Promoting Adaptive Neuroplasticity in Mild Cognitive Impairment
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Note: this protocol has been edited to focus on study methods and to update terminology since the last IRB modification 11/14/2019. Some site-specific information has been removed to enhance clarity; the methods/procedures remain unchanged.

Objectives:

Alzheimer's disease (AD) threatens to overwhelm our national healthcare resources in the coming decades [1]. The VA Healthcare System will be disproportionately affected since virtually all of the 7.6 million Vietnam Veterans will turn 65 years old in the next decade [2] and the incidence rate of dementia doubles every 5 years after age 65 [3, 4]. To mitigate the impact of AD, efforts have focused on identifying at-risk participants as well as interventions that prolong functioning and delay conversion to AD. The diagnosis of mild cognitive impairment (MCI) identifies cognitively symptomatic individuals who are likely to convert to AD [5]. Unfortunately, there has been far less progress from an intervention standpoint as existing pharmacological agents have questionable impact on cognition and conversion rates and can carry troubling side-effects [6-8].

Non-pharmacologic interventions, such as cognitive rehabilitation, offer viable treatment options that are comparatively inexpensive and carry virtually no risk. Across a series of studies funded partially through the PI's VA Career Development Awards 1 and 2, we have demonstrated that mnemonic strategies, which are cognitive techniques that utilize semantic processing to increase the organization and structure of information, can improve MCI participants' learning and memory for ecologically relevant information, such as face-name [9] and object-location associations [10]. These behavioral improvements are accompanied by increased activation within the left anterior ventrolateral prefrontal cortex (avlPFC) [11]; a region that is critical for successful memory encoding [12, 13] and that is known to play a role in working memory [14] and semantic processing [15]. ***The primary limitations*** of our work to date are that (1) MCI participants have difficulty generalizing the mnemonic strategies to novel contexts, which is critical for improving everyday functioning, and (2) that not all participants show improvement. Data from our three independent data sets, two of which are randomized controlled trials, indicate that the ability to engage the left avlPFC is critical for mnemonic strategy generalization. Thus, ***the central premise*** of the proposed study is that non-invasive brain stimulation can enhance functioning in the left avlPFC, thereby inducing adaptive neuroplastic changes and increasing the efficacy of mnemonic strategy training in participants with MCI. We intend to use transcranial direct current stimulation (tDCS) for this purpose since it uses a weak electrical current to modulate neuronal excitability, is safe, and very well tolerated [16, 17]. Critically, ***tDCS has not been used in participants with MCI or paired with mnemonic strategy training***, facts that make the proposed study truly groundbreaking.

In the proposed randomized, double-blind study, participants will complete 5 consecutive treatment sessions in which they receive either active or sham tDCS targeting the left avlPFC in combination with mnemonic strategy training or a conversational control condition (autobiographical memory recall). Participants will complete both laboratory-based and real-world memory testing and complete a self-report questionnaire to examine strategy generalization. They will also undergo fMRI scanning before and after intervention, which will provide critical information about the underlying neural mechanisms, especially whether the targeted brain region (left avlPFC) does, in fact, mediate behavioral improvement. Persistence of memory improvement and fMRI changes will be examined at a 3-month follow-up.

Specific Aims/Hypotheses:

Specific Aim 1: Examine the cognitive benefits of tDCS on mnemonic strategy generalization. *Hypothesis 1: Participants receiving active tDCS will more successfully generalize mnemonic strategies, which will be reflected by significantly greater improvement on the outcome measures, when compared to those in the sham tDCS group. Active tDCS should also result in more persistent gains when measured at follow-up.*

Specific Aim 2: Examine neuroplastic changes associated with tDCS and mnemonic strategy training. *Hypothesis 2: The behavioral improvement is mediated by increased use of the left avlPFC, as measured by fMRI.* We predict that the active tDCS group will show greater training-related increases in left avlPFC activation than the sham group (post-training vs. pre-training), and that the magnitude of activation increase in this region will correlate with the magnitude of behavioral improvement on our ecologically relevant memory tests. Finally, we will use Granger causality analysis to examine effective connectivity changes between the left avlPFC and the remainder of the brain. The extent to which active tDCS results in long-term behavioral benefits will be reflected by stable activation and effective connectivity patterns at follow-up, versus a regression toward baseline in the sham group.

Specific Aim 3: Examine the relationship between working memory, semantic processing, and mnemonic strategy generalization. *Hypothesis 3: By increasing left avlPFC activation, active tDCS will also enhance working memory and semantic processing whereas sham will not.* Subsequent analyses will determine whether one or both of these cognitive processes is vital for mnemonic strategy generalization.

Methodology

Participants: We will recruit, enroll, and randomize up to 125 participants, age 50 and older, over a 4-year timeframe from the VA Ann Arbor Healthcare System, the University of Michigan Alzheimer's Disease Center, and the surrounding community (eg.TrialMatch through Alzheimer's Association). The study team may need to consent and screen as many as 225 participants to account for high screen failures. We are also utilizing internet resources, such as social media through local businesses and organizations (eg. Barnes and Noble Facebook page) for study recruitment purposes. The internet resources will only be used to propagate awareness of the study and to supply study member contact information for those that may be interested in study participation; these sites will not collect any data. Both veterans and non-veterans will be enrolled for the following reasons:

1) The 2010 Census data show that over 93% of all Veterans are male. However, aging is a universal process and females outlive males. There is no empirical or ethical justification for limiting enrollment to just males; in fact, the scientific integrity and ecological validity of the study would be compromised by the exclusion of females.

2) Non-Veteran enrollment must include both males and females in order to avoid confounding sex and military service. Enrollment is open to participants regardless of race, gender, or social status. These are the recruitment parameters outlined in the Merit Review application, which was approved by VACO.

Inclusion criteria: Participants will receive a diagnosis of MCI based on the Albert et al. criteria [5], which are considered the "gold standard" in the field. Specifically, participants will **1)** report a subjective decline in memory (report can also be provided by an informant), **2)** demonstrate objective impairment in memory (based on Neuropsychological testing), and **3)** remain independent in activities of daily living. All participants will be stable on nootropic medications for at least 1-2 months prior to study initiation.

Exclusion criteria: A history of **1)** contributory other neurological (e.g., epilepsy, moderate - severe traumatic brain injury) or medical conditions that are known to affect cognitive functioning; **2)** significant psychiatric conditions (e.g., moderate - severe depression, bipolar disorder, schizophrenia); **3)** sensory impairments that limit the ability to take part in the study; **4)** a significant history or current use of alcohol or drug abuse/dependence. Participants will also be screened to ensure MRI compatibility (assessed using the guidelines set forth by the American College of Radiology [78]); some of the criteria for which are also reasons for excluding someone from tDCS (e.g., metallic or electronic implants). Eligible participants who cannot undergo MRI will be enrolled in the study and will complete only the stimulation and behavioral portions of the study. We have successfully used this same approach in our previous RCTs.

Recruitment: As noted, participants will be recruited from both the VA Ann Arbor Healthcare system and the University of Michigan Alzheimer's Disease Center. The primary recruitment source for the VA will be the Neuropsychology Clinic (see letter of support from Dr. Buchtel). Two methods will be used to identify potential participants. First, we will review CPRS records for this clinic from the last 6 months in order to identify those diagnosed with MCI. Once identified, we will mail an "opt in" letter to such individuals that provides information about the study and the study team's contact information. Second, we will engage in prospective recruitment for newly diagnosed participants (or more remotely diagnosed participants who are re-evaluated). This will rely on provider referral in which the provider will 1) hand the patient an approved flyer or 2) ask the patient if the provider may inform our staff of their interest via in person contact, telephone, or VA-encrypted email. Flyers will also be posted within the clinic.

The primary recruitment site for non-Veterans will be the University of Michigan Alzheimer's Disease Center (MADC). The MADC recruits participants from several sources including its memory disorders clinic, community screening events, and external referrals. Participants interested in research are maintained in an IRB-approved database (IRB# HUM00000382), which is available to the PI and his study team (see letter of support from MADC Director Dr. Paulson).

While the study team will have a designated member for recruitment efforts, all members are likely to contribute to recruitment efforts. Dr. Hampstead personally reviews all relevant information and is the final authority on whether or not participants are brought in for screening/cognitive assessment.

Screening & Cognitive Assessment: After providing informed, written consent, participants will undergo a brief neuropsychological protocol to ensure they continue meeting MCI criteria as outlined above. This protocol includes standardized measures that are shown in the Table below. Other standardized measures may be added to the protocol to characterize the nature of the patient's cognitive functioning as necessary. The PI has used this same protocol in his previous RCTs, which will facilitate direct comparisons between current and previous studies. Total time is approximately 85-120 minutes.

Measures that will be used for both primary and secondary outcome assessment will be collected during this session. These include: the Object-location touchscreen test (OLTT), the face-name generalization test, ecologically relevant memory tests that require participants to recall the location of objects within our laboratory/suite and the names of novel staff members, and the multifactorial memory questionnaire [81]. The former tests are all developed by Dr. Hampstead and are critical for assessing the generalization of the trained technique(s) to novel information. We have integrated non-invasive eye-tracking technology, via the TOBII

demonstrating and quantifying training-related changes in cognitive processing following intervention. We may also include other ecologically relevant tasks (e.g., Ecological Memory Simulations; spatial navigation task) in order to fully evaluate generalization effects. Total time for these tasks is about 30-40 minutes. Thus, total testing time is approximately 2 hours – far shorter than standard clinical neuropsychological evaluations. The PI's extensive clinical and research experience indicates that participants tolerate this protocol well. However, they will be given breaks as necessary to ensure their comfort and allowed to discontinue at any point.

The entire study team(or as many members as are present) reviews the neuropsychological results to ensure participants meet inclusion criteria (Dr. Hampstead has the final decision on whether to include a patient). This occurs via weekly laboratory meetings (or more often as necessary) that are led by Dr. Hampstead. **Eligible participants move forward into the study, details of which are provided below.**

Measure	Description	Screening (pre-treatment)	Post treatment	Follow Up (3 month)
Montreal Cognitive Assessment (MOCA)	Gross screening measure for overall cognitive functioning (~5 minutes)	x		
Wechsler Test of Adult Reading (WTAR)	Single word reading-used to establish premorbid intellectual estimates (~ 3 minutes)	x		
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Brief Neuropsychological battery that includes indices of attention, visuospatial, learning, memory, and processing speed. (~20 minutes)	x		
Emory Short Version of Wisconsin Card Sorting Test (WCST)	Assesses the ability to identify possible solution strategies and abstract problem solving(~5-15 minutes)	x		
Trail Making Test	Measures of psychomotor processing (Trails A) and set shifting (Trails B) (~3-10 minutes)	x		
Figure Ground Test	Measure of visuospatial functioning (~10 minutes)	x		
Temporal Sequencing Task	Novel temporal memory task (~5 minutes)	x	x	x
Functional Activities Questionnaire (FAQ)	Evaluates patient's ability to perform everyday tasks (ie ADL/IADLS) (~3 minutes)	x		
Geriatric Depression Scale (GDS)	Evaluates current symptoms of depression (~ 3 minutes)	x		
Multifactorial Memory Questionnaire	Self-report questionnaire that assesses confidence, contentment, and knowledge of memory strategies. (~5-10 minutes)	x	x	x
Object Location Touchscreen Test (OLTT)	Assesses the ability to learn and remember the location of objects (~ 10 minutes)	x	x	x
Face-Name Generalization Test (FNGT)	Assesses the ability to learn and remember names and faces (~10 minutes)	x	x	x
Subtests of Ecological Memory Simulation	Assesses the ability to learn and remember ecologically relevant information in areas not targeted by the mnemonic strategy (~10-20 minutes)	x	x	x

Study Procedures: Participants who are deemed eligible will undergo a total of 7 sessions within a 2-week period of time. An additional assessment will be performed at 3-months in order to examine the persistence of the training effects. Some degree of flexibility is necessary with these time frames in order to accommodate both patient and MRI availability. If needed, through the University of Michigan Fleet Services, participants may be also offered transportation in a University-registered vehicle to and from research related activities only.

Session 1:

fMRI Scanning: Activation will be assessed using both memory encoding, working memory, and semantic processing paradigms. As noted in the above figure, participants will complete scanning during Sessions 1, 7, and 8.

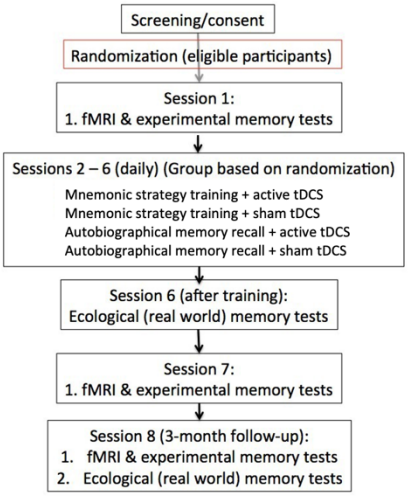
Memory encoding: Participants will complete functional runs during which they will encode novel stimuli from each of our experimental paradigms (face-name and object-location associations). Two repeated stimuli within each paradigm will be presented multiple times and will serve as the control condition. Novel stimuli will be used during each scanning session (i.e., Sessions 1, 7, 8). Run order will be randomized for each patient while stimulus list. The interaction contrast of list and time

is of primary interest (Novel (post-training > pre-training) > Repeated (post-training > pre-training) or similar contrast). *We refer to this as the encoding contrast hereafter.* Participants will complete a memory test consisting of these stimuli outside of the scanner.

Working memory: Participants will complete a standard n-back working memory paradigm, which requires participants to determine whether a given stimulus (e.g., a picture) was seen 2 stimuli ago (i.e., 2-back). In the 0-back control condition, participants simply push a button as each stimulus appears. The n-back paradigm is especially appropriate since a number of populations have shown improvement after prefrontal tDCS. The primary contrast of interest will examine the interaction between condition and time: (Post-training (2-back > 0-back) > Pre-training (2-back > 0-back). *We refer to this as the contrast for item working memory hereafter.*

Semantic processing: Participants will complete an additional semantic decision making task using the same 2-back format. The 2-back condition will require them to determine if a given picture is of the same semantic category (e.g., an animal) as the one presented 2 stimuli ago. Similar paradigms have effectively engaged the left avlPFC [80]. Using the same n-back design holds all task demands constant except for the addition of semantic processing. Thus, the primary contrast of interest will subtract out BOLD signal associated with working memory from the semantic task via the interaction contrast of task and time: (semantic (2-back post > 2-back pre) > item (2-back post > 2-back pre)). *We refer to this as the contrast for semantic processing hereafter.*

These paradigms allow us to directly examine the cognitive processes underlying mnemonic strategy use (Aim 2) as well as any tDCS-related improvements in these other cognitive abilities (Specific Aim 3).



General study design. fMRI scanning will occur during the encoding phase and will use novel stimuli each session, the order of which will be counterbalanced across participants. Alternate versions will be used and counterbalanced.

MRI Image Acquisition: All imaging will be performed at either the VA Research fMRI facilities or the fMRI laboratory located on North Campus at the University of Michigan. Total scan time will be approximately 60-75 minutes per session. Participants will also have the option to utilize the mock scanner at the University of Michigan. The mock scanner has been developed by the fMRI laboratory at the University of Michigan, and is used to get participants accustomed to a scanner environment. There are no magnetic fields associated with the scanner and no data will be collected from the mock session. Use of the mock scanner may require an additional 20 minute session, although we will try to add this on to the evaluation session. High-resolution anatomic images will be acquired using a 3D MPRAGE sequence with repetition time (TR) 2300 ms, echo time (TE) 3.9 ms, inversion time (TI): 1100ms, flip angle (FA) 8°, 176 sagittal slices of 1 mm thickness, in-plane resolution (IPR) 1x1 mm, in-plane matrix (IPM) 256x256, field of view (FOV) 256 mm. A FLAIR sequence may also be utilized to assess white matter hyperintensities. All *fMRI data* will be collected using T2*-weighted functional images acquired with a multi-band slice accelerated gradient-recalled echoplanar imaging (EPI) sequence with BOLD contrast and the following parameters: TR: 1000 ms, TE: 25 ms, FOV: 220 mm, FA: 50°, 56 axial slices of 2 mm thickness, IPR: 2.0×2.0 mm, IPM: 110×110, 32 channel head coil, 2mm isotrophic functional voxels. Resting state data have proven to be beneficial in understanding network-level changes in those with MCI. Time permitting, such data will be acquired using standard parameters (e.g., FOV = 220 mm; TR/TE 2000/25ms, flip angle = 60˚; 74 x 74; matrix size; bandwidth = 2164 Hz/pixel; 64 2.5mm interleaved axial slices covering the whole brain, 240 scan volumes). We will modify the above MRI-related parameters as necessary in order to optimize data quality and achieve study goals; such changes will occur after initial pilot testing and will be held constant throughout the trial thereafter.

Randomization: Participants will be randomized on a 1:1:1:1 ratio to either the combined active tDCS + mnemonic strategy training, sham tDCS + mnemonic strategy training, sham tDCS + autobiographical memory recall, or active tDCS + autobiographical memory recall groups using a blocked randomization schedule. Randomization will use the sealed envelope method in which a group assignment (i.e., a numeric code for the tDCS stimulation unit) is placed within a sealed envelope at the beginning of the study. Envelopes are then randomly shuffled and numbered with enrolled participants being assigned the next available number. In order to keep both participants and our staff blinded to study procedures, the PI had Soterix Medical Inc. program stimulation codes into the tDCS unit, such that half provide active and half provide sham stimulation. Study staff (i.e., research assistants/coordinators) will remain blinded until the data are analyzed.

Sessions 2 – 6:

All groups will undergo 5 training sessions on consecutive days. In order to facilitate participation, we will allow for weekend visits if necessary. Each session will last approximately 80 minutes. The first 10 minutes will be used to measure and place the tDCS electrodes. The cognitive intervention (i.e., mnemonic strategy training or autobiographical memory recall) will occur during the next 60 minutes (the first 20* minutes are concurrent with tDCS) and the final 10 minutes will be used to answer any questions. *note – an error in selecting codes such that the first 24 participants received 30 minutes of active or sham tDCS while the remaining participants received 20 minutes.

tDCS: Stimulation will be performed using a Soterix Medical Inc. tDCS unit (Clinical Trial system and HD stimulation unit) within a quiet room. Each unit automatically discontinues stimulation after the specified time has elapsed (here 20 or 30 minutes). The participant will complete a brief questionnaire about the nature and severity of any side effects (see tDCS Safety below) as well as whether they believe they received active or sham stimulation. The FDA considers these units investigational devices. Based on the safety information provided above, review of the scientific literature, and consultation with colleagues, we believe these devices are of non-significant risk (NSR).

The active tDCS protocol will provide a 30 second ramp-up period in which the electrical current is gradually increased, followed by 19 minutes of stimulation at 2mA, and finally a 30 second ramp down period during which the electrical current is gradually removed. This "dose" of tDCS is a reasonable starting place and has been used in two of the previous tDCS studies in participants with AD [71, 72].

The sham tDCS protocol will receive a 30 second ramp-up period to the full 2mA, followed immediately by a 30 second ramp down. This is an effective sham condition since it provides the sensation of stimulation but without measurable physiologic effects [16]. We will repeat this process during the 19th minute of "stimulation" in order to provide participants with a "recency" effect of stimulation.

Mnemonic strategy training condition: This phase of the training will begin at the same time as the tDCS stimulation and will persist for approximately 30 minutes after stimulation has ended. This approach capitalizes on the neuroplastic changes induced by tDCS and adaptively shapes them to reinforce the interactions necessary for successful strategy use. Participants will use the same 3-step **FRI** process described above. They will be required to independently develop the feature, reason, and image cues for each stimulus. A member of our research team will monitor and record each step of the process to ensure participant compliance. We will provide assistance and model appropriate cues as needed in order to promote successful strategy use. Participants will practice developing these cues with faces and names as well as objects and locations within each session.

Autobiographical Recall (control): This condition also begins at the same time as tDCS and persists for approximately 30 minutes after stimulation has ended. This approach acts as a control condition for the mnemonic strategy training by engaging participants in general conversation with our research team, thereby matching non-specific factors like engagement and total session time. Conversational prompts will be used to facilitate continuous dialogue if participants are unable to spontaneously generate conversation. For example, participants may be asked to discuss recent events in the news, daily life (their plans for the day/weekend, etc.), and/or historical events in their life (e.g., favorite childhood memory, their wedding day). A member of our research staff may also transcribe and subsequently analyze the dialogue for linguistic qualities by Linguistic Inquiry and Word Count or other related methods. This approach may be especially informative given that tDCS is being performed over the left inferior frontal gyrus (i.e., "Brocca's area"), which is known to be vital for speech production. Thus, it is possible that active tDCS vs. sham tDCS could facilitate speech output over the course of the 5 sessions (this possibility will be evaluated in exploratory analyses). It should be noted that we have established a method of preserving anonymity during this process; we will screen for potential identifiers listed by the Data Privacy and Security stipulations and remove all such identifiers during the transcription phase. We will then review the transcription immediately following the session to ensure there are no identifiers. In order to protect subjects' privacy, absolutely no identifiers will be recorded.

Conversations during the above sessions will be recorded using a VA approved and compliant audio digital recorder. Digital audio files will also be stored in patient files located in an encrypted virtual server on the Virtual Machine NetApp information system hard drive using Fips 40-2 validated software. This system is outlined in the approved Data Use Agreement for the study.

Session 7:

Approximately two or three days after the final training session (depending on scheduling limitations), participants will complete fMRI scanning using different versions of each type of stimuli. Participants will complete both primary and secondary outcome measures at this point as well.

Session 8:

Three months after Session 7, participants will return and will perform the ecological memory tests. They will then be escorted to the fMRI scanner, where they will perform alternate versions of our scanning paradigms. Participants will complete both primary and secondary outcome measures at this point as well.

Statistical Design:

The primary analytic technique will be regression using the SAS mixed procedure (PROC MIXED – or equivalent method), which allows the interdependence of observations to be modeled directly and can include subjects with missing data at one of the follow-up periods. PROC MIXED has the capacity to handle unbalanced data when the data are missing at random (skipped visits, patient dropout, etc). Each equation will model the change from baseline (Session 1) for one of the outcome measures of interest as a function of intervention group, post-training session (i.e., Session 7 or 8), and group*post-training session interaction. In addition, all models may include potential confounders that differ at baseline between the groups (at p=0.05*) even despite randomization (there should be few, if any, given the sample size). We will adjust p-values for significance level using the false discovery rate (FDR*). *Note – since the study began, the American Statistical Association released a position statement and associated special issue calling for the use of effect sizes and confidence intervals rather than strict p-value cut-offs. We will integrate this updated statistical conceptualization in our interpretation.

fMRI data analysis will be performed with standard neuroimaging programs (e.g., AFNI [72], FSL [73], BrainVoyager QX, SPM) and in-house programs written in Matlab (Natick, MA). Preprocessing: fMRI preprocessing will be performed according to standard methods. For group-level analyses, we will calculate voxelwise area-under-curve (AUC) in which the hemodynamic response is averaged across all voxels and time points for the contrasts described above (see fMRI scanning section). This has the benefit of providing a single value for each group in each session, thereby substantially reducing the number of contrasts and increasing power. We will examine the data in the two ways described below, using an FDR-corrected alpha.

1. The immediate post-training differences in activation change within this ROI will be examined using a 4 group X 2 time (Session 1 vs. 7) analysis of variance (ANOVA). The resulting interaction term will directly test our hypothesis that active tDCS will result in greater activation than will sham tDCS. A second such ANOVA will be performed to examine the long-term effects (i.e., Session 1 vs. 8), where the resulting interaction term will test our hypothesis that active tDCS results in a more persistent increase in activation relative to sham tDCS.
2. We will then correlate the change in activation for both the immediate and long-term effects with the corresponding average change in behavioral performance on our primary outcome measures of the OLTT and FNGT. Separate FDR corrected correlations will be performed for each group. These behavioral measures are completely independent of the fMRI data and, therefore, will provide an unbiased measure of the relationship between these variables. We predict that the active tDCS group will demonstrate more robust relationships between these variables than will the sham group.
3. To determine whether the activation changes for encoding are associated with item working memory and/or semantic processing, we will perform two separate conjunction analyses: (1) the item working memory contrast + encoding contrast; (2) semantic processing contrast + encoding contrast. These analyses will be performed within both groups using whole-brain activation.

Because we expect functional reorganization throughout the brain within both groups as a result of intervention, we intend to use Granger causality analysis (GCA) to examine changes in the effective connectivity between the left avlPFC ROI and the remainder of the brain.

Additional analyses will be completed using automated modeling software (currently in beta-version) that determines, at the individual participant level, how much electrical current reached the targeted brain region(s). This will allow us to correlate electrical current at the targeted brain region with both behavior and BOLD signal (i.e., "activation" via fMRI) and furthers our a priori intent to examine individual predictors of intervention response. Additional analyses will be completed using NeuroQuant (or comparable software) to obtain volumes of brain structures.

Additional analyses will be performed as necessary in order to fully characterize the nature of intervention-related changes.

Works Cited

1. Brookmeyer, R., et al., *National estimates of the prevalence of Alzheimer's disease in the United States.* Alzheimers & Dementia, 2011. **7**(1): p. 61-73.
2. VAplan, *Department of Veterans Affairs Strategic Plan – Refresh.* FY 2011-2015 (7/15/2010 edits).
3. Corrada, M.M., et al., *Dementia incidence continues to increase with age in the oldest old the 90+ study.* Annals of Neurology, 2010. **67**(1): p. 114-121.
4. Jorm, A.F. and D. Jolley, *The incidence of dementia: A meta-analysis.* Neurology, 1998. **51**: p. 728-733.
5. Albert, M.S., et al., *The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup.* Alzheimer's & Dementia, 2011. **7**(3): p. 270-279.
6. Daviglus, M.L., Bell, C.C., Berrettini, W., Bowen, P.E., Connolly, E.S., Cox, N.J., et al., *National Institutes of Health State-of-the-Science Conference Statement: Preventing Alzheimer's Disease and Cognitive Decline.* NIH Consens State Sci Statements, 2010 Apr 26-28. **27**(4): p. 1-30.
7. Diniz, B.S., et al., *To treat or not to treat? A meta-analysis of the use of cholinesterase inhibitors in mild cognitive impairment for delaying progression to Alzheimer's disease.* European Archives of Psychiatry and Clinical Neuroscience, 2009. **259**(4): p. 248-256.
8. Raschetti, R., et al., *Cholinesterase inhibitors in mild cognitive impairment: A systematic review of randomised trials.* Plos Medicine, 2007. **4**(11): p. 1818-1828.
9. Hampstead, B.M., et al., *Explicit memory training leads to improved memory for face-name pairs in participants with mild cognitive impairment: results of a pilot investigation.* J Int Neuropsychol Soc, 2008. **14**(5): p. 883-9.
10. Hampstead, B.M., et al., *Mnemonic strategy training improves memory for object location associations in both healthy elderly and participants with amnestic mild cognitive impairment: a randomized, single-blind study.* Neuropsychology, 2012. **26**(3): p. 385-399.
11. Hampstead, B.M., et al., *Activation and Effective Connectivity Changes Following Explicit-Memory Training for Face-Name Pairs in Participants With Mild Cognitive Impairment: A Pilot Study.* Neurorehabilitation and Neural Repair, 2011. **25**(3): p. 210-222.
12. Spaniol, J., et al., *Event-related fMRI studies of episodic encoding and retrieval: Meta-analyses using activation likelihood estimation.* Neuropsychologia, 2009. **47**(8-9): p. 1765-1779.
13. Köhler, S., et al., *Effects of left inferior prefrontal stimulation on episodic memory formation: A two-stage fMRI-rTMS study.* Journal of Cognitive Neuroscience, 2004. **16**(2): p. 178-188.
14. Nee, D., et al., *A meta-analysis of executive components of working memory.* Cerebral Cortex, 2013. **23**: p. 264-282.
15. Binder, J.R., et al., *Where Is the Semantic System? A Critical Review and Meta-Analysis of 120 Functional Neuroimaging Studies.* Cerebral Cortex, 2009. **19**(12): p. 2767-2796.
16. Nitsche, M.A. and W. Paulus, *Transcranial direct current stimulation - update 2011.* Restorative Neurology and Neuroscience, 2011. **29**(6): p. 463-492.
17. Stagg, C.J. and M.A. Nitsche, *Physiological basis of transcranial direct current stimulation.* Neuroscientist, 2011. **17**(1): p. 37-53.
18. Ferri, C.P., et al., *Global prevalence of dementia: a Delphi consensus study.* Lancet, 2005.

366(9503): p. 2112-2117.
19. *Atlanta VAMC Dementia Committee Recommendations Report.* 2009.
20. Yu, W., Ravelo, A., Wagner, T.H., Phibbs, C.S., Bhandari, A., Chen, S., Barnett, P.G. , *Prevalence and costs of chronic conditions in the VA Healthcare system.* Medical Care Research and Review, 2003. **60**(3): p. 146S-167S.
21. Alzheimer's Association [cited 2011 May 2]; Available from: www.alz.org/facts.
22. Petersen, R.C., *Mild cognitive impairment as a diagnostic entity. .* Journal of International Medicine, 2004. **256**: p. 183-194.
23. Petersen, *Mild cognitive impairment: Clinical characterization and outcome (vol 56, pg 303, 1999).* Archives of Neurology, 1999. **56**(6): p. 760-760.
24. Jack, C.R., *Alliance for Aging Research AD Biomarkers Work Group: structural MRI.* Neurobiology of Aging, 2011. **32**: p. S48-S57.
25. Brickman, A.M., Y. Stern, and S.A. Small, *Hippocampal subregions differentially associate with standardized memory tests.* Hippocampus, 2011. **21**(9): p. 923-928.
26. Strauss, E., Sherman, E.M.S., & Spreen, O. , *A compendium of neuropsychological tests: Administration, norms, and commentary – 3rd edition*. 2006, New York: Oxford University Press.
27. Jacova, C., et al., *Neuropsychological testing and assessment for dementia.* Alzheimers & Dementia, 2007. **3**(4): p. 299-317.
28. Schmand, B., et al., *Value of neuropsychological tests, neuroimaging, and biomarkers for diagnosing Alzheimer's disease in younger and older age cohorts.* J Am Geriatr Soc, 2011. **59**(1705-1710).
29. Cicerone, K.D., et al., *Evidence-based cognitive rehabilitation: Update review of literature from 1998 through 2002. .* Archives of Physical Medicine and Rehabilitation 2005. **86**: p. 1681-1692.
30. Cicerone, K.D., et al., *Evidence-Based Cognitive Rehabilitation: Updated Review of the Literature From 2003 Through 2008.* Archives of Physical Medicine and Rehabilitation, 2011. **92**(4): p. 519-530.
31. Jean, L., et al., *Cognitive Intervention Programs for Individuals With Mild Cognitive Impairment: Systematic Review of the Literature.* American Journal of Geriatric Psychiatry, 2010. **18**(4): p. 281-296.
32. Simon, S.S., J.E. Yokomizo, and C.M.C. Bottino, *Cognitive intervention in amnestic mild cognitive impairment: A systematic review.* Neuroscience and Biobehavioral Reviews, 2012. **36**: p. 1163-1178.
33. Stott, J. and A. Spector, *A review of the effectiveness of memory interventions in mild cognitive impairment (MCI).* International Psychogeriatrics, 2011. **23**(4): p. 526-538.
34. Li, H.J., et al., *Cognitive intervention for persons with mild cognitive impairment: A meta-analysis.* Ageing Research Reviews, 2011. **10**(2): p. 285-296.
35. Sitzer, D.I., E.W. Twamley, and D.V. Jeste, *Cognitive training in Alzheimer's disease: a meta-analysis of the literature.* Acta Psychiatrica Scandinavica, 2006. **114**(2): p. 75-90.
36. Verhaeghen, P., A. Marcoen, and L. Goossens, Improving memory performance in the aged through mnemonic training - a meta-analytic study. Psychology and Aging, 1992. **7**(2): p. 242-251.
37. Craik, F.I.M., Winocur, G., Palmer, H., Binns, M.A., Edwards, M., Bridges, K., Glazer, P., Chavannes, R., & Stuss, D.T. , *Cognitive rehabilitation in the elderly: Effects on memory. .* Journal of the International Neuropsychological Society 2007. **13**: p. 132-142.
38. Oswald., W.D., Rupprecht, R., Cunzelmann, T., & Tritt, K., *The SIMA-project: Effects of 1 year cognitive and psychomotor training on cognitive abilities of the elderly.* Behavioural Brain Research, 1996. **78**: p. 67-72.
39. Willis, S.L., et al., *Long-term effects of cognitive training on everyday functional outcomes in older adults.* Jama-Journal of the American Medical Association, 2006. **296**(23): p. 2805-2814.
40. Belleville, S., et al., *Training-related brain plasticity in subjects at risk of developing Alzheimer's disease.* Brain, 2011. **134**: p. 1623-1634.
41. Ramakers, I.H.G.B., et al., *The predictive value of memory strrategies for Alzheimer's disease*

in subjects with mild cognitive impairment. Archives of Clinical Neuropsychology, 2010. **25**(1): p. 71-77.
42. Stringer, A.Y., *Ecologically-oriented Neurorehabilitation of Memory Therapist Manual*. 2007, Los Angeles: Western Psychological Services.
43. Mayes, A., D. Montaldi, and E. Migo, *Associative memory and the medial temporal lobes.* Trends in Cognitive Sciences, 2007. **11**(3): p. 126-135.
44. Hampstead, B.M., et al., *Where did I put that? Participants with amnestic mild cognitive impairment demonstrate widespread reductions in activity during the encoding of ecologically relevant object-location associations.* Neuropsychologia, 2011. **49**: p. 2349-2361.

45. Hampstead, B.M., et al., *Mnemonic strategy training partially restores hippocampal activity in participants with mild cognitive impairment.* Hippocampus, 2012.
46. Bergmann, H., et al., *Distinct neural correlates of associative working memory and long-term memory encoding in the medial temporal lobe.* NeuroImage, 2012. **63**(989-997).
47. Kuhl, B., W. Bainbridge, and M. Chun, *Neural reactivation reveals mechanisms for updating memory.* The Journal of Neuroscience, 2012. **32**(10): p. 3453-3461.
48. Dennis, N.A., et al., *Effects of aging on the neural correlates of successful item and source memory encoding.* Journal of Experimental Psychology: Learning, Memory, and Cognition, 2008. **34**(4): p. 791-808.
49. Takahashi, E., K. Ohki, and D. Kim, *Diffusion tensor studies dissociated two fronto-temporal pathways in the human memory.* Neuroimage, 2007. **34**: p. 827-838.
50. Craik, F.I.M. and R.S. Lockhart, *Levels of processing: A framework for memory research.* Journal of Verbal Learning and Verbal Behavior, 1972. **11**: p. 671-684.
51. Baddeley, A., *Working memory: Looking back and looking forward.* Nature Reviews Neuroscience, 2003. **4**(10): p. 829-839.
52. Hillary, F.G., Genova, H.M., Chiaravalloti, N.D., Rypma, B., & DeLuca, J. , *Prefrontal modulation of working memory performance in brain injury and disease.* Human Brain Mapping 2006. **27**: p. 837-847.
53. Owen, A.M., Evans, A.C., & Petrides, M., *Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: A positron emission tomography study.* Cerebral Cortex, 1996. **6**: p. 31-38.
54. Cabeza, R., E. Ciaramelli, and M. Moscovitch, *Cognitive contributions of the ventral parietal cortex: an integrative theoretical account.* Trends in Cognitive Sciences, 2012. **16**(6): p. 338-352.
55. Daselaar, S.M., et al., *Posterior midline and ventral parietal activity is associated with retrieval success and encoding failure.* Frontiers in Human Neuroscience, 2009. **3**.
56. Postma, A., R.P.C. Kessels, and M. van Asselen, *How the brain remembers and forgets where things are: The neurocognition of object-location memory.* Neuroscience and Biobehavioral Reviews, 2008. **32**(8): p. 1339-1345.
57. Verwijk, E., et al., *Neurocognitive effects after brief pulse and ultrabrief pulse unilateral electroconvulsive therapy for major depression: A review.* Journal of Affective Disorders, 2012. **140**(3): p. 233-243.
58. Laxton, A.W., et al., *A Phase I Trial of Deep Brain Stimulation of Memory Circuits in Alzheimer's Disease.* Annals of Neurology, 2010. **68**(4): p. 521-534.
59. O'Reardon, J.P., H.B. Solvason, and P.G.e.a. Janicak, *Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial.* Biol Psychiatry, 2007. **62**(11): p. 1208-1216.
60. Naeser, M.A., et al., *Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open-protocol study.* Brain and Language, 2005. **93**(1): p. 95-105.
61. Brunoni, A.R., et al., *Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions.* Brain Stimulation, 2012. **5**(3): p. 175-195.
62. Fregni, F. and A. Pascual-Leone, *Technology insight: noninvasive brain stimulation in neurology - perspectives on the therapeutic potential of rTMS and tDCS.* Nature Clinical Practice Neurology, 2007. **3**(7): p. 383-393.
63. Kang, E.K., et al., *Non-invasive cortical stimulation improves post-stroke attention decline.* Restor Neurol Neurosci, 2009. **27**: p. 645-650.
64. Cerruti, C. and G. Schlaug, *Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought.* J Cogn Neurosci, 2009. **21**: p. 1980-1987.
65. Boggio, P.S., F. Bermpohl, and A.O.e.a. Vergara, *Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression.* J Affect Disord 2007. **101**: p. 91-98.
66. Fregni, F., et al., *Cognitive effects of repeated sessions of transcranial direct current stimulation in participants with depression.* Depress Anxiety 2006. **23**: p. 482-484.

67. Jo, J.M., et al., *Enhancing theworking memory of stroke participants using tDCS.* Am J Phys Med Rehabil, 2009. **88**(404-409).
68. Ohn, S.H., C.I. Park, and W.K.e.a. Yoo, *Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory.* Neuroreport, 2008. **19**: p. 43-47.
69. Fregni, F., et al., *Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory.* Experimental Brain Research, 2005. **166**: p. 23-30.
70. Boggio, P., et al., *Effects of transcranial direct current stimulation on working memory in participants with Parkinson's disease.* Journal of the Neurological Sciences, 2006. **249**: p. 31-38.
71. Boggio, P.S., et al., *Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer's disease.c.* J Neurol Neurosurg Psychiatry, 2009. **80**: p. 444-447.
72. Boggio, P.S., et al., *Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease.* Brain Stimulation, 2012. **5**: p. 223-230.
73. Ferrucci, R., et al., *Transcranial direct current stimulation improves recognition memory in Alzheimer's disease. .* Neurology, 2008. **71**: p. 493-498.
74. Elmer, S., et al., *Direct current induced short-term modulation of the left dorsolateral prefrontal cortex while learning auditory presented nouns.* Behav Brain Funct, 2009. **5**: p. 29.
75. Stuss, D.T., *Functions of the Frontal Lobes: Relation to Executive Functions.* Journal of the International Neuropsychological Society, 2011. **17**(5): p. 759-765.
76. Freitas, C., H. Mondragon-Llorca, and A. Pascual-Leone, *Noninvasive brain stimulation in Alzheimer's disease: Systematic review and perspectives for the future.* Experimental Gerontology, 2011. **46**(8): p. 611-627.
77. Brunoni, A.R., et al., *A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation.* International Journal of Neuropsychopharmacology, 2011. **14**: p. 1133-1145.
78. Kanal, E., et al., *ACR guidance document for safe MR practices: 2007.* American Journal of Roentgenology, 2007. **188**(6): p. 1447-1474.
79. Gillis, M.M. and B.M. Hampstead, *Working memory contributes to the encoding of object location associations.* Journal of the International Neuropsychological Society, 2013. **19**(S1): p. 11.
80. Ciesielski, K.T., et al., *Developmental neural networks in children performing a Categorical n-back task.* Neuroimage, 2006. **33**(3): p. 980-990.
81. Troyer, A.K. and J.B. Rich, *Psychometric properties of a new metamemory questionnaire for older adults.* Journals of Gerontology Series B - Psychological Sciences and Social Sciences, 2002. **57**(1): p. 19-27.
82. Carretti, B., et al., *Impact of metacognition and motivation on the efficacy of strategic memory training in older adults: Analysis of specific, transfer, and maintenance effects.* Archives of Gerontology and Geriatrics, 2011. **52**(3): p. E192-E197.
83. Troyer, A.K., et al., *Changing everyday memory behaviour in amnestic mild cognitive impairment: A randomized controlled trial.* Neuropsychological Rehabilitation, 2008. **18**: p. 65-88.
84. Kinsella, G.J., et al., *Early intervention for mild cognitive impairment: A randomized controlled trial.* Journal of Neurology Neurosurgery and Psychiatry, 2009. **80**: p. 730-736.
85. Granger, C.W.J., *Investigating causal relations by econometric models and cross-spectral methods.* Econometrica 1969. **37**: p. 424-438.
86. Buchel, C.F., et al.*Extracting brain connectivity*, in *Functional MRI: An introduction to methods.*, P. Jezzard, Matthews, P.M., Smith, S.M. , Editor. 2001, Oxford UP: Oxford. p. 295-308.
87. Johnson, S.C., et al., *The relationship between fMRI activation and cerebral atrophy: Comparison of normal aging and Alzheimer disease.* Neuroimage, 2000. **11**(3): p. 179-187.
88. Dickerson, B.C. and R.A. Sperling, *Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: Insights from functional MRI studies.* Neuropsychologia, 2008. **46**(6): p. 1624-1635.

89. Clement, F.B., et al. *Test-retest reliability of fMRI verbal episodic memory paradigms in healthy older adults and in persons with mild cognitive impairment.* Human Brain Mapping, 2009. **30**: p. 4033-4047