Submission Type: Modification Date: 6-4-2020

IRB #: IRB-2018-10
Title: Personalized brain activity modulation to improve balance and cognition in elderly fallers
Creation Date: 3-27-2020
Status: Review Complete
Principal Investigator: Bradley Manor

Amendment Request Form

All materials to be used with research participants must be reviewed and approved by the HSL IRB prior to implementation.

1.0 **Are you submitting *only* a change to the Study Personnel today?**

Note: this includes changes to the PI and Primary Contact

Yes

✓ No

Amendment Description

Provide a full description of the amendment and a justification for the proposed change
During the current COVID-19 pandemic, we are unable to complete our in -person follow up assessments for participants currently enrolled within this longitudinal study. We request the option of completing most of our planned in-person assessments over the phone. That is, we will call participants scheduled for assessments and complete all of our scheduled questionnaires and phone-friendly cognitive assessments.

Neuropsych measures: Over the phone we will be able to complete most of the measures to meet our cognitive aims, such as HVLT (Hopkins Verbal Learning Task); Digit Span; Verbal fluency,

and MoCA.

For participants with wifi and Zoom, we expect to be able to capture the remaining paper and pencil cognitive tests, such as the Trail Making Test and DSST (Digit Symbol Substitution Task).

Some participants will not have wifi or ability to access Zoom, and in those cases, we will not be able to capture these measures. We also will not be able to complete the gradCPT task, which requires the use of installed software on our lab laptops.

Health related questionnaires: We propose to complete all of the questionnaires over the phone. We will send the response scales to participants via email (or snail mail if needed) prior to the scheduled telephone assessment. Be believe that the strong relationships we have built with participants, together with their familiarity with these measures, will make this procedure comfortable and valid for our participants.

- SF-12 Questionnaire
- Activities of Daily Living (ADLs) Questionnaire
- Center for Epidemiologic Studies Depression Scale (CES-D)
- Medications Review
- Falls Questionnaire
- PASE
- Brief Pain Inventory (BPI)
- Falls Efficacy Scale- International (FES-I)
- Global impressions scale

2.0

Daul Task Gait and Balance: We propose to purchase several iPhone's and install our dual task gait and balance App that we have created and validated over the past three years. We will send a phone to participants who do not have their own iPhone, along with a stamped return padded envelop. For participants with their own iPhone's, we will instruct them how to install the app. We will review step by step procedures with each participant over the phone. The App is easy to use, provides animated verbal instructions to participants, and takes only a short time to complete. Specifically, using verbalized instructions, the phone is placed in the users pocket. It then guides the participant through a 45 second trial of normal walking, a 45 second trial of walking while performing a serial subtraction 'dual task,' a 30 second trial of standing with eyes open, a 30 second trial of standing with eyes closed, and a 30 second trial of standing while completing the serial subtraction task. For dual task trials, the phone instructions provide a random 3-digit starting number. The App has been used now to collect over 1000 remote gait assessments and no adverse events have been reported. Acquired data is used to capture temporal parameters of gait (e.g., stride time, dual task 'cost' to stride time), along with measures of standing postural sway. Through this process we will be able to capture numerous stated outcomes related to dual task performance that have been correlated 1:1 with R values >0.99 with the same measures collected using gold standard equipment within our laboratory (Manor et al 2018). Moreover, our participants are familiar with this dual task gait and balance assessments as they have completed them numerous times to date. All iPhone's will be disinfected before mailing to participants, and disinfected upon their return, using recommended procedures.

We will not be able to capture the following measures:

Blood pressure
Max handgrip
Timed Up and Go
Axivity Monitor.
SPPB (although capturing gait and balance data through the iPhone app will allow us to capture portions of this battery).

Section 5.1 of the Protocol form has been updated to reflect these changes.

3.0 Please click on the type of changes you are requesting

Click all that apply

- Personnel Changes
- Data Collection Materials *(e.g. surveys, questionnaires, forms, educational materials, etc.)*
- Funding *(e.g. grants, contracts, clinical trial agreements, etc.)*
- Research Design *(e.g. hypotheses, goals, aims, sample size, etc.)*
- Research Procedures *(e.g. site visits, tests or procedures to be conducted at site visits, etc.)*
- Recruitment Processes *(e.g. process and materials to recruit participants and/or their legally authorized representatives)*
- Consent Processes *(e.g. process and materials to consent participants and/or their legally authorized representatives)*
- Study Participants *(e.g. inclusion/exclusion criteria, source of participants, population, age range, duration of participation, etc.)*
- ✓ Research Site Location

Documentation (e.g. change in study title, grammar and spelling corrections, etc.)

Drugs, Devices, Ionizing and Non-Ionizing Radiation, Genetics, HIPAA Requirements, Data or Specimen Repository

Other

4.0 The study risks will:

✓ Not Change

Increase

Decrease

5.0 The study benefits will:

✓ Not Change

Increase

Decrease

6.0 Please indicate whether:

Click all that apply

The change alters the confidentiality/privacy of the participant

It is necessary to notify participants who have completed their participation

The change is due to an adverse or unanticipated event or problem

The change affects only prospective participants

The change affects the participants' commitment (ex. time, study costs, procedures, etc.)

The change involves pregnant women, fetuses, neonates, children, or prisoners

✓ The change affects previously enrolled/consented participants

Please explain

Only participant's enrolled and with upcoming or scheduled follow-up assessments will be asked to complete the modified over the phone/at home follow-up assessment

The change requires an ancillary committee approval or another institution's IRB review/approval

The change raises a conflict of interest

The change requires a waiver (ex. element of informed consent or HIPAA)

None of the above

7.0 Did you submit your *initial* application through the eIRB system?

✓ Yes

No

7.1 Online Submission forms to be changed as a result of the amendment

Please click on the online submission forms to be modified

Section 1 General Information

Section 2 Conflict of Interest

Section 3 Research Funding

Section 4 Research Project Information

✓ HSL Protocol Form for Non-Exempt Research

To make changes to the Protocol Form, please click the Protocol Form on the left sidebar.

Study Personnel Roster

Form A - Request for Waiver of Authorization to Use/Disclose Protected Health Information (PHI)

Form B - Consent Waiver Request

Form C - Use of Drugs and Biologics

Form D - Use of Devices in Research

Form E - Use of Ionizing Agents

Form F - Use of Non-Ionizing Agents

Form G - Research involving Genetic Analysis

Form H - Research Repository

Form I - HSL Department Approval (non-IFAR)

None

7.2 **Previously approved attachments to be** changed as a result of the amendment

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Recruitment Materials

Informed Consent Form

Data Collection Instruments

HSL Protocol Form

HSL Secondary Use of Data/Specimens Form

DSMB/C Charter/Manual

Data Use Agreement

Material Transfer Agreement

Agreement for Images

New Grant/Funding Application

Investigator Brochure

Sponsor Protocol

Study Procedure Manual

Other

✓ None

8.0 Are you requesting approval for *new* study materials?

Yes

✓ No

General Information

1.1 Date

07/03/2018

1.2 Protocol Title

Personalized brain activity modulation to improve balance and cognition in elderly fallers

Principal Investigator

1.3

Name: Bradley Manor
Organization: Institute for Aging Research
Address: 1200 Centre St , Boston, MA 02131-1101
Phone: 617-971-5332
Email: bradmanor@hsl.harvard.edu

Co-Principal Investigator(s)

- *Please list any HSL Co-Principal Investigator(s), if applicable.*
- *Non-HSL Co-Principal Investigators may be added on the personnel roster.*

1.4

Name: Lewis Lipsitz
Organization: Institute for Aging Research
Address: 1200 Centre St , Boston, MA 02131-1101
Phone: 617-971-5318
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Name: Junhong Zhou
Organization: Institute for Aging Research
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Name: Thomas Travison
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Primary Contact

Note: this may be a separate contact from the PI (e.g. project director), unless the PI is the only study contact. More than one primary contact can be added.

1.5

Name: Margaret Gagnon
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Address: 1200 Centre St , Boston, MA 02131-1101
Phone: 617-971-5303
Email: Gagnon@hsl.harvard.edu

Name: Amy Lo
Organization: Institute for Aging Research
Address: 1200 Centre St , Roslindale, MA 02131
Phone:
Email: AmyLo@hsl.harvard.edu

1.6 **Are there additional Study Personnel?**

✓ **Yes**

Please complete the Study Personnel Roster on the left side bar

No

Conflict of Interest

- **This section is for the identification of Conflicts of Interest for the PI and any Co-PI's.**
- **Conflicts of Interest for Co-Investigators and other study personnel will be addressed in the Study Personnel Roster.**

Does the PI or any Co-PI have a financial interest related to this research project?

2.0 "Financial Interest Related to the Research" means any of the following interests in the sponsor or competitor of the sponsor, product or service being tested, held by the individual or the individual's immediate family ("immediate family" means spouse, domestic partner, children and dependents): (1) Ownership interest of any value including, but not limited to stocks and options; (2) Compensation of any amount including, but not limited to honoraria, consultant fees, royalties, or other income; (3) Proprietary interest of any value including, but not limited to, a patents, trademarks, copyrights, and licensing agreements; (4) Board or executive relationship, regardless of compensation.

Yes

✓ No

Research Funding

3.1 **Is the research funded?**

✓ Yes

No

List all funding sources supporting the research

3.1.1

Please note: all funding applications, subcontracts and research agreements must be submitted for review with this application

Sponsor 1

Click below to find the name of Sponsor 1:
National Institute on Aging - NIA/NIH

Funding status

Choose one below:

Pending

✓ Awarded

Award Number

Provide award number assigned by sponsor.
R01 AG059089

Award Start Date

09/30/2018

Award End Date

05/31/2023

HSL Award Status

✓ Prime

Subcontract

Attach a copy of the grant/subcontract/contract funding the research

eraapplication.pdf

Has the funding agency provided a scientific review of the protocol?

✓ Yes

No

3.1.2 **Is there more than one sponsor?**

Yes

✓ No

3.2 **Has scientific review been conducted by any other reviewing entity?**

Yes

✓ No

Provide a brief description of the research project

In older adults, falls are costly, consequential and correlated with both physical and cognitive decline. Most falls occur when standing or walking. Many activities require us to stand or walk *while* performing tasks like talking or making decisions. Such "dual tasking" interferes with the control of standing and walking. This interference, or "cost," is exaggerated in older adults with previous falls and is predictive of future falls. Neuroimaging evidence indicates that standing and walking, especially when dual tasking, activate distributed brain networks including the left dorsolateral prefrontal cortex (dlPFC)—a brain region sub-serving executive function. Thus, strategies that facilitate activation of the left dlPFC and its connected neural networks hold promise to mitigate dual task costs, improve physical and cognitive function, and ultimately, reduce falls.

Transcranial direct current stimulation (tDCS) provides a noninvasive means of selectively modulating cortical excitability. We have shown in younger and older adults that a 20-minute session of tDCS designed to increase excitability of the left dlPFC reduces dual task costs and improves mobility when tested just after stimulation. We have since completed a pilot, sham-controlled trial of a 2-week, 10-session tDCS intervention targeting the left dlPFC in 20 older adults with slow gait and mild-to-moderate executive dysfunction. The intervention was successfully double-blinded and well-attended. tDCS, compared to sham, reduced dual task costs and induced trends towards improved mobility and executive function over a 2-week follow-up. We thus contend that tDCS targeting the left dlPFC holds promise to improve the control of standing and walking—and ultimately reduce falls—in older adults. Still, the size and duration of tDCS-induced benefits to older adult "fallers" have not been established. Moreover, to date, tDCS delivery has attempted to optimize current flow based on a "typical" brain and has thus *not* accounted for individual differences in skin, skull, cerebrospinal fluid and brain tissue in the aging brain. Such personalization is now possible with the current flow modeling we propose.

4.1

Our Overall Aim is to compare, in older adults with previous falls, the effects of a *personalized* tDCS intervention designed to target the left dlPFC on the dual task costs to standing and walking, and other physical and cognitive factors that are on the causal pathway to falls and important to everyday function. We will conduct a randomized, sham-controlled, double-blinded trial with assessments at baseline and post-intervention (immediate, 3-, 6-month follow-up) in 144 non-demented men and women (72 per arm) aged 65-85 years who report ≥2 non-syncopal falls within the previous year and are fearful of falling again, yet have no major neural or musculoskeletal disorders that explain their falls. The tDCS intervention will comprise 20, 20-minute sessions of tDCS over a 4-week period. Importantly, we will utilize current flow modeling from baseline structural MRIs to determine the tDCS electrode placement and stimulation parameters that optimize electrical current flow to the desired target within each participant's brain.

We hypothesize that, in older adults with previous falls and over a 6-month follow-up, a personalized tDCS intervention targeting the left dlPFC, as compared to sham, will mitigate dual task costs to the control of standing and walking and enhance other metrics of both physical and cognitive function.

INNOVATION AND IMPACT: This trial is expected to demonstrate that noninvasive modulation of

cortical excitability within the left dlPFC improves physical and cognitive factors on the causal pathway to falls in vulnerable older adults. It will also define the path for future falls prevention trials using tDCS.

4.2 **Are there external sites (outside of HSL) where the study will take place?**

✓ Yes

No

4.2.1 **List all external sites (outside of HSL) where the study will take place**

List all external locations where the research will be taking place

✓ Site 1

Provide the Name of the Institution

Beth Israel Deaconess Medical Center

List the research activities taking place at this site

Baseline and follow up MRI

List the responsible site Investigator

Mark Halko, PhD

Has IRB approval been obtained at this site?

Yes

✓ No

Is ceded review being requested for HSL to be the IRB of record for this site?

✓ Yes

Has the Institution requesting ceded review signed-on to the SMART IRB reliance system?

If you are unsure, please refer to this link.

Yes

✓ *Please complete the SMART IRB Online Cede Review Request*

No

Please complete the HSL Cede Review Request Form

No

Site 2

Site 3

Site 4

4.2.2 **Will you have more than 4 sites for this study?**

Yes

✓ No

4.3 **Click all of the sites within HSL where the research will take place**

✓ IFAR

List all research activities taking place at this site

Recruitment and screenings via telephone
Research Data Collection
Data Storage
Data Analysis

Housing Sites

Department of Medicine

Other

IMPORTANT NOTE: IF HSL WILL BE CEDING ITS REVIEW TO ANOTHER IRB, PLEASE ANSWER 'NO' or 'N/A' TO THE REMAINING QUESTIONS ON THIS FORM (e.g. 4.4 - 4.13).

4.4 **Does this project involve the collection or use of materials (data or specimens) recorded in a manner that could identify the individuals who provided the materials, either directly or through identifiers linked to these individuals?**

✓ Yes

Please complete the Protocol Form for Non-Exempt Research

No

N/A - we are requesting to cede review of this protocol to another IRB.

4.5 **Are data coming from entities covered under HIPAA?**

✓ Yes

Please describe data to be obtained

Name
Address
Telephone number
Birth date
Self- report Medical History
Baseline MRI at the Beth Israel Deaconess Medical Center

No

4.6 **Is a HIPAA waiver of patient authorization being requested?**

✓ Yes

Complete Form A

No

4.7 **Is a waiver of any required element of consent being requested?**

Yes

✓ No

4.8 **Will drugs, biologics, dietary supplements or food additives be used in the research?**

Yes

✓ No

4.9 **Will a device be used in the research?**

✓ Yes

Complete Form D

No

4.10 **Will ionizing radiation (x-rays, QCT, etc.) be used in the research?**

Yes

✓ No

4.11 **Will non-ionizing radiation (MRI, lasers, ultrasound) be used in the research?**

✓ Yes

Complete Form F

No

4.12 **Will this study involve genetic analysis?**

Yes

✓ No

4.13 Will a Research Repository be created?

Yes

✓ No

1.0 Background

Background and rationale for the research

Falls are common, costly and caused by declines in cognitive-motor function. Each year, 30-40% of older adults will fall.[1-3] Even in the absence of serious injury, a fall often leads to fear of falling,[4] self-imposed restrictions in activity, decreased socialization, and a further increase in fall risk.[5] Most falls occur when standing or walking,[6-8] and as expected, those with a history of falls tend to have worse physical function.[9-17] Fall prevention strategies targeting the peripheral muscles, nerves, bones, and joints, however, result in only modest reductions in falls.[18-21] *This ineffectiveness likely stems from a relative lack of focus on cognition and its critical role in physical function.*[22]
In particular, those with worse cognitive "executive" function (i.e., difficulty planning, making decisions, multi-tasking, inhibiting inappropriate behaviors, etc.) have worse mobility[23,24] and are more likely to fall in the future.[25,26] A workshop sponsored by the Gerontological Society of America and NIA was in fact recently dedicated to the role of cognition in age-related physical decline.[27-29] This 3-year workshop culminated in the recommendation that interventions to improve physical function and prevent falls in older adults should specifically focus on the functional integration of physical and cognitive function.[29]

The control of standing and walking—especially during dual tasking—is dependent upon the activation of specific cognitive-motor brain networks. Standing and walking are governed by complex systems comprising somatosensory, visual and vestibular elements interacting with spinal, supraspinal and peripheral motor circuitry.[23,30-35] Moreover, these activities are almost always completed in unison with other cognitive tasks such as talking, reading or making decisions. Such dual tasking disrupts standing and walking in older adults,[36-40] especially in those with a history of otherwise unexplained falls.[23,24,41-50] In this population, dual task costs to postural sway speed and area when standing, and/or gait speed when walking, predict functional capacity,[51,52] mobility[53] future falls[26,49] and even the rate of progression of cognitive impairment.[54]

The observation that older adults with a history of falls exhibit exaggerated dual task costs suggests that they have a reduced capacity to activate the required brain regions needed to maintain performance in both tasks.[55-57] Studies using fMRI, EEG and/or functional near-infrared spectroscopy (fNIRS) indicate, as expected, that standing and walking, especially when dual tasking, activate the prefrontal cortices—the primary brain regions giving rise to cognitive function.[58-68] Studies using fNIRS to measure brain activation (i.e., relative increases in oxygenated hemoglobin levels) *during* standing and walking indicate that when

compared to normal conditions, standing or walking while performing a verbalized serial subtraction task increases prefrontal cortex activation within both hemispheres, *but particularly within the left hemisphere*.[58-64,66-69] Several of these studies have further reported those who exhibit greater increases in left prefrontal activation when dual tasking exhibit lower dual task costs and better executive function.[67,68]

fMRI evidence indicates that performing two cognitive task together—as compared to performing them separately—activates additional brain regions *specifically within the left dlPFC*.[70,71] Moreover, the left dlPFC is particularly activated during performance of cognitive tasks that require both working memory and verbal processing.[72-76] 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 as a therapy to mitigate dual task costs to standing and walking, and improve other physical and cognitive outcomes on the causal pathway to falls, in older adults. tDCS modulates cortical excitability (i.e., the likelihood of neuronal firing) by inducing low amplitude current flow between two or more electrodes placed upon the scalp.[77,78] The electric fields thus polarize neuronal populations and modulate cortical excitability.[79,80] The electric fields generated by tDCS and their effects on brain tissue excitability depends upon electrode size, polarity and placement, as well as current amplitude and duration.[77]

Single-session tDCS: Twenty continuous minutes of tDCS increases brain excitability within target regions for at least 1 hour thereafter.[81,82] When delivered with the participant at rest, tDCS with the anode (positive electrode) over the left dlPFC improves performance in cognitive tasks requiring attention,[83] working memory[84-87] decision making,[88] and even dual tasking[89,90] in younger adults. Dr. Manor and his team have demonstrated that when tested just after stimulation, 20 minutes of tDCS targeting the left dlPFC reduces dual task costs to the control of standing and walking in healthy younger adults,[91] healthy older adults,[38] and in older adults with slow gait and executive dysfunction

Multi-session tDCS: tDCS interventions targeting the left dlPFC have proven effective for the treatment of depression[92,93] and chronic pain.[94] Much less is known regarding the effects of tDCS intervention in older adults without major neurologic disease. Yet, our recent work suggests that a two-week, ten-session tDCS intervention targeting the left dlPFC reduces dual task costs to both gait and balance, and, over a two-week follow-up, improves performance in several tests of physical and cognitive function in older adults with slow gait and mild-to-moderate executive dysfunction.

The proposed project is significant because it will systematically examine the effectiveness of a multi-session tDCS intervention targeting a critical brain region involved in dual task standing and walking in older adults who are vulnerable to falling. We expect to demonstrate that a personalized, multi-session tDCS intervention designed to increase the excitability of the left dlPFC improves dual tasking and other important physical and cognitive outcomes in older adults. Moreover, this trial will establish the size and duration of tDCS-induced benefits, and quantify its associated biophysical metrics via current flow modeling (i.e., average electric field

on target; see Innovation Section below). Together, these discoveries will enable future studies to 1) use neuroimaging to identify the effects of tDCS on brain activation and its relationship to function, 2) optimize tDCS as a longer-term intervention by incorporating "maintenance" tDCS after the initial intervention, and 3) further establish tDCS as a stand-alone or adjunct fall prevention strategy.

All References

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Previous (non-clinical, pre-clinical or clinical) **studies leading up to and supporting the proposed research**

Single sessions of tDCS targeting the left dlPFC reduce dual task costs and improve mobility in multiple populations: In three separate but related studies, Dr. Manor studied healthy young adults (22±2yrs),[112] relatively healthy older adults (69±5yrs),[38] and older adults with slow gait and mild-to-moderate executive function (81±10yrs) (manuscript in press). All participants completed two visits. On each visit, standing and walking were assessed both with and without simultaneous performance of a serial subtraction cognitive task, just before and after a single 20-minute session of 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 postural sway or walking speed under single task conditions. However, during dual tasking, real tDCS was associated with less postural sway speed and area when standing, and faster gait speed when walking ($p<0.01$). As a result, only real 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 increasing prefrontal cortex excitability provides at least short-term benefit to dual task performance across individuals who range widely in both age and functional capacity.

A 10-session tDCS intervention mitigates dual task costs to standing and walking, and appears to improve physical and cognitive function, in older adults with slow gait and executive dysfunction. With the explicit goal of informing this proposal, we completed a pilot, sham-controlled, double-blinded, randomized trial to examine the effects of tDCS on dual tasking, along with multiple metrics of physical and cognitive function (NCT02436915) (manuscripts in preparation). We recruited a cohort of older adults without major neurological, musculoskeletal or cardio-respiratory disease—who exhibited both slow gait and mild-to-moderate executive dysfunction as defined by preferred 4m over ground walking speed less than 1.0m/s, and a Trail Making Test B time below the 25th percentile of age- and education-based norms (See Table 1). Participants completed baseline assessments and were then randomized to receive ten, 20-minute sessions of real tDCS targeting the left dlPFC, or sham stimulation. Follow-up assessments were completed within three days of the final tDCS session and again two weeks later.

Table 1: Pilot RCT cohort characteristics (mean±SD)

	tDCS	Sham	P-value

Sample (n)	10	10	
Age (years)	83 ± 10	78 ± 10	0.35
Gender (w; m)	5; 5	6; 4	
4m gait speed (m/s)	0.73±0.17	0.72±0.14	0.96
Trail Making B (sec)	174±36	182±46	0.87
Geriatric Depression Scale (scale 0-12)	3±3	4±2.5	0.47
Mini Mental State Exam	24.1±3.4	25.5±3.3	0. 38

1.2

tDCS was delivered by the Starstim-8™ (Neuroelectrics, Corp). tDCS was designed to increase the excitability of the left dlPFC using a *non-personalized* approach: the positive electrode was placed over the F3 region of the 10-20 EEG system and the negative electrode was placed over the contralateral supra-orbital margin. Sham stimulation was designed to deliver smaller currents using the same electrode placement, so as to mimic tDCS-induced cutaneous sensations yet have minimal effect on neuronal excitability. Both interventions were well attended (9.1±0.8 of 10 sessions) and no adverse events were reported. Double-blinding procedures were highly effective: following intervention, the number of correct “guesses” of intervention assignment was no greater than that due to chance for participants, as well as study personnel administering tDCS.

Baseline and follow-up assessments included the proposed dual task paradigm and multiple tests of physical and cognitive function. At baseline, the mean (±SEM) dual task cost to standing balance (i.e., the speed of postural sway) was 50±12%. Excitingly, the real tDCS intervention group, as compared to sham, exhibited markedly reduced dual task costs over the two-week follow-up period. Despite the small sample size, similar effects or trends were observed for the dual task cost to walking speed (p=0.04), the TUG test of mobility (p=0.09), the Trail Making Test of executive function (TMTb – TMTa; p=0.11), the Montreal Cognitive Assessment (MoCA, p=0.04), and the Geriatric Depression Scale (p=0.10).

By completing this pilot RCT we have 1) strengthened ongoing collaborations between the PI and all co-investigators in this application, 2) developed state-of-the-art and scalable data management infrastructure, 3) ensured that tDCS interventions are safe, well tolerated, well attended, and can be effectively double-blinded in an older adult population similar to that proposed, and 3) enabled more accurate sample size calculations by providing estimates of inter-subject variance in the primary (and most secondary) outcomes proposed in this study, as well as the effects of tDCS intervention on these outcomes. We therefore have confidence

that we can successfully implement and complete the proposed trial and that tDCS targeting the left dlPFC (one of the proposed tDCS intervention targets) will improve dual task performance and other physical and cognitive outcomes on the causal pathway to falls in older adults.

The degree to which non-personalized tDCS is "on-target" correlates with dual task improvements, yet varies significantly across participants. A small subset of the cohort described in the previous section completed structural MRIs at baseline. Six of these participants then completed the non-personalized tDCS intervention designed to increase excitability of the left dlPFC. We used the *Stimweaver* framework to model the tDCS-induced electrical field within each participant's brain. The normal component of this field (believed to facilitate neuronal excitability) within the left dlPFC correlated closely with reductions (i.e., improvements) in the dual task costs to gait speed. However, this normal component varied considerably across participants. These pilot data give us further confidence that 1) the left dlPFC is an important target for dual task performance, and 2) personalizing tDCS to each individual's head and brain anatomy will likely maximize its effectiveness and reduce inter-subject variability.

Describe why this research is important and how it will contribute to existing knowledge

1.3

The proposed project is significant because it will systematically examine the effectiveness of a multi-session tDCS intervention targeting a critical brain region involved in dual task standing and walking in older adults who are vulnerable to falling. We expect to demonstrate that a personalized, multi-session tDCS intervention designed to increase the excitability of the left dlPFC improves dual tasking and other important physical and cognitive outcomes in older adults. Moreover, this trial will establish the size and duration of tDCS-induced benefits, and quantify its associated biophysical metrics via current flow modeling (i.e., average electric field on target. Together, these discoveries will enable future studies to 1) use neuroimaging to identify the effects of tDCS on brain activation and its relationship to function, 2) optimize tDCS as a longer-term intervention by incorporating "maintenance" tDCS after the initial intervention, and 3) further establish tDCS as a stand-alone or adjunct fall prevention strategy.

This approach recognizes the multifactorial nature of falls and tests an intervention that can enhance central nervous system compensatory mechanisms for many different falls risk factors. By improving the executive control of standing and walking, elderly fallers may be better able to adapt to the environmental stresses and physical disabilities that precipitate falls. Our participant inclusion and exclusion criteria are designed to include older adults at elevated risk of falls due to various intrinsic and extrinsic causes, but at the same time ensure that they are not so impaired that they cannot participate in or benefit from the intervention. Based on empirical evidence gathered by us and others highlighting the complex, dynamic nature of the human gait and postural control systems in aging, we expect that targeting high-level cortical elements of these systems will translate into improved dual tasking and other physical and cognitive outcomes across individuals, despite the heterogeneity of falls risks. We will test a personalized intervention specifically aimed at improving the integrated function of the involved systems and in so doing, will produce highly generalizable results that will directly lead to future trials to prevent falls within this population

Provide study objectives/aims/hypotheses

Our Overall Aim is to compare, in older adults with previous falls, the effects of a *personalized* tDCS intervention designed to target the left dlPFC on the dual task costs to standing and walking, and other physical and cognitive factors that are on the causal pathway to falls and important to everyday function. We will conduct a randomized, sham-controlled, double-blinded trial with assessments at baseline and post-intervention (immediate, 3-, 6-month follow-up) in 120 non-demented men and women (60 per arm) aged 65+ years who report ≥1 non-syncopal falls within the previous year and are fearful of falling again, yet have no major neural or musculoskeletal disorders that explain their falls. The tDCS intervention will comprise 20, 20-minute sessions of tDCS over a 4-week period. Importantly, we will utilize current flow modeling from baseline structural MRIs to determine the tDCS electrode placement and stimulation parameters that optimize electrical current flow to the desired target within each participant's brain.

Specific Aim 1: To test, in older adult "fallers," the effects of tDCS intervention targeting the left dlPFC on the dual task costs to the control of standing and walking. Standing and walking will be assessed with and without a concurrent cognitive dual task (i.e., verbalized serial subtractions). Primary outcomes will be dual task costs to postural sway speed when standing, and gait speed when walking, as these are well-established measures of functional mobility that are associated with falls.

Specific Aim 2: To test, in older adult "fallers," the effects of tDCS intervention targeting the left dlPFC on metrics of physical function that have been linked to frontal executive networks and associated with fall risk. The primary outcome will be the Short Physical Performance Battery (SPPB). Secondary outcomes will include the Timed Up-and-Go (TUG) test of mobility, fear of falling, and habitual physical activity.

Specific Aim 3: To test, in older adult "fallers," the effects of tDCS intervention targeting the left dlPFC on cognitive functions that have been linked to frontal executive networks and associated with fall risk. The primary outcome will be executive function as measured by the Trail Making Test. Secondary outcomes will be derived from tests of processing speed, working memory and sustained attention.

2.0

In the proposed trial, participants randomized to the real intervention arm will receive tDCS personalized to their individual head and brain anatomy, with the goal of generating an average electric field of 0.25 V/m within left dlPFC. Briefly, this will be done by having each participant undergo a structural brain MRI, which will be used to define the 'left dlPFC' target. The MRI will also be used to determine, through segmentation, tissue boundaries of the scalp, skull, CSF including ventricles, gray matter and white matter.[104] This information will then be imported into a software program called Stimweaver™ (Neuroelectrics Corp, Boston MA) that uses patented finite-element optimization algorithms to determine the electrode placement and current parameters required to achieve the aforementioned goal of stimulation.

Our primary hypothesis is that, in older adults with previous falls and over a 6-month follow-up, a personalized tDCS intervention targeting the left dlPFC, as compared to sham, will mitigate dual task costs to the control of standing and walking and enhance other metrics of both physical and cognitive function. In our previous study, described above in section 1.2, we found that the degree to which non-personalized tDCS is "on-target" correlates with dual task improvements, yet varies significantly across participants. A small subset of the cohort described in the previous section completed structural MRIs at baseline. Six of these participants then completed the non-personalized tDCS intervention designed to increase excitability of the left dlPFC. We used the *Stimweaver* framework to model the tDCS-induced electrical field within each participant's brain. The normal component of this field (believed to facilitate neuronal excitability) within the left dlPFC correlated closely with reductions (i.e., improvements) in the dual task costs to gait speed. ***However, this normal component varied considerably across participants.*** These pilot data give us further confidence that 1) the left dlPFC is an important target for dual task performance, and 2) personalizing tDCS to each individual's head and brain anatomy will likely maximize its effectiveness and reduce inter-subject variability.

Our secondary hypothesis is that as compared to sham, the personalized tDCS intervention targeting the left dlPFC will increase the strength of functional connectivity within the frontal-parietal executive network (the left dlPFC is a primary node within this network). Moreover, we expect that this expected tDCS-induced increase in functional connectivity will correlate with expected improvements in functional performance (i.e., our primary outcomes of dual task cost to gait speed, SPPB, and MoCA.)

3.0 Study Design

Study design (e.g. double-blind, placebo-controlled, parallel design, etc.)

3.1 We will conduct a single site, sham-controlled, double-blinded, randomized trial of tDCS. Participants will perform baseline functional assessments, as well as a MRI of the brain. They will then be assigned to a four-week, 20-session intervention of either personalized tDCS or sham (i.e., control) stimulation, via permuted block randomization stratified by sex to ensure that equal numbers of women, and equal numbers of men, are randomized to each arm. The Neuroelectrics (Cambridge, MA) Starstim-8™ tDCS system will be used to deliver the intervention, which enables blinding of both participants and study staff. Follow-up functional assessments will be performed within one week of the final tDCS session and again three and six months later. A follow up MRI of the brain will be performed within one week of the final tDCS session. Falls will be tracked throughout the entire duration of study participation using mail-in falls calendars.

Study duration (total)

3.2 *e.g. from beginning to end, the estimated timeline to complete the project*.

This is a 5 year project. We propose to complete study start up activities over the first two quarters of Year 1. Recruitment and enrollment of subjects to begin in the 3rd quarter of Year 1 and will be completed in the 2nd quarter of year 5. The study intervention, assessments, data processing and cleaning will proceed within the same timeline. Data analysis will begin in the first quarter of Year 5 and continue throughout the final grant year. Manuscript preparation and publication will occur in the final two quarters of Year 5.

Study duration for participants

3.3

Participants will be enrolled in the study for approximately 8 months, during which they will complete 27 total study visits.

4.0 Participant Selection and Withdrawal

Source of study participants

4.1

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)

Total target number of participants to be enrolled

4.2

If you are enrolling from multiple sites or cohorts, list the total target number per site and/or cohort.

We will enroll 120 individuals aged 65-85 for this study.

Inclusion criteria

Our target population will be older men and women who are vulnerable to future falls, as defined by a recent history of recurrent falls *and* fear of falling again in the future, yet who do not suffer from dementia or other major neurological, musculoskeletal or cardio-respiratory disease. We will also ensure that participants have at least mild physical and executive performance decrements, such they have room to improve on related assessments, but are not so impaired that they cannot participate nor benefit from the intervention.

4.3 Inclusion criteria:

1. Aged 65 + years.

2. Self-report of one or more falls within the past year. Falls will be defined by any event in which the individual unintentionally comes to rest on the ground or other lower level, not as a result of a major intrinsic event (e.g., syncope) or an overwhelmingly external hazard (i.e., car accident).[118]
3. Self-report of fear of falling, as defined by a "yes" answer to the yes-or-no question "Are you worried that you will fall in the future?"
4. At least some mild performance decrement in physical *and* executive function as defined by A) a score of nine or below on the SPPB (range=0-12, 12 reflecting best performance), and B) a score below the 75% of performance based upon age- and education-based norms[119] in the Trail Making Test (TMT, part B).

Exclusion criteria

Exclusion Criteria have been selected to ensure safety and optimize compliance, while minimizing confounds due to overt disease or conditions that may significantly influence study outcomes:

4.4

Exclusions based upon phone screening: Self report of 1) inability to stand or walk unassisted for 60 sec, 2) hospitalization within the past three months due to acute illness, or as the result of a musculoskeletal injury significantly affecting gait or balance (to minimize confounding due to recent fall-related injuries), 3) unstable medical condition, 4) a diagnosis of a gait disorder, Parkinson's disease, Alzheimer's disease or dementia, multiple sclerosis, previous stroke or other neurodegenerative disorder, 5) chronic vertigo, 6) myocardial infarction within the past 6 months, 7) active cancer for which chemo-/radiation therapy is being received, 8) psychiatric co-morbidity including major depressive disorder, schizophrenia or psychosis, , 9) chronic use of any sedating medications (sedatives, anti-psychotics, hypnotics, anti-depressants), or change in medication within the previous month, 10) legal blindness, or 11) contraindications to MRI or tDCS, as recorded on a standardized screening questionnaire, which include a reported history of seizures, use of neuro-active drugs, the risk of metal objects anywhere in the body, 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. Potentially eligible individuals will then complete the Telephone Interview of Cognitive Status (mTICS). We will exclude those with a score<31[120,121] to reduce likelihood of in-person exclusions due to dementia (see below).

Exclusions based upon in-person screening:

1) Mild or worse dementia defined by a Clinical Dementia Rating (CDR) score ≥1[122] as reviewed by a board certified neuropsychologist (Dr. Bonnie Wong), or 2) gait disorders due to Parkinson's disease, foot drop, lower-extremity deformity, joint replacement or severe arthritis, as identified during a gait evaluation conducted by a research nurse (M. Gagnon) and reviewed by a geriatrician and falls specialist (Dr. Lipsitz).

Participant recruitment

4.5

Describe recruitment methods

We have full confidence that we can identify and recruit 120 individuals that meet the study criteria.

We will utilize a multi-pronged approach to meet our recruitment goals.

1. We will advertise the study in the community via newspaper and posted advertisements.
2. We will post the study on websites, e.g., including the Institute for Aging website; clinicaltrials.gov; and craigslist.
3. We will send a standardized letter to potentially eligible participants from the Mobility and Brain Function Database. We will avoid over-burdening individuals within the repository by only contacting those individual who have not participated in other studies within the past 6 months.
4. We will advertise within the Hebrew SeniorLife housing sites by hanging flyers within common areas, and advertising in community newsletters.
5. We will conduct community presentations at senior housing sites.
6. We will utilize the Harvard Catalyst (CTSA) Shared Health Research Information Network (SHRINE) to identify volunteers with recent falls from Harvard-affiliated hospitals and clinics.
7. We will send a standardized letter to potentially eligible participants from the Hebrew SeniorLife outpatient database, with approval of their HSL physician.

Attach all recruitment materials

Recruitment_Flier_v1 071218.pptx

Procedures for obtaining informed consent

4.6

Include who will obtain consent and the timing of consent from recruitment

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.

Are you requesting a waiver of any required element of informed consent?

Yes; *Complete Form B - Consent Waiver Request*

✓ No

Attach the informed consent form(s)

Please download the sample consent form, fill it out and then upload attachment here.

ICF Personalized tDCS in Fallers.4_22619 stamped.docx Sample documents: Sample_ICF REV 3.29.16.docx

ICF Personalized tDCS in Fallers.4_22619 stamped.pdf

Withdrawal of participants

4.7 *Include any anticipated circumstances when participants will be withdrawn without their consent, how participants will be withdrawn, including use of any collected data and follow-up with any new/pertinent information.*

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.

4.8 **Will you be enrolling participants who may have diminished capacity to provide informed consent or to understand study procedures (now or in the foreseeable future)?**

Yes

✓ No

4.9 **Will non-English speakers be enrolled in the study?**

Yes

✓ No

5.0 Study Procedures

List the number of study visits, including procedures/tests involved at each visit

e.g. blood test, x-rays, questionnaires. If numerous study visits and procedures are involved, include a study procedure timeline.

Participants will be asked to complete 26 visits over 8 months. **All study visits, except the MRI visit, will take place at the Clinical Research Laboratory at Hebrew Rehabilitation Center, Roslindale MA. The MRI visit, visit 2, will take place at the Beth Israel Deaconess Medical Center, in the MRI Suite, 330 Brookline Ave, Boston MA. Free parking or transportation will be provided for all study visits.**

Visit 1—In-person screen and study familiarization (Up to 2.5 hours) at the Clinical Research Laboratory at Hebrew Rehabilitation Center, Roslindale, MA. Individuals deemed potentially eligible via phone screen will complete an in-person screen. All screening assessments, other than the physical exam and the CDR scale, will be administered by trained research assistants. Individuals will read and sign an informed consent form approved by the Hebrew SeniorLife IRB. Medical history, **Activities of Daily Living (ADL's**), **SF-12 (self-reported Quality of Life**) questionnaires will be complete,, and medications, blood pressure, height, body mass and years of education will be recorded. The SPPB and the TMT will be completed to ensure at least mild performance decrements in physical and executive function. Dr. Wong or a trained clinician will then administer the CDR to characterize cognitive status and rule out dementia. Dr. Lipsitz or a trained clinician will conduct a physical, neurological exam, and clinical gait assessment to rule out acute illness and overt neural or musculoskeletal causes of falls. Individuals who meet all inclusion and exclusion criteria will be enrolled. Participants will then complete the Physical Activity Scale for the Elderly to obtain self-reported levels of baseline physical activity,[132]
and the **TOPF** single word reading test of premorbid intellectual ability (1-minute administration time, to be used as an adjustor for changes in executive function).[133]

Familiarization: At the end of Visit 1, participants will first complete the proposed cognitive assessment battery **as practice** *to minimize the effects of procedural learning following the true baseline*[134] *to be completed during Visit 3 (see that section for battery details)*. Trained research assistants will administer the familiarization testing. They will not repeat the TMT, nor will they practice the Montreal Cognitive Assessment (MoCA) because it has multiple test versions that minimize confounding due to learning. Second, they will complete a 20-30 minute familiarization of the dual task paradigm (see “Dual task performance” subsection below). This procedure will 1) determine the cognitive task to be used in the assessment, thereby ensuring that it is not too difficult and/or anxiety provoking to the participant, and 2) minimize the potential for procedural-related learning to influence outcomes. First, we will determine the cognitive task to be used for each participant using a standardized procedure [30,50,135-137] in which participants are seated in a chair and asked to count backwards from 200, first by 3’s, then by 1’s. The first task in which three correct answers are provided within 15 sec will be used for testing. Participants will also receive instructions on the specific dual task testing procedures and complete several practice trials of each condition.

Visit 2—MRI exam (Up to 1 hours): We will complete both structural and functional MRIs at baseline on a 3 Tesla GE Vhi scanner with a quadrature head coil at the Beth Israel Deaconess Medical Center, located near the Clinical Research Lab. The structural MRIs will enable personalization of tDCS via current flow modeling, as well as detection of silent infarcts and white matter hyperintensities (WMHs) using T1, T2, and T2-weighted fluid-attenuated inversion recovery (T2 FLAIR) scans. The fMRI scans will measure brain activity (i.e. blood-oxygen-level-dependent (BOLD) signals).

Visit 3—Baseline assessments (Up to 2.5hrs) at the Clinical Research Laboratory at Hebrew Rehabilitation Center, Roslindale, MA :
This assessment will take place within IFAR's Clinical Research Laboratory and comprise tests of dual tasking, mobility, and cognition. Trained research assistants will administer all of the baseline assessment testing described below. Accelerometry-derived habitual physical activity will be assessed for five days after baseline. Falls-tracking will also be initiated at this visit.

Dual task performance: Procedures will follow published recommendations[24,139,140] that produce excellent test-retest reliability.[45,141-145] **We have used a similar paradigm within our research and laboratory for over ten years. Participants will complete two, 60-second trials in each of three walking conditions, and two 45 second trials in each of the three standing conditions.** For all functional tests, a trained "spotter" will stand behind or close to the subject to provide stabilizing assistance if necessary:

- Condition 1: Single task: seated cognitive task (see below for description).
- Condition 2: Single task: standing, eyes open.
- Condition 3: Single task: walking.
- **Condition 4: Single task: standing, eyes closed**
- **Condition 5: Single task: fast walking**
- Condition 6: Dual task: standing with cognitive task.
- Condition 7: Dual task: walking with cognitive task.

All standing trials will be completed on a stationary force plate (Kistler, Inc) to record postural sway (i.e., center of pressure) fluctuations throughout the trial. Participants will stand barefoot with arms at their side and feet shoulder width apart. The feet will be traced on the first trial and this tracing will be used to ensure consistent foot place throughout the study. Participants will be instructed to focus their attention on an "X" marked on a wall in front of them at eye level and will be reminded to stand as still as possible before each trial. All 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 be reminded to walk at their preferred, comfortable place prior to each walking trial.

The cognitive task will be verbalized serial subtractions from a random three-digit number between 200 and 999, to be provided to the participant prior to each trail. The type of serial subtractions (3's, or 1's will be determined in a familiarization session completed at the screening visit. Participant responses during each trial will be recorded. We have chosen serial subtractions as the cognitive dual task because: 1) it activates a distributed cortical network including the left dlPFC,[146] 2) is the most widely used dual task paradigm[24,147] and induces significant and meaningful dual task costs to both postural sway when standing and gait kinematics when walking, in older adults with and without a history of recurrent falls[30,37,38,148] 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.[145] No instructions will be given regarding task prioritization. This approach has been chosen to most closely mimic real-life situations.[24,140,147] Trial order will be randomized for each assessment

and at least 1min of rest will be provided in between trials.

Physical Function will be assessed with the Short Physical Performance Battery (SPPB).[149] which is significantly reduced in fallers and predictive of future falls. The SPPB includes measures of standing balance (timing of tandem, semi-tandem, and side-by-side stands, test-re-test correlation=0.97), four-meter walking speed (T-R-T correlation = 0.89), and ability and time to rise from a chair five times (T-R-T correlation = 0.73).[150] SPPB validity has been demonstrated by showing a gradient of risk for admission to a nursing home and mortality along the full range of the scale.[149] In the EPESE population of community-dwelling elders over age 71, the SPPB captured a wide range of functional abilities, and summary scores less than nine independently predicted disabilities in ADL and mobility at one-six years of follow-up.[150,151]

Mobility will be assessed with the TUG,[152] 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 separate trials will be recorded. This test has high test-retest reliability and discriminant validity in older adults.[153,154]

Fear of falling will be assessed by the Falls Efficacy Scale - International (FES-I) questionnaire, which asks participants how concerned they are of falling during 16 activities. It has excellent internal validity (Cronbach's alpha=0.96) and test-retest reliability (ICC=0.96).[155-157] It correlates with self-reported and assessed functional status,[158,159] the degree of self-imposed activity restriction in daily life[159,160] and future falls[161,162] in older adults.

Cognitive Assessment: Participants will complete a 30-35min battery of cognitive tests that are correlated with dual tasking,[23-25,37,163] functional capacity,[23,24] and/or falls.[25,26] We will minimize the potential for procedural learning within this battery by having participants complete the battery as "practice" at the end of the in-person screen.[134] Moreover, tests were selected that have alternate forms, or, were felt to be resistant to practice effects. 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. Tests will include the Trail Making Test (A and B) of executive function (i.e., speeded visual search, vigilance and set-shifting).[119] For this primary outcome, we will utilize the original Test B at baseline, and three alternative forms of Part B,[164] which have comparable psychometric properties, for each of the three follow-ups. Participants will also complete the MoCA test of global cognitive function,[165,166] WAIS-IV Digit Span (Forwards, Backwards) test of working memory,[167] the WAIS-IV Coding test of sustained attention and motor speed,[168] the Category and Phonemic Fluency tests of semantic knowledge and word retrieval,[169] and the Hopkins Verbal Learning Test – Revised (HVLT-R) of verbal episodic memory.[170] **gradCPT: This is a short, computer-based, valid and reliable test of sustained attention, called the gradual-onset Continuous Performance Test (grad-CPT). Data obtained from this test will enable us to further investigate the relationship between gait outcomes and attention within the recruited cohort. The grad-CPT is a computer-based test and takes about 10 minutes to accomplish. The grad-CPT has also been tested in more than 10,000 individuals across the life span (Fortenbaugh et al. 2015)**.Staff will be trained in all assessment procedures by our

5.1

co-investigator, Dr. Bonnie Wong (with ongoing supervision to ensure standard administration and scoring).

Mood will be assessed as it influences performance on clinical tests of physical and cognitive function,[171] and long-term exposure to tDCS may affect (i.e., improve) mood.[172] We will use the Center of Epidemiology Studies-Depression Scale Revised (CESD-R) scale,[173] which has been used extensively in epidemiology studies and consists of 20 questions regarding feelings of depression, worthlessness, loneliness, energy level, and fear. The CESD-R has high internal consistency (r=0.90) and a test-retest reliability of 0.51.[174]

Pain: Similar to mood, lower-extremity pain is common in older adults with previous falls,[175] interferes with function[175,176] and may benefit from tDCS.[128] Participants will complete the Brief Pain Inventory, which quantifies pain location, pain intensity and the extent to which pain interferes with daily functioning. [177] A **brief measure of chronic pain, from the Women's Health and Aging Study, will be used to assess chronic pain at baseline, three months and six months following the tDCS intervention described below.**

Reference:

Leveille SG et al, Musculoskeletal pain and risk for falls in older disabled women living in the community. J Am Geriatr Soc. 2002 Apr; 50(4):6718

Falls tracking: As the recruited cohort will have high risk of falling and related injuries during follow-up may influence physical and cognitive performance, falls will be tracked using monthly falls calendars.[118] Participants will be asked to mark the fall on the calendar and complete a form every time they fall. Staff will review calendars at each monthly follow-up visit, to discuss the incidence and characteristics of falls. Falls tracking will also provide preliminary data on falls rates by group, to be used for planning of future studies.

Habitual physical activity will be recorded for five consecutive days at baseline and the immediate, three- and six-month follow-ups using a lightweight water-proof sensor taped to participant's low-back (L5 vertebral level) (Axivity Inc., United Kingdom). This device has been validated for use in older adults of various function level.[178-180] It provides overall activity and step counts,[181] as well as accurate, automatic detection of time spent lying, sitting, standing and walking[180,182] and gait kinematics during detected bouts of walking.[178]

Visits 4-23— (Up to 40 minutes) tDCS Intervention at the Clinical Research Laboratory at Hebrew Rehabilitation Center, Roslindale, MA :

Trained research assistants will administer the tDCS intervention to the participant over twenty visits that will be completed Mon-Fri over four consecutive weeks at approximately the same time of day. **(If a participant misses sessions over the four weeks, he/she will be asked if they are willing to make-up up to three missed sessions at the end of the four week period.)**

tDCS interventions: Participants will be randomized to receive tDCS that facilitates the excitability of their left dlPFC, or sham stimulation (Figure 5). The left dlPFC was chosen because it is part of the frontoparietal control network,[123,124] a key contributor to executve function and the processing of sensory feedback for the control of actions,[58-68] and it is

activated when standing or walking—especially when dual tasking.[66-68] tDCS targeting this region has been studied extensively: it appears to mitigate dual task costs to standing and walking in older adults (See Preliminary Studies)[38,112,125] and enhances numerous aspects of cognitive-motor function when tested over shorter follow-up periods.[83-90] It has also shown efficacy for depression[92,93] and chronic pain.[94]

Personalized tDCS: Electrode placement and current parameters will be optimized to each participant by importing their MRI into *Stimweaver*, with the goal of generating an average electric field of 0.25 V/m[77] within their identified left dlPFC. The direct current delivered by any one electrode will not 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.

Personalized Sham: We will use an active sham in which very low-level currents (0.5 mA total) will be transferred between electrodes in close proximity on the scalp throughout the entire 20-minute session. This intervention will be optimized to each participant 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 to stimulation condition and does not effect functional outcomes.[101]

Intervention characteristics: Each intervention will comprise 20, 20-minute sessions of stimulation completed over four consecutive weeks. Our pilot RCT demonstrated significant effects of 10 tDCS sessions over two weeks in a similar population of older adults over a shorter follow-up period. At the same time, several well-designed trials have recently reported lasting benefits of multi-session tDCS interventions on depression,[126,127] pain,[128] stroke,[129] and Parkinson's disease,[130] which have each tested interventions ranging from 8-20 sessions. We therefore believe 20 sessions constitutes a safe and feasible intervention, and that it will maximize the duration of expected effects, yet not over-burden participants with study visits. tDCS sessions will be administered at approximately the same time of day. Participants will continue taking their medications throughout the intervention, and will be asked to inform the study team of a change in medication usage.

Double-blinding and safety procedures: tDCS will be delivered by personnel certified in tDCS administration by the Berenson-Allen Center for Noninvasive Brain Stimulation at the BIDMC, which is directed by our co-invstigator, Dr. Pascual-Leone. Similar to our most recent studies, tDCS 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 eight Pi™ gel Ag/AgCl electrodes placed on the scalp according to the 10-20 EEG convention. Study personnel administering tDCS and the participants will not be aware of tDCS intervention arm assignment. We will ensure such double-blinding by programming the tDCS software with intervention-specific stimulation codes, as supplied by personnel uninvolved in data collection, prior to study initiation. At the end of each visit, subjects will complete a questionnaire to report potential side effects (e.g., skin irritation, headache, etc).[131] In accordance with recent recommendations, the efficacy of tDCS blinding will also be assessed by asking each participant—and study team member administering tDCS—to judge whether real or sham tDCS was given, as well as their certainty of this judgment.[111] This questionnaire

will be completed at the end of the first tDCS session, at the end of the last tDCS session and at the final follow-up assessment.

Visits 24 (Up to 2.5 hours) Follow-up assessment at the Clinical Research Laboratory at Hebrew Rehabilitation Center, Roslindale, MA:
Participants will repeat the baseline assessment immediately post-intervention (within 1 week following the final tDCS visit). Trained research assistants will administer all the follow-up assessments at visit 24.

Visit 25 (1 hour) Follow-up MRI exam at Beth Israel Deaconess Medical Center Participants will repeat the baseline MRI within one week following the final tDCS visit) Transportation will be provided to and from the visit.

Visit 26 and visit 27— (Up to 2.5 hours each visit) Follow-up Assessments at the Clinical Research Laboratory at Hebrew Rehabilitation Center, Roslindale, MA: Participants will repeat the baseline assessment at three months - Visit 26, and at six months - Visit 26. Trained research assistants will administer all the follow-up assessments at visits 26-27.
3/27/20 - Due to the COVID -19 restrictions, follow-up assessments will take place over the phone. Performance measures of gait and balance will be assessed using the iPhone app developed by our team to collect gait and balance measure remotely. the app will be installed on the participant's iPhone, and if the participant does not have an iPhone, one will be provided to use for the measures.

List any additional source(s) of data to be used in the study

5.2

e.g., hospital records, clinical and office charts, checklists, pharmacy dispensing records, etc.
None

Are any procedures being performed as routine medical care?

5.3

e.g. for diagnostic or treatment purposes, etc.

Yes

✓ No

List procedures being performed solely for the research

5.4

All procedures within the protocol will be performed solely for research purposes.

Describe the methods used to protect participant privacy

5.5

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.
5. Participant confidentiality will be maintained in accordance with HIPAA regulations.
6. Only the PI and study personnel approved by the IRB and authorized to view PHI will have access to the information.
7. PHI will not be used during discussion, presentation or publication of any research data.
8. 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).

5.6 Are there data collection instruments or assessments to be used in the study?

✓ Yes

List all of the data collection instruments and assessments

Note: If any materials are not yet available, please indicate that information in this section.

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
Short Physical Performance Battery (SPPB) form
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
Clinical Dementia Rating (CDR) Form
Suicide Risk Protocol
Brief Pain Inventory
Dual Task (DT) Gait and Balance Forms
Dual Task Familiarization and Sitting Form
Blood Pressure Form
Center for Epidemiology Studies Depression Scale Revised (CESD-R)
Socio-demographics Form

Personalized tDCS Phone Screen Questionnaire
Personalized tDCS eligibility Questionnaire
MRI Safety Screening Form

Attach all instruments and assessments to be used in the study

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Assessment of Protocol Understanding Form.docx

Height and Weight Form v171318.docx

TUG form_1 71318.doc

Falls Questionnaire_v107132018.docx

Falls Efficacy Scale_I.pdf

tDCS Blinding Efficacy Questionnaire.docx

tDCS Side Effects Questionnaire.docx

SPPB Form_1 7132018.doc

Neuropsych testing response sheets.pdf

Medical History Questionnaire_1 71318.docx

Medication Review Form_1 71318.docx

TIC.pdf

MoCA-Test-English_v_1.pdf

CDR.NACCb4_tfp.pdf

Suicide Risk Assessment Protocol.pdf

Brief pain inventory_long form v1 71318.docx

DT gait assessment_1 71318.docx

Dual Task Balance Assessment_1 71318.docx

Dual Task Famililiarization and Sitting Assessment_v1 07132018.docx

Blood Pressure Form_v2.docx

CESD_R.1 71318.docx

Sociodemographic Form.docx

Personalized tDCS Eligibility Questionnaire_clean.docx

Personalized tDCS in Fallers_PhoneScreenQuestionnaire_v1_071218 IRB edits Clean version.docx

MRI RSH Safety Form ver 15_Jul2018 protected.pdf

No

6.0 Statistical Plan

Statistical Methods

6.1

Overall approach:
Exploratory analyses will be used to assess outcomes distributions, and any necessary transformations (e.g. to combat significant skew) will be performed prior to estimation of mean treatment effects. Said estimation will use **mixed effects linear regression** of post-intervention outcomes immediately following intervention and at three and six months, with random intercepts and slopes to account for serial correlation in repeated measurements on individuals; models will control for baseline outcomes as in analysis of covariance. Owing to the potential for nonlinear trends in outcomes with time, we will assume no functional form of temporal trends. Missing data will be accommodated by multiple (at least 50) imputation of missing records using algorithms to accommodate the clustered nature of the longitudinal design. Analyses will adjust for the stratified design effect (i.e. control for sex). All estimates will be accompanied by 95% confidence intervals (CIs) for the purposes of reporting in publication. Limited hypothesis testing will be performed at the 0.05 level, but emphasis will be on estimation. Owing to the focused nature of the design and prespecification of hypotheses, no interim analyses are planned, and no significance 'adjustment' will be applied for multiplicity.

Sample size determination

Include power calculations or provide justification for their absence (e.g., pilot/feasibility study).

Sample size assumptions: For sample size calculations we assume the following: 1) all participants will be included based on their randomized assignment; 2) a two-sided type-I error

probability of 0.05; 3) a cumulative attrition rate of at most 15%; 4) modest levels of intervention non-adherence and missing data, such that total missingness at six months post intervention will be at most 20%, leaving 114 participants with evaluable data at the end of follow-up, consistent with our experience in this population; and 5) analyses utilizing multiple imputation will have similar power to those using observed data, consistent with theory and prior experience. We anticipate greater power in practice owing to data obtained from the multiple follow-up measurements.

Aim-specific Analytic Plan and Power:

Aim 1 will test the effect of tDCS on dual task costs to standing and walking. The mixed-effects regression approach described above will estimate mean differences between tDCS and sham outcomes at the end of intervention and at three and six months thereafter. We will test the hypothesis that post-intervention changes in outcomes differ between randomized arms, and will additionally estimate timepoint-specific differences between arms in order to assess duration of effects. These models will control for dual-task cost to serial subtraction performance (as a time-varying covariate) to isolate the costs to gait by adjusting for potential differences in task prioritization over time. Sensitivity assessments will stratify by sex to assess empirical evidence of sex-specific effects (see below). Association between model-based estimates of subject-specific intercepts and slopes (generated as random effects) will be examined to assess the degree to which change with time is associated with the average level of function denoted by each measurement. Prior experiences suggest that 1) inter-individual standard deviation of dual-task costs under either sham or intervention will be no greater than 20%, 2) serial measures of dual task costs express substantial within-participant correlation, in excess of 0.8,[45,141-144] and 3) real tDCS intervention reduces dual task costs (Section 3.3.2.2). We assume conservatively that the proposed study will obtain serial correlation of at least 0.75. Assuming evaluable data on at least 57 participants per arm, the trial will provide **90% power to detect a mean difference of 8% between intervention and control arms** in a comparison of dual task costs at any time following cessation of intervention.[188] The trial will thus be well-powered to detect differences more subtle than the clinically-meaningful differences observed between those with and without a history of falls.[43-50] We anticipate greater power attending application of the repeated-measures analysis to all post-intervention data.

6.2

Aim 2 will test tDCS effects on physical function as primarily expressed by SPPB. Change scores between 0.5-1.3 have been proposed as the minimum of clinical significance.[149,189] We will again use the mixed-effects linear model. Based on prior trials[190,191] and data in this population[135,192] we expect that SPPB will have baseline standard deviation of 1.5 units and will exhibit high serial correlation over the repeated measurements in this design, as high as 0.9.[192] Assuming a more conservative serial correlation of 0.75, simulation studies (50,000 replicated trials) indicate that the repeated measures design will obtain 92% power to detect a mean intervention-attributable effect on SPPB of 0.5 units.

Aim 3 will test the tDCS effect on executive function measured primarily by the TMT (i.e., TMTB-TMTA); simulation studies similarly indicate that we will achieve at least 90% power to detect standardized effects of the tDCS intervention of 0.35 or greater.

Resting-state functional connectivity: Our preliminary data of a small cohort consisting of older adults with slow gait and mild-to moderate executive dysfunction demonstrated that in those receiving a 10-day tDCS intervention (n=5), there was a pre-to-post increase in the strength of functional connectivity, within the frontal-parietal executive network of 10 ± 24%. In contrast, those receiving a sham intervention (n=4), the strength of functional connectivity within this network decreased by 12± 8%. Based on this evidence, with evaluable data on 120 participants, we will have greater than 95% power to detect a similar effect of tDCS intervention on this outcome. (alpha=0.05%)

Missing data: To accommodate attrition and other sources of missingness, we will utilize the method of multiple imputation by chained equations.[193] At least 50 replicates of each missing value will be generated for inclusion in analyses. This method accommodates clustering of repeated measures at the participant level.[194] We have previously used these methods in trials of anabolic and exercise interventions in similar populations.[191,195-197]

Sensitivity analyses: To determine robustness of results we will consider the potential for confounding or effect modification according to baseline age, sex, BMI, and other covariates listed in Section 3.3.7.3. These will be addressed in secondary exploratory and regression analyses in parallel to those described above.

Insurance of scientific rigor—attention to age and sex as biological variables: The trial design is cognizant of the potential influence of age and sex on results. Randomization will be stratified by participant-identified sex classification and this will be acknowledged in all analyses. Sensitivity analyses will also be conducted to address the potential for effect modification by age and these will be reported in publication.

Data Management

6.3

Roles responsible for management, including data collection, entry, cleaning, etc. and basic procedures and safeguards to be used.

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.

7.0 Foreseeable Risks, Potential Benefits, Compensation and Costs to Participants

Potential medical risks of study procedures

7.1

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 be asked to participate in two brain MRIs. 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.

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, discomforts, inconveniences 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:

7.2

- 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 the study

7.3 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 an up to $510 stipend to help cover the costs of their time spent completing study procedures and visits. We believe that the potential benefits of establishing tDCS as a noninvasive intervention to improve executive function and mitigate the risk of future cognitive decline in older adults outweigh the potential risks, which are expected to be minor, transient and relatively rare.

Potential benefits to study population, community, or society

7.4 The observations from these studies are expected to provide important information regarding the effects of noninvasive electrical brain stimulation on both physical and cognitive function in older adults who have recently fallen due to poor balance, and who are fearful of falling again in the future. Results are also expected to provide insights into the feasibility and effectiveness of a tDCS intervention within this population, thus increasing the potential for deployment of tDCS interventions to larger numbers of older adults.

Describe any provisions for medical care and available compensation in the event of injury

7.5 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.

7.6 Will there be remuneration for participants?

e.g. goods, services, gift cards, cash, etc.

✓ Yes

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 will receive the following stipends after completing each activity:

- Visit 1: In-person screening and study familiarization - $30
- Visit 2: MRI study at the BIDMC - $50, plus transportation and/or parking reimbursement
- Visit 3: Baseline assessment visit - $45
- Visits 4 - 23: tDCS intervention visits (Twenty visits @ $10 each, will be completed Mon-Fri over four consecutive weeks = $200) **If a participant misses sessions, they may make-up up to 3 sessions for which they will be reimbursed $10 for each make-up session they complete. Participants who complete all 20 visits over the four consecutive weeks as scheduled will receive a $15 CVS gift card.**
- Visit 24: Follow up assessment (repeat of baseline) immediately post-intervention
- Visit 25: MRI study at the BIDMC - $50, plus transportation and/or parking reimbursement
- Visits 26-27: Follow up assessments (repeat of baseline visit) at 3 months post intervention, and at six months post intervention. $45 each x 2 = $90

This is total of $510 for participants who complete the entire study. (Plus a $15 gift card if all 20 tDCS Intervention visits are completed over the four consecutive weeks) Participants will be offered snacks at all study visits. Transportation will be provided for all study visits, if needed.

No

7.7 Will participants incur any costs due to participating in the study?

e.g. transportation, parking, etc.

Yes

✓ No

8.0 Safety Assessment and Study Monitoring

Definitions of adverse event and serious adverse event for the study

8.1

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 problem and adverse event reporting

8.2 *Include the method, distribution and time frame (e.g. to IRB, to DSMB, etc.*

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.

Process for data and safety monitoring

8.3 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.

8.4 **Will there be a data safety monitoring board (DSMB) or committee reviewing the research?**

✓ Yes

Has the DSMB/C charter/manual been developed?

Yes

✓ No

Indicate when the charter/manual is expected to be developed and submitted to the IRB

Note: when developed, submit the charter/manual as an amendment

Prior to the start of the study the DSMB will be established. Board members will be identified and approved by the NIA project officer within the first several months of Year 1. At the first meeting, the DSMB 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 first meeting is expected to take place in Year 1 of funding, during the study start up phase which is defined at the first 6 months of Year 1. The Board will recommend any necessary changes of the protocol to the PIs and will review and approve revisions. The Board will identify relevant data parameters and the format of the information to be regularly reported. Once approved by the DSMB, the charter/manual will be submitted to the IRB as an amendment. We anticipate that this initial meeting will take place in month 3 or 4 of Year 1, which will allow ample time for revisions to be made and approved by the DSMB and the IRB, prior to the start of recruitment.

No

8.5 Is this a Multi-site Study?

Yes

✓ No

8.6 Is there a Sponsor Protocol for this study?

Yes

✓ No

9.0 Data Handling and Record Keeping

Identifiers to be stored with data

9.1 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.

9.2 **Will codes be assigned in the place of participant identifiers?**

✓ Yes

Provide the location of the key or link to the codes

Codes will be kept in a secure locked file cabinet and password protectedspreadsheet in an Institute for Aging Research secure server.

No

Individuals (or study roles) who will have access to identifiable data, or key/link to codes

9.3

e.g. principal investigator, research assistant, data manager, etc.
The principal investigators and all study personnel with a direct role in data collection or data management will have access to the data files.

Study data storage location

9.4 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

9.5

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.

Timing of destruction of materials containing identifiers and keys/links to codes

9.6 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.

9.7 **Method for destroying materials with identifiers and keys/links to codes**

We will follow Hebrew SeniorLife/Institute for Aging Research standard protocol for research document disposal.

Record retention

9.9 *e.g. where and for how long after study completion; for guidance, please see HSL's Record Retention Policy.*

We will follow Hebrew SeniorLife's Record Management, Retention, and Destruction Guidelines. Record retention 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.

9.10 **Do you expect to use data or specimens collected as part of this research for other, future research projects?**

✓ Yes

If yes, be sure to include authorization for future use in the informed consent form

No

10. **Sending or Receiving Research Materials to/from other Institutions**

e.g. specimens, data, images.

10.1 **Will you be sending research materials to research collaborators at other institutions?**

Yes

✓ No

10.2 **Will you be receiving any research materials from research collaborators at other institutions?**

e.g. specimens, data, images.

✓ Yes

Research Material to be received by other Institution

e.g. coded participant data, biological specimens, etc.

Coded participant data from MRI scan at BIDMC

Provide the reason for receiving the research material from this Institution

e.g. data analysis, genotyping, laboratory testing, etc.

The MRI data will allow for the Personalized tDCS intervention: Electrode placement and current parameters will be optimized for each participant by importing their MRI data into the Stimweaver software.

How will research materials be provided to HSL?

e.g. secure file transfer, sample transport system, research staff, etc.

The research staff will import the coded MRI data into the Stimweaver software program.

No

10.3 **Is, or will there be a Data Use Agreement (DUA) for this study?**

Yes

✓ No

10.4 **Is, or will there be a Material Transfer Agreement (MTA) for this Study?**

Yes

✓ No

11.0 Dissemination of Results

Publication Plan

11.1 We plan to dedicate Year 5 of this grant for data analyses and manuscript preparation and submit manuscripts for publication in appropriate peer-reviewed medical journals. Additionally, will anticipate we will use the data within grant proposals to justify continued research in this area.

Plan to share individual and/or aggregate results with participants

11.2

e.g. results letter, study newsletter, etc.

The participants of this study will be informed of the results in a letter or Hebrew SeniorLife newsletter at the end of the study.

Include personnel who meet the following criteria:

- *Responsible for the design, conduct and reporting of the research*
- *Interact or intervene with study participants (e.g. conduct study procedures, obtain informed consent)*
- *Collect, receive, or obtain identifiable data/specimens, or have access to keys/codes with identifying information*

1.0 HSL Personnel

HSL personnel are employees whose primary affiliation is with HSL.

✓ HSL Person 1

Please find HSL person 1

Name: Wanting Yu
Organization: Marcus Institute for Aging Research
Address: 1200 Centre St , Roslindale, MA 02131
Phone:
Email: WantingYu@hsl.harvard.edu

Study Role

Research assistant/engineer

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

- ✓ Yes
- No

Does this person have a financial interest in the research?

- Yes
- ✓ No

✓ HSL Person 2

Please find HSL person 2

Name: Alexa Ludington
Organization: Marcus Institute for Aging Research
Address: 1200 Centre St , Roslindale, MA 02131
Phone: 617-971-5308
Email: AlexaLudington@hsl.harvard.edu

Study Role

Research assistant

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

- ✓ Yes
- No

Does the IRB office have this person's cv/resume on file?

- ✓ Yes
- No

Does this person have a financial interest in the research?

Yes

✓ No

✓ HSL Person 3

Please find HSL person 3

Name: Chun-Liang Hsu
Organization: Marcus Institute for Aging Research
Address: 1200 Centre St , Roslindale, MA 02131
Phone:
Email: ChunLiangHsu@hsl.harvard.edu

Study Role

Post-doctoral research fellow

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

✓ Yes

No

Does this person have a financial interest in the research?

Yes

✓ No

✓ HSL Person 4

Please find HSL person 4

Name: Hao Zhu
Organization: Marcus Institute for Aging Research
Address: 1200 Centre St , Boston, MA 02131-1101
Phone: 617-971-5426
Email: haozhu@hsl.harvard.edu

Study Role

Data analyst

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

✓ Yes

No

Does this person have a financial interest in the research?

Yes

Please contact the IRB Office

✓ No

✓ HSL Person 5

Please find HSL person 5

Name: Jodie Gruen
Organization: Marcus Institute for Aging Research
Address: 1200 Centre St , Framingham, MA 01701
Phone:
Email: JodieGruen@hsl.harvard.edu

Study Role

Research Assistant

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

✓ Yes

No

Does this person have a financial interest in the research?

Yes

Please contact the IRB Office

✓ No

✓ HSL Person 6

Please find HSL person 6

Name: Kelly Black
Organization: Marcus Institute for Aging Research
Address: 1200 Centre St , Roslindale, MA 02131
Phone:
Email: kellyblack@hsl.harvard.edu

Study Role

Research Assistant

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

✓ Yes

No

Does this person have a financial interest in the research?

Yes

✓ No

✓ HSL Person 7

Please find HSL person 7

Name: Nicole LaGanke
Organization: Marcus Institute for Aging Research
Address: 1200 Centre St , Roslindale, MA 02131
Phone:
Email: nicolelaganke@hsl.harvard.edu

Study Role

Research Assistant

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

✓ Yes

No

Does this person have a financial interest in the research?

Yes

✓ No

✓ HSL Person 8

Please find HSL person 8

Name: Emma Finnerty
Organization: Marcus Institute for Aging Research
Address: 1200 Centre St , Roslindale, MA 02131
Phone:
Email: emmafinnerty@hsl.harvard.edu

Study Role

Research Assistant

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

✓ Yes

No

Does this person have a financial interest in the research?

Yes

✓ No

✓ HSL Person 9

Please find HSL person 9

Name: Alvaro Pascual-Leone
Organization: Marcus Institute for Aging Research
Address: 1200 Centre Street , Boston, MA 02131-1011
Phone: 617-971-5372
Email: apleone@hsl.harvard.edu

Study Role

Co-investigator

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

✓ Yes

No

Does this person have a financial interest in the research?

Yes

✓ No

✓ HSL Person 10

Please find HSL person 10

Name: Natalia Gouskova
Organization: Marcus Institute for Aging Research
Address: 1200 Centre St , Boston, MA 02131-1011
Phone:
Email: NataliaGouskova@hsl.harvard.edu

Study Role

Statistician

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

- ✓ Yes
- No

Does the IRB office have this person's cv/resume on file?

- ✓ Yes
- No

Does this person have a financial interest in the research?

- Yes
- ✓ No

2.0 **Do you have more than 10 HSL personnel working on the study?**

- Yes
- ✓ No

Will there be any non HSL personnel working on the study?

3.0

Note: non-HSL personnel should only be added to the personnel roster if ceded review has (or will be) requested and HSL will be the IRB of record.

✓ Yes

No

Non HSL Personnel

✓ Non-HSL Person 1

Name

Mark Halko, Ph.D

Study Role

Co-Investigator

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

✓ Yes

No

Does this person have a financial interest in the research?

Yes

Please contact the IRB Office

✓ No

Non-HSL Person 2

✓ Non-HSL Person 3

Name

Bonnie Wong, PhD

Study Role

Co-investigator

Does the IRB Office have this person's current CITI certificate(s) on file?

Note: CITI certificates are valid for three years.

✓ Yes

No

Does the IRB office have this person's cv/resume on file?

✓ Yes

No

Does this person have a financial interest in the research?

Yes

✓ No

Non-HSL Person 4

Non-HSL Person 5

4.0 **Do you have more than 5 Non-HSL personnel working on the study?**

Yes

✓ No

Form A - HIPAA Request for Waiver of Authorization to Use/Disclose Protected Health Information (PHI)

1. Does the research need to be conducted with PHI?

✓ Yes

Provide explanation of why PHI is necessary to conduct the research

We will obtain contact information from individuals recruited via advertisement during the phone screen, to be able to maintain contact with them, and arrange transportation for them, during study participation. The PI will maintain an electronic version of the PHI data which will be stored in a password-protected file on the Hebrew SeniorLife server. Paper forms will be kept in a locked file cabinet located in the PI's office.

We request the ability to identify potential participants through review of HSL outpatient medical records. We will contact the MD of any patient who meets the study eligibility criteria by encrypted email, to ask permission to contact these patients . If the MD approves, we will then reach out to the individual by mail via the attached letter along with a study brochure. The individual can then respond to us if they would like to learn more about the study or want to participate.

No

2. Reason for Request

✓ Review of PHI (Medical record, computer files, etc.)

Requesting a waiver of informed consent

✓ In preparation for recruitment of research subjects

Please click all that apply.

✓ Review of appointment logs/schedules

✓ Review of existing database of PHI

Review of other lists

✓ Other

Specify the reason for the request

The study team requests the ability to ask and record PHI to enable communication with potential and enrolled subjects.

3. **Who will have access to PHI?**

List the role or name of persons on the research protocol who will have access to PHI

All study personnel responsible for recruitment and data collection and participant follow up activities may have access to PHI during the study.

List the total number of charts/subject data to be accessed/reviewed

If intervention and control groups, dyads, etc. include numbers for all types of participants

We anticipate conducting approximately 1500 phone screens, and 432 in person screens, as our past experiences recruiting similar cohorts suggest one-third of these individuals will be interested, eligible and enroll in the trial.

Dates of access to PHI

Start Date (can be approximate)

09/04/2018

End Date (can be approximate)

06/30/2023

4. **Types of PHI to be Accessed**

Mark all appropriate PHI to be accessed

✓ Names

Click which applies:

Viewing Only *(not recording names)*

✓ Recording Names

✓ Telephone Numbers

Click which applies:

Viewing Only *(not recording telephone numbers)*

✓ Recording Telephone Numbers

Fax Numbers

✓ Address/Residence

Click which applies:

Viewing Only *(not recording addresses/residences)*

✓ Recording Addresses/Residences

Social Security Number

Medical Record Number

Health Plan Beneficiary Number

Identifying Photographic Images

✓ Medical Diagnoses

Click which applies:

Viewing Only *(not recording medical diagnoses)*

✓ Recording Medical Diagnoses

Medical Records

Medication List

Device Identifier, serial number

Biometric Identifier (finger, voice prints)

✓ Geographic Subdivision Smaller than State (e.g. street, city, zip code)

Click all that are appropriate

✓ Street

Click which applies:

Viewing Only *(not recording street)*

✓ Recording Street

✓ City

Click which applies:

Viewing Only *(not recording cities)*

✓ Recording Cities

County

Precinct

✓ Zip Code

Click which applies:

Viewing Only *(not recording zip codes)*

✓ Recording Zip Codes

✓ Elements of Dates (e.g. birth, admission, discharge, age over 89, etc.)

Click all that are appropriate

✓ Birth

Click which applies:

Viewing Only *(not recording birth dates)*

✓ Recording Birth Dates

Admission

Discharge

Procedure

Death

Age over 89 years

Other

5. **Will PHI be sent to Investigators at Institutions outside of Hebrew SeniorLife?**

Yes

✓ No

Describe your plan to protect the PHI from unapproved use or disclosure

6.

- Each subject will be given a unique study identification number and data will not include any of the subject's PHI.
- All subject-identifying information will be stored and managed on a secured database server.The information will be password protected.
- Subject confidentiality will be maintained in accordance with HIPAA regulations.
- Only the PI and/or study personnel who are approved by the IRB and authorized to view the PHI for study related activities - study recruitment, data collection and participant follow up activities - will have access to the information.
- PHI will not be used during discussion, presentation or publication of any research data.

7. **Describe your plan to destroy identifiers/PHI at the earliest opportunity, or provide a justification for retaining identifiers**

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

8. **Principal Investigator Certification**

I certify that PHI will not be reused or disclosed to any other person, or business or organization except as required by law, for oversight of the research project, or for other research specifically approved by the IRB.

- ✓ Yes
- No

I agree to abide to the Minimum Necessary Requirement (to use only the information reasonably necessary to accomplish the purpose of the project stated on this form).

- ✓ Yes
- No

1.0 Principal Investigator Information

1.1 Investigator experience with studies involving the use of devices, and in what capacity

(e.g. principal investigator, site investigator, collaborator, etc.)

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

1.2 Investigator experience directing studies that involve the use of devices

Dr. Manor has directed numerous study protocols, currently HSL IRB approved, utilizing the devices currently proposed for use in this study.

1.3 Does the Investigator have financial interest in the device(s) being used in this research study?

(e.g., royalty, patent or stock options, etc.)

Yes

✓ No

2.0 Product Information

2.1 Please click on the number of devices you will be using in this study

1

2

✓ 3

More than 3

Form D.1 Device 1

1.0 Product Information

Name of the Device

1.1

Provide the full name, and if there is a marketed or brand name also include this information here

Starstim

Type of Device

Describe the device and its purpose for being used in the research

1.2 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.

1.3 Device Manufacturer Name

Neuroelectrics

Device Manufacturer Contact Information

1.4

tel:+34 93 254 03 66
fax:+34 93 212 64 45
http://www.neuroelectrics.com

Device Sponsor

1.5

e.g. manufacturer, principal investigator, funding entity, etc.

N/A

Attach a copy of the Device Brochure

1.6

NE_Starstim32.pdf

NE_UM_Part01_Enobio.pdf

NE_UM_Part02_Electrode.pdf

NE_UM_Part03_NIC.pdf

STARSTIM_Brochure150806.pdf

2.0 FDA Status of the Device and Risk Assessment

2.1 The Device being used in this study is:

Marketed, and FDA approved for this indication or use

Marketed, but lacks FDA approval for this indication or use

✓ Not marketed, Non-FDA approved

2.2 Has the FDA made a risk determination for the study?

Yes

✓ No

2.3 Has the Sponsor made a risk determination for the study?

Yes

✓ No

2.4 The FDA has placed restrictions on this Device:

Yes

✓ No

List commonly reported adverse effects or problems with the Device

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:

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

2.5 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

3.0 Study Information

Method/route/mode of Device administration

3.1 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.

3.2 The route of administration is consistent with the FDA approval

Yes

No

✓ N/A FDA Approval is not required

The Population in which the Device will be used:

3.3

Click all that apply

✓ Geriatric Population (over 65 years of age)

Adults (ages 18 years to 64 years)

Pregnancy women and/or neonates

Children

Other

Healthy persons

Persons with an illness or condition for which the Device was designed or is being tested

3.4 **Duration of Device use for study participants**

The device will be used to apply 20 minutes of tDCS to the participant's scalp in each of 20 separate study visits.

3.5 **Schedule of Device administration, including changes in frequency, or strength of the Device**

During the 20 minute tDCS session, the direct current delivered by any one electrode will not exceed 2.0mA; the total amount of current from all electrodes will not exceed 4mA.

3.6 **Will the participants be operating the Device?**

Yes

✓ No

3.7 **Describe any special instructions required in order to use the Device**

N/A

Describe any special restrictions for using the Device

3.8

e.g. do not use near water, persons cannot have history of high blood pressure, etc.

N/A

3.9 **Describe the procedures for monitoring device functionality and participant adherence**

The device is connected to a computer software program that continuously monitors device functionality.

4.0 Device Supply, Distribution and Storage

4.1 The Device is available:

By prescription only

✓ Over the counter

Available only through Study Sponsor

Other

4.2 The Device will be stored and administered at HSL

✓ Yes

Describe the plan for storage, security and distribution of the Device, as well as accounting for its use and return (if applicable).

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.

No

4.3 List any special storage and handling requirements of the Device

N/A

4.4 Costs of Product to study participant

✓ There is no cost to the participant for the study Device

The Device will be charged to the participant?s insurance company
This information must be provided in the consent form, including any short or long-term implications to the participants for the billing of their insurance company.

The participant will pay for the Device

Form D.2 Device 2

1 Product Information

Name of the Device

1.1

Provide the full name, and if there is a marketed or brand name also include this information here

Mobility Lab

Type of Device

1.2

Describe the device and its purpose for being used in the research

The Mobility Lab system allows the user to wirelessly record human movement from multiple synchronized monitors.

1.3 Device Manufacturer Name

APDM Movement Monitoring Solutions

Device Manufacturer Contact Information

1.4

web: support.apdm.com
email: support@apdm.com
telephone: 888-988-APDM (2736)

Device Sponsor

1.5

e.g. manufacturer, principal investigator, funding entity, etc.

N/A

Attach a copy of the Device Brochure here

1.6

MobilityLab_UserGuide.pdf

2.0 FDA Status of the Device and Risk Assessment

2.1 The Device being used in this study is:

- Marketed, and FDA approved for this indication or use
- Marketed, but lacks FDA approval for this indication or use
- ✓ Not marketed, Non-FDA approved

2.2 Has the FDA made a risk determination for the study?

- Yes
- ✓ No

2.3 Has the Sponsor made a risk determination for the study?

- Yes
- ✓ No

2.4 The FDA has placed restrictions on this Device:

- Yes
- ✓ No

2.5 List commonly reported adverse effects or problems with the Device

There are no adverse effects associated with this passive recording system.

3.0 Study Information

Method/route/mode of Device administration

3.1

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.

3.2 **The route of administration is consistent with the FDA approval**

Yes

No

✓ N/A FDA Approval is not required

3.3 **The Population in which the Device will be used:**

Click all that apply

✓ Geriatric Population (over 65 years of age)

Adults (ages 18 years to 64 years)

Pregnancy women and/or neonates

Children

Other

Healthy persons

Persons with an illness or condition for which the Device was designed or is being tested

3.4 **Duration of Device use for study participants**

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.

3.5 **Schedule of Device administration, including changes in frequency, or strength of the Device**

N/A

3.6 **Will the participants be operating the Device?**

Yes

✓ No

3.7 **Describe any special instructions required in order to use the Device**

N/A

Describe any special restrictions for using the Device

3.8

e.g. do not use near water, persons cannot have history of high blood pressure, etc.

N/A

Describe the procedures for monitoring device functionality and participant adherence

3.9

The device is connected to a computer software program. This program configures the device and completes a performance assessment at the beginning of each trial of data collection.

4.0 Device Supply, Distribution and Storage

4.1 **The Device is available:**

By prescription only

✓ Over the counter

Available only through Study Sponsor

Other

4.2 **The Device will be stored and administered at HSL**

✓ Yes

Describe the plan for storage, security and distribution of the Device, as well as accounting for its use and return (if applicable).

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

No

4.3 List any special storage and handling requirements of the Device

N/A

4.4 Costs of Product to study participant

✓ There is no cost to the participant for the study Device

The Device will be charged to the participant?s insurance company *This information must be provided in the consent form, including any short or long-term implications to the participants for the billing of their insurance company.*

The participant will pay for the Device

Form D.3 Device 3

1.0 Product Information

Name of the Device

1.1

Provide the full name, and if there is a marketed or brand name also include this information here

AX3

Type of Device

Describe the device and its purpose for being used in the research

1.2 The AX3 is an accelerometer that incorporates a real time clock and temperature sensor. It is used to detect movement, vibrations and orientation changes in all 3 axis with precision, and able to record up to 21 days of continuous data. It is small and lightweight [23 x 32.5 x 7.6 mm] and weighs 11 grams and waterproof. The device has been validated for use in older adults of various functional levels. It provides overall activity and step counts as well as accurate, automatic detection of time spend lying, sitting, standing and walking and gait kinematics during detected bouts of walking.

The purpose of using this device in the current research is to collect habitual physical activity data over 5 days at baseline and the immediate follow-up, three and six month follow-up period.

1.3 Device Manufacturer Name

Axivity

Device Manufacturer Contact Information

1.4

Office Address

Axivity Ltd
Jam Jar Studio 3
Hoults Yard
Walker Road
NE6 @HL
United Kingdom

Contact Details

info@axivity.com

Telephone: +44 (0) 191 6031526
Fax: +44 (0) 191 6031565

Device Sponsor

1.5

e.g. manufacturer, principal investigator, funding entity, etc.
Principal Investigator

Attach a copy of the Device Brochure here

1.6

AX3_Data_Sheet.pdf

2.0 FDA Status of the Device and Risk Assessment

2.1 The Device being used in this study is:

Marketed, and FDA approved for this indication or use

Marketed, but lacks FDA approval for this indication or use

✓ Not marketed, Non-FDA approved

2.2 Has the FDA made a risk determination for the study?

Yes

✓ No

2.3 Has the Sponsor made a risk determination for the study?

✓ Yes

No

The sponsor considers this Device to be:

2.3.1

Please review the FDA Information Sheet on Significant and Non-Significant Risk Devices

✓ *A non-significant risk (NSR) to participants*

An NSR device study is one that does not meet the definition for an SR device study (see below).

Provide an explanation of this determination and any other information that may be helpful to the IRB.

(e.g. description of the device, reports of prior investigations with the device, the proposed investigational plan, subject selection criteria, etc.)

The device is a non-significant risk wearable external activity monitor that has been used and validated in previous studies of older functionally impaired adults. In the current research, we will utilize the device in the same manner as has been reported previously, i.e, the device will be placed and secured at the participant's low back, at the level of the L5 vertebra. In our current studies, participants report that once placed, it is not noticeable nor does it impact daily life, and is in fact, easy to forget it is in place. All enrolled participants will be asked to wear the activity monitor as describe below in section 3.5.

Listed below are several publications of studies utilizing the device.

Del Din S, Hickey A, Hurwitz N, Mathers JC, Rochester L, Godfrey A. Measuring gait with an accelerometer-based wearable: influence of device location, testing protocol and age. *Physiological measurement.* 2016;37(10):1785-1797.

Ladha C, Del Din S, Nazarpour K, et al. Toward a low-cost gait analysis system for clinical and free-living assessment. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference.* 2016;2016:1874-1877.

Clarke CL, Taylor J, Crighton LJ, Goodbrand JA, McMurdo ME, Witham MD. Validation of the AX3 triaxial accelerometer in older functionally impaired people. *Aging clinical and experimental research.* 2016.

Feng Y, Wong CK, Janeja V, Kuber R, Mentis HM. Comparison of tri-axial accelerometers step-count accuracy in slow walking conditions. *Gait & posture.* 2017;53:11-16.

A significant risk (SR) to participants

Under 21 CFR 812.3(m), an SR device means an investigational device that:

? Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

? Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare

of a subject;
? Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
? Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

2.4 **The FDA has placed restrictions on this Device:**

Yes

✓ No

2.5 **List commonly reported adverse effects or problems with the Device**

None

3.0 Study Information

Method/route/mode of Device administration

3.1 This activity monitor will be placed and secured by a trained research assistant. The device will be placed as previously described, to the participant's lower back, at the level of the L5 vertebra. The device is lightweight and waterproof, and thus does not interfere with activities of daily living, such as bathing or showering. After wearing the device for 5 days at home, the device will be removed from the participant's lower back by the study research assistant.

3.2 **The route of administration is consistent with the FDA approval**

Yes

No

✓ N/A FDA Approval is not required

3.3 **The Population in which the Device will be used:**

Click all that apply

- ✓ **Geriatric Population** (over 65 years of age)
- **Adults** (ages 18 years to 64 years)
- **Pregnancy women and/or neonates**
- **Children**
- **Other**
- **Healthy persons**
- **Persons with an illness or condition for which the Device was designed or is being tested**

3.4 **Duration of Device use for study participants**

Each participant will be asked to wear the device at 4 time-points, over 5 days each, for a total of 20 days altogether.

3.5 **Schedule of Device administration, including changes in frequency, or strength of the Device**

Habitual physical activity will be recorded for five consecutive days at baseline (Visit 3) and at the immediate post-intervention (Visit 24), three (Visit 25) and six month (Visit 26) follow up period.

3.6 **Will participants be operating the Device?**

- **Yes**
- ✓ **No**

3.7 **Describe any special instructions required in order to use the Device**

None

Describe any special restrictions for using the Device

3.8

e.g. do not use near water, persons cannot have history of high blood pressure, etc.

None

3.9 Describe the procedures for monitoring device functionality and participant adherence

The device will be charged prior to each use

4.0 Device Supply, Distribution and Storage

4.1 The Device is available:

By prescription only

✓ Over the counter

Available only through Study Sponsor

Other

4.2 The Device will be stored and administered at HSL

✓ Yes

Describe the plan for storage, security and distribution of the Device, as well as accounting for its use and return (if applicable).

The device will be stored in a locked cabinet within the Clinical Research Laboratory. Only research assistants or members of the study team responsible for placing and monitoring the devices will have access to the locked cabinet.
The device will be applied and secured to a participant in accordance to standard practice, it will be taped to the participant's lower back (at the L5 vertebral level) at the start of the activity monitoring period. The device serial number, date of application and date of removal and participant ID will be tracked for each use.

No

List any special storage and handling requirements of the Device

4.3

n/a

4.4 Costs of Product to study participant

✓ There is no cost to the participant for the study Device

The Device will be charged to the participant's insurance company
This information must be provided in the consent form, including any short or long-term implications to the participants for the billing of their insurance company.

The participant will pay for the Device

Product Information

1.0

Please click on the number of Non-Ionizing Agents (e.g. MRI, ultrasound, laser, etc) to be used in this study

- ✓ 1
- 2
- 3
- More than 3

F.1 Use of Non-Ionizing Agent 1

1.0 Non-Ionizing Source Information

1.1 Provide the name of the procedure

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.

1.2 Provide the name of the institution where the procedure will be performed

Beth Israel Deaconess Medical Center

2.0 Participant Exposure

2.1 Participants to undergo the procedure

(e.g. all participants, randomized participants, etc.)
All participants enrolled will undergo a baseline MRI visit.

2.2 Part(s) of the participant's body to be exposed to the non-ionizing agent

Head

Exposure Parameters

Please include (as applicable):

- *MRI: Static magnetic field strength (Gauss), SAR: average and peak RF heating, rate of magnetic field strength change with time (dB/dt) relative to gradient, and acoustic noise (decibels)*
- *Ultrasound: Frequency (Hz) and intensity (W/cm2)*

- *Lasers or Ultraviolet: Power output (W/cm2), wavelength (nm) and tissue exposure (J/cm2)*

2.3

Baseline structural MRIs will enable personalization of tDCS via current flow modeling, as well as detection of silent infarcts and white matter hyperintensities (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 for tDCS personalization: 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 FreeSurfer combination pipeline and the Lesion Segmentation Tool for SPM,[138] 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^{o}, 1 mm^{3} isotropic resolution, matrix= 256X256; **T2:** 283 s, TR/TE= 3200/284 ms, 1 mm^{3} isotropic resolution, matrix=256X256; **T2 FLAIR:** 422 s, TR/TE=6000/388 ms, flip angle=120 ^{o}, thickness=1.0 mm, 0.49x0.49 mm in-plane resolution, matrix=512X512.
BOLD MRI will utilize a standard echo-planar imaging sequence with the following parameters: repetition time/echo time (TR/TE) = 1050/34.8ms; 65° flip angle; 230×230mm field of view (FOV) with a 104×104 acquisition matrix; thickness/gap (THK)=4mm/1mm with 2x2 mm^{2} in-plane resolution. *Anatomical MRI* will be acquired after the BOLD sequences with the T2-weighted FLAIR sequence (TR/TE/TI = 6000/279/2100ms, 1.0mm isotropic res, 256x256mm, 160 slices/slab) and a 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence (TR/TE/TI = 7.8/3.1/600ms; 1.0mm slice thickness, 52 slices; bandwidth = 122Hz per pixel; 10° flip angle; 240´240mm FOV with 256´192 acquisition matrix).

2.4 Describe the number of visits at which participants will undergo the procedure, and the duration of exposure at each study visit

There will be two MRI visits, up to 1 hour in duration for each visit.

2.5 Is the exposure in the study considered routine?

✓ Yes

No

2.6 **Are the participants engaged in other research projects or medical care that involves additional exposure?**

- Yes
- ✓ No
- Unsure