Combining tDCS and Neurorehabilitation to Treat Age-related Deficits of Mobility and Cognition: UPfront Walking Study

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Protocol

1. Project Title

Combining tDCS and neurorehabilitation to treat age-related deficits of mobility and cognition: UPfront Walking Study

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3. Abstract:

Loss of mobility and cognitive ability are serious conditions that threaten the independence of older adults. Importantly, both of these conditions are mechanistically linked by impairment of frontal lobe brain function. Frontal lobe dysfunction has been implicated as a factor contributing to gait deficits in some individuals with Alzheimer's disease, frontotemporal dementia and vascular dementia. There is a critical gap in knowledge about what therapeutic strategies are effective for maintaining or reinstating function in this critical brain region in order to preserve physical and cognitive health in older adults. The goal of our research is to develop a novel therapeutic intervention to enhance both mobility and cognition via neuroplasticity of frontal/executive control circuits. We will engage neuroplasticity of frontal circuits in two ways. The first is through neurorehabilitation with "complex walking tasks" (CWTs), such as obstacle crossing, obstacle avoidance and walking on non-uniform surfaces. CWTs are a potent behavioral approach for engaging prefrontal circuits. Furthermore, CWTs are crucial to successful ambulation in the home and community settings and therefore provide an ecologically valid therapeutic approach. The second approach that we will use to engage neuroplasticity of frontal circuits is anodal transcranial direct current stimulation (tDCS). Anodal tDCS is a safe, non-invasive neuromodulation technique. It has previously been shown to induce excitatory effects on brain tissue and, in single-session assessments, to improve performance during complex walking tasks. tDCS has also been shown to be an effective adjuvant for enhancing the effects of cognitive training. The objective of this study is to calculate effect size, establish variance of response and demonstrate feasibility of the experimental interventions in order to plan for a full scale clinical trial. Participants will include thirty older adults who demonstrate evidence of frontal/executive impairment. Participants will be randomized to one of three groups: 1) standard walking neurorehabilitation with sham tDCS ('standard/sham' group), 2) complex walking neurorehabilitation with sham tDCS ('complex/sham' group), or 3) complex walking neurorehabilitation with active anodal tDCS ('complex/active' group). Functional near infrared spectroscopy (fNIRS) will be used to explore intervention-induced changes in prefrontal cortical activity. Assessments will be conducted at baseline, post-treatment and 3-month follow up. We propose the following specific aims:
Specific Aim 1: Determine preliminary efficacy for recovery of mobility and cognitive function.
Specific Aim 2: Demonstrate feasibility/safety of tDCS as an adjuvant to rehabilitation.
Specific Aim 3: Explore the relationship between prefrontal activity and behavioral outcomes
The data collected here will provide the information needed to justify and plan a future full scale clinical trial to assess the relative efficacy and underlying mechanisms of each intervention approach.

4. Background:

Age-related mobility deficits and/or cognitive deficits are present in a large proportion of older adults. Those who have mobility deficits have higher rates of morbidity and mortality, more hospitalizations, poorer quality of life, and are less likely to remain independent. Those who have cognitive deficits experience reduced ability to perform instrumental activities of daily living and have a reduced quality of life. Standard therapeutic approaches are insufficient for addressing age-related impairment of physical and cognitive function. There is a clear and urgent need for alternative or adjuvant strategies that can directly target specific mechanisms of impairment in order to yield greater gains. Deficits in cerebral function are known to affect cognition, and are also likely to be an important mechanism contributing to mobility deficits. Physical interventions that are designed to target cerebral mechanisms may not only improve walking function, but may also improve cognitive function. Directly combating age-related dysfunction of frontal/executive circuits may considerably enhance mobility and cognitive function.

The important role of cerebral structure and function on walking and cognitive ability is made clear by the often devastating effects of overt neurological injury/disease such as stroke, traumatic brain injury, Parkinson's disease and Alzheimer's Disease. A less appreciated issue is that older adults also exhibit substantial but sub-clinical impairments of cerebral structure and function. These impairments include (but are not limited to) reduced intracortical excitability, reduced cortical thickness, loss of gray matter volume and increased presence of white matter hyperintensities [42-49]. Accumulating evidence indicates that age-related degradation of the brain is a common and important factor contributing to decline of mobility and cognition.

Frontal cerebral circuits are particularly important because they have broad effects on executive functions that are important to planning, initiating and coordinating both cognitive and motor behaviors. Our recent research suggests that older adults who exhibit a greater level of prefrontal cerebral activity (measured by fNIRS) during complex walking tasks also perform those tasks better. Evidence also indicates that the prefrontal cortex and other frontal lobe brain regions are particularly susceptible to age-related dysfunction. The prefrontal cortex is an important component of multiple major cerebral circuits that have been linked to walking function.

Neurorehabilitation of Walking

Neurorehabilitation is a behavioral therapeutic approach for enhancing the neural control of task performance. Our neurorehabilitation intervention for walking will incorporate many evidence-based principles of motor recovery including:

Restoration of function: We seek to restore walking function through neuroplastic adaptations of locomotor circuitry. We will discourage the use of compensatory movement strategies or assistive devices because such approaches may limit or counteract the neurophysiological adaptations that we seek to promote.

Specificity of training: Rehabilitation is most effective when targeting specific neural circuits that underlie behavioral deficits.

Sensory input to the nervous system: Sensory input in this context refers to movement strategies that promote task-appropriate afferent activity. A number of proprioceptive and somatosensory factors are known to be important for triggering initiation and performance of gait cycle events. These include achieving sufficient limb loading and leg extension to promote robust forward propulsion, followed by sufficient maximal hip extension to trigger the initiation of

swing phase. Therapists will emphasize appropriate body weight shifting and limb loading, hip extension and symmetry during key events/phases of the gait cycle.
Intensity, Repetition and Progression of training: Neuroplasticity requires repeated and intense practice. Furthermore, progression of intensity ensures a high training stimulus even as capability improves.

We will use two neurorehabilitation interventions: steady state walking (control intervention) and complex walking tasks (experimental intervention). The objective of the complex walking task intervention is to engage frontal/executive circuits to induce beneficial activity-dependent neuroplasticity (e.g., synaptic connectivity). We have previously shown that complex walking tasks are a potent approach for engaging prefrontal cortex during walking. Furthermore, complex walking tasks are important and ecologically valid because they are crucial to successful mobility in the home and community environments.

Transcranial Direct Current Stimulation (tDCS) and augmentation of mobility and cognition
tDCS will be used to induce positive neuromodulation of frontal/executive circuits to make them more amenable to the "activity-dependent neuroplasticity" that is known to occur with behavioral neurorehabilitation. Specifically, tDCS may facilitate the efficacy of our walking neurorehabilitation intervention by strengthening the synaptic connections within the recruited circuits. Deeper frontal circuits may also experience neuromodulation through applied field effects. tDCS involves the application of a weak electrical current through two or more electrodes placed on the scalp. The principal mechanism of action is subthreshold modulation of neuronal membrane potentials, which alters cortical excitability and neuronal activity dependent on the current flow direction through the target neurons. We propose that integrating anodal tDCS into a neurorehabilitation intervention will increase its effectiveness. Indeed, the neurocognitive literature reveals evidence that modulatory effects accumulate when tDCS is applied during multiple, consecutive sessions, and that tDCS effects are most prominent when a consolidation period is allowed. Furthermore, applying tDCS during practice of the desired functional task has been found to trigger effects that outlast the stimulation period and facilitate longer term neuroplasticity.

5. Specific Aims:

Specific Aim 1: Determine preliminary efficacy for recovery of mobility and cognitive function.

Primary Mobility Outcome: Figure-of-eight walking test (Figure-8 Walk Test)

Primary Cognitive Outcome: Composite executive score on NIH EXAMINER battery (EXAMINER)

Hypothesis 1a: Effect sizes for improvement in the *Figure-8 Walk Test* will be greatest for *complex/active*, followed by *complex/sham*, followed by *standard/sham*.

Hypothesis 1b: Effect sizes for improvement on EXAMINER will be greatest for *complex/active*, followed by *complex/sham*, followed by *standard/sham*.

Specific Aim 2: Demonstrate feasibility/safety of tDCS as an adjuvant to rehabilitation.

Hypothesis 2: The study interventions will not significantly differ for adherence, retention, or adverse events.

Specific Aim 3: Explore the relationship between prefrontal activity and behavioral outcomes

fNIRS of prefrontal cortex will be used to quantify changes in prefrontal/executive activity during performance of the *Figure-8 Walk Test* and *EXAMINER* test to probe mechanisms of response to the interventions.

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6. Research Plan:

Study Overview

All study procedures will be conducted at the University of Florida.
Up to thirty older men and women will be enrolled in the intervention component of this study. A larger number will be enrolled for onsite screening, because some will fail the screening tests and not proceed to the study intervention. Volunteers will undergo the following sequence of events:

- *Telephone Screening*: Volunteers will be screened by telephone to determine if they meet basic enrollment criteria including age and general health status.
- *1st Informed Consent and Onsite Screening*: Volunteers who pass the phone screen will be invited to participate in on-site screening. Informed consent for screening will be obtained. Mobility function and cognitive screening will be conducted, including 10m walk speed and tests from the cognitive battery of the NIH Toolbox. Other criteria listed in Table 6 will also be evaluated. Screening will be conducted over two visits lasting approximately 4 hours and 3 hours, respectively. A third visit may sometimes be needed if all assessments cannot be completed in the two visits
- *2nd Informed Consent and Baseline Assessment*: Qualifying volunteers will be invited to participate in the full study. They will attend a baseline assessment session which will include Informed Consent for full study participation and tests of the primary and secondary study outcomes including Figure-8 walk test and NIH EXAMINER battery of executive function. Secondary outcomes will also be evaluated as described in the Research Plan. This visit will last approximately 3 hours.
- *Rehabilitation Intervention*: Enrolled participants will receive 18 sessions of neurorehabilitation, which will be combined with either active or sham tDCS. These sessions will be completed over the course of 6 weeks. Each session will last about 75 minutes from arrival to departure.
- *Post-Intervention Assessment*: At the completion of the neurorehabilitation program, participants will attend a post-therapy assessment session that is identical to the baseline assessment.
- *Three month follow up Assessment:* Three months after completing the neurorehabilitation program, participants will attend a 3-month follow up assessment session that is identical to the baseline and post-treatment assessments.

Telephone Screening

Participants will be screened by telephone to determine if they meet the following inclusion criteria:

- over the age of 65
- able to walk independently without a walker (canes are OK)

- find it physically tiring to walk a quarter mile, or climb two flights of stairs, or perform household chores. (<u>At least one</u> of these should be true).
- do not feel severe pain in legs when walking (i.e., pain that prevents performing daily walking tasks).
- In the past six months, have not fractured or broken a bone.
- have not been diagnosed with an overt injury or illness to the central nervous system (Parkinson's disease, Alzheimer's disease, stroke, brain injury, spinal cord injury, etc.).
- do not have a terminal illness.
- do not have uncontrolled high blood pressure.
- do not have severe arthritis, such as awaiting joint replacement
- do not have current cardiovascular, lung or renal disease; diabetes; terminal illness
- have not had myocardial infarction or major heart surgery in the previous year
- have not had cancer treatment in the past year, except for nonmelanoma skin cancers and cancers having an excellent prognosis (e.g., early stage breast or prostate cancer)
- do not have a current diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder
- not currently participating in physical therapy for lower extremity function or cardiopulmonary rehabilitation
- not currently enrolled in any clinical trial
- not recently enrolled in a clinical trial that may affect physical or cognitive abilities
- not planning to relocate out of the area during the study period
- no known contraindications to non-invasive brain stimulation and/or MRI including metal in the head, pacemaker, known abnormal cranial fissures/holes.

<u>1st Informed Consent and Onsite Screening</u>

Upon arriving to the research site, participants will undergo informed consent for screening and functional assessments. All questions from the phone screening will be repeated, and additional health/medical screening criteria will be evaluated as noted in the table below. As part of screening, we will explain in the detail the full study protocol including rehabilitation intervention with transcranial direct current stimulation.

Screening will usually occur over two separate study visits, occurring within a span of about 1-2 weeks. The following assessments will be conducted during the screening visit:

- 10-meter walking speed
- NIH Toolbox: A subset of the NIH Toolbox cognitive battery will be conducted, with emphasis on tests of attention, executive functions, and working memory. This testing can be completed in 30 minutes.
- Activities Specific Balance Confidence Scale: The ABC Scale is a 16-item questionnaire that gauges confidence (on a scale of 0-100%) on various balance and walking tasks relevant to household and community ambulation.
- Tests of foot tactile sensation. This includes touching a vibrating probe to the foot, as well as pressing plastic probes or monofilaments (similar to hairbrush bristles) of various size/stiffness to the sole of the foot to determine sensitivity of sensation.
- Resting blood pressure
- Basic visual examination with standard eye chart
- Height, weight, age, sex
- Obtain list of medications that the participant is currently using

- Walking test with active or sham transcranial direct current stimulation (tDCS). For full details about tDCS, please see section below (Rehabilitation Intervention; Transcranial direct current stimulation). This test serves two purposes. One is to allow the participants to experience tDCS prior to enrolling in the study intervention. This will help to fully inform the participants and may help us to avoid drop-outs. The second purpose is to allow us to collect cross sectional data to assess whether active tDCS aids with motor learning in the context of walking. This is consistent with the overall aims of the study. The walking test will involve a walking course of 40 foot length where there will be small foam obstacles to step over and soft mats to walk across. We will ask the participants to walk at their fastest safe speed. They will be asked to do this task 10-15 times in a row, with approximately 1-2 minutes of rest in between every walking trial. Performance on each walking trial will be measured as walking speed.
  During this test, participants may be asked to wear an accelerometer (activity monitor) so we can assess how smoothly they walk. They may also be asked to wear sensors on their fingers that measure skin conductivity, which is a probe of sympathetic nervous system arousal.
- Videos and/or photos may be taken during assessments to document the functional abilities of participants, and for possible use in research presentations or education. At the time of consent, participants will choose what their videos/photos can be used for. We will avoid capturing images of the participants face, and will delete any such images that are accidentally captured.

Following the screening visit, study staff will evaluate performance/responses relative to the following study enrollment criteria. Individuals who meet all criteria will be invited to enroll in the full study (i.e., the rehabilitation intervention).

Screening Criteria

Inclusion criteria

- preferred 10m walking speed < 1.0 m/s
- less than 50th percentile rank (age and education corrected score) on NIH toolbox executive assessments: Card Sort Test and Flanker test
- Willingness to be randomized to either intervention and to participate in all aspects of study assessment and intervention

Exclusion criteria

- Contraindications to non-invasive brain stimulation and/or MRI including metal in the head, pacemaker, known abnormal cranial fissures/holes.
- difficulty communicating with study personnel
- uncontrolled hypertension at rest (systolic > 180 mmHg and/or diastolic > 100 mmHg)
- Low vision that cannot be corrected by wearing glasses. Low visual will be operationally defined as visual acuity less than 20/70 on a standard eye chart, or difficulty performing complex walking tasks due to visual conditions affecting accurate navigation around and over obstacles (self-reported or observed by examiner).
- use of medications that are known to modify tDCS effectiveness including those with anticholinergic, GABAergic, or glutamatergic properties; or sodium channel blockers.
- illiterate, due to the likelihood of difficulties performing some of the cognitive tasks
- non-English speaking, due to the likelihood of difficulties following instructions during therapy and during assessments
- clinical judgment of investigative team

At the discretion of the Principal Investigator, any individual may be deemed ineligible for further participation in any component of this study if there are concerns about the individual's capability to perform study procedures or if it may be unsafe for the volunteer to participate in the study. Furthermore, minor exceptions to the inclusion/exclusion criteria may be permitted at the discretion of the Principal Investigator if those exceptions do not influence participant safety. For example, small deviations from the target range of walking speed or cognitive performance. This is important to ensure that individuals are not excluded for insignificant reasons and to facilitate meeting enrollment benchmarks.

2nd Informed Consent and Baseline Assessment

Participants will complete a 2nd informed consent in order to take part in the full study procedures. All study procedures will be described in detail and all questions will be answered.

Assessment sessions

Assessments will be conducted at the following time points:
Baseline - generally within two weeks before starting the intervention
Post-Intervention – generally within one week after completing the intervention
3-month follow-up - generally about three months after completing the intervention

The following assessments will be completed at each intervention:

Walking and Balance Tests

Figure-8 Walk Test: this test involves walking in straight and curved paths and was designed to represent walking skill in everyday life [92]. It has been shown to be associated with executive functions and performance on various other mobility-related tests in older adults [92].
Other "complex" walking tasks: Participants will be asked to perform a battery of walking tasks that are designed to be similar to conditions that are encountered in the home and community settings. These tasks may include walking over/around obstacles, walking while carrying an object, walking in dim lighting, walking while performing a cognitive task, walking up/down stairs, walking over a soft foam surface (exercise mats), walking backwards, gait initiation, gait termination, and/or similar tasks, and/or or a combination of these tasks.

Quiet standing on a force platform: This test measures center of pressure and sway during quiet standing with eyes open and with eyes closed.

Berg Balance Scale: A 14-item scale designed to measure balance of the older adult in a clinical setting.

During these tests, prefrontal cortical activity will be recorded with functional near infrared spectroscopy, which is described below. Participants may also be asked to perform these tasks while wearing textured shoe insoles that mildly increase sensation from the soles of the feet.

Cognitive Tests

NIH EXAMINER: this is a computer based standardized assessment that tests the cognitive/executive domains of planning, set shifting, working memory, inhibition, and fluency. It calculates separate factor scores for each domain as well as a composite executive score.
Tower of Hanoi: the objective of this puzzle is to move a stack of differently sized disks from one rod to another while obeying the following rules: only one disk can be moved at a time; a disk can only be moved if it is the uppermost disk on a stack; no disk may be placed on top of a smaller disk. The time and number of moves to complete the puzzle will be recorded.

Trail making Tests A & B: The task requires a subject to connect a sequence of 25 consecutive targets on a sheet of paper or computer screen, similar to a connect-the-dots puzzle. There are two parts to the test: in the first, the targets are all numbers (1, 2, 3, etc.) and the test taker needs to connect them in sequential order. In the second part, the subject alternates between numbers and letters (1, A, 2, B, etc.). The goal of the test is for the subject is to finish both parts as quickly as possible, with the time taken to complete the test being as the primary outcome*.*
Digit Span Test: memory span is the longest list of items that a person can repeat back in correct order immediately after presentation. The task is known as digit span when numbers are used.

During all cognitive tests, prefrontal cortical activity may be recorded with functional near infrared spectroscopy, which is described below.

Functional near infrared spectroscopy (fNIRS)

fNIRS is a safe non-invasive technology for indirectly assessing cortical activation based on changes in blood flow and oxygenation. Sensors are placed on the forehead, and produce infrared light that is able to pass through the skull and is absorbed or reflected by blood and other tissues in the head. Infrared light is considered safe and there is no sensation association with this procedure. Calculations made from the relative amount of light absorption/reflection provide an estimate of the metabolic activity level of underlying cortical tissue. We will use a commercially available fNIRS monitor (Octamon by Artinis Medical Systems).

Sympathetic nervous system activity measured by skin conductance

During any walking or cognitive task, participants may be asked to wear sensors on their fingers that measure skin conductivity, which is a probe of sympathetic nervous system arousal.

Rehabilitation Intervention

Participants will take part in a 6-week, 18-session neurorehabilitation led by qualified and trained study personnel. Participants will be randomized to one of three groups: 1) standard walking neurorehabilitation with sham tDCS (‘*standard/sham’ group*), 2) complex walking neurorehabilitation with sham tDCS (‘*complex/sham’ group*), or 3) complex walking neurorehabilitation with active anodal tDCS (‘*complex/active’ group*). Training logs will be maintained to gauge the content and intensity of training. To control for intensity, participants will maintain a rating of perceived exertion of 4 (moderate to strong) on the Borg Category/Ratio Scale during walking. Exertion will be adjusted by modifying walking speed and/or by modifying the rest time between walking bouts. Training logs will also include information on attendance and adverse events. From these logs we will determine adherence (# of sessions attended), retention (completion of rehabilitation and post-therapy assessment) and number of adverse events.

Complex Walking Task Intervention

Two of the three experimental groups will train using complex walking tasks. All of the complex walking tasks that we use have been used previously in our research protocols and/or have been previously reported in the rehabilitation research literature and/or are components of validated clinical instruments. Accordingly, all of the tasks have been demonstrated to be feasible and appropriate for use in our cohort. The following walking tasks will be used: over obstacles, navigating around obstacles, changing speeds, on soft surfaces (exercise mat), in dim lighting, while conversing with the therapist, up/down ramps and climbing/descending stairs.

Progression of training over the course of the intervention will be accomplished by combining these tasks to increase complexity.

Steady State Walking Intervention

The steady state walking intervention will be conducted similarly to the complex walking intervention, but training will be limited to performance of typical steady state walking.

Transcranial Direct Current Stimulation (tDCS)

During therapy session, all participants will receive active or sham tDCS, which is a mild form of non-invasive brain stimulation. The electrode placement for the tDCS is designed to engage the frontal lobes bilaterally. tDCS will be applied and operated by research personnel listed in myIRB (with all required training in human subjects research) who have been thoroughly trained in the use and safety of tDCS by the investigative team.

Active tDCS: For each session, a Soterix Direct Current Stimulator will apply up to 30 minutes of 2.0mA direct current through two biocarbon rubber electrodes encased in saline soaked 5cm^2 sponges (10cc of 0.9% saline solution) placed over the frontal cortices at F3 and F4 (based on the "10-20 system" of brain mapping). Current inflow will occur on the right (F4), and outflow on the left (F3). Impedance quality will be ≤10kΩ to insure proper stimulation of brain tissue.
Sham tDCS: Sham stimulation is performed with the same device and all procedures will be identical except for the duration of stimulation. Participants will receive 30 seconds of 2 mA of direct current stimulation at the beginning of the session. Participants habituate to the sensation of tDCS within 30-60 seconds of stimulation. This procedure provides the same sensation of tDCS without the full duration of stimulation, making it a highly effective sham procedure.

During assessment or rehabilitation sessions, videos and/or photos may be taken during to document the functional abilities of participants, and for possible use in research presentations or education. At the time of consent, participants will choose what their videos/photos can be used for. We will avoid capturing images of the participants face, and will delete any such images that are accidentally captured.

Post-Intervention Assessment and 3-Month Follow-Up Assessment

The procedures will be identical to what is described for the baseline assessment

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7. Possible Discomforts and Risks:

As with all physical activity, there is a risk of falling while we test or train walking ability. Falls can lead to injuries ranging from minor to serious. It is also possible that participants could experience musculoskeletal injury such as an ankle sprain. It is possible that the participant may experience fatigue, soreness, and discomfort due to physical activity associated with this study. These are unlikely to be worse than what he/she would experience due to increased physical activity outside of our study. These are normal responses to exercise and most discomfort would generally disappear within a matter of days. In general, walking exercise is strongly recommended for all adults, including elderly adults with medical conditions.

Transcranial direct current stimulation is considered safe but some people do experience some side effects. The most common side effects are itching and tingling or mild discomfort at the area of stimulation, and headache. Other possible but uncommon side effects include dizziness and nausea. Whenever an electrical stimulation is applied to the body, it could possibly cause a

seizure or abnormal heartbeat, but this has never occurred with the transcranial direct current stimulation parameters used in this study. tDCS will be applied and operated by research personnel listed in myIRB (with all required training in human subjects research) who have been thoroughly trained in the use and safety of tDCS by the investigative team.

fNIRS is considered safe. The infrared light used in assessment is not known to cause any harm to alter the brain in any way. The sensors are secured to the participant's head using adhesive tape, which may cause minor skin irritation in some people, or more substantial irritation in people who are sensitive/allergic to adhesives. We will check with participants about any known sensitivities to adhesives.

There is a risk that participants may find cognitive and functional tests challenging or uncomfortable if they have difficulty succeeding with the tasks. Participants may skip any question that they do not wish to respond do.

8. Possible Benefits:

There is no direct benefit to the participant.

9. Conflict of Interest:

None.

10. Statistical Analysis Plan

This is an R21 study that is designed to acquire data for planning a full scale clinical trial. Summary statistics will be provided for all primary measures, as well as for demographic and clinical characteristics. For the primary outcome of each hypothesis, group mean differences and standard deviations will be used to calculate effect sizes. With this information we will be able to conduct a power analyses to plan for a future full-scale clinical trial.

Data and Safety Monitoring Plan

Data Safety Monitoring Board

This study will use the Pepper Safety Committee for data and safety monitoring. This committee, henceforth called the Data Safety Monitoring Board (DSMB) is used for most studies that are affiliated with the UF Claude Pepper Older Americans Independence Center. The three members of this committee have no affiliation with the study. The committee meets every 6 months.

The PI will provide the DSMB with access to all relevant study data, documents and progress information. The PI and designated staff will attend the DSMB meetings and will be responsible for preparing and presenting data reports from the study.

The DSMB has the following charges:

- The initial task of the DSMB is to review the study protocol with regard to recruitment, randomization, intervention, subject safety, data management, plans for auditing of subject records, quality control and analysis plans, and to identify needed modifications. The DSMB then identifies the relevant data parameters and the format of the information to be regularly reported.
- Review data over the course of the trial relating to recruitment, randomization, compliance, retention, protocol adherence, trial operating procedures, forms completion, intervention effects, gender and ethnic/racial minority inclusion and subject safety.

- Identify problems relating to safety over the course of the study. Inform study PI via written report.
- Identify needs for additional data relevant to safety issues and request these data from the study investigators.
- Propose appropriate analyses and periodically review developing data on safety and endpoints.
- Make recommendations regarding recruitment, treatment effects, retention, compliance, safety issues and continuation of the study.
- Send the Program Administrator and PI written reports following each DSMB meeting. These reports may address all issues reviewed by the DSMB.
- The study PI is responsible for distributing the report to the local IRB.

The DSMB may convene an executive session at any time. The PI, project director, and project officer would attend these meetings. Any additional requirements pertaining to the DSMB will be determined by the NIA.

Adverse Event Reporting

Adverse events (including expected, unexpected, serious and non-serious) will be tracked in a cumulative table. Adverse events will be reported according to the guidelines of the University of Florida Institutional Review. Specifically, adverse events that are serious and unexpected (see definitions below) will be reported to the UF IRB within 5 working days of when study personnel learned about it. Reports of adverse events that are not serious or that are expected (e.g., muscle soreness) will be added to the cumulative adverse event table and reported to the UF IRB annually.

A *serious adverse event* is any adverse event that results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolonging existing hospitalization,
- a persistent or significant disability/incapacity,
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when the event may jeopardize the patient or subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.
An *unexpected adverse event* is any adverse event that not consistent with the current investigator brochure, protocol, consent form, or is not part of the normal disease progression. In addition, known adverse events may occur more frequently than expected. If so, then this meets the definition of “unexpected” and must be reported to the IRB.

Protection Against Risk

Staff training: All personnel will be thoroughly trained in the study procedures by the Principal Investigator or other appropriate member of the research team, and will complete all required trainings concerning human subjects research at the University of Florida. Personnel involved with administering tDCS will be trained in the lab of Dr. Woods, who has extensive experience with this technology.

Health monitoring and medical response: Volunteers at risk of health problems due to recent history of medical conditions (e.g., serious cardiac or pulmonary conditions) will be excluded, as noted above in the inclusion/exclusion criteria. Any adverse events will be recorded and monitored as required by our University of Florida Institutional Review Board. On-site medical

services will be available in the event of adverse events occurring during screening or assessment visits. Subjects will be able to terminate a study session at their request at any time without prejudice. Minimization of risk during neurorehabilitation and assessments will be accomplished by monitoring vital signs, with prescribed criteria for termination of the testing session. Vital signs will be monitored before, during and after assessment. Contraindications for participation will include resting heart rate >100 bpm or <50 bpm, resting systolic blood pressure >180 mmHg or <100 mm Hg or resting diastolic blood pressure >100 mmHg. Indications to terminate physical activity will include heart rate that exceeds age-predicted maximum (220-age), sudden drop in heart rate exceeding 15 bpm, systolic blood pressure >220 mmHg or <100 mmHg, or diastolic blood pressure >110 mmHg. Other criteria for termination include subject complaints of shortness of breath, light-headedness, dizziness, confusion, severe headache, dyspnea or onset of angina. Should the session be halted, the subject will be asked to rest while BP and HR are monitored and will resume only if BP and HR return to acceptable values. If any of these conditions persist after rest, the patient's primary physician will be called and patient referred for evaluation. If the patient complains of angina at rest, loss of consciousness occurs, or cardiac arrest, emergency medical services through 911 will be called immediately. Portable defibrillators will be available.

Confidentiality: Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented. Confidentiality of data will be maintained by using research identification numbers that uniquely identify each individual. Safeguards will be established to ensure the security and privacy of participants' study records. Appropriate measures will be taken to prevent unauthorized use of study information. Data other than demographic information will not use names as an identifier. The research ID number will be used. The research records will be kept in a locked room in the study site. The files matching participants' names and demographic information with research ID numbers will be kept in a locked file that uses a different key from that of all other files. Only trained and certified study personnel will have access to these files, and they will be asked to sign a document that they agree to maintain the confidentiality of the information. Electronic records will be stored on password protected network server maintained by the university information technology department. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we access personal health information and medical records only after receiving signed informed consent.

Safety during neurorehabilitation: Neurorehabilitation sessions will be led by a licensed physical therapist or other qualified staff member assigned by the Principal Investigator. The intensity and duration of walking activity will be carefully monitored to ensure that it is appropriate to the participant's capabilities. Participants will wear a gait belt during neurorehabilitation, which will better enable the therapist and/or assistants to provide support in the event of a loss of balance. Falls or near-falls during neurorehabilitation will be tracked on the therapy log and reported to the PI and DSMB.

tDCS Safety: Our protocol uses stimulation parameters that are considered standard practice, and have been used safely in prior research. The FDA has ruled that the tDCS stimulator used in this study is a "non-significant risk" device. The most common side effects of tDCS are slight itching, tingling, and reddening of the skin under the electrode. Participants typically habituate to itching or tingling sensations within 60 seconds of stimulation. Less common symptoms of stimulation are headache or nausea. Both headache and nausea have been reported to stop when stimulation is terminated. To minimize risk associated with tDCS, participants will be monitored throughout stimulation sessions and asked to report any discomfort. If scalp sensation is uncomfortable, stimulation levels will be decreased to a comfortable level or will be

stopped. In the event of a headache, stimulation will be decreased to a comfortable level (where the headache or nausea is no longer present) or will be stopped. All tDCS sessions will be administered and continually supervised by a trained experimenter.

fNIRS Safety: fNIRS poses no safety risk. Infrared light from the fNIRS device is not harmful and elicits no sensation. Sensors may be secured to the skin using adhesive tape, which could lead to mild skin irritation in those who are sensitive to adhesives. If a person indicates or displays such a sensitivity, we will avoid using adhesive tape and instead use elastic fabric or straps to secure the sensors.

Questionnaire administration: Questionnaire data are collected in secure spaces where the interview cannot be overheard. Participants will be informed that they are not required to answer questions that they do not wish to answer.