

Protocol/Project Summary

Title: Brain & Cognitive Changes after Reasoning Training in Individuals with Cognitive Complaints

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INTRODUCTION AND PURPOSE: This proposal is to conduct a study to obtain data regarding the benefits of different types of interventions (i) reasoning training following transcranial direct current stimulation (tDCS) (ii) reasoning training following sham transcranial direct current stimulation (tDCS) on frontal- lobe mediated cognitive measures of executive control in adults with memory complaints, in the absence of dementia. In addition to behavioral assessment of cognition, the project will employ (i) Magnetic Resonance Spectroscopy (MRS) to measure changes in brain energy metabolism and Magnetic Resonance Imaging (MRI) to measure global brain blood flow and connectivity and (ii) electroencephalogram (EEG), to evaluate intervention outcomes.

The primary hypothesis is that individuals receiving tDCS prior to brain training will have a stronger response to brain training than those in the sham tDCS group. We further hypothesize that short, intensive dosages of reasoning training will enhance performance in trained area of cognition and will generalize to untrained domains as measured by frontal lobe-mediated measures of executive control (also referred to as fluid intelligence) of working memory, inhibition, switching, fluency, and nonverbal reasoning.

With reasoning training we expect increases white matter integrity between temporal and frontal lobe regions as measured by Fractional Anisotropy (FA) in the Diffusion Tensor Imaging (DTI) sequences. With MRS we expect to characterize changes in brains with mild cognitive impairment which are not seen with conventional MRI imaging, including changes in concentration of metabolites (such as phosphocreatine, inorganic phosphate, etc), ATP energy production, redox potential and cellular pH. Also, in the EEG assessments, we expected changes in N2, P3, and N4 ERP components in the reasoning training groups compared to the wait-listed control group. Importantly, we expect these changes to be more prominent in the reasoning training following tDCS than the reasoning training group alone.

BACKGROUND: In the United States 67.1 million individuals are age 55 or older (U.S. Census Bureau). The negative effects of cognitive decline in seniors will produce an enormous economic burden at individual, state and national levels, since this age group is one of the most rapidly growing segments of our population. One of the biggest risk factors faced by this population is decline in brain function. Interventions that promote functional independence, postpone hospitalization, and reduce the need for formal care will not only extend independent living and improve quality of life for seniors but will also save health care dollars. Thus far, the majority of the studies have focused on interventions that target specific brain functions such as memory, problem solving, etc. (Ball et al., 2002; Jobe et al., 2001; Mahncke, 2006). A significant potential exists to modify the structure and function of the aging human brain given intensive mental stimulation. Age-related cognitive decline has consistently been identified on frontal lobe measures of executive control such as reasoning. Concomitantly, a greater vulnerability of frontal brain networks, which subserve executive control functions, has also been identified with aging. Preliminary evidence highlights the potential of cognitive training to modify and strengthen brain and cognitive function in seniors. Evidence from our lab indicates that frontally mediated, gist-based reasoning (defined as the ability to combine detail information to construct abstract meanings) offers a promising cognitive domain to train in both healthy agers and individuals who have lower baseline cognitive performance.

In addition, new findings from cognitive training-induced neuroplasticity reveal a significant potential for the human brain to modify its structure and function well into old age via intensive cognitive training. Emerging research by our group (Anand, et al., 2011) and others indicate that such cognitive training programs may be most useful in individuals who have lower baseline cognitive performance. There are emerging, data-driven findings that suggest that we will be able to prevent modest decline and strengthen cognitive capacities in seniors. The key challenge is elucidating what types of training will be successful in enhancing cognitive function into late life and what are the brain state changes associated with successful training.

Limitations from prior studies of cognitive training in seniors show minimal if any generalization effect of cognitive training to untrained cognitive functions (Meron, et al., 2015). That is, individuals seem to get better on the specific cognitive area trained, such as memory, vocabulary; however, the training does not generalize to achieve a more global cognitive benefit (Elder and Taylor, 2014).

Transcranical Direct Current Stimulation (tDCS) is a form of neurostimulation which uses constant, low current delivered (2 mA) directly to the brain area of interest via electrodes (size electrodes: 35 cm²). TDCS is widely used to evaluate cortical functions (Nitsche et al. 2008; Matsumoto et al. 2010; Nitsche and Paulus, 2011; Zaehle et al. 2011; Polanía et al. 2011; Stagg and Nitsche 2011; Brunoni et al. 2012a) and has also been proposed as a therapeutic procedure in various diseases (Hoy and Fitzgerald 2010; Zyss; 2010; Benninger et al. 2010; Freitas et al. 2011; Brunelin et al. 2012; Brunoni et al. 2012b; Berlim et al 2013).

Tests on healthy adults demonstrated that tDCS can increase cognitive performance on a variety of tasks, depending on the area of the brain being stimulated. Application of tDCS has further been shown to improve verbal speed, fluency and naming with stimulation sites ranging from left and right temporal and frontal regions (Elder and Taylor, 2014). Improvement of working memory, learning, and long-term memory by tDCS has been demonstrated in healthy subjects (Kuo and Nitsche, 2012). Improvement of working memory in patients treated by tDCS was reported using the digit-span test and the go-no go task (Fregni et al., 2006; Boggio et al., 2007).

TDCS is also used as a therapeutic procedure to improve functions in adults with Mild Cognitive Impairment and Alzheimer's disease (Kulzoq et al., 2014; Hsu et al., 2015). A review of the research supports that individuals with Alzheimer's disease benefited from tDCS suggesting that noninvasive brain stimulation may be effective in individuals with cognitive decline due to physiological or pathological changes (Elder and Taylor, 2014; Hsu et al., 2015). Furthermore, research supports the possibility that tDCS may be able to reverse pathological brain activity and thereby delay the progression of disease in MCI. This study hopes to explore the ability of tDCS to enhance the cognitive functioning of Individuals with cognitive complaints.

CONCISE SUMMARY OF PROJECT: Up to 50 individuals with memory or cognitive complaints between the ages of 50 and 80 years will be recruited for this study and may be randomized into 1 of 2 groups. These groups are reasoning training following transcranial direct current stimulation (tDCS) and reasoning training following sham transcranial direct current stimulation. The primary hypothesis is that individuals receiving tDCS prior to brain training will have a stronger response to brain training than those in the sham tDCS group.

Response to training will be measured by improved cognitive function and neural change as measured by standardized and experimental measures of cognition, MRI and EEG. A group level comparison will be done to compare the groups. Each group may consist of up to 25 participants. Participants will be comprehensively screened to rule out individuals who may have cognitive complaints which may be due to other issues such as depression, brain injury or possible dementia. Participants will be recruited from Center for BrainHealth database, as well as through flyers handed out to members of the community who attend lectures related to brain health and express an interest in future and ongoing research studies, and by means of advertisements placed in local newspapers, radio, television and magazines, and the Center for BrainHealth website. Additionally, some participants may be referred by Dr. Mary Quiceno at the Alzheimer's Disease Center (ADC) of University of Texas Southwestern Medical Center. Dr. Quiceno is study personnel who will be reviewing participant criteria for amnestic MCI in conjunction with the clinicians, and also oversees the ADC.

STUDY PROCEDURES: The experiments described below will be undertaken with the understanding and written consent of each subject. Participants will only include people who are fluent speakers of English, as not all of the standardized and experimental cognitive tests have been normed for non-English speakers. Participants may be asked to participate in the cognitive screening and/or reasoning training portions of the study. Investigators will be blinded to which group the participants are randomized. The procedures for the study are explained below:

- **Phone Screening (20 minutes)**

A phone screening will consist of a brief medical questionnaire to determine eligibility for the study. Individuals who are not native English speakers or who have a history of learning disability, stroke, cognitive impairment, epilepsy, brain tumors, major psychiatric illness, alcoholism and substance abuse will be excluded from the study. Individuals with uncontrolled diabetes, uncorrected hearing, uncorrected vision will also be excluded from the study, as well as glaucoma, and macular degeneration. Individuals with a score of four or above on the Ohio State University TBI Identification Method (Short Form), or those who have incurred a brain injury in the past year will be excluded. The AIRC MR screening questions will be asked verbally to ensure potential participant can take part in the imaging portion of the study, including certain MR-safe metals should metal be located outside of the radio-frequency coil, or deemed safe in the current 7T literature. Metal implants will be evaluated on a case by case basis by the AIRC Medical Director, and study PI to determine eligibility. Individuals who pass the phone screening will be asked for contact information of a family member to complete a memory questionnaire.

- **Clinical Dementia Rating Scale (Memory Questionnaire) (30 to 40 minutes)**

The Clinical Dementia Rating (CDR) can be completed on the phone with the potential participant's family member and then completed with the participant. It includes general questions about memory, daily function and life engagement. After completing the questionnaire, individuals may be invited to schedule a time for the cognitive screening.

- **Cognitive Screening and Neuropsychological Assessment (Approx. 180 minutes)**

A clinician from the Center for BrainHealth will consent the participant and answer any questions before beginning the screen. The screening will consist of a medical questionnaire and MMQ which participants are given to bring into the appointment, the Mini Mental State Examination (MMSE), Geriatric Depression Scale, Auditory Selective Learning, Wide Range Achievement Test (WRAT), Logical Memory (LM) subtest, and the California Verbal Learning Test (CVLT). Participants will also undergo hearing and vision screening. Further testing for neuropsychological assessment will include standard neuropsychological measures such as the Boston Naming Test (BNT), Controlled Oral Word Association Test, Digit Span Forward and Backward (DSFB), Delis-Kaplan Executive Function System, Trails A & B, Similarities, and the Wechsler Test of Adult Reading (WTAR). Testing will also include experimental measures such as the Test of Strategic Learning, and Verbal Problem Solving, a cognitive and physical activity questionnaire, the Cognitive Reserve Index questionnaire (CRIq), and demographic scale numbers as assessed by the NAM-POWERS-BOYD Occupational Scale. Neuropsychological testing will take place on three separate occasions, so that assessment is conducted pre and post reasoning training, and three months post training. The testing will be done at the Center for BrainHealth at 2200 W. Mockingbird Lane, Dallas, Texas. When a person has been seen at the ADC within the past six months, the Cognitive Screen and Neuropsychological Assessment will be shortened. Standardized neuropsychological tests will be accessed from the ADC with their permission, in order to shorten the assessment time. While participants are not being referred from Baylor AT&T Memory Center, if they have undergone testing during the past six months and would like to offer consent to have these neuropsychological batteries accessed, they will be able to do so at the consent process. At the initial neuropsychological assessment, participants will initial a portion of the consent form that indicates their willingness to undergo genotyping, with genetic information collected via a buccal swab. This is a simple procedure in which a participant's saliva is collected on a swab similar to a cotton tip swab, and sealed in a container identified with them individually and preserved for analysis. No blood sample is required. Samples will be sent to Inova Fairfax Hospital for genotyping purposes. Some participants who have already participated in the testing will be called back if they indicate willingness to the additional procedure. At the reconsent, these participants will indicate that they will only be offering a saliva sample at the time of the consent by initialing a statement on the new form, in addition to a new HIPAA form. Both consent forms will be kept for these participants, based on study procedures that were agreed to at the time of their initial consent.

All participants who agree to participate in reasoning training will undergo EEG, and Magnetic Resonance evaluation before and after training.

- EEG (Approx. 90 Minutes)

Each participant may undergo up to three EEG sessions, before beginning the study, at completion of the study, and three months after completing the study. Each EEG testing session may last from 60 to 90 minutes, depending upon the pace of the participant response times. All skin preparation equipment coming into contact with one's skin is thrown away after a single use, and electrodes and caps are cleaned and disinfected immediately after

use in accordance with published guidelines. EEG experiments will be conducted at the Center for BrainHealth.

- Phase 1 (Approx. 30 minutes). The electrode cap will be placed on the participant's head. Though the cap itself causes no more physical discomfort than a lycra swimcap, the application process takes time because all electrodes (up to 128) must be able to read the electrophysiological responses from the participant's scalp with a specific level of accuracy (5 kOhms). To achieve this level electrolyte gel will be added to the participant's cap. Once this level is achieved for 95% of the electrodes the experiment will begin.
- Phase 2. (Approx. 30 minutes). The participant will be asked to sit as still as possible and attend to the words/pictures that follow. For each task, the participant will be given instructions specific to that task. Because of the noise potentially recorded with neurological data, participants will see many repetitions of the same stimuli. Participants will be instructed to push the yes/no button or button 1/button 2 on the response box to indicate their response. The stimuli will be presented in blocks of 5-10 min. 2-3 minute breaks will be given between blocks for participants to rest if desired.
- Phase 3. (Approx. 5 minutes). Once the experiment has ended, the cap will be carefully removed. Participants will be offered a towel to dry their hair, and given the opportunity to wash their hair if desired.
- Debriefing. (Approx. 2-5 minutes). Participants are told about the study, and given documents pertaining to the reasoning training, and other appointments. They will be given an opportunity to ask the investigator questions about the study and their participation. They will then be thanked and debriefed.

- Magnetic Resonance Evaluation (Approx. 75 Minutes)

Participants who clear the MR safety screening will complete two MR sessions per time points (i.e. pre and post reasoning training) in the study. The first scan will be conducted at 3T Philips Acheiva Scanner (30 minutes) and the second scan will be done on 7T Philips scanner (about 45 minutes) for a total of 60 minutes. For both scans, the participant will be asked to stay still and awake in the scanner, with head placed in a pad-cushioned coil. The scanner normally makes a loud noise during the procedure, so the participant will wear hearing protection (ear plugs) for the scan. While in the scanner, the participant can be heard and seen by the technologist performing the scan. For further safety, a rubber socket will be wrapped around one of the fingers of the participant to allow monitoring of the heart rate and blood oxygen level during the scan. The scanner is located at the Advanced Imaging Center, UTSW, 2201 Inwood Rd., Dallas TX 75390. Imaging and testing may be done on separate days to facilitate scheduling and so as not to over-tire the participants.

Magnetic Resonance Imaging (MRI) – The MRI session will be conducted on 3T Philips Acheiva scanner. The MRI scan protocols include high resolution T1 image (MPRAGE) Diffusion Tensor Imaging (DTI), pseudo-Continuous Arterial Spin Labeling (pCASL), Phase Contrast (PC) and TRUST MRI. The total scan time will be 30 minutes.

Magnetic Resonance Spectroscopy (MRS) – The MRS session will be conducted on 7T scanner. The MR protocols on 7T include a 31P MRS. The scan time will be 45 minutes.

- tDCS (25 minutes each session, 200 minutes total)

Prior to the reasoning training, participants will undergo tDCS. Participants will receive 20 minutes of tDCS using 2mA or less targeting the inferior frontal gyrus prior to each of their 8 reasoning training sessions for a total of 160 total combined minutes. This time does not include set up time which should take no more than 5 minutes each session (an additional 40 minutes for all sessions). For the sham tDCS group, the device will be turned off after 30s. These parameters for sham stimulation were chosen based on previous reports that the perceived sensations on the skin, such as tingling, usually fade out in the first 30s of active tDCS (Nitsche et al., 2003b; Paulus, 2003). During stimulation, there will be a control task to ensure that participants are all involved in the same level of cognitive stimulation during training. During each of the twenty minute sessions they will be presented with a section of one of the British Broadcasting Corporation (BBC) series entitled Planet Earth. The series is a popular nature documentary ([https://en.wikipedia.org/wiki/Planet_Earth_\(TV_series\)](https://en.wikipedia.org/wiki/Planet_Earth_(TV_series))) from 2006 which is moderately stimulating and entertaining, without requiring high resources and causing participants to tire prior to reasoning training. We think it is important than participants are engaging the same cortical network while being stimulated, to ensure variance is due largely to tDCS group assignment. A different episode will be presented each time, with care not to select anything which may be overly arousing for most participants. All session will be administered at Center for BrainHealth, 2200 W. Mockingbird Lane, Dallas, Texas 75235.

The tDCS and tDCS sham sessions will be delivered for 20 minutes immediately prior to each of the 8 separate reasoning training sessions.

- Reasoning Training (60 minutes)

Intervention protocol will encompass reasoning training (described below). One group will receive reasoning training following transcranial current stimulation (tDCS), the second group will receive sham tDCS.

- Reasoning training alone: Brain training for this group will be delivered in small groups of 3-5 individuals over a four-week period (two 1-hour session per week – total 8 hours). The training is strategy based rather than content-based so that the focus is not content specific or situation dependent. Furthermore, gist-based reasoning has been linked to frontal lobe activation and to measures of executive function. Potentially, the learned strategies could be applied across a variety of living contexts such as attending lectures, going to the movies, following new stories, planning and carrying out a project, and understanding brochures outlining changes in health care benefits, to name a few. The strategy instruction is

hierarchical and dynamically interdependent, with each strategy building upon previous strategies to transform the concrete meaning into abstracted gist-based meanings through reasoning and inferencing. Constructing meaning at a higher level of abstraction promotes learning which is more efficient and long lasting. Participant will be given homework to complete between each group session. The take home activities are to provide opportunities for the participants to practice the strategies. Groups will be conducted by trained clinicians at UTD Center for BrainHealth or at locations in the community. Participants will be evaluated prior to the beginning of the 8 intervention sessions, at its conclusion, and three months post.

- Participants will receive either tDCS or sham tDCS for 20 minutes prior to reasoning training.

CRITERIA FOR INCLUSION OF SUBJECTS: Selection criteria will include healthy male and female adults between the ages of 50 to 80 years, with cognitive complaints in the absence of dementia. Subjects to be screened and enrolled may be individuals in the community who respond to flyers handed out at the lectures related to brain health, and who respond to advertisements in local newspapers, radio, television and magazines. Selection criteria may also include participants who can tolerate at least hour long training sessions, who can participate in tasks involving motor abilities such as use of at least one arm and hand, those individuals with a score of three or below on the Ohio State University TBI Identification Method (Short Form), provided the injury was not in the last year, and who can safely have an MRI, including certain MR-safe metals should metal be located outside of the radio-frequency coil, or deemed safe in the current 7T literature. Metal implants will be evaluated on a case by case basis by the AIRC Medical Director, and study PI to determine eligibility.. No racial/ethnic groups will be excluded, although the patients must be able to speak, read, and comprehend English well enough to participate in the testing and training sessions, since the assessments are not normed or translated in other languages at this time.

CRITERIA FOR EXCLUSION OF SUBJECTS:

Subjects will be screened for any condition or illness that would interfere with participation or make participation potentially harmful. Individuals who have any significant health, neurological, or psychiatric illness, or history of substance abuse will be excluded. Individuals are not appropriate for the study if they meet any of the following criteria: someone who is left-handed, not proficient in reading, comprehending, and speaking English, has pre-existing cerebral palsy, females who are not post-menopausal, mental retardation, autism, epilepsy, schizophrenia, pervasive developmental disorder, thyroid diseases, diabetes, claustrophobia, pregnancy, non-correctable vision problems. Individuals with major depression, psychosis, active behavioral disorder, uncontrolled epilepsy, and individuals with a score of four or above on the Ohio State University TBI Identification Method (Short Form), or those who have incurred a brain injury in the past year will be excluded. Participants will not be included in the absence of cognitive complaints.

In addition, participants will be administered a standard MRI prescreening form (attached as UT Southwestern Advanced Imaging Research Center (AIRC) MAGNETIC RESONANCE

(MR) PROCEDURE SCREENING FORM FOR RESEARCH SUBJECTS) to assess the presence of any MR contraindications (i.e., unsafe metal or medical devices within/on the body) and to screen for significant health, neurological, or psychiatric illness and for a history of substance abuse, including alcohol. Exclusions for metal safety include questionable ferrous implants, bullets, BB's, shrapnel, any metal within the volume of the radio-frequency coil unless it is currently represented in the literature as safe at 7T levels.

SOURCES OF RESEARCH MATERIAL: Materials to be obtained for research purposes can include cognitive test data, neuropsychological test data, physical assessment data, language skills test data, health records, imaging data. Center for BrainHealth at The University of Texas at Dallas will obtain IRB approval from their institution and UTSouthwestern. Training sessions will take place at the Center for BrainHealth, or through online training sessions. Data from these activities will be recorded at Center for BrainHealth and UTSouthwestern Imaging Center and housed at BrainHealth.

RECRUITMENT OF SUBJECTS: The Research Coordinators at the Center for BrainHealth may distribute flyers to members of the community who attend lectures and state an interest in future and ongoing research. In addition, the Center for BrainHealth will potentially place advertisements in local newspapers and magazines, and on the Center for BrainHealth website and social media accounts to reach other members of the community also interested in future and ongoing research. The Center for BrainHealth will schedule assessment and study procedures for individuals who respond to the aforementioned flyers and ads. Study coordinators and investigators involved in this study will have contact with the participants throughout this study. If the patient agrees to participate and meets the preliminary study criteria, then informed consent will be obtained during the first meeting at the Center for BrainHealth. The patient must be able (of age and cognitively competent) to sign the informed Consent and HIPAA Authorization. The subjects will be provided detailed information about the study including purpose, procedures, and possible risks and benefits of participating, their time commitment to the study, as well as a copy of consent forms, and study coordinator contact information.

POTENTIAL RISKS

There are no known risks associated with the behavioral and psychological testing other than fatigue and frustration. If the participant's responses to questionnaires or the information they provide to study personnel indicate suicidal thoughts or actions, the researchers are obligated to notify authorities. They will refer the participant to a psychiatrist. There are no known risks or adverse effects resulting directly from exposure to magnetic fields and radio frequency energy used in this study other than a feeling of claustrophobia, fatigue or discomfort from lying still during the scanning process. Although there is no evidence of any risk to pregnant women, we will exclude women who are pregnant or suspect they may be pregnant.

Exposure to high magnetic fields may have effects on the normal electrical activity of the body including changes in nerve and heart function. Changes in the heart rate or rhythm could occur. Blood pressure, temperature, and pulse rate may change. Studies with an 8 Tesla MRI have not shown any significant effects.

The participants will be asked not to move the head quickly in the magnetic field to avoid potential sensation of dizziness, occurring in 30% or more of subjects. The participants may experience a metallic taste while entering or leaving the scanner. This is also a relatively

common sensation. The participants may experience a headache during or after the scan. This is infrequent and occurs in about 5% of volunteers. Another less common occurring is seeing tiny light flashes when the eyes are closed. In studies at 8 Tesla, 1 subject out of 200 has vomited as the result of being in the scanner.

Exposure to the rapidly changing magnetic fields could cause twitching of the subject's muscles. This effect, known as peripheral nerve stimulation (PNS), is temporary.

As with all MRI, any metal in the body or in clothing represents a risk. Metallic objects can be accelerated by the magnetic field and become dangerous. A metal implant or foreign object in the body could be displaced by the magnetic field. There can be increased heating near metal structures. Safety screening for unsafe metals by the PI and AIRC Director in conjunction with the 7T development plan will ensure this risk is minimized. Potential risks of EEG are possible scalp irritation resulting from the cap of sensors, boredom and fatigue. If the participant becomes excessively uncomfortable, the experimenter will stop the experiment at any time.

Participants undergoing tDCS may experience the following side effects but such are still considered to represent a minimal risk. 1) The most common side effect is temporally local redness of the skin direct under the electrode. This disappears within 1 hour. 2) They may experience itching at the site of the electrode, which also passes within an hour. 3) A small number of patients have a slight feeling of dizziness when starting the stimulation. This lasts only a few seconds and does not affect balance after stimulation. 4) Very rarely, temporary skin damage, or a burn may occur under the electrode. This gives a darkening or peeling of the top layers of skin, which normalizes after a week and heals. The size of such etch is a few millimeters. This is harmless, however, with the current that we will handle, this risk is minimal. 5) On the safety side, transcranial direct current stimulation is considered safe.

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

SUBJECT SAFETY AND DATA MONITORING: The risks associated with specific study procedures will be thoroughly explained to participants. The risks of the cognitive assessment will be mitigated by using highly trained personnel who provide encouragement; schedule breaks, and provide a supportive environment for the study participant. The project staff will explain all procedures, including the time required. Care will be taken to minimize any feelings of anxiety and discomfort that may be aroused. The patients will not be pushed to perform beyond their capacities. They will be encouraged to take breaks if they become tired or frustrated. The participant will have the option to terminate participation at any time during the study. Participants will be encouraged to put on scrubs (provided by MR facility) to minimize the danger of missed metal items. During the fMRI, subjects will be able to communicate through the intercom built into the scanner. The procedure will be stopped if the subject is unable to complete the study or shows any signs of intolerance such as frequent movements. Reassurance will be provided as needed and they will be reminded that their continued participation in the study is completely voluntary. In the event of severe adverse effects (e.g. headache, nausea, ear problem

due to noise), participants will be removed from the study and appropriate follow-up instituted. Potential heat tissue is present in all magnetic resonance imaging. The amount of power is monitored with appropriate built-in instrumentation to assure the specific absorption rate (SAR) is under FDA standards. In any event of system failure or problems scanning will stop.

Participants will be monitored by a clinician during administration of tDCS. Should the participant become dizzy or experience other side effects during the procedure, reassurance will be provided and they will be encouraged to continue. In the case of a itching or burning sensation, participants will be encouraged to move the arm band, and inform researchers of any irritation. If necessary, the procedure will be discontinued. If there is a burn which occurs that is evident to participant or researchers and warrants treatment, the participant will be referred to seek immediate treatment with the Urgent Care center, or follow up with their primary care physician.

PROCEDURES TO MAINTAIN CONFIDENTIALITY: Every effort will be made to maintain the confidentiality of study records. Only the researchers will have access to any personally identifying information, that is, contact information for each participant (i.e., an email address or phone number). This information will not be stored with the participant data. An identification number will be assigned to each participant so that it will be possible to identify information to be shared with other researchers as described in the HIPAA. In data analysis, each participant will be identified by this number. All research materials with identifiable data, consisting of detailed health questionnaires, neuropsychological testing, and consent and HIPAA forms, will be kept in locked cabinets in the Center for BrainHealth at UTD and imaging data obtained from UTSW will be stored at UTD following research compliance standards. Genetic information will be sent to Inova Fairfax Hospital for genomic analysis to identify candidate genes. Participant identifying information, such as name, address, and phone number will not be provided to the researcher at this university. Some other testing information may be provided for the purpose of understanding genetic protection and risk factors. The data from the study may be published, but all information will be deidentified and compliant with research confidentiality standards. The confidentiality of the data will be maintained within the legal limits. Only associates listed on the study will have access to identifying data. The Research Coordinator, the Principal Investigator, and co-investigators will have access to the data and to the codes, along with designated research associates. The researchers will destroy the personal identifiers upon completion of data collection for the study.

POTENTIAL BENEFITS: Participants may not benefit from enrolling in this study. However, they may benefit from the training sessions by improving their thinking ability, memory and learning skills and by feeling an increase in self-esteem, as a result. In addition, the information obtained from this pilot study may be of benefit to patients in future, as the investigators may gather more information about the interventional strategies to help healthy adults, in addition to risk and protection factors which may be part of genetic profiles.

RISK/BENEFIT ASSESSMENT: The disadvantages to being in this study include: time commitment, travel, and the physical and emotional challenges related to assessments and trainings. The maximum time planned for each of the MRI/MRS scan is 1 hour and each of neuropsychological and experimental behavioral assessment session is up to 2 hours not including time for commuting and scheduling for a total of 6 hours for participating in the study. Although the 7T MRI scanner is not FDA approved for clinical use, the scanner will be operated

within the FDA guidelines for high-field imaging. The procedures and training sessions could take less time, but the investigators want to prepare the participants for the possibility of the maximum time commitments. TDCS is a non-invasive technique which has been shown to be safe in healthy subjects in several research centers in previous investigations, with no impact to participant well-being. Individuals with a history of seizures, pregnancy, cardiac history or those who have a pacemaker will be excluded as a precaution. A referral plan is in place for those who have topical skin damage from tDCS. There is a risk of breach of confidentiality, although investigators are taking careful precautions to prevent this. Participants are informed of the risks prior to signing the consents.

BIOSTATISTICS:

Our primary hypotheses for all outcome measures, including imaging and EEG, involve interactions of experimental group with pre- and post-assessment time periods. We expect that tDCS-SMART will have larger post-training improvements for behavioral outcomes, EEG components, and imaging biomarker changes relative to tDCS-SHAM. These will be assessed by simple interaction tests in general statistical linear mixed models with concerted efforts to control a false positive rate inflation from multiple testing. For the latter we will utilize some modality-specific methods (e.g., conditional cluster-level inference for imaging), in addition to false discovery rate control.

Fifty participants will be recruited for this study, 25 in each group. Outcome measures, including imaging and EEG will be obtained to assess the efficacy of tDCS for a larger clinical trial. This number is based on a relatively large effect size taken from a meta-analysis of tDCS studies summarized in Price et al. (2015) Brain Stimulation, wherein some Hedge's g values were in the 0.9-1.0 range for some verbal memory and fluency measures. Given those values, we obtain a power level of 0.8 for single degree-of-freedom interaction tests. For those outcomes having lower power, we will obtain accurate effect sizes for a larger trial."

References

Alsop D.C. and Detre J.A. (1996). Reduced Transit-Time Sensitivity in Noninvasive Magnetic Resonance Imaging of Human Cerebral Blood Flow. *Journal of Cerebral Blood Flow & Metabolism*, 16, 1236–1249. doi:10.1097/00004647-199611000-00019

Altmann, A., Tian, L., Henderson, V.W., Grecius, M.D., Sex Modifies the APOE-Related Risk of Developing Alzheimer's Disease. *Ann Neurol*, 75 (4): 463-73. Doi:10.1002/ana.24135

Anand, R., Chapman, S.B., Rackley, A., Keebler, M., Zientz, J., & Hart, J., Jr. (2011). Gist reasoning training in cognitively normal seniors. *International Journal of Geriatric Psychiatry*, 26 (9), 961-968. Doi:10.1002/gps.2633

Aslan S., Xu F., Wang P.L., Uh J., Yezhuvath U.S., van Osch M., Lu H. (2010). Estimation of labeling efficiency in pseudo continuous arterial spin labeling. *Magn Reson Med.*, 63(3), 765-71.

Ball, K., Berch, D.B., Helmers, K.F., Jobe, J.B., Leveck, M.D., Marsiske, M., Morris, J.N., Rebok, G.W., Smith, D.M., Tennstedt, S.L., Unverzagt, F.W., Willis. S.L. (2002). Effects of Cognitive Training Interventions with Older Adults: A Randomized Controlled Trial. *JAMA*, 2088 (18); 2271-2281.

Benninger, D. H., Lomarev, M., Lopez, G., Wassermann, E. M., Li, X., Considine, E., & Hallett, M. (2010). Transcranial direct current stimulation for the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 81(10), 1105-1111. doi: 10.1136/jnnp.2009.202556

Berlim, M. T., Van den Eynde, F., & Daskalakis, Z. J. (2013). Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *J Psychiatr Res*, 47(1), 1-7. doi: 10.1016/j.jpsychires.2012.09.025

Boggio, P.S., et al. (2007). Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression. *J Affect Disord*, 101(1-3), p. 91-8.

Brunelin, J., Mondino, M., Haesebaert, F., Saoud, M., Suaud-Chagny, M. F., & Poulet, E. (2012). Efficacy and safety of bifocal tDCS as an interventional treatment for refractory schizophrenia. *Brain Stimul*, 5(3), 431-432. doi: 10.1016/j.brs.2011.03.010

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., . . . Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul*, 5(3), 175-195. doi: 10.1016/j.brs.2011.03.002

Brunoni, A. R., Zanao, T. A., Ferrucci, R., Priori, A., Valiengo, L., de Oliveira, J. F., . . . Fregni, F. (2013). Bifrontal tDCS prevents implicit learning acquisition in antidepressant-free

patients with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*, 43, 146-150. doi: 10.1016/j.pnpbp.2012.12.019

Elder, G.J., Taylor, J.P. (2014). Transcranial magnetic stimulation and transcranial direct current stimulation: treatments for cognitive and neuropsychiatric symptoms in the neurodegenerative dementias? *Alzheimers Res Ther*. 6(9), 74. doi: 10.1186/s13195-014-0074-1

Fregni, F., et al. (2006). Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. *Depress Anxiety*, 23(8), 482-4.

Freitas, C., Mondragon-Llorca, H., & Pascual-Leone, A. (2011). Noninvasive brain stimulation in Alzheimer's disease: systematic review and perspectives for the future. *Exp Gerontol*, 46(8), 611-627. doi: 10.1016/j.exger.2011.04.001

Geda, Y.E., Topazian, H.M., Roberts, L.A., Roberts, R.O., Knopman, D.S., Pankratz, S., Christianson, T.J.H., Boeve, B.F., Tangalos, E.G., Ivnik, R.J., and Petersen, R.C. J. (2011). Engaging in Cognitive Activities, Aging and Mild Cognitive Impairment: A Population-Based Study. *Neuropsychiatry Clin Neurosci*. 23(2), 149–154. doi:10.1176/appi.neuropsych.23.2.149. Hoy, K. E., & Fitzgerald, P. B. (2010). Brain stimulation in psychiatry and its effects on cognition. *Nat Rev Neurol*, 6(5), 267-275. doi: 10.1038/nrneurol.2010.30

Hsu W-Y., Ku Y., Zanto T.P., Gazzaley A. (2015). Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis. *Neurobiology of Aging*, 36(8) 2348–2359. doi:10.1016/j.neurobiolaging.2015.04.016

Jobe, J.B., Smith, D.M., Ball, K., Tennstedt, S.L., Marsiske, M., Willis, S.L., Rebok, G.W., Morris, J.N., Helmers, K.F., Leveck, M.D., Kleinman, K. (2001). ACTIVE: a cognitive intervention trial to promote independence in older adults. *Control Clin Trials*, 22 (4), 453-79.

Kulzow, N., et al. (2014)., An object location memory paradigm for older adults with and without mild cognitive impairment. *J Neurosci Methods*, 237, 16-25.

Kuo M.F., Nitsche M.A. (2012). Effects of transcranial electrical stimulation on cognition. *Clin EEG Neurosci.*, 43(3),192-9. doi: 10.1177/1550059412444975.

Lei H., Ugurbil K., Chen W. (2003). Measurement of unidirectional Pi to ATP flux in human visual cortex at 7T by using in vivo 31P magnetic resonance spectroscopy. *PNAS* 100(24), 14409-14.

Mahncke, H.W., Connor, B.B., Appelman, J., Ahsanuddin, O.N., Hardy, J.L., Wood, R.A., Joyce, N.M., Boniske, T., Atkins, S.M., Merzenich, M.M. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: A randomized, controlled study. *PNAS*, 103 (33): 12523-12528.

Matsumoto, J., Fujiwara, T., Takahashi, O., Liu, M., Kimura, A., & Ushiba, J. (2010). Modulation of mu rhythm desynchronization during motor imagery by transcranial direct current stimulation. *J Neuroeng Rehabil*, 7, 27. doi: 10.1186/1743-0003-7-27

Meron, D., et al. (2015). Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability. *Neurosci Biobehav Rev*.

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 Stimul*, 1(3), 206-223. doi: 10.1016/j.brs.2008.06.004

Nitsche, M. A., & Paulus, W. (2011). Transcranial direct current stimulation--update 2011. *Restor Neurol Neurosci*, 29(6), 463-492. doi: 10.3233/RNN-2011-0618

Nitsche, M.A. Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F., Paulus, W. (2003). Pharmacological Modulation of Cortical Excitability Shifts Induced by Transcranial Direct Current Stimulation in Humans. *Journal of Physiology*. 553(1), 293–301. doi: 10.1113/jphysiol.2003.049916

Polania, R., Paulus, W., & Nitsche, M. A. (2012). Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Hum Brain Mapp*, 33(10), 2499-2508. doi: 10.1002/hbm.21380

Ren J., Sherry A.D., Malloy C.R. (2014). Amplification of the effects of magnetization exchange by 31 P band inversion for measuring adenosine triphosphate synthesis rates in human skeletal muscle. *Magn Reson Med*. doi: 10.1002/mrm.25514.

Ren J., Sherry A.D., Malloy C.R. (2015). (31) P-MRS of healthy human brain: ATP synthesis, metabolite concentrations, pH, and T1 relaxation times. *NMR Biomed*, 28(11), 1455-62.

Ren J., Yang B., Sherry A.D., Malloy C.R. (2015). Exchange kinetics by inversion transfer: integrated analysis of the phosphorus metabolite kinetic exchanges in resting human skeletal muscle at 7 T. *Magn Reson Med*, 73(4), 1359-69.

Richardson, J., et al.(2014) Feasibility of using high-definition transcranial direct current stimulation (HD-tDCS) to enhance treatment outcomes in persons with aphasia. *NeuroRehabilitation*.

Sridharan D., Levitin D.J., and Menon V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *PNAS*, 105(34), 12569–12574. doi: 10.1073/pnas.0800005105

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist*, 17(1), 37-53. doi: 10.1177/1073858410386614

Vemuri, P., Lesnick, T.G., Przybelski, S.A., Knopman, D.S., Roberts, R.O., Lowe, V.J., Kantarci, K., Senjem, M.L. Gunter, J.L., Boeve, B.F., Petersen, R.C., and Jack, C.R. Jr. (2012). Effect of Lifestyle Activities on Alzheimer Disease Biomarkers and Cognition. *Ann. Neurol.*, 72, 730–738. doi: 10.1002/ana.23665

Vemuri, P., Lesnick, T.G., Przybelski, S.A., Knopman, D.S., Machulda, M., Lowe, V.J., Melke, M.M., Roberts, R.O., Gunter, J.L., Senjem, M.L., Geda, Y.E., Rocca, W.A., Petersen, R.C., and Jack, C.R. Jr. (2016) Effect of intellectual enrichment on AD biomarker trajectories. *American Academy of Neurology*, 86, 1–8.

Xu F., Uh J., Brier M.R., Hart J., Yezhuvath U.S., Gu H., Yang Y., Lu H. (2011). The influence of carbon dioxide on brain activity and metabolism in conscious humans. *Journal of cerebral blood flow and metabolism*. 31, 58–67.

Zaehle, T., Sandmann, P., Thorne, J. D., Jancke, L., & Herrmann, C. S. (2011). Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. *BMC Neurosci*, 12, 2. doi: 10.1186/1471-2202-12-2