Title: Optimizing transcranial direct current stimulation (tDCS) to improve dual task gait and balance in older adults

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This protocol was prepared to meet the IRB requirements for a protocol. A prior application from Cayuse was submitted to transfer the study to Advarra for initial approval.

Brief description of the Research Project

Standing and walking are almost always completed in unison with other cognitive tasks such as talking, reading or making decisions. The ability to perform this important type of "dual tasking" is critical to daily activities and dependent upon one's capacity to effectively activate appropriate brain networks that include the left dorsolateral prefrontal cortex (dlPFC). Transcranial direct current stimulation (tDCS) is a safe, noninvasive technology that can selectively modulate brain excitability (i.e., the likelihood of activation) by passing low-level currents between electrodes placed upon the scalp. We have demonstrated through a series of studies that a single, 20-minute exposure of 'conventional' tDCS targeting the left dlPFC—administered via two large sponge electrodes—reduces dual task costs to metrics of standing postural control and gait, when tested immediately following stimulation. Still, we and others have also observed relatively high between-subject variability in the effects of this conventional bipolar form of tDCS. We contend that this variability in effectiveness arises in part from relatively diffuse and unspecific current flow when using large sponge electrodes, in combination with individual variability in head and brain anatomy that significantly alters current flow and the generated electric field in the target brain region. In this project, we will 1) apply recent advances in tDCS modeling and administration to model the electric fields generated by conventional tDCS in older adults using their individual structural brain MRIs, and 2) develop and test an multi-channel tDCS montage designed to optimize current flow to the left dlPFC (i.e., 'optimized' tDCS). Our Specific Aim is to examine the immediate after-effects of conventional tDCS, optimized tDCS, and sham stimulation on dual task standing and walking in older adults. Our study population will be older men and women without overt disease or illness, yet with poor baseline dual task performance defined as a dual task cost (i.e., reduction) to gait speed of at least 10% induced by simultaneously performing a serial subtraction task when walking. We hypothesize that across participants, the effect of conventional tDCS on dual task standing and walking performance will correlate with a specific component of the electric field generated over the left dlPFC target. We also hypothesize that optimized tDCS will induce A) greater effects on dual task standing and walking performance as compared to conventional tDCS and sham stimulation, and B) these effects will be more consistent across individuals as compared to conventional tDCS. This project will provide important insights into tDCS "dosage" that will enable us and many other researchers to better understand, control, and optimize this form of noninvasive brain stimulation to individual head and brain anatomy. It is also expected to demonstrate that optimized tDCS, as compared to the conventional approach, significantly improves the size and consistency of observed benefits to dual task standing and walking in vulnerable older adults.

Background and rationale for the research

Dual tasking is essential to mobility and dependent upon cognitive-motor brain networks. Standing and walking are almost always completed in unison with cognitive tasks such as talking or making decisions. Such dual tasking disrupts standing and walking in older adults,[1-10] and those with relatively high dual task costs report worse functional capacity[11,12] and perform worse on tests of mobility[13] and executive function.[14-16] Moreover, older adults—even in the absence of overt neurological disease—who walk >18-20% slower when performing a serial subtraction cognitive task, as compared to walking quietly, are more likely to fall[9,16] and suffer cognitive decline[17] in the future.

Observed dual tasks costs suggest that some older adults are unable to effectively activate the brain networks required to maintain performance in both tasks.[18-20] fMRI, EEG and functional near-infrared spectroscopy (fNIRS) studies indicate that standing and walking, especially when dual tasking, activate

the prefrontal cortices.[21-31] Studies using fNIRS during standing and walking indicate that when compared to normal conditions, walking while performing verbalized serial subtractions increases prefrontal cortex activation,[21-27] particularly within the left hemisphere.[29-32] Moreover, older adults who exhibit greater increases in left prefrontal activation when dual tasking tend to exhibit lower dual task costs.[30,31]

fMRI evidence indicates that performing two non-motor cognitive tasks together—as compared to performing them separately—activates additional brain regions specifically within the left dlPFC.[33,34] Moreover, the left dlPFC is particularly activated during performance of cognitive tasks that require both working memory and verbal processing.[35-39] We thus contend that while the control of standing and walking likely calls upon the bilateral dlPFC and its connected neural networks, the left dlPFC is important to one's ability to safely stand and walk while completing cognitive tasks that require verbalization—an ability central to daily living activities.

tDCS holds promise for improved dual tasking in older adults. tDCS induces low amplitude current flow between electrodes placed upon the scalp.[40,41] Generated electric fields polarize neuronal populations and modulate cortical excitability.[42,43] While the effects of tDCS on cortical excitability depend upon electrode size, polarity and placement, as well as current amplitude and duration,[40] 20 minutes of anodal (i.e., excitatory) tDCS increases excitability within target regions for up to 4 hours.[44,45] Conventional, bipolar tDCS using sponges to target the left dlPFC by placing the anode over the F3 region of the 10-20 EEG placement system and the cathode over the contralateral supraorbital margin. It has been shown to improve performance in cognitive tasks requiring attention,[46] working memory[47-50] decision making,[51] and non-motor cognitive dual tasking[52,53] in younger and/or older adults, when tested immediately following stimulation. Our team has published a series of studies indicating that this form of tDCS improves metrics of dual task standing and walking in cohorts of healthy younger adults,[54] healthy older adults,[55] and in older adults with functional limitations and "at-risk" dual task costs[56].

This project will combine brain imaging, advanced current flow modeling and state-of-the-art instrumentation to understand and optimize tDCS as a therapeutic strategy. Despite benefits to dual tasking at the group level, we have observed that the effects of tDCS tend to vary considerably across older adults—and observation ubiquitous to tDCS research to date.[40,57-59] We contend that a significant portion of this variability stems from an inability to ensure that, due to interpersonal differences and the use of large sponge electrodes, the desired electrical fields actually reach the desired brain locations in a controlled manner.[60-62] Moreover, this concern is amplified for older adults, as there is high inter-individual variance in skin, skull, brain and cerebrospinal fluid (CSF) anatomy, and each of these factors influence current flow.

In this project we will establish the relationship between the electric field generated by conventional, sponge-based tDCS and its effect on dual task performance. In doing so, we will provide first-of-it-kind insight into the degree of inter-subject variability in generated electric field in older adults, as well as the component(s) of this field that underlie observed functional benefits. We have hypothesized, based upon the evidence described above, that 1) when using conventional tDCS, the average nE over the left dlPFC 'drives' observed dual tasking improvements, and therefore, 2) multichannel tDCS that optimizes flow to this region will maximize benefit and reduce variance. If these hypotheses are supported, our project will establish a methodology and analytical pipeline to understand, control, and optimize tDCS dosage—a discovery with significant applications to our work and that of the entire field of noninvasive brain stimulation. If our hypotheses are not supported, our electric field mapping approach will nevertheless produce an invaluable dataset from which voxel-based and other computational and

statistical approaches may be used to test additional hypotheses to advance our understanding and optimization of tDCS.

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Previous Studies leading up to and supporting the proposed research

Single sessions of conventional tDCS targeting the left dlPFC reduce dual task costs and improve mobility: In multiple separate but related studies, we studied healthy younger adults (22±2yrs),71 healthy older adults (69±5yrs),55 and older adults with slow gait and executive dysfunction (81±10yrs).56All participants completed two visits. On each visit, standing and walking were assessed with and without simultaneous performance of a serial subtraction task, before and after a 20-minute session of conventional tDCS targeting the left dlPFC on one visit, and sham stimulation on the other visit, in random order. In all three cohorts, stimulation did not alter standing posture or gait under single task conditions. However, during dual tasking, tDCS reduced postural sway speed and area when standing, and increased gait speed when walking ($p<0.01$). Thus, only tDCS reduced the dual task cost (i.e., percent change from single to dual tasking) to these outcomes (sway speed: $p<0.1$; sway elliptical area: $p<0.02$; gait speed: $p<0.01$). Together, these data give us confidence that conventional tDCS designed to increase left dlPFC excitability enhances dual task performance across individuals who range widely in both age and functional capacity.

The immediate after-effects of conventional tDCS on dual task walking performance are beneficial yet relatively variable across older adults with high baseline dual task costs to gait speed. We extracted data from all older adult participants described in the previous section who had “at-risk” baseline dual task costs to gait speed of >20% despite no overt disease or illness (n=20; 12 women; dual task cost $\mu\pm\sigma$=26±13%; age=75±6 years). Conventional tDCS targeting the left dlPFC reduced the dual task cost to gait speed in all but one participant, and at the group level, significantly reduced this outcome as compared to sham stimulation ($p=0.002$). While the mean absolute pre-to-post change in dual task cost from pre-to-post tDCS was 12 percentage points, the standard deviation of change was 10 with a range of 35. These data demonstrate that 1) we can recruit older adults with poor dual task performance, 2) conventional tDCS holds promise to improve dual task performance in these vulnerable individuals, and 3) the effects of tDCS, while beneficial, are quite variable across individuals.

The degree to which conventional tDCS is “on-target” correlates with dual task improvements, yet varies across participants. We completed a pilot RCT in which 20 older adults with slow gait and mild-to-moderate executive dysfunction, yet who were without overt disease or illness, were randomized to a 2- week, 10-session conventional tDCS intervention targeting the left dlPFC (NCT02436915).56 tDCS, compared to sham, reduced dual task costs to gait speed and postural sway speed, and improved cognition as assessed by the Montreal Cognitive Assessment (MoCA), at a two-week follow-up ($p<0.05$). Twelve participants also completed a baseline structural brain MRI. Six of these were then randomized to tDCS. We used Stimweaver with each MRI to model generated electric fields based upon the electrode placement and flow parameters used for the intervention. The normal component of the electric field (nE) averaged over the left dlPFC varied considerably, and, correlated closely with reduced dual task costs to gait speed at follow-up ($r2=0.80$, $p<0.05$). In contrast, the nE over the right dlPFC did not correlate with dual task changes (not shown). These data give us confidence that the left dlPFC is an important target for dual task performance, and optimizing tDCS will likely maximize its effectiveness and reduce inter-subject variability.

Research Importance and how it will contribute to existing knowledge

This project is significant because it will combine brain imaging, advanced current flow modeling and state-of-the-art instrumentation to understand and optimize tDCS as a therapeutic strategy. In this project we will establish the relationship between the electric field generated by conventional, sponge-based tDCS and its effect on dual task performance. In doing so, we will provide first-of-it-kind insight into the degree of inter-subject variability in generated electric field in older adults, as well as the component(s) of this field that underlie observed functional benefits.

We propose to test a noninvasive and safe intervention, namely tDCS, to improve dual task performance—an important factor on the causal pathway to functional decline in older adults. Our approach is innovative in several ways.

We will use advanced tDCS technology to deliver optimized interventions. Our collaborator, Dr. Ruffini, has developed a method called Stimweaver to optimize multichannel tDCS montages.[63,64] This method calculates tDCS electric fields (including components normal and tangential to the cortical boundaries) using a multi-layer finite element model of a realistic head derived from individual's structural MRI. Here, we will use Stimweaver to model and study the electric fields generated by conventional tDCS and optimized tDCS. .

In addition to sponge-based sham, we will employ an optimized sham protocol to maximize blinding and minimize staff bias to intervention. The proposed project will compare—using a within-subject design—conventional tDCS delivered via sponges with optimized tDCS delivered via an array of eight gel electrodes. Each participant will thus also be exposed to two different sham interventions. First, we will implement a conventional sponge-based sham protocol in which tDCS will be delivered for a short period of time before it is "ramped" down to zero for the remainder of the session[57]. This "inactive" sham was adopted because cutaneous sensations associated with tDCS diminish quickly.[69,70] Second, we will implement an optimized gel-electrode-based "active" sham in which the Stimweaver optimization algorithm will be used with the objective of creating a null electric field on the target (left dlPFC) with the constraint that some electrodes deliver low-level currents that still induce cutaneous sensations. This method creates similar cutaneous sensations and skin redness as tDCS so that putative peripheral effects are present in both. Our group has used this method successfully for double blinding and it has produced no behavioral effects.[66]

Study Objectives, Aims and Hypotheses

We propose a randomized, double-blinded, 'within-subject' study design to test the effects of optimized and conventional tDCS. We will obtain complete datasets on 30 women and men aged 65-85 years who exhibit "at risk" dual task costs to gait speed (i.e., >10% reduction), yet without dementia or other overt neurological or musculoskeletal disease. Anatomical and functional MRIs of the head will be optional. Participants will complete four visits separated by one week, during which they will receive one of four 20-minute interventions in random order: conventional tDCS and sham stimulation using sponge electrodes, and optimized tDCS and an "active" sham stimulation using gel electrodes (further described below). Dual tasking will be tested before stimulation, after stimulation, and again one hour later. Primary outcomes will be dual task cost to gait speed when walking, and postural sway speed when standing. Secondary outcomes will include single and dual task metrics of standing and walking separately, as well as cognitive task performance within the dual task paradigm.

Specific Aim: To conduct a "within-subject" cross-over study to determine the acute effects of single sessions of optimized tDCS, conventional tDCS, and sham stimulation on dual task standing and walking in 30 older adults who are free of overt disease yet who present with poor baseline dual task performance.

Hypothesis 1: Across participants, the effect of conventional tDCS on dual task standing and walking performance will significantly correlate with the average of the nE component over the left dlPFC.

Hypothesis 2: Optimized tDCS will induce A) greater improvements on dual task standing and walking performance as compared to conventional tDCS and both sham conditions, and B) these effects will be more consistent across individuals as compared to conventional tDCS.

Study Design

We will conduct a "within-subject," double-blinded, randomized controlled study comparing the after-effects of single sessions of conventional tDCS, optimized tDCS, and two different sham conditions on dual task performance in men and women aged 65-85 years with poor baseline dual task performance. Participants will have the option to complete a structural and functional brain MRI. They will complete four visits during which they will receive one of the four interventions in random order. Visits will be separated by one week to ensure washout of tDCS effects on brain physiology. Dual tasking will be tested before tDCS, after tDCS and again one hour later.

Study Duration (total)

One year

Study Duration for participants

Up to 8 weeks

Participant Selection

Participants will be recruited from the Boston area community, senior housing facilities in urban and suburban areas, research recruitment repositories including the "Mobility and Brain Function" repository, multiple clinics at the BIDMC, and advertisements within regional media outlets and website posting (IFAR and clinicaltrials.gov).

We aim to obtain complete datasets in 30 participants. We expect to enroll 36 individuals to achieve this aim.

Inclusion criteria

- Men and women aged 65-85 years;
- Poor dual task performance, defined as a preferred gait speed that is >10% slower when walking and simultaneously performing verbalized serial subtractions (i.e., dual tasking), as compared to walking normally (i.e. single tasking).

Exclusion criteria

- Unwillingness to cooperate or participate in the study protocol;
- An inability to walk or stand for 30 continuous seconds without an assistive device;
- A diagnosis of a gait disorder, Parkinson's disease, Alzheimer's disease or dementia, multiple

sclerosis, previous stroke or other neurodegenerative disorder,
- Self-report of acute illness, injury or other unstable medical condition;
- Any report of severe lower-extremity arthritis or pain, physician-diagnosis of peripheral neuropathy, or other peripheral neuromuscular disease that may confound the effects of tDCS on gait or postural control;
- Use of antipsychotics, anti-seizure, benzodiazepines, or other neuroactive medications;
- Severe depression defined by a Geriatric Depression Scale score greater than 11;
- Any report or physician-diagnosis of schizophrenia, bipolar disorder or other psychiatric illness;

Participant Recruitment

We have full confidence that we can enroll 36 participants and obtain at least 30 compete datasets on individuals that meet the stated inclusion and exclusion criteria. We anticipate needing to conduct approximately 180 phone screens and 108 in-person screens, as our past experiences recruiting similar cohorts suggest a third of these individuals will be interested, eligible and enrolled in the study. We will aim to recruit a cohort of older men and women that is representative of the older population living in the greater Boston Metropolitan area. We will do so by taking advantage of extensive research recruitment repositories, our close connections with clinical programs and large housing facilities within both urban and suburban areas, and advertisements within regional media outlets. We will implement several strategies to minimize burden and maximize retention and compliance: we will develop personal relationships between participants and study staff, schedule appointments at convenient times, give reminders for each visit, provide food and beverages when appropriate, and compensate participants for their time. IFAR has dedicated on-site parking for study participants.

Obtaining Informed Consent

Interested individuals will be asked to provide verbal consent to complete initial eligibility screen during a phone conversation with study personnel. Potentially eligible participants will then schedule an in-person screening procedure. Potential participants may be emailed or snail-mailed (per request, and according to their preference) a copy of the informed consent for them to review at their own pace prior to the in-person screening. Written informed consent will be obtained by study personnel at the beginning of this in-person screening procedure.

Withdrawal of Participants

If during the course of their study enrollment, a participant develops a new medical condition that would make participation in the study contraindicated, as determined by a study physician (Dr. Lipsitz), the participant will be informed of this and withdrawn from the study. All data collected prior to withdrawal will be maintained in the study data set.

Study Procedures

Visit 1—screening: baseline functional characterization: Individuals deemed potentially eligible via phone screening will complete an in-person screen. They will read and sign an informed consent form approved by the Hebrew SeniorLife IRB. A medical history questionnaire will be completed and medications, blood pressure, height, body mass and years of education will be recorded. A brief dual task assessment will be conducted in which participants complete two, 30-second trials of walking at preferred speed: one normally (i.e., single task) and another while performing verbalized serial subtractions of 3s from 500 (i.e., dual task). Participants will be eligible if their average gait speed is ≥10% slower when dual tasking than single tasking. Individuals who meet all eligibility criteria will be

enrolled.

Enrolled participants will then complete several tests to characterize relevant aspects of cognition, mobility, mood, and physical activity, as follows.

Cognition will be assessed with a 60-65min battery of tests that are correlated with dual tasking (1,6,15,72,73), functional capacity (6,72), and/or falls (16,73). All tests have excellent psychometric properties and normative data covering the range of demographic characteristics of our proposed sample, with minimal ceiling and floor effects. Cognitive tests will include

- Montreal Cognitive Assessment (MoCA) of global cognitive function (74,75)
- Trail Making Test (A and B) of executive function (i.e., speeded visual search, vigilance and set-shifting) (76)
- WAIS-IV Digit Span (Forwards, Backwards) test of working memory (77)
- WAIS-IV Coding test of sustained attention and motor speed (78)
- Category and Phonemic Fluency tests of semantic knowledge and word retrieval (79)
- Hopkins Verbal Learning Test – Revised (HVLT-R) of verbal episodic memory (80)
- Gradual-Onset Continuous Performance Task (gradCPT) - a highly valid and reliable computer test to examine one's sustained attention. We propose to add the gradCPT in our existing protocol to help understanding the interplay between attention and gait in older adults.

Mobility will be assessed with the following tests:

- the timed up-and-go (TUG (81) which requires the participant to stand up from a chair, walk three meters, turn around, walk back and sit down. The average time to complete two trials will be recorded. This test has high test-retest reliability and discriminant validity in older adults (82,83)
- Short physical performance battery (SPPB) - includes measures of standing balance, four-meter walking speed, and ability and time to rise from a chair five times.

Self-report of mood, pain, physical activity and function will be assessed as each influences clinical tests of physical and cognitive function:

- Mood will be assessed with the Center of Epidemiology Studies-Depression Scale Revised (CESD-R) scale (86) which has been used extensively in epidemiology studies and consists of 20 questions regarding feelings of depression, loneliness, energy level, and fear. The CESD-R has high internal consistency (r=0.90) and a test-retest reliability of 0.51 (87).
- Self-reported physical activity will be assessed with the Physical Activity Scale for the Elderly (PASE) (88).
- Cognitive Reserve Questionnaire - a metric of education and intellectual activities pursued throughout one's lifetime.
- Brief Pain Inventory (BPI) - used to measure location and severity of bodily pain, as well as the impact of pain on general well-being.
- Falls Questionnaire - used to track the number of falls participants have had in the past 6 months.
- Geriatric Depression Scale (GDS) - a measure of depression in older adults.

Visit 2 (optional)—Functional and Structural MRI: Baseline MRIs will enable current flow modeling, which considers silent infarcts, white matter hyperintensities (WMHs), and functional connectivity. T1, T2, T2- weighted fluid-attenuated inversion recovery (T2 FLAIR), and resting-state functional scans will be completed on a 3T GE system with a quadrature head coil at the Beth Israel Deaconess Medical Center. Two T1 datasets will be acquired: one with fat-suppression to optimize brain and CSF

segmentation and another one without it to optimize skull and skin segmentation. Field-of-view will encompass all the head with coverage up to C1/2 vertebrae and without head cropping. Silent brain infarcts will be identified as focal lesions appearing hyperintense on T2 and hypo-intense on T2 FLAIR scans. White matter lesions will be identified as periventricular and subcortical regions appearing hyper-intense on T2 FLAIR. Lesion diameters/volumes will be calculated using an in-house AFNI and FreeSurfer combination pipeline and the Lesion Segmentation Tool for SPM,89 with manual edits as necessary. All volumes will be normalized as a percentage of the total brain parenchyma volume. Parameters: T1: 362 s, TR/TE=2530/3.32 ms, flip angle=7o, 1 mm3 isotropic resolution, matrix= 256X256; T2: 283 s, TR/TE= 3200/284 ms, 1 mm3 isotropic resolution, matrix=256X256; T2 FLAIR: 422 s, TR/TE=6000/388 ms, flip angle=120o, thickness=1.0 mm, 0.49x0.49 mm in-plane resolution, matrix=512X512.

Visit 3-6—Effects of tDCS on dual task performance: These visits will be separated by one week. Each participant will complete each of their assessments at approximately the same time of day. On each visit, participants will randomly receive one of four different 20-minute tDCS interventions. They will complete a dual task paradigm before tDCS and immediately after tDCS.

tDCS: Each participant will be exposed to a single session of conventional tDCS, optimized tDCS, and two shams, delivered using the Startim-8™ device and software (Neuroelectrics Corp, Cambridge MA). This system enables custom amounts of current to be delivered via conventional 25 cm^2 sponges or through an array of up to eight Pi™ (3 cm2) gel Ag/AgCl electrodes placed on the scalp according to the 10-20 EEG convention. This system also enables blinding of study personnel and participants to the type of stimulation being administered. Staff and participants will complete a blinding questionnaire after each session. Participants will complete a short side effects questionnaire at the beginning and end of every session,[90] on which they will be asked to state whether they received tDCS or sham intervention on that visit, and their confidence in this belief.

Conventional tDCS: The anode will be placed over F3 and the cathode over the contralateral supraorbital margin (Figure 5). At the beginning of stimulation, the current will be increased manually from 0.1 mA, in 0.1 mA increments over 60 seconds, up to a maximum of 1.8 mA. Participants will be instructed to notify study personnel if and when they feel any uncomfortable sensation. The ramp-up will be stopped at this point and for the remainder of the session tDCS will be delivered at an intensity of 0.1 mA below the highest level reached. At the end of each session, current will be automatically ramped down to 0.0 mA over a 60 second period. The same ramp-up/ramp-down procedures will be used across the other active conditions.

Conventional sham: A conventional sham will be used to maximize blinding of conventional sponge-based stimulation. The same sponge placement, ramp-up procedure, and session duration described above will be used; however, current will be automatically ramped down 60 seconds after ramp-up.[91]

Optimized tDCS: This intervention will utilize eight gel electrodes with placement and current parameters optimized to the cohort , with the goal of generating an average nE over the dlPFC of the same size as the one delivered by a conventional montage using sponges in an average subject at 1.5 mA of current (we will use prior data from older adults to define this average target).. The direct current delivered by any one electrode will however never exceed 2.0 mA; the total amount of current from all electrodes will not exceed 4 mA. Each 20- minute session will begin and end with a 60-second ramp up/down of current amplitude to maximize comfort.

Optimized sham: An active sham will be used in which very low-level currents (0.5 mA max) are

transferred between the same electrodes used in the active condition throughout the entire 20-minute session. This intervention will be optimized to deliver currents designed to not significantly influence their cortical tissue, but still mimic the cutaneous sensations induced by tDCS. We have shown that this active sham effectively blinds participants and operators to stimulation condition and does not affect functional outcomes.[66]

Pre/post tDCS assessments: Participants will complete a dual task paradigm before, immediately after, and one hour after tDCS administration. Procedures will follow published recommendations [6,92,93] that produce excellent test-retest reliability.[94-99] We have used this paradigm within our research and laboratory for over ten years. Participants will complete two, 60-second trials in each of six conditions:

- Condition 1: Single task: seated cognitive task (see below for description).
- Condition 2: Single task: standing.
- Condition 3: Single task: walking.
- Condition 4: Dual task: standing with cognitive task.
- Condition 5: Dual task: walking with cognitive task.
- Condition 6: Single task: fast walking

Standing trials will be completed on a force plate (Kistler, Inc) to record postural sway (i.e., center of pressure) fluctuations. Participants will stand barefoot with arms at side and feet shoulder width apart. The feet will be traced on the first trial and this tracing will be used to ensure consistent placement throughout the study. Participants will focus on an "X" marked on a wall and will be reminded to avoid extraneous movements. Walking trials will be completed around a 25m indoor track. Prior to testing, participants will be outfitted with wireless biosensors, each containing a triaxial accelerometer, goniometer and magnetometer, on the sternum, low back, wrists and ankles to record gait kinematics (Mobility Lab™, APDM Inc). Participants will walk at their preferred, comfortable pace prior to each walking trial. For the fast walking trials, participants will walk as fast as they can walk safely. The cognitive task will be verbalized serial subtractions of 3's from a random three-digit number between 200 and 999 (e.g., 500, 497, 494, etc.). Participant responses during each trial will be recorded. We have chosen this task because: 1) it activates a distributed cortical network including the left dlPFC,100 2) is the most widely used dual task paradigm 6,101 and induces meaningful dual task costs to postural sway when standing and gait kinematics when walking in older adults,[1,55,102,103] 3) has been used by our team and will thus enable comparison of current results to those from past studies, and 4) is reliable and minimally influenced by learning after familiarization.[99] No instructions will be given regarding task prioritization. This approach has been chosen to most closely mimic real-life situations.[6,93,101] Trial order will be randomized for each assessment and at least 1min of rest will be provided in between trials.

Participant Privacy

The following are the planned procedures for effectively protecting against and minimizing loss of participant privacy:

1. Phone screenings will be conducted in a private office space.
2. Study visits will be conducted in private rooms located within laboratory.
3. Each participant will be given a unique study identification number and data will not include any of the participant's PHI. 4. All participant-identifying information will be stored and managed on a secured database server. The information will be password protected.
4. Participant confidentiality will be maintained in accordance with HIPAA regulations.
5. Only the PI and study personnel approved by the IRB and authorized to view PHI will have access to the information.

6. PHI will not be used during discussion, presentation or publication of any research data.
7. Files containing PHI data collected for recruitment and screening purposes will be kept in locked, secured filing cabinets accessible only to designated study personnel (research assistants and investigators).

Data Collection Instruments

Assessment of Protocol Understanding

Height and Weight Form

Timed Up and Go (TUG) Form

Falls Questionnaire Falls Efficacy Scale - I Questionnaire

tDCS Blinding Efficacy Questionnaire

tDCS Side Effects Questionnaire

Neuropsychology Cognitive Testing - Trail Making Task (TMT); Montreal Cognitive Assessment (MoCA); Wechsler Adult Intelligence Scale (WAIS IV) - digit span (forwards/backwards), Coding test, and Category/Phonemic Fluency; Hopkins Verbal Learning Test - Revised (HVLT-R)

Medical History Questionnaire

Medication Review Form

Suicide Risk Protocol

Dual Task (DT) Gait and Balance Forms

Dual Task Brief Gait eligibility assessment

Dual Task Familiarization and Sitting Form

Blood Pressure Form

Center for Epidemiology Studies Depression Scale Revised (CESD-R)

Socio-demographics Form

Optimizing tDCS Phone Screen Questionnaire

Optimizing tDCS eligibility Questionnaire

MRI Safety Screening Form

Physical Activity Scale for the Elders

Activities of Daily Living Questionnaire

Short Form 12 Health Questionnaire

Cognitive Reserve Questionnaire

Uses of Device

Starstim

The Principal Investigator (Dr. Brad Manor) has utilized each of the proposed devices extensively in numerous research studies.

StarStim is a transcranial current stimulation device. The device is powered by a 9 volt battery. Transcranial Current stimulation (tCS) is a neurophysiological technique capable of modulating the excitability of the neuronal tissue of the central and peripheral nervous system through the application, for a finite time length, of an electrical field. This electric field is generated by the application of weak electrical currents through the scalp and into the brain. It has been demonstrated that the technique is safe and potentially beneficial if used within the known bounds of current intensity, density and duration.

tDCS has been widely used during the last decade demonstrating non-significant risk to participants (Brunoni, Fregni, & Pagano, 2011). In a comprehensive review of studies published from 1998 to 2008 that was authored by an international panel of experts, it was concluded that "extensive animal and human evidence and theoretical knowledge indicate that the currently used tDCS protocols are safe" (Nitsche et al., 2008). Side effects associated with tDCS according to the most recent data available (Brunoni, Fregni, & Pagano, 2011; Nitsche et al., 2008; Antal et al, 2007; Moliadze, Antal, & Paulus, 2010; Brignani, Ruzzoli, Mauri, & Miniussi, 2013) are:

1. Sensations reported by subjects under the electrodes: (These sensations can sometimes continue throughout and for a brief period following completion of the tDCS but usually resolve shortly after the initiation of tDCS)
    - Mild tingling (20-70%)
    - Light itching (30-40%)
    - Slight burning (10-22%)
    - Discomfort or mild pain (10-18%)
2. Other effects that can occur both during and after tDCS include:
    - Mild fatigue (15%)
    - Skin redness (20%)
    - Headache (10-15%)
    - Difficulties in concentration (11%)
3. Additionally the following rare side effects have been described:
    - Nausea (<1%)
    - Nervousness (<1%)
4. Although it has never been reported in tDCS, seizures are a theoretical risk. Individuals with a history of seizures and/or a diagnosis of epilepsy will therefore be excluded from this study

References:

Antal, A., Brepohl, N., Poreisz, C., Boros, K., Csifcsák, G. & Paulus, W. Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. Clin J Pain 2008; 24(1):56-63. http://doi.org/10.1097/AJP.0b013e318157233b

Brignani, D., Ruzzoli, M., Mauri, P., & Miniussi, C. (2013). Is transcranial alternating current stimulation effective in modulating brain oscillations? PloS One, 8(2), e56589. http://doi.org/10.1371/journal.pone.0056589

Brunoni, A.R., Fregni, F., & Pagano, R. L. (2011). Translational research in transcranial direct current stimulation (tDCS): a systematic review of studies in animals. Reviews in the Neurosciences, 22(4), 471â481. http://doi.org/10.1515/RNS.2011.042

Moliadze, V., Antal, A., & Paulus, W. (2010). Boosting brain excitability by transcranial high frequency stimulation in the ripple range. The Journal of Physiology, 588(Pt 24), 4891â4904. http://doi.org/10.1113/jphysiol.2010.196998

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., & Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. Brain Stimulation, 1(3), 206â223. http://doi.org/10.1016/j.brs.2008.06.004

The device will be used to record EEG and apply transcranial direct current stimulation (tDCS) to the participant's scalp via gel electrodes. The device will be operated by study personnel who have obtained certification for administration of tDCS.

The device will be stored in a locked cabinet within the Clinical Research Laboratory at the Hebrew Rehabilitation Center. Dr. Brad Manor will monitor device usage by study personnel.

Mobility lab

The Mobility Lab system allows the user to wirelessly record human movement from multiple synchronized monitors. There are no adverse effects associated with this passive recording system.

The device is secured to the participant's wrists, ankles, sternum and waist with elastic straps. The device records multiple characteristics of movement during trials of standing and walking. The device will be used to collect movement data during multiple trials of standing and walking (approximately 60 minutes in total) on 4 separate study visits. The device is connected to a computer software program. This program configuresthe device and completes a performance assessment at the beginning of each trial of data collection.

Uses of Non-Ionizing Agents

MRI

MRI consisting of structural and functional scans. A structural MRI scan provides anatomical information of the brain, while the functional MRI provides information about the activity of the brain. These types of scans are a part of routine MRI procedures.

Baseline structural MRIs will enable current flow modeling, as well as detection of silent infarcts and white matter hyper intensities (WMHs), and the BOLD fMRI will enable characterizing the brain functional network at resting state. T1, T2, and T2-weighted fluid-attenuated inversion recovery (T2 FLAIR)scans will be completed on a 3T GE system with a quadrature head coil at the Beth Israel Deaconess Medical Center, located near the Clinical

Research Lab. Two T1 datasets will be acquired: one with fat-suppression to optimize brain and CSF segmentation and another one without it to optimize skull and skin segmentation. Field-of-view will encompass all the head with coverage up to C1/2 vertebrae. Silent brain infarcts will be identified as focal lesions appearing hyper-intense on T2 and hypo-intense on T2 FLAIR scans. White matter lesions will be identified as periventricular and subcortical regions appearing hyper-intense on T2 FLAIR. Lesion diameters and volumes will be automatically calculated using an in-house AFNI and Free Surfer combination pipeline and the Lesion Segmentation Tool for SPM with manual edits as necessary. All volumes will be normalized as a percentage of the total brain parenchyma volume.

Parameters: T1: 362 s,TR/TE=2530/3.32 ms, flip angle=7°,1 mm3 isotropic resolution,matrix= 256X256; T2: 283 s,TR/TE= 3200/284 ms, 1mm^2isotropic resolution,matrix=256X256; T2 FLAIR:422 s, TR/TE=6000/388 ms, flip angle=120°, thickness=1.0 mm, 0.49x0.49 mmin-plane resolution, matrix=512X512. BOLD MRI will utilize a standard echo-planar imaging sequence with the following parameters:repetitiontime/echo time (TR/TE)= 1050/34.8ms; 65° flip angle;230×230mm field of view (FOV) with a104×104 acquisition matrix;thickness/gap (THK)=4mm/1mm with 2x2mm^2 in-plane resolution. Anatomical MRI will be acquiredafter the BOLD sequences with the T2-weighted FLAIR sequence(TR/TE/TI = 6000/279/2100ms, 1.0mm isotropicres, 256x256mm, 160 slices/slab) and a 3D magnetization preparedrapid gradient echo (MP-RAGE) sequence (TR/TE/TI = 7.8/3.1/600ms; 1.0mm slicethickness, 52 slices; bandwidth = 122Hzper pixel; 10° flip angle; 240x240mm FOV with 256x192acquisition matrix).

There will be one optional MRI visit, approximately 50 minutes in duration.

Data Management

All data collected for analysis will be de-identified and assigned a unique study number. Data collection forms will be kept in a locked file cabinet in the office of the PI at Hebrew SeniorLife. Data will be entered and stored on a password-protected secure server at Hebrew SeniorLife.

The Institute for Aging Research primarily employs the REDCap system to facilitate data management operations. REDCap is a full-featured clinical trials data management system (DMS) accessible to data entry and data analysis workstations using secure Web technologies. The REDCap product is developed and maintained by Vanderbilt University in cooperation with REDCap Consortium members, including Hebrew SeniorLife. HSL hosts and maintains a dedicated instance of REDCap for use across our research enterprise. Each research study is provided separate project workspace in which all of the study data are stored in a MySQL relational database on the private corporate network behind several firewalls and located physically within the HSL data center.

Data collected will be stripped of identifiers. Data will be assigned a code number and no personal identifying information will be associated with study data in any format, including electronically. Only the investigators will know information about a particular subject. Identifying information about a subject will be stored in locked computer files and cabinets and will not be used during the discussion, presentation, or publication of any research data.

Data will be kept on a secure, password protected Hebrew SeniorLife server in a REDCap Database. Only study members at the Hebrew SeniorLife site will have access to the REDCap database. All

hard copy forms will be kept in a locked filing cabinet that only study members will be able to access.

We will follow the current Hebrew SeniorLife Record Management, Retention, Disposition and Destruction Guidelines for this study. Identifiers will be kept for 7 years following the completion of the study. At this time destruction of materials containing identifiers and keys will be completed.

We will receive the coded participant data from MRI scan at BIDMC. The MRI data will allow for participant MRI to be imported into the Stimweaver software.

Foreseeable Risks, Potential Benefits, Compensation, and Cost to Participants

Potential medical risks of study procedures:

TESTS OF WALKING AND PHYSICAL FUNCTION: The proposed walking tests have been adapted from the large-scale, population-based MOBILIZE Boston study (PI: L. Lipsitz) and multiple completed and ongoing clinical studies within the Clinical Research Laboratory at IFAR. They have been designed to be safe for individuals of varying risk and conditioning levels including older adult fallers. The physical activity associated with these tests is of low to moderate intensity. Potential risks include strains, sprains, muscle soreness, and light-headedness. In rare instances, more serious side effects such as an injurious fall may occur. For all functional tests, a trained "spotter" will stand behind or close to the subject to provide stabilizing assistance if necessary. Subjects will be instructed to stop performing or skip any test that makes them feel uncomfortable. Adequate rest will be given in between each test, and any reusable equipment will be cleaned with disinfectant after each use.

MAGNETIC RESONANCE IMAGING (MRI): Participants will have the option to participate in one brain MRI. They will rest in a horizontal position on the imaging table that slides into a magnetic field. All studies performed under this protocol will not exceed the FDA guidelines for magnetic resonance in any way. Therefore, the risks assumed by the participant are the same as in any noninvasive protocol involving whole body MRI. The presence of metal objects could cause a burn injury, but by following strict MRI exclusion guidelines, this risk will be minimized. Participants may feel claustrophobic or anxious during the procedure and they may experience musculoskeletal or back discomfort lying on the scanner table. The MRI makes loud banging noises as it takes images. Under some circumstances nerve stimulation may occur, which may be experienced as a mild twitching reaction in limbs and/or lower back muscles. Such effects are rare and scan settings are kept well below the levels where such effects are known to occur. MR imaging also requires the use of radio waves that can cause a mild warming similar to exposure to hot weather. Body temperature may increase but by less than two degrees Fahrenheit. Participants will be instructed to inform MRI personnel should they experience discomfort due to warming and the procedure will be stopped.

We may need to contact a participant's health care provider to ask him/her for documentation related to whether it is safe for the participant to have an MRI of their brain. For example, if they have had cataract surgery, we would need to verify the name, make, and model of the lens that was implanted. This is for safety purposes. If we need to contact a participant's health care provider, we will ask the participant for their written permission to do so.

TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS): tDCS has been widely used during the last decade demonstrating non-significant risk to participants. Expected side effects include:

1) Sensations reported by subjects under the electrodes: (These sensations can sometimes continue throughout and for a brief period following completion of the tDCS but usually resolve shortly after the initiation of tDCS)

- Mild tingling (20-70%)
- Light itching (30-40%)
- Slight burning (10-22%)
- Discomfort or mild pain (10-18%)

2) Other effects that can occur both during and after tDCS include:

- Mild fatigue (15%)
- Skin redness (20%)
- Headache (10-15%)
- Difficulties in concentration (11%)

3) Additionally the following rare side effects have been described:

- Nausea (<1%)
- Nervousness (<1%)
- Although it has never been reported in tDCS, seizures are a theoretical risk. Individuals with a history of seizures and/or a diagnosis of epilepsy will therefore be excluded from this study.

Potential psychosocial (non-medical) risks of study procedures:

TESTS OF MENTAL FUNCTION: Risks associated with answering these cognitive test questions are minimal, but participants may experience mental fatigue and/or anxiety during this form of testing.

INCONVENIENCES: We will minimize the risk to subjects in this study by excluding those with conditions listed in the exclusion criteria. The proposed protocol requires multiple visits and therefore considerable participant burden with respect to time and effort. Our study team has a strong track record of successful clinical research requiring similar participation, and retention has been high in these projects.[118,205] The Clinical Research Laboratory at IFAR is located next to a cafeteria and equipped with comfortable seating, a TV, movies, books and magazines to keep individuals occupied during resting periods. Several additional strategies will be employed to minimize participant burden and maximize adherence to the protocol. We will:

- Develop a personal relationship between participants and members of the staff by matching research assistants with individual participants.
- Schedule appointments at convenient times with familiar staff.
- Explain to participants all aspects of their participation and follow up. We will demonstrate and practice study procedures before beginning data collection.
- Provide reminders of all appointments and follow-up phone calls. Include personal notes in the participant's data file to remember events in the life of the participant; these can be commented on at the next visit (e.g., birthday, birth of a grandchild).
- Provide snacks during all visits.
- Provide transportation for all visits, if required
- Provide valet or dedicated, on-site parking spaces.
- Compensate participants for visits.

Potential benefits to individual participants as a result of participating in the study:

Participants may not receive any significant health benefit from participation, although some may benefit from knowledge of their health status, as well as potential therapeutic effects of tDCS.

Participants will be provided up to a $300 stipend to help cover the costs of their time spent completing study procedures. Specifically, they will receive the following amounts for each visit completed:

Visit 1A - In-person screening $25

Visit 1B- Baseline assessment $25
Visit 2 – Optional MRI visit - $50
Visits 3- 6: Brain stimulation and Dual tasking assessment visits – one visit per week over 4 weeks; $50 for each visit = total of $200

Participants will receive a check in the mail within eight weeks of study participation.

Potential benefits to study population, community or society:

We believe that the potential benefits of understand and optimizing tDCS as a noninvasive intervention to improve dual task standing and walking in older adults outweigh the above-outlined potential risks to participants, which are expected to be minor, transient and relatively rare.

Provisions for medical care and available compensation in the event of injury:

Any subject who suffers an adverse event during the conduct of study protocols at Hebrew SeniorLife will be given immediate medical care at the Hebrew SeniorLife by the medical investigators, and, if the event meets the definition of a serious adverse event, the participant will be removed from the study, and will be referred to their primary care physician for ongoing care. The treating provider will bill the insurance company or other third parties, if appropriate, for the care a participant receives for any injury. We will try to have these costs paid for, but the participant may be responsible for some of them. For example, they may be responsible for payment of any deductibles and co-payments required by the insurer. There are no plans to provide any compensation for an injury beyond what is described above, should one occur.

If the event does not meet the criteria of a serious adverse event, and the participant is willing and able to continue, he/she will be able to continue and complete the study.

Definitions of Adverse Events and Serious Adverse events for the study

An adverse event is any untoward medical occurrence in a participant, whether or not is is causally related to the study. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the study. Adverse events will be recorded on the appropriate case report forms and source documents. The investigator and/or trained staff member will evaluate all adverse events as to their severity and relation to the test article. The severity of adverse events will be graded as follows:

- Mild: Awareness of a sign or symptom but easily tolerated.
- Moderate: Discomfort sufficient to cause interference with usual activity or to affect clinical status.
- Severe: Incapacitating with inability to do usual activity or to significantly affect clinical status.
- Life Threatening: The participant was at immediate risk of death from the adverse event as it occurred.

The Investigator will also assess the relationship of any adverse event to study, based upon available information, using the following guidelines:

- 0 = Unlikely: No temporal association, or the cause of the event has been identified.
- 1 = Possible: Temporal association, but other etiologies are likely to be the cause; however, involvement of the study procedures cannot be excluded.
- 2 = Probable: Temporal association, other etiologies are possible, but not likely.

A serious adverse event is any experience that results in any of the following outcomes: death, is life threatening, inpatient hospitalization or prolongation of hospitalization, a persistent or significant disability/incapacity. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unanticipated problems and adverse events will be reported according to the Hebrew SeniorLife's IRB written guidelines for interventional studies. Serious adverse events will be reported to the Hebrew SeniorLife's IRB within 24hrs by fax or email, with a written report submitted within 5 business days of learning of the event, and submission of the incident via the eIRB system within one week of learning of the event. This form will record any adverse symptoms and/or study protocol deviations.

All adverse events/study incidents will be reported to the HSL IRB, according to policy, within 5 business days of learning of the event, and to submit the incident via the eIRB system within one week of learning of the event.

Data Safety Monitoring Board

Only those listed on the approved IRB protocol will have access to subject data. Subject data will be coded and locked in a file cabinet in a locked office. Identifying information will not be used during discussion, presentation or research publication. The criteria for discontinuing a participant's participation include the participant's request, as well as any unexpected life-threatening or potentially disabling event, including syncope, an injurious non-accidental fall, hemodynamic collapse, stroke, transient ischemic attack, dysrhythmia, renal insufficiency, angina, myocardial infarction, anaphylaxis, acute hemorrhage, or hospitalization for acute illness. Any adverse events that take place during testing will be reported by the PI (Dr. Brad Manor) to Dr. Lewis Lipsitz, Director of Institute for Aging Research, Professor of Medicine at HMS and Chief of Gerontology at BIDMC and recorded in the database. Drs. Manor and Lipsitz will have primary responsibility for monitoring participant safety in the trial. The investigators will be responsible for reviewing each adverse event in a timely fashion, and reporting all incidents to the DSMB in accordance with the established DSMB charter, and preparing a summary report. Any adverse events will be reported to the Hebrew SeniorLife IRB according to written guidelines.

Dissemination of Results

Results will be disseminated through publications in peer-reviewed medical journals, presentations at national meetings, and announcements on the HSL website and other public media.

To comply with the dissemination of NIH-funded clinical trial information, we will register this clinical trial at ClinicalTrials.gov. We will ensure that results information is submitted to ClinicalTrials.gov as outlined in the policy, and according to the specific timelines stated in the policy. We also will ensure that informed consent documents for this clinical trial will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov. Hebrew SeniorLife's Institute for Aging Research has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.