Home-based Transcranial Direct Current Stimulation for Pain Management in Persons with Alzheimer's Disease and Related Dementias

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PROTOCOL TITLE:

Home-based Transcranial Direct Current Stimulation for Pain Management in Persons with Alzheimer's Disease and Related Dementias

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	3.1.2022	Adding a telephone MoCA as an additional screening tool	No

Table of Contents

1.0 Study Summary

Study Title	Home-based Transcranial Direct Current Stimulation for Pain Management in Persons with Alzheimer's Disease and Related Dementias
Study Design	Double-blind, randomized, sham-controlled, parallel group (1:1 for two groups) design.
Primary Objective	The purpose of this project is to assess the effect of the self-administered transcranial direct current stimulation (tDCS) in 40 older adults with ADRD
Secondary Objective(s)	The specific aims are the following: evaluate the preliminary effects of home-based M1-SO applied tDCS on clinical pain in persons with early-stage ADRD (specific aim 1); evaluate the preliminary effects of home-based M1-SO applied tDCS on pain related cortical response in persons with early-stage ADRD (specific aim 2); and evaluate the feasibility and acceptability of home-based M1-SO–applied tDCS for pain management in persons with early stage ADRD (specific aim 3).
Research Intervention(s)/ Investigational Agent(s)	tDCS
IND/IDE #	N/A
Study Population	Older adults with early-stage Alzheimer's Disease and Related Dementia (ADRD)
Sample Size	40
Study Duration for individual participants	3 months, including follow-up phone interviews
Study Specific Abbreviations/ Definitions	tDCS, transcranial direct current stimulation; ADRD, Alzheimer's Disease and Related Dementia, SMC, Safety Monitoring Committee

2.0 Objectives

The purpose of this project is to assess the feasibility, acceptability, and preliminary effects of this novel nonpharmacological treatment option in persons with ADRD. The specific aims are the following: evaluate the preliminary effects of home-based M1-SO applied tDCS on clinical pain in persons with early-stage ADRD (specific aim 1); evaluate the preliminary effects of home-based M1-SO applied tDCS on pain-related cortical response in persons with early-stage ADRD (specific aim 2); and evaluate the feasibility and acceptability of home-based M1-SO applied tDCS for pain management in persons with early-stage ADRD (specific aim 3). Outcome measures include clinical pain, pain-related cortical response using functional near-infrared spectroscopy, and participant experience and side effects using questionnaire.

3.0 Background*

The World Health Organization has highlighted dementia care as one of its highest priorities. Alzheimer's disease and Related Dementias (ADRD) is characterized by progressive and global deterioration in cognitive functions,15 and more than 5.5 million people in the United States have ADRD. Persons with ADRD are often elderly and have many age-related sources of pain (e.g., radiculopathy and arthritis), with approximately 60% reporting chronic pain. Aside from behavioral and psychological symptoms of dementia (BPSD), pain is the most cited cause for decreased quality of life in persons with ADRD. Moreover, our group and others showed that pain in ADRD is associated with neuropsychiatric symptoms and a decline in cognitive functioning. Primary treatment options for pain management comprise mainly the prescription of analgesic medications; however, existing pharmacological approaches often produce significant adverse events (e.g., constipation, confusion, behavioral disorders, psychomotor retardation, and falls), and the treatment benefits may decrease over time (e.g., drug tolerance development). Furthermore, many studies suggest that alterations in pain related brain mechanisms may contribute to chronic pain. Indeed, neuroimaging studies have revealed increased pain-related brain activation in people with chronic pain, and alterations in pain related brain mechanisms have been associated with chronic pain and disability in older adults. Therefore, there is growing interest in nonpharmacological interventions targeting pain-related brain function in this population. Noninvasive brain stimulation, such as transcranial direct current stimulation (tDCS), has received significant attention as treatment of pain in chronic conditions owing to its neuromodulatory effects in the central nervous system. tDCS involves the application of low-amplitude direct electric current to the head in a noninvasive and painless manner, which modulates the resting membrane potentials of neurons, altering the excitability of the targeted cortical area. Hundreds of clinical trials have demonstrated that tDCS is safe and well tolerated within the established current intensities and durations. For pain treatment, stimulation is typically delivered multiple times with the anode electrode placed over the primary motor cortex of the left hemisphere and with the cathode electrode placed over the contralateral supraorbital region. A panel of experts of the International Federation of Clinical Neurophysiology published evidence-based guidelines in which they recommended 20-minute tDCS using 2 mA electrical current intensity for possible efficacy among populations with chronic pain.

Therefore, we will examine the effect of tDCS in persons with ADRD. Our hypothesis is that remotely supervised tDCS at home will decrease clinical pain.

4.0 Study Endpoints*

The study endpoint is 3 months, including monthly follow-up telephone assessments for 3 months after the completion of intervention.

5.0 Study Intervention/Investigational Agent

tDCS with a constant current intensity of 2 mA will be applied for 20 minutes per session daily for 5 days via the Soterix 1x1 tDCS mini-CT Stimulator device (Soterix Medical Inc., NY; 6.5 inches long, 3 inches wide, 0.7 inches thick) with headgear and 5x7 cm saline-soaked surface sponge electrodes. The FDA has ruled that the aforementioned tDCS stimulator is a "non-significant risk" device, a requirement for Investigational Device Exceptions. The sponge electrodes snap into the custom headgear, which is secured to the participant's head for simple and fail-safe electrode preparation. This single-position headgear with clearly labeled sponge markers eliminates room for user error and helps conserve the placement of the montage. Participants can only administer a stimulation session via the Soterix 1x1 tDCS mini-CT Stimulator device after being provided a single-use unlock code by the research staff once proper contact quality is achieved (only the on/off button will be adjustable by the study participants; they will not be able to adjust the device settings). After the participant enters the unlock code, the screen on the device will show a timer that counts down the minutes until the end of the session. At 20 minutes, the device will turn off automatically, and study staff will instruct the participant to remove the headset and discard the sponges and to safely store all materials for the next session. For sham stimulation, the electrodes will be placed in the same positions as for active stimulation, but the stimulator will only deliver 2 mA current for 30 seconds. This sham stimulation method has been shown to be reliable and indistinguishable from active treatment.

6.0 Procedures Involved*

Alzheimer's disease and Related Dementias (ADRD) affects more than 5.5 million individuals in the United States. Approximately 60% of persons with ADRD experience chronic pain, and pain is the second most commonly cited reason for decreased quality of life in persons with ADRD. Our group and others showed pain in ADRD is associated with behavioral and psychological symptoms of dementia. The current standard of care comprises mainly the prescription of analgesic medications, which often produce significant adverse effects. Moreover, recent evidence suggests that alterations in pain-related brain mechanisms may contribute to chronic pain. Therefore, there is growing interest in nonpharmacological interventions targeting pain-related brain function in this population. One promising treatment is tDCS with the anode over the primary motor cortex and the cathode over the contralateral supraorbital area (M1-SO applied tDCS), as it can change brain activity in a noninvasive, painless, and safe way. We will investigate the effects of home-based, remotely supervised, M1-SO applied tDCS on clinical pain in 40 persons with early-stage ADRD using an experimenter- and participant-blinded,

randomized, sham-controlled, parallel group (1:1 for two groups) pilot clinical trial. The central hypothesis is that home-based, remotely supervised tDCS will decrease pain. This hypothesis will be tested by pursuing the following specific aims: evaluate the preliminary effects of home-based M1-SO applied tDCS on clinical pain in persons with early-stage ADRD (specific aim 1); evaluate the preliminary effects of home-based M1-SO applied tDCS on pain related cortical response in persons with early-stage ADRD (specific aim 2); and evaluate the feasibility and acceptability of home based M1-SO–applied tDCS for pain management in persons with early stage ADRD (specific aim 3). We will also obtain data, as an exploratory aim, to investigate whether tDCS reduces behavioral and psychological symptoms of dementia. The proposed study will directly investigate the effects of home-based, remotely supervised tDCS in 40 persons with ADRD using an experimenter- and participant-blinded, randomized, sham-controlled, parallel group (1:1 for two groups) pilot clinical trial. Caregivers will set up and administer home-based tDCS for persons with ADRD and must be present at each home-based session, and participants will be remotely supervised by trained research staff at each stimulation to ensure the use of proper technique. Primary outcome (clinical pain assessed by the MOBID-2) will be performed by the caregivers. Caregivers will be trained at the in-person baseline visit to use tDCS devices and to perform outcome measures. tDCS session will be not performed if the caregiver is not available, and it needs to be the same caregiver throughout the trial. The proposed research is significant because it is expected to provide valuable insight into an exciting new modality of nonpharmacological pain management that is easy, safe, and noninvasive with minimal side effects.

Participants will do remotely-supervised tDCS at their home or private room for 5 days under real time supervision by the research staff. Data will be collected by study staff across several points using equipment and resources available at Dr. Ahn's (PI's) laboratory at Florida State University (see Table below). The primary endpoint will be clinical pain (MOBID-2) collected after the final intervention session. Participants will visit Florida State University two times, and each visit will take approximately 2 hours.

Research subjects/caregivers will be called one day prior to their scheduled study visit and asked a series of COVID-19 related questions covering topics such as isolation and quarantine, vaccination status, symptoms, test results, and exposure. And then subjects will be notified about the FSU COVID-19 precautions. Consent materials will be modified to include a statement to the effect that no in-person activity may involve any individual (human research participants (human subjects) or study staff—vaccinated or unvaccinated) who (1) tests positive for COVID-19 or (2) has been in close contact with someone who has COVID-19, within at least the past 10 days of the positive COVID-19 test or close contact; that prospective subjects will be screened for this purpose; and that for any in-person research activity the use of masks is strongly recommended (and may be required in certain locations) as is a full COVID-19 vaccination.

Table 1. Timetable for Collection of Data

		Week 1	F1	F2	F3

Stimulation Session	Baseline	1	2	3	4	5			
MMSE	X								
Medical History Questionnaire	X								
Clinical Pain (MOBID-2): primary outcome	X	X	X	X	X	X	X	X	X
Clinical Pain (NRS): secondary outcome	X	X	X	X	X	X	X	X	X
BPSD (CMAI, NPI): secondary outcome	X					X	X	X	X
Pain-related cortical response (fNIRS): secondary outcome	X					X			
tDCS experience questionnaire: secondary outcome						X			
Patient satisfaction (CSQ-8): secondary outcome						X			
Side effects questionnaire: secondary outcome		X	X	X	X	X			

Note: F, Weekly follow-up phone assessment after completion of tDCS treatment; MMSE, Mini-Mental Status Exam, MOBID, Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale; BPSD, behavioral and psychological symptoms of dementia; CMAI, Cohen-Mansfield Agitation Inventory; fNIRS, functional near-infrared spectroscopy; CSQ, Client Satisfaction Questionnaire.

- MMSE. MMSE will be used to exclude people with severely diminished cognitive function (i.e., Mini-MentalStatus Exam score ≤ 15).
- Medical History Questionnaire. All participants will complete a thorough questionnaire to collect demographic and medical history details, including age, sex, height, weight, duration of knee OA,current and past treatments for knee OA, comorbid conditions, and current medications.
- Clinical pain will be measured to rate patients' pain via the Mobilization-Observation-Behavior Intensity-Dementia (MOBID-2) scale from 0 to 10, which will be primary outcome measure for data analysis purposes. The MOBID-2 is a well-validated measure with good ability to detect painchange in persons with ADRD. We also measure clinical pain by asking participants to rate their average pain over the past 24 hours via NRS from 0 (no pain) to 100 (worst pain imaginable), following Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations for clinical trials involving chronic pain. NRS is appropriate for use among older adults with mild to moderate dementia.
- BPSD. NPI will be used to obtain information on behavioral and psychological symptoms of the patients. NPI comprises 12 items that are summed to yield an overall score of 0-144 (each item will be rated frequency X severity, totaling 0 – 12), with higher scores indicating greater symptoms. We also collect CMAI, which is comprised of 29 items that are summed to yield an overall score of 29-203 (each item will be rated 7-point scale of frequency). Trained research staff will conduct the NPI interview. In terms of training, two raters (one primary and one back-up) conduct mock administrations to each other. Same rater will conduct the assessment with the subjects for fidelity. PI will

review NPI and CMAI and will not refer subjects for clinical review based on the result.

- A multichannel fNIRS imaging system (LIGHTNIRS, Shimadzu, Kyoto, Japan) will be used to determinechanges in regional cerebral blood flow in response to thermal stimuli applied to the right forearm of participants. The illumination and detection optodes will be arranged in a geometrical layout that will cover the prefrontal and somatosensory cortex regions bilaterally, consistent with locations investigated in previous studies. For evoked pain scans, low-intensity thermal stimuli at the thermal pain threshold level will be applied for a few seconds during multiple scanning runs, followed by an approximately equivalent interval of no stimulation, which is commonly used in pain related neuroimaging studies since thermal hyperalgesia is an important component of chronic pain. A temperature-controlled pain generator (Medoc TSA-II Neurosensory Analyzer) will be used to produce thermal stimulation through a 16 mm □16 mm thermode. We expect to observe reduced pain-evoked activation in the active tDCS group in the prefrontal and somatosensory cortices. To minimize the inconvenience to participants, we will deliver thermal stimuli that are below the individual's pain tolerance level and set the cutoff temperature at 50°C. These procedures will ensure maximum patient safety and comfort while allowing successful and reliable imaging of the pain-related cortical response.
- We will collect data on the tDCS experience via a questionnaire, adapted from Gillick et al. and Cha et al., at the conclusion of tDCS treatment on a 0 (strongly disagree) to 10 (strongly agree) scale: 1) It was easy to prepare the device and accessories; 2) The device was unnecessarily complex; 3) The device was easy to use; 4) I felt the video conferences with a technical person were helpful; 5) I would imagine that most people would learn to use this device quickly; 6) The device was cumbersome to use; 7) I felt confident using the device; 8) I needed to learn a lot of things before I could get going with this device; 9) The effectiveness of the treatment increased over the course of treatment; and 10) Overall, I felt that transcranial electrical stimulation treatment benefited me. Participants/caregivers will also be encouraged to elaborate on their answers in free form. In addition, we will measure participant satisfaction with treatment using the Client Satisfaction Questionnaire (CSQ-8). The CSQ-8 comprises eight items that are summed to yield an overall score of 8-32, with higher scores indicating greater satisfaction. Moreover, we will evaluate the presence and severity of possible side effects of treatment at the end of each session on a 0 (not at all) to 10 (highest degree) scale. The participants will be asked in an open-ended manner whether they experienced any side effects, and they will then be asked specifically about tingling, itching sensation, burning sensation, pain at the stimulation site, fatigue, nervousness, headache, difficulty concentrating, mood change, and changes in vision or visual perception. If any side effects are reported, the degree of relatedness to the intervention will be assessed on a 5-point scale. This approach has been used in our previous study and frequently in other studies.

7.0 Data and Specimen Banking

N/A

8.0 Sharing of Results with Subjects*

We will publish research results at the peer-reviewed journal and/or scientific conferences. After completion of the study, results may be shared to research subjects if they want.

9.0 Study Timelines*

The duration of an individual subject's participation in the study is three months including follow-up phone assessments. The estimated date for the investigators to complete this study is 02/01/2023.

10.0 Inclusion and Exclusion Criteria*

A maximum of 40 persons with early-stage Alzheimer's disease and related dementias (ADRD) will be enrolled. Participants who are 50 to 90 years old will be considered eligible if they (1) have early- stage ADRD, (2) have caregiver-reported chronic pain (average pain in the past 3 months ≥ 3 out of 10), (3) have a caregiver willing to participate in the study who sees the participant at least 10 hours/week, (4) can speak and read English, and (5) have no plans to change medication regimens during the trial. The diagnosis of early-stage ADRD will be verified by PI based on Mini-Mental Status Exam score (generally 16-23), the blind/telephone version of the Montreal Cognitive Assessment (MoCA, generally 16-26), or Clinical Dementia Rating scores (generally 0.5-1.0). We will assess the use of medications that can influence responses to tDCS (e.g., selective serotonin reuptake inhibitors, beta-blockers) and include them as covariates in our statistical models. Participants will be excluded if they have any concurrent medical conditions that could confound the interpretation of outcome measures, pose a safety risk for any of the assessment or tDCS procedures, or preclude the successful completion of the protocol. Specific exclusion criteria are: (1) history of brain surgery, brain tumor, seizure, stroke, or intracranial metal implantation, (2) alcohol/substance abuse, (3) severely diminished cognitive function (i.e., Mini-Mental Status Exam score ≤ 15), and (4) hospitalization within the preceding year for neuropsychiatric illness. Participants who do not have a device with internet access will be provided a smartphone to use during the study.

11.0 Vulnerable Populations

N/A

12.0 Local Number of Subjects

The number of subjects who are expected to be enrolled and screened is 24, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.) is 20. The total number of subjects to be accrued locally is 20, since we completed data collection for 20 subjects at the University of Texas Health Science Center at Houston before PI (Dr. Ahn) moved to Florida State University.

13.0 Recruitment Methods

Participants will be recruited in Leon County under the direction of the PI. We will advertise around local institutions and communities by advertisement study flyers. PI will

oversee participant screening and recruitment. We will share recruitment materials with potential study participants, and those patients who contact the study team for more information about the study will be approached by study investigators or trained study personnel for further determination of eligibility screening requirements and informed consent either in-person at a scheduled baseline visit. We will also recruit through the Institute for Successful Longevity participant registry, as well as contacting previous participants of Dr. Sheffler's study who have consented to be contacted for future research studies. MMSE will be used to exclude people with severely diminished cognitive function (i.e., MMSE score $\leq$ 15), and we will get the consent from the subject whose MMSE score is above 15. In addition to the MMSE cutoff, to ensure participant understanding of the study procedures, participants will be required to accurately describe the purpose and requirements of their participation in the study following review of the informed consent form.

Subjects will receive up to $240 in gift cards for completing the entire protocol, and they will receive partial payment if they do not complete the entire study. For each self-brain stimulation, subjects will receive $30 and an additional $30 for each visit to our testing center and $10 for each follow-up phone assessments.

14.0 Withdrawal of Subjects

Participation in this study is completely voluntary. All participants will be informed of the nature of the procedures and associated risks. Also, participants will be informed that they can withdraw from the study at any time by calling study team at 850-644-2647 and that this will have no adverse impact on the study or on their own future medical treatment.

15.0 Risks to Subjects

tDCS. The PI has extensive experience with tDCS interventions. Participants will be instructed to inform the experimenter of any discomfort during tDCS. To minimize risk associated with tDCS, participants will be asked to report any discomfort, and the examiner will monitor participants throughout the stimulation sessions. All tDCS sessions will be remotely supervised by a trained experimenter. Participants may stop at any time. tDCS has not been shown to cause seizures nor lower the seizure threshold in animals. There are no reports of seizure induced by tDCS in human participants in the literature. However, this may not be true for epilepsy patients, whose seizure threshold rates are likely abnormal. Thus, history of seizure is an exclusionary criterion for our study.

Demographic and clinical survey questionnaires. The potential risk of the questionnaires involves participants' feelings of discomfort or unease when reading or responding to survey questions that are personal. Throughout each questionnaire, participants will be reminded that participation is completely voluntary, they can refuse to answer any question, and they can stop at any time. Breaks will be given if needed. Research staff who collect data will have previous training in the conduct of all survey questionnaires.

Functional near-infrared spectroscopy. Optical fibers will be secured to the participant's scalp using the cap's grommets. Although there is no designed measure that protects the participants from the risk of discomfort due to prolonged wearing of headgear, we will assess the participants' level of discomfort through direct question immediately after wearing the headgear and periodically during the experiment. Participants will be instructed that they can discontinue the procedure if they experience any discomfort or unpleasant effects.

Thermal stimulation. The primary potential risk of thermal stimulation involves burning of the skin; however, we will be using the Medoc TSA-II Neurosensory Analyzer to create thermal stimulation. The TSA-II is covered under FDA 510K #K922052, which mandated both hardware and software safety limits that prevent burning of the skin. The following precautions will be employed in the proposed study: 1) participants will be informed that they can withdraw their arm from the stimulator at any time; 2) the experimenter will continuously monitor stimulus temperature and can manually discontinue stimulation at any point; and 3) the stimulator has a built-in shut-down system to prevent the delivery of prolonged or high-intensity stimuli. Inconvenience to participants will be minimized by delivering brief stimuli that are below the individual's thermal pain tolerance level. These procedures will ensure maximum patient safety and comfort while allowing successful and reliable imaging of the brain.

16.0 Potential Benefits to Subjects*

Brain Stimulation have been shown to reduce pain in some older adults. We cannot promise any benefits to participants in this research. However, this study will help us to understand whether self-brain stimulation will reduce pain in older adults with Alzheimer's Disease and Related Dementia, which might lead to better treatment for people with such condition.

17.0 Data Management* and Confidentiality

PI has substantial experience in the design and implementation of data management procedures that provide accurate recording and storage of data, participant confidentiality, and timely analysis. Based on our experience, we believe that the major data management and analysis needs for the proposed project can be met by using a high-end PC, equipped with SPSS and SAS for Windows and appropriate spreadsheet programs. All data files will be automatically backed up daily.

The data entry system will require a login identification and password to gain access to the data. Where appropriate, validation and range rules will be applied to the actual entry fields. Only the PI and designated research staff will be able to view the data in its raw state.

All data files will be automatically backed up daily. We will ensure data changes are documented and there is no deletion of entered data. Data will be accessible only by research team members via an encrypted and password-protected computer, and we will prevent unauthorized access to data.

Confidentiality will be protected by assigning each participant a number, which will be used in all data tabulation and subsequent publications. The list linking this number to the participant's identity will be maintained in a password-protected data file, accessible only by authorized research personnel associated with the human testing components of this project. The PI will oversee the compliance of the study, maintaining strict adherence to the requirements of the law, research protocols, and health information security. Only trained research team members designated in the IRB- approved study protocol will collect data. REDCap (http://www.project-redcap.org) will be used to capture and store participant data, accessible only by research team members via an encrypted and password-protected computer. All research data will be labeled using the participant's unique identifier. No name or other identifying information will be used on research data. All paper data (e.g., participant contact information, consent forms) will be placed in a locked file cabinet within 24 hours of their acquisition.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Dr. Ahn, the PI, will have the primary responsibility for monitoring study research staff, who will receive training on the study design, recruitment, and protocol prior to study initiation. The research staff will attend weekly meetings with the PI and monthly team meetings during data collection with the PI and co-investigators to discuss any study-related issues regarding recruitment and follow-up data collection. These meetings will be used to discuss experiences with the intervention participants, provide consultation, ascertain whether the research staff are following study protocols, evaluate and reinforce cultural competence, and identify any potential adverse events. Dr. Miao, the study statistician, will coordinate data management and analysis.

The Safety Monitoring Committee (SMC), which was approved by NIH, will be responsible for overseeing activities related to implementing the clinical trial to ensure patient safety, conformance to the clinical protocol, overall performance of the trial components, and integrity of the data being collected. The SMC will meet prior to the start of enrollment and then annually to review study progress (e.g., recruitment, retention, and safety procedures) and participant safety concerns and as needed to adjudicate any adverse events. All meeting materials will be considered privileged by SMC members. The SMC will comprise 3 members with expertise in neuromodulation, statistics, and geriatric clinical research: Ricardo Jorge, MD, professor of psychiatry and behavioral sciences at Baylor College of Medicine; Nikhil Padhye, PhD, associate professor and biostatistician at the UTHealth Cizik School of Nursing; and Jessica Lee, MD, Assistant Professor, Geriatric and Palliative Medicine, UTHealth McGovern Medical School. The SMC members are independent of the project. These members are appropriately qualified to review the scientific design and conduct of the study, to evaluate safety and risks to participants, to interpret data statistically, and to make recommendations concerning the continuation, modification, suspension, or termination of the study.

19.0 Provisions to Protect the Privacy Interests of Subjects

A number of data integrity procedures will be used to ensure the validity and integrity of the data and the safety of all participants involved in the study. All procedures involving human participants will be performed at the PI's laboratory at FSU. Relevant data and safety information obtained from each study participant will be verified against the original source documents by the study coordinator, and any identified discrepancies will be reviewed at the weekly meetings. All identifying information will be archived on a password-protected server in password-protected folders and files. Only study staff will have access to these files. We will use the double data entry module in REDCap for self-report data (e.g., questionnaires).

Computer-generated reports of variable frequencies and participant lists will be reviewed, leading to possible corrections to coding or entry. After data within a given group are checked for accuracy, the data will be stored in the password-protected folders.

Adherence to the study protocol will be promoted throughout the trial. Of note, the research team will receive proper training using detailed manuals of procedures for all aspects of the proposed research, including treatment protocols and participant interaction, in a step-by-step fashion. All study personnel will be trained before study initiation, and the PI will carry out weekly supervision of the research team's adherence to protocols. These procedures were successfully implemented in our previous studies.

20.0 Compensation for Research-Related Injury

This study poses minimal risks because (1) the discomfort is transient in nature and generally subsides immediately after the procedure; (2) participants are instructed that they may stop any procedure at any time with no adverse consequences; and (3) the level of discomfort experienced by participants is below their tolerance level. Also, risks will be minimized by adhering to our exclusion criteria, and the study physician will have full discretion to exclude participants who may be at excessive risk. There will be no compensation in the event of research related injury.

21.0 Economic Burden to Subjects

There will be no costs that subjects may be responsible for because of participation in the research.

22.0 Consent Process

Subjects will participate in the study only after they provide verbal and signed consent. MMSE will be used to exclude people with severely diminished cognitive function (i.e., MMSE score ≤ 15), and we will get the consent from the subject whose MMSE score is above 15. In addition to the MMSE cutoff, to ensure participant understanding of the study procedures, participants will be required to accurately describe the purpose and

requirements of their participation in the study following review of the informed consent form.

23.0 Process to Document Consent in Writing

Trained research personnel will obtain consent in a private room where participants feel comfortable. Informed consent will be documented in writing via the participants' and investigators' signatures.

24.0 Setting

The research team will conduct the research at the PI's research lab at the FSU.

25.0 Resources Available

This study, funded by NIH, was approved by the IRB at the University of Texas Health Science Center at Houston. On this R15 project, all the data will be collected at the Dr. Ahn's laboratory at FSU. Adequate equipment and resources are available in the Ahn laboratory to carry out the procedures and accommodate the personnel described in this proposal.

26.0 Multi-Site Research

N/A