**Title: Modulating brain activity to improve goal-directed physical activity 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.*

## Purpose

Although the majority of older adults are aware of the compelling evidence that regular exercise is critical to the maintenance of health into old age, most do not meet recommendations for daily exercise. This lack of engagement in 'goal-directed' physical activity stems from numerous interrelated factors including lack of motivation, depressed mood, and cognitive "executive" impairments that diminish one's ability to regulate behavior over time. Intriguingly, each of these factors has been linked to the function of brain networks that include the left dorsolateral prefrontal cortex (dlPFC). Transcranial direct current stimulation (tDCS) is a noninvasive and safe means of modulating the excitability of specific brain regions and their connected neural networks. tDCS designed to facilitate the excitability of the left dlPFC has been shown to improve motivation, mood, and multiple aspects of executive function in healthy adults. We thus hypothesize that tDCS holds promise to increase goal-directed physical activity in older adults.

We aim to conduct a pilot randomized controlled trial on the feasibility and effects of a 2-week, 10-session tDCS intervention targeting the left dlPFC on physical activity and community mobility, over a two-month period following the setting of a personalized physical activity goal, in relatively physically-inactive older adults without overt illness or disease.

## Background

Regular physical activity is an extremely effective, safe, and modifiable means of health promotion, especially in old age. Yet, nearly 60% of older adults do not reach recommended amounts of daily physical activity.[1] Although there are many factors contributing to physical inactivity in older age, three main barriers are lack of motivation,[2] depressed mood,[3,4] and poor executive function.[5,6] Recent neuroimaging studies have linked each of these barriers to functional integrity and/or activation of the left dorsal lateral prefrontal cortex (dlPFC) and its connected neural networks.[7-13] As such, strategies designed to facilitate activation of the left dlPFC hold promise to reduce barriers to physical activity and thus, increase such goal-directed behavior in older adults.

Transcranial direct current stimulation (tDCS) is a non-invasive device to modulate cortical excitability (i.e. the likelihood of neuronal firing) by inducing current flow between two or more electrodes placed upon the scalp.[14,48] tDCS enables selective facilitation of brain tissue excitability by using electrodes placed on the scalp to deliver low-amplitude electrical currents that polarize populations of cortical neurons. The electric fields generated by tDCS and their effects on brain tissue depend upon electrode size, polarity, and placement, as well as current amplitude and duration.[14] A single 20-minute session of tDCS with the positive electrode over the F3 region of the 10-20 EEG placement system and the negative electrode over the contralateral supra-orbital margin facilitates left dlPFC excitability and its connected neural networks for at least one hour following stimulation.[15] Such effects on excitability have been observed in younger and older adults of varying cognitive status.[16,17] Moreover, multiple exposures to tDCS over a relatively short time period (e.g., 10 once-daily sessions within two weeks) induces longer-lasting increases in both cortical excitability[18,19] and cerebral perfusion.[20]

tDCS designed to facilitate the excitability of the left dlPFC, improves motivation, mood, and even executive function in numerous populations including older adults. In particular, studies have suggested that single- and or multi-session interventions of this form of tDCS:

- Increases the willingness of healthy adults to exert physical and cognitive efforts for rewards,[21] Induces lasting improvements in mood, even in older adults with moderate-to-severe depression,[22,23]
- Enhances multiple aspects of executive function relevant to goal-directed behavior, including working memory,[24] selective attention,[25] task switching,[26] multitasking,[27] problem solving,[27] and decision making.[29] Our team has demonstrated that this form of tDCS improves gait and balance—abilities critical to exercise and falls self-efficacy[30]—in older adults (details below).

We have demonstrated through a series of studies that tDCS improves executive function, as well as the executive control of gait and balance, in older adults.[31-34] Most recently, we reported that in a small sample (n=20) of non-demented ambulatory older adults without overt illness or disease, yet who presented with mild-to-

moderate executive dysfunction at baseline, that a two-week tDCS intervention targeting the left dlPFC, as compared to sham stimulation induced clinically-meaningful improvements in the Montreal Cognitive Assessment (MoCA), and particularly within the executive function sub-score of this exam.[31] Moreover, tDCS, as compared to sham, improved the ability to stand and walk, especially while engaging in an additional cognitive task (i.e., verbalized serial subtractions of 3 from a random 3-digit number). This ability to "dual task" is a sensitive predictor of both falls and cognitive decline in the future[38-42] and is critical to safe mobility during physical activity. Furthermore, dual tasking requires multiple higher-level cognitive executive functions,[42-47] including working memory, mental flexibility, and self-control, that are together needed to initiate and ultimately sustain physical activity in the presence of distractors. These results, combined with the aforementioned reports that this form of tDCS may also improve motivation and mood, gives us confidence that 1) a 2-week tDCS intervention is safe and feasible for older adults of varying functional status, and that 2) such an intervention will likely induce numerous functional benefits that will together translate into improved effectiveness of a goal-directed physical activity behavioral intervention.

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## Participant Selection

Number of Subjects: 32 participants in total (16 participants per group, two groups: counseling+ real stimulation, counseling + sham stimulation)

### Inclusion criteria

- Men and women aged 65 – 85 years
- Live in subsidized housing in Boston area communities
- Meet at least one the following: 1) self-report of exercising, on average, less than 150 minutes of at least moderate-intensity exercise per week, as determined by phone-screen completion of the International Physical Activity Questionnaire-Short Form (IPAQ short), or 2) self-report 'room to improve' and the motivation to increase their current physical activity levels.

### Exclusion criteria

- An inability to ambulate without the assistance of another person (canes or walkers allowed)
- Self-report of falls for more than twice over the past six months.
- Self-report of physician-diagnosed dementia, more than moderate cognitive impairment defined as a Montreal Cognitive Assessment (MoCA) score <18, or an inability to understand the study protocol as determined by study staff
- A clinical history of stroke, Parkinson's disease or parkinsonian syndromes, multiple sclerosis, normal pressure hydrocephalus or other movement disorder affecting gait
- Any report of severe lower-extremity arthritis or physician-diagnosis of peripheral
- neuropathy
- 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
- Any unstable medical condition
- Contraindications for tDCS, including reported seizure within the past two years, use of neuro-active drugs, self-reported presence of specific implanted medical devices (e.g., deep brain stimulator, medication infusion pump, cochlear implant, pacemaker, etc.), or the presence of any active dermatological condition, such as eczema, on the scalp

### Participant recruitment

We will leverage our established relationships within the Boston area subsidized housing providers to recruit older individuals living in low income senior housing. We will meet with housing site administrators, and post flyers within these communities. We will also attend community meetings to raise awareness and meet with resident council members to discuss the study. We will hold informational gatherings to allow housing site

residents to attend and obtain one-on one information about the study.  We will also place flyers (attached) within local senior living communities and/or advertise in local media outlets targeting senior citizens (e.g., 50+ Advocate).

Those displaying interest in participation will complete an initial phone screening which will provide an overview of the study and a series of questions related to initial inclusion and exclusion criteria (attached). Participants who are potentially eligible based upon the phone screen will be scheduled for the first study visit, which will begin with a formal consent process and further in-person screening procedures.

### Consent Process

Individuals will contact the study team at the number provided on the study advertisement. A research assistant will give an overview of the study to the individual. At this point, the individual will be asked if they are interested in participating. They will then be asked if they have time to complete a 10-minute over-the-phone screening questionnaire based on the inclusion and exclusion criteria. If so, the research assistant will continue the screening (see attached phone screening form). If the potential subject does not have time, the PI will obtain their contact information and a more convenient time to call the potential subject back. If the participant meets all criteria of the study, the formal in-person study visit will be scheduled. For these individuals, we will send a copy of the informed consent in the mail or via email (based on the participant's preference). This will allow the participant time to review the consent form prior to their study visit.

On the day of the scheduled visit, the Research Assistant will review the informed consent with the participant and answer any remaining questions. If the participant would like to continue, the participant and the research assistant will sign the consent form. The PI and/or the Research Assistant will provide a copy of the signed consent form for the participant to keep for their records.

## Screening Procedures

Phone screen:

Interested individuals will first complete a phone screen, which will include the International Physical Activity Questionnaires (IPAQ)-short to determine their physical activity level.

Visit 1: In-person screen and introduction (1 hour); Participant's Housing Site

Those potentially eligible will complete an in-person visit (Visit 1). This visit will take place in the participant's housing site, in a comfortable and private location that will be arranged in advance by the research team. Written informed consent will be obtained at this time. A medical history questionnaire will be completed, medications, blood pressure, height, body mass and years of education will be recorded, and the MoCA will be administered. Eligible individuals will then be enrolled in the study.

Physical Activity Monitoring: At the end of Visit 1, participants will be provided with a FitBit™ activity tracker and familiarized with its functionality. The FitBit Alta wireless and waterproof activity tracker wristband (https://www.fitbit.com) will be used to record physical activity, including step counts and minutes of moderate-to-vigorous activity. Participants will be asked to wear theFitBit™ every day, removing it only at night to recharge the battery. Participants will wear the FitBit™ for 2 weeks. Baseline physical activity will then be recorded over this two-week period as participants go about their normal daily lives.

Community Mobility Monitoring: At the end of Visit 1, participants will be also provided a global positioning system (GPS) device (Columbus V990) to wear for the entire study period. They will be asked to take it with them whenever they leave their home and keep it on their person. Devices will be returned at the end of the study. Data will be downloaded to a secure computed and saved with only the study ID number. No personally identifying information will be included in the GPS data files.

## Baseline Procedure

Visit 2: Baseline Assessment Visit (~ 1.5 hour); Participant's Housing site

Baseline Assessments: (90 minutes) The assessments described below have been designed to capture information on motivation, barriers, and self-efficacy related to physical activity, mood, cognition, and mobility.

A 20-minute battery of validated questionnaires will be used to assess motivation for physical activity (Exercise Self-Regulation Questionnaire, SRQ-E), self-efficacy for exercise (SCI Exercise Self-Efficacy Scale, SES-E), self-efficacy for walking (Self Efficacy for Walking Scale, SES-W), barriers to exercise (Barriers Self-Efficacy

Scale, BARSE), mood (15-item Geriatric Depression Scale), cognitive reserve (Cognitive Reserve Questionnaire)

A 40-minute battery of tests will assess global cognitive function (MoCA), executive function (Trail Making Test A and B), working memory (WAIS-IV Digit Span Forwards and Backwards), sustained attention and motor speed (gradCPT and WAIS-IV Coding test), verbal learning (Category and Phonemic Fluency tests), and episodic memory (Hopkins Verbal Learning Test.Revised, HVLT-R). These tests were selected because they are sensitive to cognitive status and/or self-regulation in older adults, are suitable for repeat testing as they have alternate forms or are resistant to practice effects, have excellent psychometric properties and normative data, and have minimal ceiling and floor effects.

A 30-minute battery of functional tests will be completed. Dual task standing and walking will be assessed following recommendations that produce excellent test-retest reliability in older adults. Participants will complete two, 60-second trials in each of six conditions: 1) Single task—seated cognitive task (see below for description); 2) Single task—standing; 3) Single task—walking; 4) Single task-fast walking; 5) Dual task—standing with cognitive task; 6) Dual task—walking with cognitive task. The cognitive task will be verbalized serial subtractions of 3's from a random three-digit number between 200 and 999. Participant responses will be recorded. We have chosen this task because it activates a distributed cortical network including the left dlPFC,67 induces meaningful dual task costs to both gait and posture in older adults, and is reliable and minimally influenced by learning in older adults. All trials will be completed using the portable Mobility Lab™ motion capture system (APDM, Seattle WA). Walking trials will be completed in a long hallway. Participants will be reminded to walk at their preferred, comfortable pace. During the fast walking trials, participants will be reminded to walk as fast as they can walk safely. Assistive devices will be allowed for trials of walking (but not standing). Finally, functional mobility will be assessed by the Timed Up-and-Go (TUG) test, which correlates with mobility disability73 and has excellent inter- and intra-rater reliability. Participants will be randomized to tDCS intervention arm (to begin at Visit 3) at this time and the behavioral intervention will be initiated at the end of Visit 2.

Visit 3: <u>First Personalized Counseling Session (~0.5 hour); Participant's housing Site</u>
Behavioral intervention to promote physical activity (~30 min): We will utilize a modified version of a personalized, goal-based counseling approach to promote physical activity in older adults. Briefly, a physical therapist (Dr. Amy Lo) or a nurse (Peggy Gagnon) will complete a face-to-face counseling session with each participant, tailored to their state of readiness to increase physical activity levels. Dr. Lo or Peggy will provide the participant with a goal to increase their average daily step count by 20% from baseline, review their stated barriers to exercise and provide them with a list of strategies they may use to augment their step counts throughout each day. The participant will also be encouraged to spend time each day to plan their walking activities for the next day. Dr. Lo and the research staff will conduct both in-person and telephone counseling

sessions, as noted above in Figure 1, over the eight week follow-up period to discuss challenges and provide additional tips for increasing physical activity. Regular calls will be scheduled once a week for alternate weeks (i.e., weeks 3,5,7 and between assessment visits and in-person counseling visits (i.e., weeks 2,4,6,8, and 10). The goals of these regular telephone calls will be to check in, review and discuss activity performance, and answer any questions the participant may have regarding their efforts to increase physical activity

Physical Activity Monitoring: All participants will continue to use the FitBit™ to track their activity during the entire eight week follow-up period. At the end of visit 2, they will be instructed how to synchronize the FitBit™ to their computer or smartphone, and will be instructed to do this each day. If participants do not have access to a computer or smartphone, the research team will synchronize the participant's FitBit™ during scheduled in-person sessions. Research staff will confirm compliance and data uploads by pre-registering each FitBit and monitoring its activity via the company's website.

Participants will receive regular behavioral intervention calls from the study staff throughout their study enrollment, until the final study visit, Visit 15. Participants will be given contact information for the study team members, so that they may reach the study team if needed at anytime between scheduled study activities.

**Experimental Procedures**

Visits 4-13: tDCS Brain Stimulation visits (30 minutes); Participant's Housing site

Participants will complete 10 twenty minute brain stimulation sessions (Monday-Friday) over the next two weeks.

tDCS intervention: Similar to our preliminary study, this intervention will consist of 10, 20-minute sessions delivered on Monday-Friday over two weeks. Stimulation will be delivered using the Startim-8™ device and software (Neuroelectrics Corp, Cambridge MA), which enables custom amounts of current to be delivered through an array of up to eight Pi™ gel Ag/AgCl electrodes placed on the scalp according to 10-20 EEG convention. This system also enables the blinding of study staff and participants to stimulation type. At the end of the first session and every other session thereafter, participants will complete a side effects questionnaire.51 A blinding efficacy questionnaire will also be completed after the final session, on which participants state whether they believe they received tDCS or sham and their confidence in this belief.

Real tDCS: Similar to our preliminary studies, tDCS will be delivered via six gel electrodes with placement and current parameters optimized based on a standard brain to maximize the average normal component of the generated electric field over the left dlPFC. Current delivered by anyone electrode will 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.

Sham stimulation: An ‘active’ sham will be used in which very low-level currents are transferred between the same electrodes used in the active condition throughout the 20-minute session. However, currents will be designed to mimic the cutaneous sensations induced by tDCS yet not significantly influence cortical tissue. This approach effectively blinds participants and operators to stimulation condition and does not affect functional outcomes.52

Visit 14: Follow-Up Assessment (1.5 hours); Participant's Housing site

Follow-up assessment, as described above in Visit 2, will be completed immediately after and 2 weeks after the tDCS intervention.

Visit 15, 16 and 17: Follow-up Personalized Counseling visits (30 minutes); Participant's Housing site

Three bi-weekly in-person counseling sessions will be completed after the tDCS intervention.

Visit 18: Final Assessment visit (1.5 hours); Participant's Housing site

Final follow-up assessments, as described above in Visit 2, will be completed after 6 weeks of the tDCS intervention.

At the end of visit 18, we will provide the opportunity for participants to continue tracking their FitBit information for up to additional 3 months. If the participant agrees, we will keep the tracking option available for the study team to track the retention of the intervention. The study team will terminate this tracking service by the end of the retention phase.

**Materials for recruitment and study conduct**

StimFit_Recruitment_Flier_20200108_clean.pptx
StimFit_Recruitment_Flier_notabs_20200108_clean.pptx
StimFit_Recruitment_letter_20200205_tracked IRB edits_clean.doc
Assessment of Protocol Understanding Form.docx
International Physical activity Questionnaire IPAQ short procedure Q by Q and questions.docx
MOCA.pdf
Stim-Fit_Phone_Screen_2020205_clean.docx
Stim-Fit_tDCS_Eligibility_Questionnaire.docx
The PAR Q.docx
gradCPT Instructions_FrailAdults.docx
N-Back_Instruction.docx
TRAILS_V1.pdf
TRAILS_V2.pdf

Trails_v3_corrected.docx

Digit Span.pdf

Blood Pressure Form_42219.docx

DT Balance Assessment 42219.docx

DT familiarization and sitting assessment 42219.docx

DT gait assessment 42219_AlipgEdit.docx

GDS15.pdf

Height and Weight Form 42219.docx

Medical History Questionnaire_1 71318.docx

Medication Review Form_1 42219.docx

Sociodemographic Form 42219.docx

TUG form 42219.doc

BARSE.pdf

ESES worksheet_exercise_self-efficacy_scale_eses_0.docx

SEW_DUR.pdf

SRQ-Exercise_short.pdf

WHAS Pain Questions.docx

tDCS Blinding Efficacy.docx

tDCS Side Effects Questionnaire.docx

Cognitive Reserve Questionnaire.pdf

## Data Analysis and Data Monitoring

### Data Analysis

This study will enroll 32 participants. We have conservatively planned for approximately 20% attrition and have thus based our statistical plan on complete datasets of n = 26.

Assessment of feasibility endpoints will be based on sample computations, including the screened to enrolled ratio, retention rate, assurance of blinding, and safety assessment (see above). Adverse events (AE) will be organized according to the MedDRA classification system and reported in each DSMB communication both by MedDRA System Organ Class (SOC) and overall. Both the number of individuals with one or more of AEs within each SOC, as well as the total count of all AEs within each SOC, will be reported. These will be accompanied by point and 95% confidence interval estimates of the proportion of individuals who would experience AEs and the total count of AEs per person-time within each SOC, respectively. The latter computation will acknowledge clustering at the level of the participant by using generalized estimating equations (GEE) in estimation with robust variance estimates used for computing confidence intervals.

We will use variance decomposition to generate estimates of within and between-individual variation in functional outcomes that would potentially be used in a subsequent trial (see above), along with confidence interval estimates for said variance measures, in order to assist in planning of the subsequent study. We will also conduct an exploratory analysis of the of mean change in these endpoints using mixed-effects linear regression of all time points, with a random effect included at the participant level in acknowledgement of serial correlation of repeated measures. Dependent variables will be the change in outcomes related to average daily activity from baseline to the six-week post-tDCS follow-up period, as well as the change in laboratory-based functional outcomes from baseline to each planned follow-up visit.

Feasibility outcomes:

The proposed sample size was motivated by our experience in similar pilot studies, the need to develop a sufficiently detailed profile of the background population and convincing demonstration of the feasibility of our protocols, the anticipated drop-out rate, and the need to make resource and sample size estimations for the subsequent trial. We anticipate, based on prior work, that we will screen between 5 and 15 individuals for each participant enrolled. Enrollment of 32 individuals will allow us to determine to within 1 individual the expected number of participants screened to enrolled in the subsequent trial using an 80% confidence interval; similarly, we will be able by the same method to estimate the probability a given participant will complete intervention to within 0.10.

Functional outcomes:

Assuming type-I error probability = 0.05 and cumulative attrition and missingness approximately = 20% (i.e.

evaluable data on 26 participants with complete data, the design will obtain 90% power to detect standardized differences [ratio of mean within–participant difference on endpoints to the standard deviation (SD) of same] of at least 0.41, and 80% power to detect effects of 0.36 or greater.

Our primary functional endpoint is habitual physical activity defined as average daily step counts derived from a FitBit wristband. As no prior study has investigated the change in total steps per week as a result of this type of intervention, we estimate the SD of the intervention-attributable change based on prior data on changes in weekly step counts in other conditions. Given that a prior study of pulmonary rehabilitation demonstrated a SD of 150 steps per week,84 we will have 90% power to detect changes as small as 62 steps per week, and 80% power to detect 54 steps per week.

**The GPS data will be analyzed by the team at the University of Pittsburgh. The GPS data were downloaded to a secure computer and saved with only the study ID number. Our team will upload the GPS data to the secure server at the University of Pittsburgh. No other identifiable information will be provided to the team at the University of Pittsburgh.**

## Data Storage and Confidentiality

### Data Storage

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 HebrewSeniorLife.

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 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.
Data security measures

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. All data are password protected and only the principal investigator or the study staff with a direct role in data collection or data management will have access to the data files and codes.

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.

### Confidentiality

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

- Phone screening will be conducted in a private office space.
- Study visits will be conducted in private rooms located within the participant's housing site.

- Each participant will be given a unique study identification number and data will not include any of the participant's PHI.
- All participant- identifying information will be stored and managed on a secured database server. The information will be password protected.
- Participant confidentiality will be maintained in accordance with HIPAA regulations.
- Only the PI and study personnel approved by the IRB and authorized to view PHI will have access to the information
- PHI will not be used during discussion, presentation or publication of any research data.
- Files containing PHI data collected for recruitment and screening purposes will be kept in locked, secured file cabinets accessible only to designated study personnel (research assistants and investigators.

## Risks/ Benefit Assessment

### Risks

Possible risks associated with physical activity:

Participants will be provided with a personalized goal to increase their average daily physical activity (i.e., step counts) during the study period. Participants are thus expected to increase their physical activity during this period. This activity is expected to be of low to moderate intensity. Potential risks are minimal and most likely transient, including strains, sprains, muscle soreness, light-headedness and physical fatigue. In rare instances, more serious side effects such as an injurious fall may occur.

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.

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.

Tests of mental function:

Risks associated with answering the cognitive test questions are minimal, but participants may experience mental fatigue and/or anxiety during this form of testing.

Minimizing Inconvenience

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. 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.

COVID-19:

During the COVID 19 quarantine and social distancing procedures, precautions will be taken to minimize contact when possible by performing teleconferencing and frequent check ins with participants on a remote basis.

**Potential Benefits**

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 completing a behavioral intervention to increase physical activity. Participants will be provided a $160 stipend to help cover the costs of their time spent completing study procedures. They will also have the option to keep the Fitbit device that they use in the study.

We believe that the potential benefits of establishing tDCS as a noninvasive intervention to improve goal-directed physical activity in physical inactive older adults significantly outweigh the above-outlined potential risks to participants, which are expected to be minor, transient and relatively rare.

The observations from these studies are expected to provide important information regarding the effects of noninvasive electrical brain stimulation on goal-directed physical activity in older adults. Results are also expected to provide insights into the feasibility and effectiveness of such intervention within this population, thus increasing the potential for deployment of tDCS interventions to larger numbers of older adults.

### Costs incurred during the study for medical care/injury

Any subject who suffers an adverse event during the conduct of study protocols will receive the medical care necessary to treat the adverse event. If we cannot provide the care directly, we will arrange for the medical care to be provided to the subject. 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

### Payment to Participants

Describe the type remuneration and the timing of remuneration to study procedures e.g. participants will be provided with $50 per study visit, to be distributed as visits are completed, etc.
Participants receive up to $160 for taking part in this study. Participants will also receive a FitBit and will be able to keep it when the study has ended if they wish. Specifically, participants will receive the following amounts for each visit completed:

Visit 1 - In-person screening visit - $10 Visit 2 – Baseline visit - $10
Visits 3- 12: Brain stimulation– 10 visits over two weeks; $10 for each visit= total of $100
Visits 13-14: Follow-up assessment visits - $10 for each visit = $30 total for completion of all 3 follow-up visits.

Visit 15: Final in-person counseling session - $10 Visit 16: Final follow-up study assessment - $10
Participants will receive a check in the mail within eight weeks of study participation.

### Participant Withdrawal

Participation may be terminated at the discretion of the PI, if the PI feels that study discontinuation is necessary to protect the participant, or that there are unmanageable factors which will interfere significantly with the study procedures and/or interpretation of results. The study participant will be informed of this and withdrawn from the study. The participant can, at any time, request the study be terminated and to be withdrawn. Any previously collected data prior to termination/withdrawal will be maintained in the study data set.

### Adverse Event Reporting

An adverse event is any untoward medical occurrence in a participant, whether or not it 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:

Serious adverse events will be reported to the IRB, as well as the identified Safety Monitor, within 24hrs by fax or email. A related written report will be submitted within 5 business days of learning of the event, and a submission of the incident to the IRB system will be completed within one week of learning of the event. This form will record any adverse symptoms and/or study protocol deviations.

All other adverse events/study incidents will be reported to the HSL IRB and identified Safety Monitor, according to policy, within 5 business days of learning of the event. A related submission of the incident will be completed via the eIRB system within one week of learning of the event.

### Safety Monitoring

Safety monitoring procedures will be implemented and reviewed by a Safety Monitor (to be determined upon Notice of Grant Award), in accordance with NIA safety policies for human intervention studies.

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. These adverse events will be recorded in accordance with IRB requirements and included in the study database. If a determination about

continued participation cannot be made according to these criteria, the adverse event report will be faxed to the un-blinded Safety Monitor, who will make the final decision.

Prior to the start of the study the Safety Monitor will review the IRB approved protocol, procedure manual and informed consent documents, with regard to participant safety, recruitment, randomization, intervention, data management, quality control, and confidentiality. The Safety Monitor will recommend any necessary changes of the protocol to the PIs and will review and approve revisions. The Safety Monitor will identify relevant data parameters and the format of the information to be regularly reported.

The Safety Monitor will then meet biannually with the investigators to review standardized reports. He/She will review the progress of recruitment and retention of participants, compliance with the protocol, and operating procedures. If they raise concerns about safety issues, they may request additional data and propose specific analyses. They will make recommendations to the PIs regarding recruitment, retention, compliance, and safety issues, and will

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 and adverse event reporting

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

All other adverse events/study incidents will be reported to the IRB and Safety Monitor, according to policy, within 5 business days of learning of the event. A related submission of the incident will be completed via the eIRB system within one week of learning of the event. Safety monitoring procedures will be implemented and reviewed by a Safety Monitor (to be determined upon Notice of Grant Award), in accordance with NIA safety policies for human intervention studies.

Prior to the start of the study the Safety Monitor will review the IRB approved protocol, procedure manual and informed consent documents, with regard to participant safety, recruitment, randomization, intervention, data management, quality control, and confidentiality. The Safety Monitor will recommend any necessary changes of the protocol to the PIs and will review and approve revisions. The Safety Monitor will identify relevant data parameters and the format of the information to be regularly reported.

The Safety Monitor will then meet biannually with the investigators to review standardized reports. He/She will review the progress of recruitment and retention of participants, compliance with the protocol, and operating procedures. If they raise concerns about safety issues, they may request additional data and propose specific analyses. They will make recommendations to the PIs regarding recruitment, retention, compliance, and safety issues, and will send a written report to the Program Administrator following each meeting. The Safety Monitor will be sent reports of research activity and summaries of safety monitoring information before each meeting.

### Participant discontinuation

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. These adverse events will be recorded in accordance with IRB requirements and included in the study database. If a determination about continued participation cannot be made according to these criteria, the adverse event report will be faxed to the un-blinded Safety Monitor, who will make the final decision.

## Publication Plan

We will register this clinical trial at ClinicalTrials.gov. 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. 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.