

TITLE: Transcranial Direct Current Stimulation for Freezing of Gait in Parkinson's Disease

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1) Protocol Title

Transcranial Direct Current Stimulation for Freezing of Gait in Parkinson's Disease

2) IRB Review History

N/A

3) Objectives

The goal of this research is to quantify the effects of unilateral anodal transcranial direct current stimulation (tDCS) in patients with Parkinson's Disease (PD) and freezing of gait (FOG). We will test the effects of unilateral transcranial direct current stimulation (tDCS) in combination with locomotor training.

Aim1. Quantify the effects of tDCS on freezing of gait in patients with PD. tDCS will be administered together with locomotor training to patients with PD and with FOG. Temporal and spatial gait kinematics will be measured using a portable accelerometer-based system. The primary outcome will be gait velocity. Secondary outcomes will be Timed Up and Go Test (single and dual-task), the freezing of gait questionnaire, Unified Parkinson Disease Rating Scale (UPDRS), and percentage time spent with FOG during the timed up and go (TUG), and postural sway while standing (single and dual-task).

Aim2. Quantify the effects of anodal direct current stimulation on cortical excitability of the motor cortex. Effects of anodal tDCS will be assessed in patients with PD and with freezing of gait. Transcranial magnetic stimulation (TMS) will be used to probe cortical excitability and plasticity of motor cortex pre and post intervention.

Aim3. Evaluate the cortical/subcortical changes induced by tDCS. We will use magnetic resonance spectroscopy (MRS) to identify changes in brain glutamate and GABA in patients with PD and FOG.

4) Background

The neurological mechanisms underlying gait dysfunction and in particular freezing of gait (FOG) are unknown, but it is thought that impaired gait automaticity may cause patients with Parkinson's Disease (PD) to rely more heavily on cortical control for locomotion. It has been postulated that interventions that restore the normal excitability of the motor cortex would be associated with better motor function ¹(1). Noninvasive techniques such as transcranial direct current stimulation (tDCS) have been employed in various neurological conditions to modulate the cortical excitability and with improved functional outcome.

Studies of transcranial direct stimulation suggest that tDCS improves function presumably by activating central neuromodulatory mechanisms ²(2) and spinal locomotor pattern generating circuitry ³(3). The current proposal seeks to combine tDCS and locomotor training to assess effects in walking in patients with PD. tDCS decreases the threshold for neuronal excitability and has neuromodulatory effects on cortical and subcortical structures improves the motor and cognitive functions in PD ⁴(4). We hypothesize that tDCS in combination with locomotor training will reduce freezing of gait. The effects on cortical excitability will be quantified using TMS and neurotransmitter changes associated with this intervention will be explored using MR spectroscopy.

The long-term goal of this project is to develop strategies for persons with PD that will facilitate optimal restoration of walking function. These studies are significant in that they will advance the field as relates to: 1) development of optimal strategies to improve walking function in patients with PD, and 2) understanding the dysfunction neural networks involved in FOG. The studies are innovative in that they: 1) determine the value of using tDCS as a conditioning intervention to modulate the excitability of the nervous system and thereby improve responsiveness to training, 2) seek non-pharmacological approaches for managing FOG and 3) explore the mechanism of action of tDCS on FOG.

Identifying noninvasive therapies for walking would bring a significant benefit for patients with PD, increase quality of life and decrease burden on caregivers. This research is relevant for the aging population in the United States and may be beneficial for patients with other neurological conditions such as frontal gait disorders, patients with white matter disease and cognitive impairment. Identifying the best stimulation parameters with the least side effects will set the stage for future clinical trials.

5) Inclusion and Exclusion Criteria

Patients with Parkinson's Disease as determined by the UK Brain Bank Criteria and Hoehn and Yahr (H&Y) stages 2-3 will be considered for enrollment. Patients will be screened at the University of Miami Movement Disorders Clinic by the Principal Investigator (PI) and his team.

Inclusion Criteria:

- Ages 18- 80
- Parkinson's Disease Hoehn and Yahr stages 2-3
- Presence of Freezing of Gait as per the freezing of gait questionnaire.
Participants will qualify if they report 2 or more episodes of freezing per week

- Stable medication regimen
- Time to complete Timed up and go (TUG) between greater than 12 seconds

Exclusion criteria:

- Medical or orthopedic conditions that would interfere with gait training for 30 minutes
- Unable to perform timed up and go
- History of seizures
- Implanted deep brain stimulator, pacemaker or any other electronic device
- Dementia as defined by mini-mental state examination (MMSE) equal to or below 24
- Adults unable to consent, individuals who are not yet adults (infants, children, teenagers) pregnant women and prisoners will not be considered for participation

6) Number of Subjects

Forty subjects with PD and FOG will be recruited. Subjects with diagnosis of PD according with UK PD brain bank criteria, H &Y stage 2-3 and presence of FOG will be considered for the study.

7) Study-Wide Recruitment Methods

Potential subjects will be recruited from the clinics at the University of Miami-Movement Disorders Research Center, other health care providers in the Miami community and the local Miami community through support groups and public spaces. An experienced clinical trial team is currently in place to assure that the studies are conducted in a manner which allows for accurate, efficient and timely collection of data and provides a safe and pleasant environment for the patients. The Clinical Trial Staff have all received training and certification to conduct clinical trials from the University of Miami Research Administration and have been trained and currently follow Good Clinical Practice Guidelines to assure the safety and protection of study participants. The Center currently works closely with the National Parkinson Foundation and all of its local chapters and support groups to facilitate patient recruitment through multiple resources provided to the Center by the National Parkinson Foundation.

The study investigators will discuss the study with patients who have been diagnosed with Parkinson's Disease and meet the eligibility criteria. Patients with Parkinson's

Disease H&Y stage 2-3, on a stable medication regimen and without major medical problems (i.e., cardiac problems, malignancy, h/o of seizures) will be candidates for the study. The subjects will be provided with an overview of the objectives and procedures, and with an informed consent form in their language. If patients agree to participate in the study a screening visit will be scheduled to assess the eligibility for participation.

8) Study Timelines

Each individual selected to participate will participate in a baseline evaluation visit, 9 training visits, and post-test evaluation visit. Evaluation visits are estimated to be 3 hours, and training visits 45minutes.

Visit #1- Pre-test assessment including gait, postural sway, cognition and TMS measures will be collected. Participants may divide this into two sessions, to accommodate for a shorter test duration.

Visit #2-9- Participants will participate in a 30 minute gait training protocol administered by trained personnel with tDCS augmentation. These visits will be scheduled 3 times per week for 3 weeks totaling 9 training sessions.

Visit #10- Post-test gait, postural sway, cognition and TMS measures will be collected. Participants may divide this into two sessions to accommodate for a shorter test duration.

We estimate the study will be completed in one year.

9) Study Endpoints

- Primary outcome change in walking speed
- Secondary outcomes are:
 - Freezing of gait: freezing of gait questionnaire, time spent with freezing of gait
 - Motor function: motor scores of Parkinson's Disease- UPDRS (part 3)
 - Locomotor function (biomechanical analysis [Gait Mobility Lab system]): 10 meter walk (speed and stride length), TUG (single and dual-task), postural control (postural sway)
 - Neurophysiological: motor threshold of the primary motor area as measured by TMS, and Glutamate/GABA ratio, as measured by MRS.
 - Neuropsychological: backward digit span, oral version of the trail making test, Montreal cognitive assessment (MOCA), and the consonant trigrams test

10) Procedures Involved

A feasibility study will be performed to evaluate the influence of tDCS in conjunction with locomotor training (LT) in participants with PD. Participants will undergo a battery

baseline assessments, followed by 3 weeks of locomotor training associated with tDCS. After training, participants will undergo a battery of post-test assessments.

On the first visit (baseline assessments), all outcomes outlined in section 9 (Study Endpoints) will be performed. Baseline and post-test assessments will be performed by the study personnel and under the supervision of the principal investigator and co-investigator at the Department of Neurology, University of Miami Miller School of Medicine.

Locomotor training (LT) will take place following the pre-test assessment. Participants will engage in locomotor training 3 times per week, in 30 minute sessions, for a total of 9 sessions. During LT, participants will receive non-invasive tDCS (2mA, Phoresor device) applied to the supplementary motor area of the hemisphere controlling the weaker leg, utilizing superficial small electrodes applied to the participant's scalp. Stimulation will be administered under the supervision of the co-investigator, whom has expertise in brain stimulation and has a track-record that includes the use of tDCS in neurological populations. LT will be administered by a licensed physical therapist at the University of Miami Wellness Center (medical campus and/or coral gables campus).

Following the 3-week training, participants will undergo post-testing, wherein they will repeat all outcomes outlined in section 9 (Study Endpoints).

Data Analysis:

Outcome measures (primary and secondary) post-training will be compared to pre-training values. The data will be inspected for homogeneity of variance and normality of distribution. We will test for significant changes in outcomes of motor function, locomotor function, neuropsychological performance and neurophysiological outcome measures from pre-test to post-test. Statistical analysis will be performed using the Statistical package for the Social Sciences 15.0 (SPSS, Chicago, Illinois). A paired t-test will be used to compare the effects from pre-intervention to post-intervention. The significance level for the study will be set at alpha < 0.05.

Testing Procedures

Assessments will be performed while participants are ON medication.

Gait speed and stride length - These outcomes will be measured during the 10 meter walk and TUG using the Gait Mobility Lab System (APDM device). The best 3 recordings out of 5 measurements will be used for quantification.

TUG - Will be measured using a stopwatch, and the Gait Mobility Lab System (APDM device). For healthy subjects the mean value of TUG is 9.52 sec with SD of 1.38 while for Parkinson's patients the mean value of TUG is 13.83 sec SD 4.41. The best 3 recordings out of 5 measurements will be used for quantification. **Postural control:** postural sway will be quantified during quiet standing, and quiet standing while

performing a serial subtraction task using the Gait Mobility Lab System (APDM device). The best 3 recordings out of 5 measurements will be used for quantification.

FOGQ - Freezing of gait Questionnaire (FOGQ) will be administered by a trained member of the study team. It consists of 16 items regarding gait and falls and is reported as a score from 0-16.

UPDRS - United Parkinson's Disease Rating Scale (UPDRS) will be performed by a trained member of the study team. The UPDRS contains 4 sections. Part 1 assesses the non-motor aspects of daily living, part 2 assesses motor aspects of daily living, part 3 is a motor examination of PD and part 4 quantifies the presence of motor complications like dyskinesias, fluctuations or dystonia.

Neurophysiological assessment- We will use single pulse TMS to evaluate the excitability of the primary motor area utilizing the Magpro X100 device and a figure-of-eight coil. Surface electrodes will be placed on the first dorsal interosseous (FDI), and motor evoked potentials will be elicited to determine threshold of activation and amplitude of response at stimulator intensity of 120% of motor threshold.

MR spectroscopy will be performed with a 3T magnet. Single-voxel acquisition method will be used to acquire data from the primary motor cortex to measure glutamate and glutamine. An in-house developed software by Dr. Maudsley ⁵(19) will be used to quantify metabolites from such TE-averaged spectra with simulated spectral prior generated using the NMR parameters of the metabolites of interest- figure1 ⁶(20). GABA in the medial primary motor cortex region will be measured using a published edited single-voxel MR spectroscopic method ⁷(21).

Intervention and Training Procedures

tDCS intervention: anodal tDCS of the supplementary motor area of the hemisphere controlling the weaker leg (determined by verbal report) will be delivered during every training session (total time=30 mins, intensity=2mA) while participants are in the ON state of their medication schedule.

Locomotor Training: The training paradigm will focus on strategies for which there is evidence of effectiveness in persons with PD. Briefly, during the first week, individuals practice the primary motor task, and motor dual tasks (DTs), receive frequent feedback and make use of auditory and visual cues. On the second week, cognitive-motor DTs are introduced and visual and auditory cues are decreased or removed in an effort to increase the challenge and to aid the individual in establishing an internal representation of the requirements necessary to carry out the walking training. Tasks increase in complexity in weeks 2 and 3 to promote transference of possible gains in gait performance to other motor behaviors found daily life without dependence on external stimuli.

11) Data and Specimen Banking

N/A

12) Data Management

We estimated the power based on a range of sample sizes, effect sizes at a 0.05 significance level with a two-sided t test. A total sample size of at least 40 PD patients will achieve at least 80% power to uncover an effect size of 0.94 at a significance level of 0.05 for a two-sided test. This effect size is corresponding to a mean difference of 15% (15.2cm/s) given that the square root of the within mean square error is 16. We performed the power analysis using PASS 2008 Software (NCSS, Kaysville, UT). For the data analysis, we will estimate the effect of tDCS on changes in gait velocity, TUG and UPDRS score using mix-effects models. All analyses will be conducted using SAS (version 9.2, SAS Institute Inc., Cary, NC).

All data files will be secured at the University of Miami. Data management will be monitored by the PI on an on-going basis.

Paper records:

Paper records will be housed in a locked file cabinet, in a locked room, with controlled access. Only the PI and associated research staff will have access to the records. Each participant will be assigned a unique study ID number. This ID is affixed to all data forms and is kept separate from the individual's identifying information, except in one electronic file which is password-protected and accessible only by the PI.

Study participants will not be specifically identified in any publication of the research results.

Records will be kept for 7 years after completion of the study, at which time they may be destroyed.

13) Provisions to Monitor the Data to Ensure the Safety of Subjects

Data Monitoring:

Data and safety monitoring will be the primary responsibility of the Co-Investigator, with on-going oversight by the study PI. All participant personal and medical information will be treated as confidential and safeguarded in accordance with the Privacy Act of 1974 and the Health Insurance Portability and Accountability Act of 1996 (HIPAA) which protects the privacy of individually identifiable health information, and identifiable information being used to analyze patient safety events and improve patient safety.

Safety:

Safety of participants will be monitored by the Co-Investigator on an on-going basis and reviewed by the study PI on a weekly basis. The study PI will be informed immediately of any suspected adverse effects.

All testing and training procedures will be performed by qualified personnel at the University of Miami Wellness Center (miller school of medicine and/or coral gables), which is located minutes from an emergency room.

In the event of a non-serious adverse reaction during participation in the study, a staff medical physician will be immediately paged or the participant will be escorted to the emergency room. In the event of an emergency, the EMS will be activated; first responders will immediately initiate basic emergency procedures and continue until EMS arrives.

Adverse effects reporting:

The principle investigator will comply with the required annual reporting of non-serious and serious adverse events to the IRB, General Clinical Research Center (GCRC), and Research Subject Advocacy (RSA) program of the University of Miami.

14) Withdrawal of Subjects

The following clinical criteria will be used for withdrawing a participant from the study: The principal investigator will withdraw participants who become ineligible to participate in the study (as per study inclusion and exclusion criteria), or if there is a safety concern for the participant or study investigators including seizure, pain or intolerable side effects.

15) Risks to Subjects

1) There is a risk of seizure associated with the use of transcranial magnetic stimulation (TMS), but this is considered remote (less than 1 in 10,000) provided that there is no history of: a) epilepsy; b) seizure; c) head injury, or d) stroke.

There is a risk of movement of implanted biomedical devices, therefore, subjects would not be appropriate for this study if they have: metal plates, blood vessel clip or any implanted biomedical device in your head. There is no risk involved regarding implanted plates or screws in the cervical spine. Subjects will be screened for history prior to inclusion.

2) Transcranial magnetic stimulation (TMS) – Subjects will feel a local twitch of the scalp and neck and involuntary movement of their left leg, provided there are sufficient numbers of intact descending fibers to conduct the electrical signal. Information of interest includes the magnitude of the contraction. The FDA considers the single-pulse TMS system a “non-significant risk” device. Although the risk for seizure is low with single pulse TMS, all study personnel are trained in how to respond appropriately to a seizure, by keeping the subject safe during the event and activating emergency medical response. As all TMS procedures will be performed at the Center of Neurology, the study PI and medical personnel will be present in the building to assist with additional needs.

All subjects will be screened during the initial evaluation to ensure that they do not have implanted metal devices in the head, to decrease the risk of any potential adverse events. A mild and transient headache can occur (approximately 1 in 4 subjects) and there have been no adverse reactions in any of the more than 100 subjects we have studied using TMS to date. It should be emphasized that TMS is now in widespread use around the world, both for electrophysiological testing and more recently for certain forms of therapy.

- 3) The stimulation protocols relating to the study are similar to those used in previous studies. Subject may experience minor irritation from the tDCS electrodes over the stimulation sites. Mild redness over stimulation sites occurs in some subjects and generally subsides within 15 minutes. This will be monitored closely following removal of the stimulator in initial trials. Subjects may also be advised that they may feel a tingling current in the general area of stimulation. Subjects may also feel temporary muscle soreness following participation due to increased muscle soreness due to increased lower limb activity demands and intensity of activity. There are no documented studies reporting adverse side effects of tDCS.
- 4) People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. We will screen for these conditions prior to the study with an MRI Safety Questionnaire, and if the patient has any risk factors, will not receive an MRI scan. If there is a question about the presence of metal objects in your body, subjects will be excluded from participation. In addition, we will ask subjects to remove all magnetic objects (e.g. watches, coins, jewelry, credit cards) before entering the MRI scan room. Otherwise, there are no known long-term risks or consequences of MRI scans.

14) Potential Benefits to Subjects

It is unknown whether subjects will benefit from this research study although previous studies have demonstrated that functional gait training has been shown to improve gait parameters in individuals with locomotion dysfunction due to Parkinson's Disease.

16) Vulnerable Populations

N/A

17) Multi-Site Research

N/A

18) Community-Based Participatory Research

N/A

19) Sharing of Results with Subjects

The study results will be shared with the scientific community and will be published.

20) Setting

Patients will be screened at the UM Movement Disorders Clinic. The research will be performed at the University of Miami Wellness Center (miller school of medicine and/or coral gables campus). MRIs will be performed at UM Applebaum Center by Dr. Govind Varan.

21) Resources Available

Dr. Joyce Gomes-Osman. PhD, PT is a research neuroscientist with extensive experience in clinical research and non-invasive brain stimulation approaches, which include transcranial magnetic stimulation (TMS) and electroencephalography (EEG). Dr. Gomes-Osman has a publication record that include studies utilizing non-invasive brain stimulation to characterize the neurophysiology and induce neurostimulation (as a potential therapeutic approach) in individuals with neurologic impairments from spinal cord injury. Her experience in clinical trials are a result of 6 years working at the Miami Project to Cure Paralysis, University of Miami, where she was a project coordinator for two R01 grants, while working on her doctoral studies. Dr. Gomes-Osman has expanded her knowledge in Neurology and non-invasive brain stimulation techniques during her postdoctoral fellowship with Dr. Alvaro Pascual-Leone, an internationally recognized leader in this field, at the Berenson-Allen Center for Non-Invasive Stimulation at Beth Israel Deaconess Medical Center at Harvard Medical School. She remains affiliated as a research scholar, and is currently conducting studies to investigate the effects of aerobic exercise on neuroplasticity and cognitive function in healthy individuals. In addition, she is a lecturer at the “Intensive Course in Transcranial Magnetic Stimulation”, organized by this Center.

Dr. Corneliu Luca has experience with persons with Parkinson's Disease and sees patients in the Movement Disorders Clinic at UM where many patients with freezing of gait are referred. He is currently funded by the American Academy of Neurology and will spend 25% of his time for this project.

Dr. Jordyn Rice, PT, DPT is the lead physical therapist in this study. She is a research assistant in the Neuromotor and Plasticity lab currently working to complete her PhD studies in Physical Therapy under the neuromotor track. She has a clinical background working in a variety of settings including outpatient orthopedics and neurology, acute care in the trauma ICU at a level 1 trauma center, and inpatient neurological and post trauma rehabilitation at the Shepherd Center in Atlanta, GA.

22) Prior Approvals

N/A

23) Recruitment Methods

Participants will be recruited from the Movement Disorders Clinic at UM.

24) Compensation

Participants who complete all visits will receive an incentive of \$85 total which will also aide in offsetting the cost of parking and transportation.

25) Local Number of Subjects

We will study a total of 40 participants to achieve adequate power and account for potential variability within our sample.

26) Confidentiality

The site Investigator will assure that the privacy of subjects, including their personal identity and personal medical information, will be maintained at all times according to Health Insurance Portability and Accountability Act (HIPAA). Subjects will be identified by code numbers on case report forms and other documents.

27) Provisions to Protect the Privacy Interests of Subjects

Efforts will be made to limit the use and disclosure of personal information, including research study and medical records, to people who have a need to review this information. The sponsor, monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your medical records to conduct and oversee the research.

Principal investigator and study members will have access to study documents. Documents will be secured in a closed office where PI and study members have access.

28) Compensation for Research-Related Injury

Patients may be exposed to risk of injury from participation in this study. If injury occurs, treatment will in most cases be available. If patients have insurance, the insurance company may or may not pay for these costs. If they do not have insurance, or the insurance company refuses to pay, study patients will be expected to pay. Funds to compensate for pain, expenses, lost wages and other damages caused by injury are not available.

29) Economic Burden to Subjects

As this is an investigational study, there is no cost to subjects for participating, nor will their insurance be billed for any of the procedures performed during the study. In the event the a subject will require medical treatment as a result of their participation in this study, which is unforeseen, their insurance company may or may not cover the expenses associated, and if they refuse to pay the subject will be responsible for the costs.

Participants will be required to attend 3 weekly visits, and endure associated expenses with transportation and parking initially, but will be offset by the incentive given when completing study visits.

30) Consent Process

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR). The informed consent explains the procedures and requirements of the study, together with any potential hazards/risks. Each subject will sign such an informed consent form or give oral consent/proxy. The subject will be assured of the freedom to withdraw from participation in the study at any time. The Investigator will retain the original signed consent form and provide each subject with a copy of the signed consent form and make sure that the patient understood the consent form.

The investigators will follow “SOP: Informed Consent Process for Research (HRP-090).”

31) Process to Document Consent in Writing

Investigators will be following “SOP: Written Documentation of Consent (HRP-091).” Consent Form attached.

32) Drugs or Devices

The devices used for tDCS and TMS are FDA approved and available at the Neuromotor Rehabilitation Research Laboratory at the University of Miami Miller School of Medicine Professional Arts Center (PAC). Only authorized personnel has access to the equipment and will be used only on subjects and be used only by authorized investigators. See attached.