Cover Page

Official Title: HOMEStudy: Development of a Home-based Self-delivered Prehabilitation Intervention to Proactively Reduce Fall Risk in Older Adults

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Protocol

1. Project Title

Development of a Home-based Self-delivered Prehabilitation Intervention to Proactively Reduce Fall Risk in Older Adults

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3. Abstract:

The effects of aging are multifaceted including structural and functional impairments of the central nervous system which often result in reduced mobility, quality of life, and independence. Neurorehabilitation is an effective approach for enhancing motor function, but a challenge for this field is the ability to produce sufficient neuroplastic change and lasting behavioral improvements. Even in the best clinical settings, it may not be feasible for practitioners or patients to dedicate the time and financial resources needed to enact adequate progress. Moreover, older adults often do not receive preventative neurorehabilitation. Rather, interventions usually follow hospitalization resulting from an adverse event. Development and implementation of innovative preventative approaches (prehabilitation) to maintain mobility function and independence for aging adults may promote a significant clinical paradigm shift. Therefore, the long-term goal of this proposed research is to establish a prehabilitation approach to reduce fall risk and preserve mobility function. Prehabilitation has the potential to help all older adults particularly prior to major health/life events that are associated with fall risk, such as planned surgeries (e.g., joint replacement) and adaptations to ones living environment (e.g., moving to a new home). Prior to testing a prehabilitation intervention in those special populations, we first seek to conduct a pilot study to develop the protocol, establish feasibility, and acquire evidence of preliminary efficacy. Our prehabilitation intervention is designed to be self-delivered by individuals in their own home and includes two components: motor imagery of complex walking tasks (e.g., movements needed to walk throughout a home), and brain neuromodulation via transcranial direct current stimulation (tDCS). Motor imagery incorporates both mental imagery and action observation. Mental imagery is the act of mentally rehearsing a motor action without physically performing the observed movement(s). Another component of motor imagery is action observation, which is the act of visually observing a movement(s) being correctly performed. tDCS is a form of non-invasive brain stimulation which delivers a mild electrical stimulation via electrodes placed on the scalp. tDCS influences neuronal membrane potential, which can make brain neurons more likely to fire in response to a behavioral intervention (e.g., motor imagery). Both approaches are intended to promote the effects of activity-dependent plasticity and Hebbian learning in the brain (“neurons that fire together, wire together”). When motor imagery and tDCS are self-delivered at home with telehealth support, there lies the potential to offer a convenient and cost- effective means to proactively improve functional mobility in older adults. These approaches may be particularly beneficial for under-served older adults including those with low socioeconomic status and/or living in rural areas where barriers exist in receiving specialized medical services. Thus, home-based therapies offer

a unique and pragmatic way to enhance mobility prior to an incident occurring. Moreover, through necessity and technological advancements, our capacity to monitor and intervene within the home has greatly improved. Providing a necessary framework for new approaches targeting mobility and independence for our aging neighbors. To test the following aims for this intervention-based pilot study we will collect data from 30 fall prone older adults who will be randomly assigned to either an active (i.e., real) or sham (i.e., false) tDCS group.

4. Background:

Falls are the leading cause of injury related deaths among people over the age of 65. Roughly 1 in 4 older adults experience a fall annually, with 20-30% of those experiencing moderate- to-severe injuries, resulting in nearly 30,000 deaths, 3 million emergency room visits, and 800,000 hospitalizations. Of the falls that occur, 55% happen at home during commonly performed activities of daily living. While not all falls require medical attention, those that do, inherit large healthcare-related costs with a reported $50 billion spent on fall-related post injury treatments for older adults. Aside from expense, diminished mobility within free-living environments poses a risk for older adults trying to sustain autonomy and independence. The proposed study is significant because falls are largely preventable; however, the current standard of care only initiates for recovery, rather than as a preventative measure. Therefore, implementation of prehabilitative measures for at risk older adults to safeguard against devastating falls and loss of independence are the target population for this research.

For the proposed study, motor imagery (MI) will refer to the combined use of action observation and mental imagery. Action observation and mental imagery are frequently implemented to promote and enhance motor learning, and particularly effective when practiced in series9. Action observation refers to watching another individual perform a task, allowing the observer to obtain information about the task requirements and think about the associated motor strategies necessary for completion. Mental imagery refers to the mental rehearsing of various actions and sensations of a particular task, without physical movement. Studies have shown that practicing both types of rehearsing together enhances motor leaning and motor control for upper limb, lower limb, and whole-body functional tasks. A recently published report showed that older adults recovering from a total hip replacement who engaged in post-surgical MI demonstrated greater locomotor improvements two months post-surgery compared to their counterparts participating in standard of care rehabilitation. Further, neuroimaging studies have shown that MI augments neuronal activity, indicating a robust neural response and exciting possibilities for providing safe task-practice and Hebbian neuroplasticity (“neurons that fire together wire together”), which involves the reorganization of neural circuits in response to practice and experience. We are not proposing that MI is superior to conventional physical practice, but rather than MI is a safer alternative for exposing older adults to complex walking conditions in a self-delivered home-based intervention. Moreover, we propose that self-administered MI and neuromodulation via transcranial direct current stimulation (tDCS) will demonstrate compliance and feasibility due to its safety, convenience, and low-cost relative to fall related medical and rehabilitation expenses.

Achieving task-specific improvements to motor behavior requires neuroplasticity. Consistently, reviews show that MI in motor behavior and motor learning paradigms facilitate activity-dependent neuroplastic adaptation. For instance, functional brain imaging studies have demonstrated overlapping neural networks (e.g., frontoparietal network) and similar neural connectivity patterns in primary motor and motor associated brain regions when comparing action observation and mental imagery to physical practice. Further, neurophysiological adaptations have shown similar increases between MI and physical practice in cortical and

spinal excitability for increasingly complex tasks such as performing wrist flexion and extension exercises to shooting a free-throw in basketball. Additionally, neuromuscular activation via electromyography (EMG) has been observed during imagined (i.e., instructed to abstain from physical movement) dumbbell lifting movements. Demonstrating similar muscle activation responses (although different activation amplitudes) for nine upper limb muscles fundamental to the movement (i.e., agonist, antagonist, synergist, and fixator muscles). Moreover, differential EMG responses were recorded for imagined 'heavy' vs. 'light' dumbbell lifts. Together indicating that MI engages common neural circuits, neurophysiological substrates, and neuromuscular activation patterns compared to physical performance, which we propose can be leveraged to increase activity-dependent neuroplasticity and influence motor performance.

Transcranial Direct Current Simulation (tDCS) is a safe and non-invasive brain stimulation technique which induces a relatively weak electrical current to a targeted region of the brain, influencing neuronal membrane potential. In the proposed study we will examine feasibility and develop a protocol for combining MI with tDCS in a home-based, self-delivered intervention. The rationale for combining tDCS with MI is that this approach might provide a more robust activation of the neural circuits important to task performance, thus driving a greater neuroplastic response. Therefore, when brain circuits are excited simultaneously by MI and excitatory tDCS, those circuits may be strengthened to a great extent through Hebbian neuroplasticity. Additionally, tDCS appears to be most effective when applied in conjunction with task-relevant neural activity and over multiple sessions (as we propose to do). For instance, prior studies have shown that excitatory tDCS occurring during a postural stability (i.e., balance) MI paradigm significantly improved postural stability performance. Importantly, prior studies report that home-based, self-delivered tDCS (alone, not combined with MI) is safe and feasible. This literature has evaluated numerous populations spanning multiple neurological conditions and impairments (e.g., Parkinson's disease, ALS, stroke, multiple sclerosis, Alzheimer's disease, Mild Cognitive Impairment, osteoarthritis, fibromyalgia, and depression). There are now several review articles describing best practices for home-based, self-delivered tDCS. Among the most recent was a review article titled "*Supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice*". The proposed objectives will provide the necessary experience and pilot data to justify conducting a more robust future study.

5. Specific Aims:

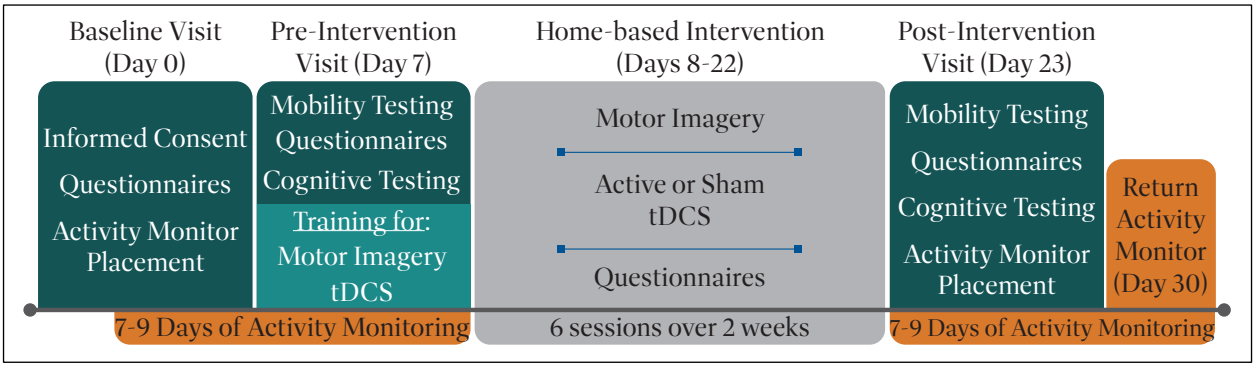
Aim 1: Establish the feasibility and acceptability of delivering a telehealth-based motor imagery and tDCS intervention for improving mobility. *Hypothesis 1*: Participants will effectively self-deliver the motor imagery and tDCS intervention, based on 80% of participants demonstrating high rates of compliance, safety, and the usability of the technology. Structured questionnaires will be used to assess each component separately for both motor imagery and tDCS.

Aim 2: Determine the extent to which motor imagery and prefrontal tDCS augments objective functional mobility outcomes. *Hypothesis 2*: Participants who receive active as opposed to sham tDCS will demonstrate moderate effect sizes ($d \geq 0.72$) for functional mobility improvement. Specifically, older adults who receive active tDCS will demonstrate shorter sit-to-stand duration, reduced postural sway area, shorter 360˚ turn duration, shorter timed up and go duration, and faster gait speed.

Aim 3: Determine the extent to which motor imagery and prefrontal tDCS influences physical activity intensity and sedentary time. *Hypothesis 3*: Participants who receive active as opposed to sham tDCS will demonstrate moderate effect sizes of $d \geq 0.72$ for duration of walking bouts, intensity of walking bouts (as measured by metabolic equivalents (METs)), and a reduction in total daily sedentary time.

6. Research Plan:

Study Overview



This prospective cohort study will incorporate a double-blind, randomized design to assess whether home-based MI and active tDCS improves functional mobility and home-based physical activity behavior. For this pilot study 34 older adults (aged ≥70 years) with a self-reported risk of falling will be randomly assigned to either the active or sham tDCS group. Following the group assignment participants will complete six home-based MI intervention visits over a two-week period coupled with prefrontal active or sham tDCS. Prior to, and following the home-based intervention participants will complete laboratory testing. The first laboratory visit (Baseline Visit) will include informed consent, questionnaires, and physical activity monitor placement. The second laboratory visit (Pre-Intervention Visit) will include functional mobility testing, questionnaires, cognitive testing, and familiarization training for the home-based intervention. This visit will also include the removal of the activity monitor. The post-Intervention third laboratory visit will include mobility testing, questionnaires, cognitive testing, and application of the physical activity monitor for an additional week of activity monitoring. For physical activity monitoring participants will wear the activity monitor for 7-9 days prior to and after the intervention sessions.

Up to 34 typical older men and women will be asked to participate in this study. An additional 10 participants (estimated) may enroll in the intervention but discontinue participation before completing the protocol. A larger number (up to 75) may participate in screening by telephone and/or onsite but will fail the screening tests and not proceed to the study intervention. Participants will undergo the following sequence of events:

- *Telephone Screening*: Participants will be screened by telephone to determine if they meet basic enrollment criteria including age and general health status. If patients authorized us to view their medical records, those records may be examined to verify absence of exclusion diagnoses, to obtain complete/accurate medication lists.
- *Informed Consent and Baseline Visit*: Participants who pass the phone screen will be invited to participate in on-site baseline visit where informed consent will be obtained. Demographic information, physical abilities (i.e., fall risk), cognitive function, questionnaires, and health/safety screening will be conducted. This single visit will last approximately 1.5 hours. Qualifying participants will be invited to participate in the full study.
- *Activity Monitor Placement*: Participants will have a small and light weight activity monitor placed on their right thigh using a clear waterproof adhesive tape at two time points during the study. Participants will wear this activity monitor for 7-9 days prior to and after the intervention. The monitors are secured in such a way that participants can shower and sleep with the monitors secured to their leg.

- *Pre-Intervention Visit:* Participants will undergo mobility testing while with wearing wireless inertial sensors. For mobility testing participants will be asked to complete the Mini Balance Evaluation Systems Test (Mini BESTest) which assess 6 different balance control systems. Participants will be asked to complete a series of 2-minute walk trials either at their natural walking pace, their fast-walking pace, or while performing a secondary mental task. Participants will perform a variety of 90-degree, 180-degree, and 360-degree turns. Participants will complete the clinical test of sensory interaction on balance (CTSIB) which is performed by having participants stand with their feet together on either a firm or foam surface with their eyes open or closed. Participants will be asked to perform the five time sit-to-stand, and the timed up and go test, which requires participants to stand up from a seated position then walk three meters, turn around walk back to the chair and sit back down. The pre-intervention assessment will last about 2 hours. Participants will also complete a series of computerized tests assessing cognition. Lastly, participants will be trained on how to perform the home-based intervention. This will entail how to secure the transcranial direct current stimulation (tDCS) headband, turn on and activate the tDCS stimulator, and how to perform the motor imagery paradigm.
- *Study Intervention Visits:* Participants will attend 6 intervention sessions in which will be self-delivered within their own home. They will practice motor imagery tasks comprised of watching an individual complete commonly performed motor tasks correctly (i.e., standing up and sitting down from a chair, walking throughout a house, turning, walking outside) then imagine performing the same task without actually moving their body. During this task participants will receive either active or sham transcranial direct current stimulation (tDCS) to the frontal portion of their brain. Participants will be asked to complete questionnaires about how the motor imagery and tDCS went each day. Each session will last approximately 30 minutes.
- *Post Intervention Visit:* Participants will complete the same testing protocol as the Pre-Intervention visit. This will include using the wireless inertial sensors to complete the Mini-BESTest and measure gait, turning, balance, sit-to-stand, and the timed up and go. Participants will complete the same cognitive tests battery as the Pre-Intervention visit along with a debriefing questionnaire asking about their thought on the intervention and which group (active or sham) they felt they were assigned. Lastly, participants will have the activity monitor secured to their thigh for an additional week to measure changes in physical activity after completing the intervention. After the week of activity monitoring participants will be asked to return the activity monitor to the laboratory.

Telephone Screening

Participants will be screened by telephone to determine if they meet the criteria outlined below. Participants who qualify for the study will be informed that any identifiable information collected during this study will be securely stored and that they will be given a unique participant identification number. Conversely, participants who do not qualify (i.e., screen out) for the study, their information will not be stored.

Inclusion criteria

- Age 70 - 95 years of age
- Self-report having a risk of falling. Fall risk will be determined by asking whether the participant has had (and recovered from) a fall related injury in the previous year or had fallen two or more times in the previous year or if the participant is afraid of falling because of their balance or walking. (This criterion is based on the 2020 NEJM study: “A Randomized Trial of a Multifactorial Strategy to Prevent Serious Fall Injuries”)

- Self-report of *"some difficulty with walking tasks, such as becoming tired when walking a quarter mile, or when climbing two flights of stairs, or when performing household chores."*
- Willingness to be randomized to either study group and to participate in all aspects of the study assessment and intervention.
- Living in the community and able to travel to the research site.
- Ability to independently assemble and put on the tDCS headband or incorporate the involvement of a willing study partner (e.g., a spouse, family member, or friend) who agrees to assist with this task during each home intervention session.
- Access to an internet-connected computer or television capable of playing videos with sound located in a quiet area with a comfortable stationary chair.
- Able to provide informed consent.

Exclusion criteria

- Diagnosed neurological disorder or injury of the central nervous system, or observation of symptoms consistent with such a condition (spinal cord injury, Alzheimer's, Parkinson's, stroke, etc.)
- A score of 23 or lower on the Montreal Cognitive Assessment (MoCA)
- Contraindications to non-invasive brain stimulation (e.g., metal in head, wound on scalp)
- Use of medications affecting the central nervous system including, but not limited to, benzodiazepines, anti-cholinergic medications, and GABAergic medications.
- Severe arthritis, such as awaiting joint replacement
- Cardiovascular disease that is either uncontrolled or limits participants ability to complete light aerobic mobility assessments, lung disease requiring supplemental oxygen, or renal disease requiring dialysis; uncontrolled diabetes; terminal illness
- Myocardial infarction or major heart surgery in the previous year
- 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)
- Current diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder
- Difficulty communicating with study personnel (including people who cannot speak English)
- Uncontrolled hypertension at rest (systolic > 180 mmHg and/or diastolic > 100 mmHg)
- Bone fracture or joint replacement in the previous six months
- Current participation in physical therapy for lower extremity function or cardiopulmonary rehabilitation
- Current enrollment in a clinical trial that may influence the results of either study, discretion up to the study investigators.
- Clinical judgment of investigative team

Informed Consent and Baseline Visit

Upon arriving to the research site, participants will undergo informed consent. We will explain the full study protocol including transcranial direct current stimulation, motor imagery, activity monitor, and the home-based intervention.

All questions from the phone screening will be repeated, and additional health/medical screening criteria will be evaluated. This will include:

- Resting blood pressure

- Height, weight, age, sex, education level, socioeconomic status
- Medical history
- Obtain list of medications that the participant is currently using
- Montreal Cognitive Assessment (MoCA)

Following the baseline visit, study staff will evaluate performance/responses relative to the study enrollment inclusion/exclusion criteria. Individuals who meet all criteria will be invited to enroll in the full study.

Participants who qualify without exemption will be invited to participate. Participants who agree to participate will complete a series of questionnaires and have the activity monitor secured to their thigh at the end of the baseline visit or at the participants preferred time. The activity monitor will be secured to the participant for 7-9 days prior to the pre-intervention study visit.

Questionnaires:

- Activities Specific Balance Confidence Scale: 16-item questionnaire that gauge's confidence (on a scale of 0-100%) on various balance and walking tasks relevant to household and community ambulation.
- Movement-specific Reinvestment Scale: questionnaire that asks about the extent to which a person directs conscious attention to control of movement.
- Trailmaking Test – paper-based test where the person must "connect the dots" between numbers or between alternating letters and numbers.
- Sleep quality assessed by the Pittsburgh Sleep Quality Index, which is a questionnaire about sleep-related habits and experiences.
- Motor Imagery Questionnaire (revised second edition) (MIQ-RS), which is a questionnaire asking about one's ability to imagine performing self-initiated movements.
- Short Form – 36, which is a set of 36 questions aimed at assessing self-reported measures of health.
- Katz Index of Independence – is a set of questions aimed at assessing one's level of independence when performing activities of daily living.
- Montreal Cognitive Assessment – is a rapid screen of cognitive abilities designed to detect mild cognitive dysfunction.

At the discretion of the Principal Investigator, any individual may be deemed ineligible for further participation in 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, if a participant does not have an internet connection but is able to use a USB drive to watch the motor imagery videos. This is important to ensure that individuals are not excluded for insignificant reasons and to facilitate meeting enrollment benchmarks.

Pre-Intervention Visit

Mobility Assessment

Performance on walking tests will be assessed using wireless inertial sensors, force plates, and/or an electronic walkway. The wireless inertial sensors are secured to the body using Velcro and elastic straps ensuring a snug placement. Data from the wireless inertial sensors is wirelessly streamed to a laboratory computer which allows for offline movement calculations.

We will use commercially available wireless inertial sensors (Opal by APDM) and software (MoveoExplorer by APDM).

Various assessments of mobility performance will be made during the pre-intervention visit. Mobility tasks will include assessments of walking, turning, balancing, and sit-to-stand performance. For walking, participants will be asked to complete three, two-minute walks at their normal, fast, and while performing a secondary cognitive task (such as walking while counting backwards by 7's). Turning tasks will include, 90 degree turns, 180 degree turns and 360 degree turns. Balance will be assessed using the Mini-BESTest and the Clinical Test of Sensory Integration on Balance (CTSIB). The Mini-BESTest is a 14-item test that assess four domains of dynamic balance. The CTSIB includes four 30 second balance trials where participants are either standing on the firm ground or on a compliant foam pad with their eyes open or closed. Sit-to-stand performance will be assessed via the five time sit-to-stand and timed up and go.

Cognitive Function Assessment

We will administer the Cognitive Assessment Battery from Cambridge Brain Sciences, which includes up to 12 cognitive tests. All are short, simple, computer-based assessment that assess domains of cognitive such as spatial working memory, response inhibition, and reasoning. Specific examples include:

- Digit Span Test – determine the longest list of numbers that a person can remember.
- Visuospatial working memory – remember the sequence and location of items that appear and disappear from the screen.

Video, photos, and voice recordings

During this study, videos and/or photos may be taken during to document the functional abilities of participants, and for possible use in research presentations or education. We may also use voice recordings to capture performance on cognitive assessments such as a verbal fluency task performed during walking. At the time of consent, participants will choose what their videos/photos/recordings can be used for. We will avoid capturing images of the participants' faces and will obscure or delete any such images.

Home-based tDCS and Motor Imagery Visits

Motor Imagery Task

Each of the six motor imagery sessions will include roughly 35 minutes of action observation and mental imagery (combined, termed motor imagery) task practice. Participants will be asked to sit in a quite location without distraction, on a sturdy chair (not a recliner) in front of a computer or television screen. The motor imagery tasks are generated from the clinically based functional mobility assessments, which demonstrate strong psychometric properties and resemble activities of daily living (e.g., sit-to-stand, 360˚turn, walking and turning, and balancing). Additionally, we will incorporate ecologically applicable walking environments such as navigating outside spaces (e.g., the home, parking lots, community parks). On their computer or television screen participants will actively watch a video of each task being performed correctly from both a first- and third-person perspective. Then participants will be instruction to

mentally imagine performing the task (Figure 2). Participants will practice action observation ("seeing the movement"), and mental imagery ("mentally rehearsing the feelings of the movement") in separate but related trials. This sequence facilitates the vividness of the motor imagery practice. For action observation, participants will familiarize themselves to the task by watching a video of the test being performed correctly from both perspective (total duration of 1 min). Participants will then imagine performing the task via action observation from the 1st person perspective (1 min) and 3rd person perspective (1 min). Participants will then be instructed to close their eyes and imagine performing the task via mental imagery, from the 1st person perspective then the 3rd person perspective, each for 1 minute. This will provide participants roughly 5 minutes of motor imagery practice per task for a total duration of 35 minutes. Participant will be able to pause the program between trials if a break or rest is needed.

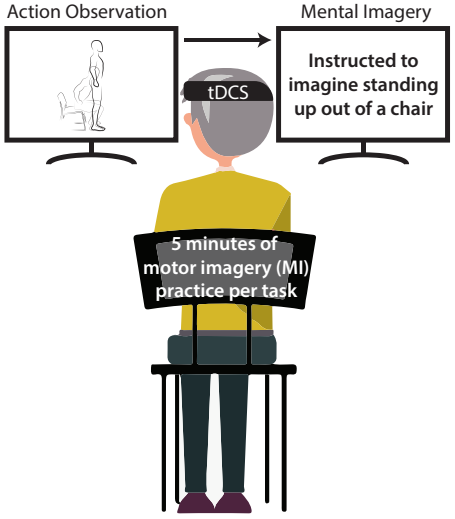


Figure 2: example of at home intervention set-up

Home-based tDCS during Motor Imagery Practice

Participants will be randomized and counterbalanced (i.e., equal numbers in each group) to receive either active or sham tDCS, which will be delivered simultaneously during the motor imagery practice sessions. Home-based and self-delivered tDCS has been shown to be safe and feasible for both neurologically impaired and healthy populations. A Soterix Clinical Trials tDCS unit will be used for delivery of stimulation. Figure 3 illustrates the tDCS head gear, which is easy to place, user friendly, and very lightweight. Participants will be provided single-use "SNAPpad" sponge electrodes (5x7 cm) which are individually sealed and come pre-saturated with the optimal amount of conductive saline solution. The electrode sponges snap onto a pre-configured "SNAPStrap" head gear, which is adjustable for each participants head size ensuring a secure and consistent fit for all of the motor imagery intervention sessions. To ensure consistency of electrode placement throughout the intervention participants will be provided hands on instruction during the pre-intervention visit and will also be provided instructional documentation (i.e., picture diagrams and videos). This will ensure participants are familiar with snapping the electrodes and placing the headgear while they are at home. Participants will also be provided instruction for operating the handheld tDCS unit. The unit is very user friendly and has large easy to read numbers and interface.


Figure 3. tDCS headband in the optimal placement for intervention visits

Each participant will be given six unique (one for each intervention session) 5-digit number sequences which will be used to initiation the stimulation for each intervention session. The unique number sequences are created using a third-party to ensure double-blind randomization. Therefore, neither the participant nor the researchers will know which participants are receiving active or sham stimulation.

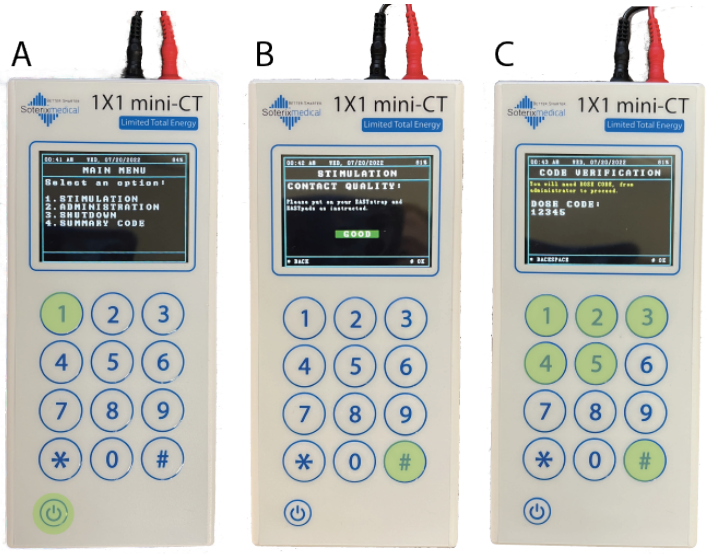


Figure 4. Operating the tDCS unit.
A) participant will first be instructed to press the power button, then number 1 – 'stimulation'. B) Upon placing the headband (shown in Figure 3) participants will be provided information regarding the contact quality (good, moderate, poor), and instructed to press the # sign. C) participants input the individualized stimulation code followed by the # sign to initiate the stimulation.

Active tDCS: Twenty minutes of 2.0mA direct current through two biocarbon rubber electrodes encased in saline soaked 5cm2 sponges placed over the frontal cortices at F3 and F4 (based on the international "10-20 system" of standardized brain electrode placement). 2.0mA was

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 2.0mA of direct current stimulation at the beginning of each rehabilitation session. Since participants habituate to the sensation of tDCS within 30-60 seconds of stimulation, this procedure provides the same sensation of active tDCS.

Telehealth Support: To ensure participants can place the headband and initialize each tDCS session the study staff will coordinate with the participant to ensure a staff member is available by telephone to answer any questions.

Questionnaires:

- CHAMPS Physical Activity Questionnaire for older adults, which assesses weekly frequency and duration of various physical activities typically undertaken by older adults.
- Daily Vividness of Imagined Tasks Questionnaire – is a set of questions aimed at assessing ones ability to imagine the tasks during the home-based study sessions
- tDCS Sensation Questionnaire – is a set of question assessing the amount of sensation for various feelings a participant felt during the tDCS session.

Post Visits

Participants will return to lab approximately 1 day after completing the home-based tDCS and motor imagery protocol. The Post-Intervention visit will be very similar to the Pre-Intervention visit, including each of the components listed above in the Pre-Intervention Visit section along with one additional questionnaire. After the mobility, cognitive assessments, and questionnaire, the activity monitor will again be placed on participants thigh for 7-9 additional days of activity monitoring. At the conclusion of the 7-9 days (depending on whether the day falls on a weekend) participants will be asked to drop off the activity monitor to the laboratory.

Questionnaire:

- Debriefing Questionnaire – is a set of question asking whether the participant felt like the stimulation and motor imagery influenced their performance. Also, this questionnaire asks participants to guess which group they felt they were randomized to.

Possible Discomforts and Risks:

For the laboratory-based mobility assessment there is a risk of falling. 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.

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

Transcranial direct current stimulation (tDCS) has been used by many prior studies and has an excellent record of safety and tolerability. The most often reported effect is tingling or itching sensations at the site of electrode placement, which may be accompanied by redness of the skin. Some people also report headache or a feeling of fatigue. All these effects dissipate quickly, and tDCS has not been reported to have prolonged negative consequences. A recent literature review article compiled data from all tDCS clinical studies performed from 1998 to August 2010. Of 209 studies (172 articles, encompassing almost 4000 subjects), active tDCS and sham tDCS did not differ in the frequency of adverse effects that were observed. The most common adverse effects were headache, itching, burning sensation (without actual injury), discomfort and tingling, occurring in 10-40% of patients regardless of treatment group. Additionally, numerous reviews have demonstrated that self-delivered home-use of tDCS is safe and feasible.

This study involves laboratory based physical activity including functional mobility assessments. As with all physical activity, there is a risk of adverse events such as injury to muscles/bones/joints, cardiovascular events, and falling. To mitigate fall risk participants will be continuously spotted by trained research personnel during laboratory based functional mobility testing. Specifically, to ensure safety for participants while turning, research personnel will first place a gait belt around the waist of participants for best spotting practices. Additionally, personnel will be within arm's reach, facing the participant while moving in the opposite direction of the turn to ensure the ability to provide multiple points of contact (i.e., hip and shoulder support) in cases of lost balance. Physical activity also may lead to discomfort such as fatigue and muscle soreness which are normal occurrences with exercise. This study also involves cognitive assessments. There is a risk that participants will be unhappy or embarrassed with their perceived performance during the assessments. There is also a slight risk that personal, or health information could be revealed inappropriately or accidentally. Depending on the nature of the information such a release could upset or embarrass the participant. There are no alternative procedures for this study. The only alternative is not to participate. Research participants are free to withdraw at any time, with no negative repercussions.

There is a slight risk that the medical grade adhesive used to secure the activity monitors to the thigh might cause skin irritation or a rash. In such instances participants will be asked to stop wearing the activity monitor.

8. Possible Benefits:

There is no direct benefit to the participant.

9. Conflict of Interest:

None.

10. Statistical analysis and sample size calculations
This pilot study is designed to assess feasibility and acceptability of a telehealth-based motor imagery and tDCS intervention (aim 1) and to acquire preliminary data to plan and conduct power analyses for a larger study (aims 2 and 3). To assess feasibility and acceptability, summary statistics will be assessed for compliance, safety, usability, and recruitment measures. For aim 2 and 3 we are not hypothesizing statistical significance between active and sham tDCS groups but rather anticipate that effect sizes will support a directional effect. Based on the UF Older Americans Independence Center (OAIC) Biostatistics Core's recommendations, we will use the following statistical design:

For Hypothesis 1: the future statistical design to inform feasibility and acceptability will be based on 80% of participants demonstrating compliance, safety, and usability of technology.

For Hypothesis 2: the future statistical design that will be informed by the present pilot data is a two-sample t- test to investigate the pre- and post-intervention functional mobility outcome differences for both the active and sham tDCS groups. To assess the size of the observed effects between active and sham tDCS, Cohen's *d* values will be reported for each functional mobility response variable. Effect sizes will be defined as small (d = 0.20), medium (d = 0.50), and large (d = 0.80).

For Hypothesis 3: the future statistical design that will be informed by the present pilot data is a two-sample t- test to investigate the pre- and post-intervention physical activity time, intensity, and sedentary time differences for both the active and sham tDCS groups. To assess the size of the observed effects between active and sham tDCS, Cohen's *d* values will be reported for physical activity time, intensity, and sedentary time. Effect sizes will be defined as small (d = 0.20), medium (d = 0.50), and large (d = 0.80).

Data and Safety Monitoring Plan

Adverse Event Reporting

Adverse events will be reported according to the guidelines of the University of Florida Institutional Review.

Reporting within 5 days of the PI becoming aware will apply to adverse events that meet <u>all</u> the following criteria:

- Serious
- Unexpected
- Related or the Relationship is "more likely than not"

Adverse events will be added to the cumulative event table and reported at continuing review when they meet either of the following criteria:

- Serious (but expected) and related or the relationship is “more likely than not”.
- Unexpected (but not serious) and related or the relationship is “more likely than not”.

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 is 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.

Health monitoring and medical response: Volunteers at risk of health problems due to recent history of medical conditions (e.g., serious cardiac or serious 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. 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 subject complaints of shortness of breath, light-headedness, dizziness, confusion, severe headache, dyspnea or onset of angina. If any of these conditions are greater than mild or 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 are 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 laboratory mobility testing: Participants will wear a gait belt during all mobility related tasks. This will better enable the therapist and/or assistants to provide support in the event of a loss of balance. Falls will be tracked and reported to the PI and IRB even if there is no injury associated.

Home-based tDCS Safety: Our protocol uses stimulation parameters that are considered standard practice, and have been used safely in prior research. 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. To minimize risk associated with tDCS, participants will be asked to monitor and report any discomfort following tDCS stimulation sessions. If stimulation sensation is uncomfortable, participants will be instructed to remove the tDCS head strap and stop the stimulation.

tDCS has been used extensively in both lab-based and home-based intervention protocols. Therefore, safety is well established, and guidelines are available to promote safe usage in both settings. A recent review article was published in the leading neuromodulation journal *Brain Stimulation*, entitled "**Supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice**". This publication developed an 8-item list of recommendations for home-based delivery of tDCS. Here we describe how the proposed study addresses each of these points:

1. Electrode Placement: Consult the literature and consider carefully how to best position the electrodes to achieve the desired effect.
   The F3-F4 (as designated by the "10-20 system" of standardized brain electrode placement) electrode montage that we will use has been widely studied. Based on current density models, F3-F4 electrode placement delivers broad and roughly symmetrical current flow to the anterior frontal lobes. The intensity and duration settings are believed to produce net excitation under both the anode and cathode electrodes based on transcranial magnetic stimulation and MRI- based connectivity analysis in prefrontal cortex findings.
2. Monitoring: Participants receiving tDCS remotely should be monitored for as many sessions as reasonable to assure that the experimental protocol is being followed precisely.
   We will implement this monitoring using a developed plan. This begins by having a familiarization session which will occur during the pre-intervention study visit in the laboratory. Here the research staff will carefully train the participant to set up the tDCS electrodes and headgear. This process is facilitated by using Soterix SNAPpad electrodes and SNAPstrap headgear, which are specifically designed for simple home-based self-administered tDCS. Participants will be asked to take a photo of themselves (i.e., a selfie) with the electrode and headgear set up at each session then email/text

message the photo to study staff. This will allow staff to view these photos (generally on the same day) and provide corrective feedback if necessary.

3. Tolerability: Adverse events must be recorded. Well-defined procedures should outline how to address typical and atypical reported adverse events. If a participant is unable to tolerate the pre-specified amperage of stimulation and the study design does not permit reduction of the dose, then the participant must be prevented from moving forward in the study.
   tDCS protocols have been used on many thousands of research participants around the world and have not been linked to serious side effects. Our protocol uses stimulation parameters that are considered standard practice and have been used safely in our laboratory's prior research. The most common side effects of tDCS are slight itching, tingling, and reddening of the skin under the electrodes. Participants typically habituate to these sensations within 30-60 seconds of stimulation. For every session, participants will complete a questionnaire that asks about the presence and severity of side effects. From prior experiments within our laboratory typical side effects include mild sensations of burning or tingling at the stimulation site (e.g., rating of 3 or less on a 10- point scale), and/or a mild headache. The latter may be due more to tightness of the headgear assembly rather than to the tDCS itself. If a participant is unable to tolerate or for any reason does not like the stimulation, we will prevent the participant from continuing the study. For such instances they will be documented and included for feasibility outcomes.
4. Dose: Dose is optimized based on study hypothesis (brain target) and prior work in the literature.
   In the present study we will deliver both active and sham tDCS. For active stimulation we will deliver twenty minutes of 2.0mA direct current will be administered through two biocarbon rubber electrodes encased in saline soaked 5x7 cm sponges placed over the frontal cortices at F3 and F4 (based on the international "10-20 system" of standardized brain electrode placement). Current inflow will occur on the right (F4), and outflow on the left (F3) frontal cortices. 2.0mA was chosen based on prior research demonstrating that this parameter helps to reduces neuronal membrane polarization. Sham stimulation is performed with the same device and all procedures will be identical except for the duration of stimulation. The sham group participants will receive 30 seconds of 2.0mA direct current stimulation at the beginning of each rehabilitation session. Since participants habituate to the sensation of tDCS within 30-60 seconds of stimulation, this procedure provides the same sensation as active tDCS in the absence of any meaningful dose of stimulation. It is therefore a highly effective sham procedure.
5. Training: Standardized training for both the research staff and research participant should be required and outlined by the protocol.
   Personnel involved with administering tDCS will receive comprehensive training from Dr. Swanson (Principal Investigator) or Dr. Clark (Study Mentor). This will include extensive practice of head measurements on foam head models and on other lab members, to ensure proper location of stimulation electrodes. They will also have thorough training in the use of all related equipment/supplies.
   The research participants will undergo a more focused training pertaining to placement of stimulation electrodes and operation of the stimulation device. This process is facilitated by using Soterix SNAPpad electrodes and SNAPstrap headgear, which are specifically designed for simple home-based self-administered tDCS. Likewise, the stimulator itself is designed for ease of use. The participant only needs to enter a six-digit code on the keypad to initiate the pre-programmed stimulation dosage. We will also create training videos that participants can watch at their leisure to review study procedures. These videos will be posted online, and if requested provided on a USB flash drive.

6. Environment: Participants ought to complete treatment sessions in a distraction-free setting.
   Participants will be instructed to ensure that the motor imagery/tDCS environment is free from unrelated distractions. Pets must be confined to a separate room. Non-study related entertainment devices including televisions, radios, or portable music devices cannot be used during training. The participant must refrain from conversations so as not to be distracted during the training tasks.
7. Evaluation: Specific research outcomes assessment should be conducted at time points decided a priori.
   As described in the Research Plan the primary outcomes are to establish feasibility of home-based self-delivered tDCS (Aim 1) and to determine whether active tDCS along with MI enhances functional mobility (Aim 2) and physical activity intensity and sedentary time (Aim 3).
8. Minimum Device Specifications: Device monitoring that blocks or moderates stimulation if impedance is too great to conduct a current as intended between the electrodes. Medical grade materials should be used in the production of any device build that is used for research or clinicians. Doses should be delivered by devices with precision and accuracy. Device should have a capacity for researchers and clinicians to pre-program and lock the dosage that will be delivered to users. Safety features should be implemented into a device build to ensure that essential protections are provided to the patient. These include the ability to abort a session or limiting the device's ability to stimulate in situations of high resistance. The device should be user friendly and intuitive as appropriate for patients with disability (i.e., those with limited vision or cognitive ability. Examples include large fonts and texts used on the device and clear indication as to how to abort stimulation sessions).
   All the device specifications mentioned here are included in the stimulation device that we will use for our study. Our device is manufactured by Soterix Medical Inc, which is a worldwide leader in tDCS equipment. We will use the "1x1 tDCS mini-CT" device, which is specifically design for convenient and safe at home-delivery of tDCS in clinical trials.

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.