Medical University of South Carolina
Protocol

PI Name: Gonzalo J. Revuelta, DO

Study Title: Effects of Neuromodulation and Rehabilitation of the Locomotor Network in Freezing of Gait

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A. SPECIFIC AIMS

Aim 1: To determine the effects of supplementary motor area low frequency repetitive transcranial magnetic stimulation (SMA LF-rTMS) + rehabilitation compared to rehabilitation alone on the locomotor network in patients with PD and FoG.

Hypothesis: SMA LF-rTMS followed by rehabilitation will decrease connectivity between mesencephalic locomotor region (MLR) and SMA more so than rehabilitation alone.

Aim 2: To determine the effects of SMA LF-rTMS + rehabilitation compared to rehabilitation alone on FoG severity in patients with PD and FoG.

Hypothesis: SMA LF-rTMS followed by rehabilitation will improve FoG severity (as measured by objective and subjective markers of FoG severity) more so than rehabilitation alone.

B. BACKGROUND AND SIGNIFICANCE

FoG is a debilitating condition, which occurs in the majority of patients with PD[1-3]. FoG often leads to falls, hospitalizations, or nursing home placement and has been found to be the most important predictor of poor health-related quality of life[2, 4-6]. Current treatment strategies aim to optimize response to available medical or surgical therapies; however, responses are limited, inconsistent and short lived. Previous rehabilitation strategies have yielded only modest improvements in gait parameters not FoG specifically, and there is no evidence of sustained efficacy. As our knowledge of the pathophysiology grows, we begin to understand that FoG is not purely a dopaminergic circuit phenomenon. Preliminary evidence from our group and others support the notion that FoG is a network dysfunction with significant contribution from cortical structures. Our observation of the reversibility of FoG following immobilization supports the plausibility of network modulation and rehabilitation as a therapeutic approach.

By characterizing locomotor network dysfunction in FoG before and after cortical inhibition and rehabilitation we can provide further evidence of increased cortical governance as a major contributor to

the pathophysiology of FoG. Furthermore, the pilot data gathered here will not only support the feasibility of neuromodulation of the locomotor network, but will support the use of cortical inhibition as a therapeutic approach to FoG. We believe that with our current understanding of the locomotor network, we can target the supplementary motor area (SMA) in a non-invasive way with rTMS, and normalize locomotor network activity. This approach will mimic the immobilization periods, releasing cortical control in a targeted manner. Once this maladaptive process is removed, patients will be primed to walk without cortical interference. This provides a therapeutic window where rehabilitative approaches designed to increase automatic gait. By performing this combined cortical inhibition and gait training repeatedly we propose we will achieve network normalization and reverse FoG while gaining considerable knowledge regarding FoG pathophysiology, neuromodulation and rehabilitation.

C. PRELIMINARY STUDIES

Preliminary Studies: We performed functional and diffusion MRI on 46 patients with PD, 22 patients with FoG and 24 PD controls. There was increased functional connectivity between PPN and multiple structures (including the SMA) within the motor network in FoG compared to PD-controls (see figure 1). We also found a significantly increased fiber count with diffusional kurtosis imaging (DKI) based tractography on tracts originating in the left PPN and ending in the SMA (see figure 2). Overall our data demonstrates the feasibility of the use of functional and structural MRI for evaluating these networks in our hands, as well as supporting the central hypothesis of increased cortical control.

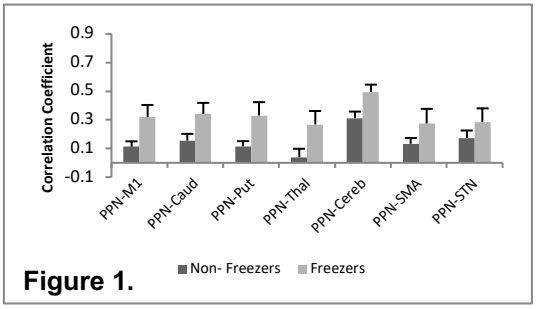

Figure 1.

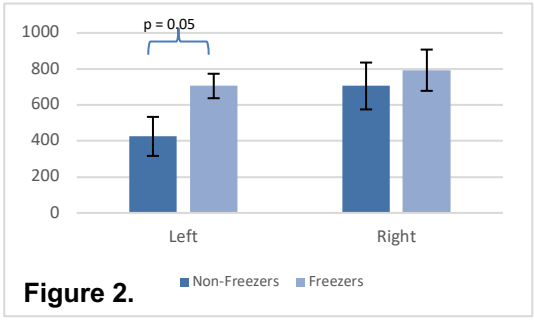

Figure 2.

We looked at dual task interference for velocity, step length, time to turn and overall task time on 23 subjects from our cohort that had full set of gait analysis data. We found dual task interference to be greater in patients with FoG compared to PD controls, particularly in the off medication state, and for the overall task and turning task (see Figure 3). This data supports the notion that dual task interference, particularly for turning is an important marker for FoG severity, and can be used as an effective outcome measure in our study.

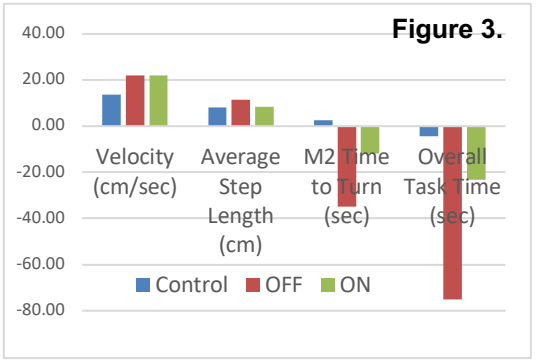

Figure 3.

D. RESEARCH DESIGN AND METHODS (including data analysis)

Imaging Protocol: Subjects will undergo identical imaging protocols before and after intervention. For structural imaging deterministic fiber-tracking algorithm based on DKI will be used, with a seeding region placed at the PPN to the ending region at the SMA. The anisotropy threshold for all subjects will be set at 0.20, angular threshold at 40 degrees, and step size at 1.5 mm. Tracks with length less than 60 mm were discarded and a total of 10000 seeds were placed. For fMRI, subjects will have eyes closed at rest (resting state or RS fMRI). BOLD time series will be extracted via SPM 12's marsbar toolbox from predetermined regions of interest (ROIs) including the left PPN, STN, pallidum, cerebellum, putamen, caudate, primary motor cortex, SMA, and thalamus. Time course correlations will be performed to determine a correlation coefficient between the PPN and locomotor network ROIs. For the interleaved TMS/BOLD protocol patients will lay supine in the MRI scanner with a TMS coil mounted in the MR head coil. Resting motor threshold (RMT) will be obtained, and the coil will be adjusted from the motor cortex to the SMA. Participants will then receive a run of TMS/BOLD (12 single pulses with 12 second interpulse interval at 110% RMT).

Table 1
Summary of Activities:
Screening Visit
Cognitive Assessment Questionnaires
Baseline Gait Analysis
Baseline MRI Visit
RS fMRI
Diffusion MRI
Interleaved TMS/BOLD
Intervention x 10 days
1Hz rTMS
Dual task training
Treatment questionnaire (day 10 only)
Post-Tx Gait Analysis
Post-Tx MRI Visit
Phone assessments (nFOGQ 1, 2 & 3 months)

Patient Selection: Subjects meeting diagnostic criteria for PD and documented FoG will be recruited from the MUSC Movement Disorder Clinic by clinical staff. Subjects with contraindications to MRI, or TMS (no history of seizures, no metal implants in head, no pregnancy) dementia, or inability to complete the walk 30 feet in the off state without assistance will be excluded. Questionnaires to assess cognitive, quality of life (PDQ39) and FoG assessments (nFOG-Q[7]) will be administered at screening visit and post intervention. Standard motor (Unified PD rating scale; UPDRS) assessments will be performed at the time of gait analysis (see Table 1). Women of childbearing potential will have a urine pregnancy test.

rTMS Protocol: Active rTMS will be delivered to the bilateral SMA region at the following parameters: 1 Hz, 1200 total pulses, 110% resting motor threshold (rMT), 20 minutes total for ten total sessions. Sham stimulation will be administered using the Magventure B-65 placebo system in which the sham side of the coil was placed over the pre-SMA (no magnetism delivered) and electricity is delivered to scalp stimulating electrodes in the same pulse sequence as active stimulation replicating stimulation sensation. This device is FDA approved for Depression. Participants will be given a questionnaire to complete about their thoughts on the treatment. This will occur on the last day of the intervention period (10th day of intervention).

Rehabilitation Protocol: Subjects will undergo ten, 20 minute, dual task training sessions immediately following each rTMS session. Dual task training will consist of repetitive trials of straightaway walking and turning while adding increasingly difficult concurrent cognitive tasks (working memory language and calculation). Subjects will be instructed to focus on the cognitive task, not on their gait with the goal of improving gait without increasing error rate on the cognitive task. Variations of this protocol have been successfully implemented in this patient population[8, 9].

Trial Design and outcomes: Subjects will be randomized to either active rTMS + rehabilitation or rehabilitation alone at a 2:1 ratio (10 active: 5 control). An additional 6 patients will be randomized to either active rTMS + rehabilitation or rehabilitation alone at a 1:2 ratio (2 active: 4 control). This will bring total number of subjects to 12 active and 9 control. The primary outcome measure will be dual task interference for turning.

Gait Assessment/Analysis Protocol: Gait is assessed at baseline and post intervention. Subjects will walk on an electronic walkway (GaitRite + M[2]) which will capture straightaway walking and turning, in the off medication and on medication state, under single and dual task conditions (2 trials each), capturing multiple spatiotemporal parameters. Dual task interference for overall task time (timed up and go), step length, velocity and nFOG-Q scores will be secondary outcomes. Gait assessment will be videotaped.

Statistical analyses: The sample size estimation is based on the primary (mechanistic) aim (Aim 1), since the effect size of the clinical aim (Aim 2) has not yet been established. A two group t-test with a 0.05 two-sided significance level will have 80% power to detect the difference between a treatment group mean of 0.11 and a control group mean of -0.06 assuming that the standard deviation is 0.10, when the sample sizes in the two groups are 12 and 9, respectively (a total sample size of 21). The mean and standard deviation estimates are based upon the functional connectivity strength for the FOG+ and combined control groups as reported in Fling et al 2014[10]. The observed treatment effects on FoG severity of the treatment group, as compared to the control group, will be used to determine the effect size of this therapy, and estimate the sample size for future trials aiming to determine efficacy.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

Participants will range in age from 18-80 years of age. Patients will be recruited from the Movement Disorders clinic at MUSC. The subject population will consist of people with a diagnosis of Parkinson's disease, as defined by UK Brain Bank diagnostic criteria for Parkinson's disease that have FOG as identified by item 14 of the UPDRS. Parkinson's disease commonly affects both men and women of all ages. Since Parkinson's disease does not discriminate gender or age, subjects classified as "vulnerable" may be included. Our study population reflects the demographics of this population and area that meet the inclusion criteria.

As subjects are seen for their medical treatment in the Movement Disorders Clinic, we will request their consideration to participate in the study. We will review the premise of the study as well as consent form and address any questions or concerns to the subject's satisfaction assuring them that participation will not affect their current or future medical care. The subjects will be given a copy of the consent in clinic to read. If the subject is interested in participating, they will be scheduled for a screening visit. If the subject has not had an opportunity to read the consent at home, they will be given the opportunity to do so at screening and again the study protocol will be explained, and questions will be answered. If the subject decides to participate they will sign the written institutional IRB approved consent form as well as the HIPAA authorization at that time. All information and data will be stored in a locked office in the Movement Disorders Office, only accessible by the study staff.

In some cases, there may be some subjects that do not have a scheduled appointment during the months designated for the study and we will need to contact the subjects by telephone to offer the opportunity to participate in the study. They will be contacted by the treatment team first, if interested they will then be contacted by the study team. If the subject is interested, we will schedule a screening visit (as described above) in order to review the study in person with the subject. If the subject wishes to proceed then we will complete and sign the consent form and HIPAA authorization and proceed with the remaining study visits.

Our only "vulnerable" population that will be sampled in this study is the elderly with the concern of co-morbid conditions that may affect their ability to participate; however, the inclusion criteria specifies that they will be able to physically participate in the study. We will not be excluding any gender or race/ethnic population that fits the inclusion criteria. Our sampling will reflect the population of the Movement Disorders clinic. No children are involved in this study. There will be no collaborating sites involved.

b. Sources of Materials

Once potential subjects are identified and agree to enroll in the study they will be requested to sign the HIPAA authorization and informed consent. They will be assigned a sequential subject number for identification purposes and all subsequent materials collected will contain only their subject number. The research material that will be obtained during the study is noted above and will be kept in individual data binders assigned to each subject.

c. Potential Risks

The subject may voluntarily withdraw from the study at any time. This decision will have no impact upon their current or future medical care in our facility.

The physical risks to the subjects related to the Gait Assessment protocol are similar to those risks present when walking down the sidewalk. Subjects that are asked to delay the time they take their

morning medications or turn off their DBS device may feel their Parkinson's symptoms for a longer period of time on the morning of that visit. Patients are often asked to delay their morning medications when evaluated in our clinics as part of standard practice. In order to minimize this delay these visits are scheduled first thing in the morning. Physical risks would include musculoskeletal injury due to fall or overexertion. A harness will be used when subjects walk on the treadmill and a physical therapist will be walk along side the patient when subjects are walking on the electronic walkway or hallway.

Loss of Confidentiality Risk**:** There is a potential risk of loss of confidentiality with this study. The video will show your face as you walk. The videotape will be stored on a secure, password-protected server at MUSC, and only MUSC staff will have access to it.

The physical risks to the subjects related to the MRI are primarily related to movement of any iron containing items in the MRI room, or of any iron containing implant. Patients with iron containing implants are excluded from the study. Precautions have been taken to eliminate this risk. Iron containing items are not allowed in the MRI room. Patients may also experience discomfort or emontional stress related to the MRI. These discomforts are primarily related to the feelings of claustrophobia or loud noise generated by the MRI scanner. Patients are provided with ear plugs and are educated about the procedure beforehand to reduce discomfort.

The following is a summary of TMS related risks:

Physical: There are minimal risks associated with rTMS, which are further minimized when proper screening is completed. Nonetheless, there are several physical risks associated with rTMS. In very rare circumstances seizures can be induced by TMS but all instances of TMS induced seizures were isolated and no long term inducement of seizures has resulted from TMS. There are also a host of physical side effects associated with rTMS, which vary drastically by location of stimulation. These include but are not limited to: headaches; scalp soreness; ear discomfort; hearing loss; fainting or faintness; and muscle pains. Among published rTMS studies that targeted the pre-SMA or vertex, no seizures have been reported. Previous research has reported that rTMS to the pre-SMA is well tolerated. Fainting may also occur during exposure therapy, although this is rarely reported.

Potential risk of a seizure: In designing this experiment, we have followed the latest safety guidelines for TMS. Despite these precautions, there is a very small chance that you could have a seizure as a result of rTMS. Eight seizures have been noted in previous studies, with six of them occurring in healthy volunteers without any history of seizures, brain tumors or traumatic brain injuries. All of these seizures have occurred during rTMS with the participant in the treatment chair and a trained operator on hand. All seizures have stopped by themselves without any medication. No participants have had any problems after the seizures. MUSC has a plan for dealing with fainting and seizures, and every TMS researcher is familiar with it. If you have a seizure, you will be made to lie down with your legs elevated. An emergency response team will be called. Most seizures, including those caused by rTMS, last less than 60 seconds and do not require any medication. A neurologist will evaluate you once you recover from the seizure. Any participant who has a seizure cannot continue with the study.

Potential for scalp discomfort and headaches: Some people report mild discomfort when the magnetic pulses are applied over the scalp. A small number of people (~5%) report headache following rTMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies.

Potential worsening of mood with TMS: rTMS is an FDA-approved therapy for treatment-resistant depression. There is no evidence that rTMS causes depression or worsens mood. We will work closely with you to familiarize you with the TMS equipment and setup to help with anxiety you may have about

the procedures. The Brain Stimulation Laboratory team members at MUSC are experienced with the proposed procedures and are among the leading experts in the field of brain stimulation and TMS.

Other potential effects of TMS on brain tissue: TMS is thought to be safe, with no brain damage, despite extensive use in humans and other animals. We have reported a safety study looking at the MRI scans before and after 2 weeks of daily left prefrontal TMS for depression. No structural changes were found in left prefrontal lobe of patients who received active TMS compared to placebo. We have also performed an MRI diffusion imaging study before and after TMS/fMRI and found no deleterious effect of TMS on brain tissue at the site of stimulation.

Potential hearing loss: The TMS coil generates a high-energy click that may cause hearing damage. Humans exposed to TMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours. Foam earplugs can protect against these changes and will be worn during TMS sessions.

Potential changes in cognitive function: There have been no reports of long-term changes (more than a minute) in cognitive function (memory, attention, etc.) in TMS studies. Safety studies specifically looking for these changes did not find any effects of TMS with the exception of one open study in which healthy volunteers were exposed to 150 trains of TMS at different site of stimulation in an experiment that lasted more than 3 hours. There was a significant decrease in scores on a logical memory test. The stimulation parameters exceeded the recommended safety range and there was no control for patient fatigue or other non-specific effects.

Safety in case of pregnancy: This protocol will exclude pregnant women. The risks of using TMS with pregnant women are currently unknown. Please inform the research team if you are pregnant or think that you might have become pregnant during the study. A pregnancy test will be performed before the experiment begins.

Unknown Risks: TMS is an experimental procedure that has not been approved by the FDA as anything other than a therapy for treatment-resistant depression. The Principal Investigator will let you know if they learn anything that might make you change your mind about participating in the study.

Social and Economic: The treatment design will require that all participants attend daily, 1 hour treatment sessions for 3 concurrent weeks during each work day (Mon. - Fri.). This may cause disruption of normal social and work schedules and may even result in work hours lost. To minimize this potential problem, sessions will be scheduled around the participant's personal schedule.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Subjects who meet the inclusion/exclusion criteria will be recruited from the Movement Disorders Clinic. Consent will be obtained by the study personnel. All research data and informed consents will be collected and stored in a locked office in the Movement Disorders office only accessible to the study staff. A source document worksheet will be utilized to document the consent process including HIPAA authorization and ensure each patient has been cleared medically by their treating physician and specialist if deemed necessary. A copy of the informed consent and HIPAA authorization will be given to the subject for their personal records.

b. Protection against Risk

The participation of human subjects in research falls under the jurisdiction of federal regulations (45 CFR 46 and 21 CFR 50 and 56). MUSC investigators are granted the privilege of working with human

subjects under normal assurance to the government that such research complies with regulations protecting human subjects. The university has a federal-wide assurance for research with human subjects (FWA 00001888, Feb 2002), and is in compliance with federal policy governing use of human subjects. Individuals involved in human subject research at MUSC are required to complete the Collaborative IRB Training Initiative (CITI) offered on-line by the University of Miami. All human subject protocols are reviewed through an academic Institutional Review Board (IRB) process. The Office of Research Integrity coordinates the activities of three IRB committees. The MUSC IRB is accredited by the Association for the Accreditation of Human Research Protection Programs.

This study does not require subjects to exercise or exert themselves in any way, the gait training protocol expects patients to maintain self selected speed, however it does challenge their gait by having them perform cognitive tasks while walking, always accompanied by a therapist. Patients will be monitored throughout the study for the development of any adverse events. An adverse event related to study procedures would be the development of new onset symptom directly related to the gait analysis or MRI procedures. A serious adverse event would be defined as any event that jeopardizes the subject's health, requiring hospitalization, resulting in significant, persistent disability, birth defects, congenital anomaly or resulting in a life threatening event or death. Should any medical complications arise during active testing, the test will be stopped and immediate medical care will be rendered. The subject could be directed to one of our on-campus emergency rooms to further administer care if needed. Additionally, the subject will have the ability to stop active testing (ie the treadmill or MRI) at any point during the testing (treadmill has an emergency stop button and patients can communicate with MRI technician) and would be able to dis-enroll from the study altogether at any point during the time of the study. To protect confidentiality, subjects will be assigned a unique study identifier. This is in order to eliminate identifying Protected Health Information (PHI) on all data collection sheets, including participant diaries and investigator records. All signed consents and source document worksheets pertaining to the study will be stored in a locked office in the Movement Disorders Research Office. During the course of the study, user access to this information and participant identifiers will be restricted to staff associated with the study. Computerized data will be stored on a secure, password protected, network.

Participants must meet specific medical and historical screenings (e.g., no history of seizures, no metal implants in head, no pregnancy) to minimize risks associated with repetitive transcranial magnetic stimulation (rTMS). Participants will complete a TMS safety screening that includes a series of basic health and history questions that are used to thoroughly mitigate risk of injury from TMS. The TMS safety screening is based on internationally agreed upon standards of safety. The screening will be administered in interview format to candidate participants and to enrolled participants.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

By completing this study subjects will be able to understand better the severity of the freezing of gait, how the currently prescribed medications and stimulation affects it, and will also have information about their cognitive abilities. This information can be provided to their treating physicians to help guide treatment decisions. Furthermore, the proposed intervention may be of benefit for their walking.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Identifying an effective means of measuring FoG severity will make it possible to test the efficacy of multiple potentially effective therapeutic agents. Understanding the pathways most related to FoG via our imaging protocols would yield potential therapeutic targets for this condition. Finally, collecting pilot data on this specific intervention may yield sufficient data to justify a larger trial.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

The participant is at minimal risk during the intervention; however, safety precautions will be taken by securing medical clearance for all participants. During the Motion Analysis and gait training portion of the study, subjects will be attended by the research therapist at all times. We do not anticipate any cardiovascular discomfort since subjects will not be asked to exert themselves in any way. Lab technician will take all necessary precautions including the use of a harness to avoid falls. Additionally, the participant will be aware that they may discontinue the study at any time. Subjects will be aware of all possible side effects at the time of screening and will be instructed to notify the PI or Co-PI immediately if they experience a side effect.

Internationally recommended TMS screening procedures will be completed prior to in person screening, during in person screening/enrollment, and prior to each rTMS session to minimize the chance that participants are at risk for severe risks associated with rTMS (e.g., seizures). Short term side effects such as migraine headaches can be minimized by recommending that participants take an OTC pain killer (e.g., Ibuprofen) on their own volition.

If an emergency should present, the facility is located on the MUSC campus with 24-hour access to the MUSC Emergency Room that is staffed by an emergency response team.

If during assessment of a subject's UPDRS score, the subject is found to be severely depressed or suicidal, the investigator will verify the patient's current mental health status and ensure the patient is directed and transported to the nearest psychiatric emergency services immediately or arrange for expedited evaluation by psychiatric services if the patient is not actively suicidal.

Data will be kept stored in a locked office in the Movement Disorders Research Office. During the course of the study, user access to this information and participant identifiers will be restricted to staff associated with the study. Computerized data will be stored on a secure, password protected, institutional approved database.

F. REFERENCES/LITERATURE CITATIONS

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G. CONSULTANTS

n/a

H. FACILITES AVAILABLE

The Center for Rehabilitation Research in Neurological Conditions houses two separate laboratories for assessing gait, and has facilities in the third floor hallway that are typically used for gait training. The lab is equipped with state of the art equipment capable of various measures of gait and movement.

The clinical research program is housed in 208B Rutledge Avenue at the Murray Center for Research in Parkinson's Disease, together with clerical support personnel and office machinery. The Program also sees outpatients in the Rutledge Tower, a 158,000 sq foot modern complex for ambulatory care. The clinical laboratory is also house in the building with a staff experienced in the performance of clinical trials, under the direction of a Clinical Research Coordinator. Portable digital video recording is present in the Neurology Clinic as well as video studio in the research facility. The performance site complies with regulations cited in 45 CFR Part 46.

3T MRI scanners are available in the Center for Biomedical Imaging at 30 Bee Street or Rutledge tower.

The Brain Stimulation Lab (BSL) is a series of labs and offices (>3000 square feet) primarily located on the 5th floor of the Institute of Psychiatry (IOP). BSL studies use electromagnetic approaches as either research tools investigating neuroscience questions or as investigational or FDA approved treatments for brain diseases. Techniques actively being used by BSL researchers and their collaborators include: transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), electroconvulsive therapy (ECT), deep brain stimulation (DBS) and epidural cortical stimulation (epCS). TMS is a non-invasive technique for mapping brain functions and possibly treating neurospychiatric disorders such as Parkinson's disease, chronic pain and depression. MUSC's BSL team has been a world leader in TMS research since 1995, performing basic research studies using TMS as well as using TMS in clinical trials, such as an NIMH-sponsored study of depression (OPT-TMS) and studies of TMS to inhibit pain, determine if TMS can change food cravings, and determine if TMS can help modify symptoms in stroke patients. ECT, VNS and TMS are clinical services offered within the BSL. BSL researchers at MUSC were the first in the world (in 1998) to implant VNS devices in patients with major depression who had not adequately responded to traditional antidepressants. DBS and epCS are more invasive than TMS or VNS, but are less invasive than traditional brain surgery, where the brain is permanently lesioned. DBS of the thalamus is approved for the treatment of Parkinson's disease and the BSL has studies underway using DBS or epCS for treatment resistant depression. Members of the BSL team overlap and collaborate with the Center for Advanced Imaging Research (CAIR). In some instances, brain stimulation techniques are delivered in conjunction with fMRI studies to examine relevant circuitry.

Current equipment in the BSL includes 14 TMS machines, some of which are historical display pieces: a 1993 Cadwell® High Speed MES-10 (with a water-cooled figure-8 coil), a Dantec® MagPro (with a figure-8 and a round coil) and newer Dantec machine, four NeoPulse Neotonus® Model 3600 stimulators (with solid focal coils and sham coils), a Magstim® Rapid, Super-Rapid and Bistim machines (with figure-8 and double- cone coils). We also have a new Brainsway H-coil device and a Neuronetics Neurostar machine. For determining motor thresholds, the BSL has a Dantec® Cantata EMG machine and a laptop computer with MacCRO Spike software and Colborne amplifiers. The ECT suite has two MECTA Spectrum 5000Q machines and a Thymotron IV. Desktop computers with 22"

LCD monitors run Brainsight®, a software program for frameless stereotaxy used for image-guided targeted TMS.

The laboratory also contains a resting ECG analysis system, phlebotomy chair, exam table refrigerator, automated blood pressure monitor, ophthalmoscope, and an L-shaped counter with two sinks. There is a nasal oxygen supply and an emergency cart. The BSL has 3 image analysis workstations networked directly to the Center for Advanced Imaging Research (CAIR) for rapid image data analysis and transfer of functional imaging data needed to guide TMS placement using Brainsight. The BSL psychometrician utilizes a designated neuropsychological testing room containing desktop and laptop computers to run neurocognitive and attention test software such as the CPT, PsyScope.1.2.1, visual working memory task, WCST, etc.

Previous studies in the BSL have ranged from clinical trials in unipolar depression, bipolar affective disorders, borderline personality disorder (BOPD), chronic pain and acute laboratory pain, to challenge studies in generalized anxiety disorder, post-stroke aphasia, Tourette's syndrome, Parkinson's disease and schizophrenia. There are numerous studies as well integrating TMS with functional imaging (SPECT tracers injected in this lab or interleaved TMS/fMRI studies in the CAIR). Additionally the BSL was funded through the Defense Advanced Research Projects Agency (DARPA) to perform sleep-deprivation studies in healthy adults and use within-individual fMRI-guided TMS to determine if TMS can produce improvements in performance.

Inter-TMS-administrator reliability is established across all clinicians and scientists involved in studies to insure safety and standardization of TMS delivery and minimal, standardized interaction with research patients during TMS delivery. TMS treatment is logged in terms of the number of magnetic stimuli exposure for both study patients and researchers present in the room. Weekly meetings are held to discuss clinical and research related issues as well as to share the latest scientific findings and to discuss future projects related to the field. The BSL also serves as the international editorial office headquarters of Brain Stimulation, Basic, Translational and Clinical Research in Neuromodulation, published by Elsevier

I. INVESTIGATOR BROCHURE

n/a

J.APPENDIX

n/a