that are unexpected, related or possibly related to a subject's participation in the research and suggests that the research places subjects or others at greater risk of harm than was previously known or recognized constitute Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) and must be reported directly to the IRB (in addition to the DSMB). Finally, all deaths will be reported to the IRB within 24 hours of learning of the death, unless the death is expected (e.g., due to disease progression).

12.0 Withdrawal of Subjects

Subjects may be withdrawn from the study without their consent, including stopping participation for safety reasons. For example, if during placement or operation of the tDCS or sECoG electrodes it becomes evident that continuing with the study protocol would present risk in excess of that outlined in this document, data collection for that subject may be terminated even if the planned DBS procedure is continued. These conditions may include damage to nearby structures such as the skin (for tDCS) or the cortical surface (for sECoG). At any time, subjects may also express desire to withdraw from the study. We will instruct the patients that, to withdraw from the study, all they need to do is to contact one of the members of the study team and express the desire to be excluded from the study.

13.0 Risks to Subjects

It is important to note that neither the tDCS nor sECoG electrodes will penetrate the brain at any time. Both electrodes will remain outside the brain itself. The tDCS electrodes will remain on top of the scalp; the sECoG electrode will remain underneath the skull and on top of the brain

surface (see Figure 1, Step 3). Only the DBS electrode performed for standard of care treatment will penetrate the brain. Research staff will follow up with each participant by phone within a week of the procedure to make sure the participants are not having any problems. Additionally, research staff will review each participant's medical record at 30 days after the procedure to collect information on clinical outcomes and any additional treatments, tests or procedures the participant may have had in the postoperative period.

Nevertheless, this study still poses certain risks as outlined in the following sections:

tDCS

Commonly reported side effects of tDCS occur at the site where the electrodes are placed: local scalp itching (30.4%),[16, 17] tingling or burning sensations (70.6%), transient headaches or stimulation-induced skin lesions (11.8%)[18, 19] and contact dermatitis (1.5%).[20] Report of headache or scalp lesion on visual inspection during the stimulation will trigger immediate removal of the electrodes, withdrawal of the patient from the study, and continuation with the DBS procedure. Furthermore, the electrodes will be sterilized with ethylene oxide prior to the procedure and will be secured in place with iodine-impregnated adhesive film, which will serve as an additional measure against any possible infection.

sECOG

Insertion of electrodes onto the brain surface may precipitate bleeding from a ruptured blood vessel, damage to nearby structures, and increased risk of infection due to foreign body. These risks were outlined in a recent study (Panov et al, 2017) documenting 200 cases of sECoG insertion during DBS surgery in which all study related procedures took place in 20 minutes or less.[15] In this study, 2 sECoG electrodes were unable to be inserted due to resistance and 8 others were associated with some complication, none of which were directly related to sECoG placement. The overall complication rate (again unrelated directly to sECoG insertion) was 5% (which is equivalent to the overall complication rate of DBS surgery without sECoG insertion) and **no infections related to the sECoG electrode occurred.** Nevertheless, to mitigate the risk of infection associated with sECoG placement, we will limit the total time dedicated to this study to 20 minutes. These electrodes come prepackaged sterilely and will be handled using standard operating room sterile procedure. Moreover, large cortical veins noted on preoperative imaging during surgical planning and/or any resistance detected during insertion will trigger immediate removal of the electrode, withdrawal of the patient from the study, and continuation with the DBS procedure.

VR goggles

Immersion in a virtual environment using a head mounted display has been associated with potential discomfort and health risks. In most cases, health implications are minor and consist of mostly temporary discomfort. Several studies have associated stereoscopic 3D viewing with eyestrain, visual discomfort and fatigue. However, Pölönen et al. concluded that viewing 3D environments for up to 2 hours is a relatively comfortable experience across all age levels, with short breaks reducing the risk of eyestrain and changes in visual function.[22] The Samsung Gear VR, which shares many characteristics with the Oculus Rift headset used in this project, was successfully used over a prolonged time in an inpatient setting with no severe adverse events. However, patients often described the headset as uncomfortable and difficult to focus.[23] To mitigate this risk, subjects in this study will wear the VR goggles for no more than 20 minutes. Awake, frameless DBS subjects will be instructed to notify a member of the IRB-approved

research team present in the operating room if they experience eyestrain, visual discomfort, discomfort associated with the headset and/or difficulty focusing. If awake, frameless DBS subjects report of any of these symptoms, the headset and electrodes will be removed and the standard of care DBS procedure will continue. Any data acquired will be retained for analysis.

Behavioral task

The primary risk from performing intraoperative behavioral tasks is fatigue. Patients will be asked to perform the reach-and-point motor task no more than twice. Patients will be asked during the interval if they need further rest and will be granted time (1 minute) to do so upon their request. Report of further fatigue will trigger immediate removal of the VR headset and electrodes, withdrawal of the patient from the study, and continuation with the DBS procedure.

Photography and videography

Awake, frameless DBS patients will be videotaped during performance of the task. We will also photograph the surgical site as well as any other aspect of the subject's research participation that will help us correlate the patient's condition with the ECoG data. In all, the videos and photos we record can include the full face, upper body, arms, legs and surgical site. Asleep patients will not undergo video recording, however we will still photograph the surgical site in these patients. Photography and videography carry a risk of loss of privacy. Photos and videos will be stored on a secure server. Only approved study personnel will have access to these files.

Fluoroscopy

In addition to the fluoroscopy images that will occur as part of clinical care for the placement of the DBS electrode, there may be additional fluoroscopy images that occur to evaluate the placement of the research electrodes. Effective radiation dose is measured in milliSieverts (mSv). Background radiation exposure from the environment (e.g., cosmic rays from space) is approximately 6 mSv per year. Each fluoroscopic image is approximately 5 microSieverts (μSv). According to the US Department of Energy, up to 50 mSV are allowed per year in adult radiology workers. Beyond this limit, additional radiation carries an increased risk of cancer. To mitigate this risk, the fluoroscopy will be administered by a certified radiation technologist who will use the lowest dose necessary for the image. Also, if the research electrode placement is captured in one of the fluoroscopic images taken as part of clinical care for the placement of the DBS electrode, no additional fluoroscopic images for research will be required.

Loss of Confidentiality

Additional risks include loss of confidentiality. To mitigate this risk, a linking database associating the participant ID and patient identifiers will be maintained separately from the research data on a password protected server and only IRB-approved personnel will have access to the linking database.

14.0 Potential Benefits to Subjects or Others

This research is not expected to provide direct benefit to individual subjects but may lead to improvements in care for patients suffering from movement disorders in the future. A successful study outcome may contribute to this improvement and may be used in future subjects undergoing similar procedures.

15.0 Sharing of Results with Subjects

Due to the extensive amount of time needed for data processing, it will not be possible to disclose individual study results to subjects or their healthcare providers. Incidental findings and other results of diagnostic tests associated with routine care of subjects will be shared with the subject and their physician by phone, writing and/or electronic medical record communication by the PI.

16.0 Drugs or Devices

The tDCS (not FDA-approved), sECOG (FDA-approved, packaged as a single-use sterile device, designed and marketed for direct contact with the brain) and VR goggle (not considered a medical device) devices will be stored in the PI's laboratory located in the Clinical Sciences building at MUSC. On the day of data collection, all devices will be transported to the operating room at MUSC then immediately transported back to the PI's laboratory at the conclusion of the recording.

17.0 References

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