Title: Enhancing Spatial Navigation using Non-Invasive Brain Stimulation
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PI: Benjamin M. Hampstead, PhD, ABPP/CN

Objectives: Remembering how to travel from one location to another is critical in everyday life, yet this vital ability declines with normal aging and can be further affected by conditions that disproportionately affect older adults, such progressive dementia. Human and animal research has shown that two distinct memory systems interact during navigation. The first, referred to as allocentric navigation, is flexible and uses spatial knowledge of key features or landmarks to develop and use a mental map of the environment. This approach involves brain regions that are critical for new learning and memory but that decline with age. The second, referred to as egocentric navigation, is inflexible and relies on "habit" memories that link specific features with specific directions. This approach relies on brain regions that are critical for "automatic" responses and that are relatively unaffected by age.

The main problem is that allocentric navigation declines with age and is accompanied increased dependence on egocentric navigation. This change increases the risk of becoming disoriented or "lost" when traveling in unfamiliar areas or even when traveling new routes in familiar areas. Therefore, **the main goal** of this project is to examine whether non-invasive brain stimulation, specifically transcranial direct current stimulation, can improve allocentric navigation in cognitively intact older adults and those who have been diagnosed with mild cognitive impairment (MCI) – a clinical precursor to Alzheimer's type dementia.

Specific Aims/Hypotheses:

Specific Aim 1: Examine the effects of high definition tDCS (HD-tDCS) on both allocentric and egocentric memory test performance. We predict that participants will perform more accurately following active HD-tDCS when compared to sham HD-tDCS.

Specific Aim 2: Examine the neurophysiologic response to HD-tDCS using fMRI. We predict that active HD-tDCS will increase BOLD signal in a behaviorally meaningful way regardless of diagnostic group (i.e., healthy control vs. MCI). Critical questions about the restorative vs. compensatory effects of tDCS in those with MCI will be examined by contrasting BOLD signal change between the groups

Methodology

Participants: We will enroll up to 60 older adults (age 50+), who are right handed and MRI compatible, from the VA Ann Arbor Healthcare System, the University of Michigan Alzheimer's Disease Center (MADC), and the surrounding community. Enrollment is open to participants regardless of race, gender, or social status.

Inclusion criteria: Patients will receive a diagnosis of MCI based on the Albert et al. (2011) criteria. Specifically, patients 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 patients will be stable on nootropic medications for at least 1-2 months prior to study initiation.

By definition, healthy controls (HC) will be free of objective memory test impairment (i.e., all scores within normal limits on the standardized testing protocol below).

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); 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: 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 of MCI patients at the VA will be the Neuropsychology Clinic while HC will be recruited from the general VA community via postings/flyers in approved areas. 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, which is available to the PI and his study team. This database includes individuals who are cognitively intact (HC) and those with MCI.

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 (for patients) or that they are, in fact, cognitively intact (for the HC). This protocol includes standardized measures that are shown in the table below. Other measures may be added to the protocol to characterize the nature of the patient's cognitive functioning as necessary. Participants will be given breaks as necessary to ensure their comfort and are allowed to discontinue at any point for any reason.

Measure	Description	Screening Session
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
Temporal Sequencing Task	**Novel Temporal Memory Task (~5 minutes)**	X
Functional Activities Questionnaire (FAQ)	Evaluates patient's ability to perform everyday tasks (i.e., ADLs/IADLs) (~3 minutes)	X
Geriatric Depression Scale (GDS)	Evaluates current symptoms of depression (~3 minutes)	X
Multifactorial Memory Questionnaire (MMQ) & Memory Assessment Clinics – self report (MAC-S)	Self-report questionnaires that assess perceived memory complaints (~15minutes)	X
Object Location Touchscreen Test (OLTT)	Assesses the ability to learn and remember the location of objects (~10 minutes)	X

Screening protocol.

Eligible participants move forward into the study, details of which are provided below.

Study Procedures:

Eligible participants will undergo 2 sessions within a 2-week period of time. Some degree of flexibility is necessary with these visits in order to accommodate both patient and MRI availability.

Once determined to be eligible, participants will be randomized to one of two groups within their respective diagnostic groups. The first group will receive active HD-tDCS during session 1 and then sham HD-tDCS during session 2. The second group will receive the opposite order.

Participants will first receive 20 minutes of HD-tDCS at 2mA or sham as appropriate to the assigned condition. Participant specific codes are entered into the Soterix Medical Inc Clinical Trial unit thereby ensuring participants and study staff are blinded to stimulation condition. Stimulation will be performed using a Soterix Medical Inc. tDCS unit (Clinical Trial system with attached 4x1 HD stimulation unit) within a quiet room. The unit automatically discontinues stimulation after the specified time has elapsed (here 20 minutes). The patient 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 active tDCS protocol will provide an initial ramp-up period in which the electrical current is gradually increased, followed by 20 minutes of stimulation at 2mA, and finally a ramp down period during which the electrical current is gradually removed.

The sham tDCS group will receive a ramp-up period to 2mA followed immediately by ramp down period. This is repeated at the end of the session.

fMRI Scanning: After completing HD-tDCS, participants will be escorted to the MRI machine where they first undergo a resting-state fMRI scan and then complete the spatial navigation task. Structural imaging data were collected through a GE MR750 3T magnetic resonance system (GE, Milwaukee, WI) with a 32-channel phased array head coil. Sequence parameters for acquisition were: Field of view (FOV) = 256, Matrix = 256 × 256, 156 slices per volume, 1 mm3 voxel size, TR = 12 ms, TE = 5 ms, TI = 500 ms, flip angle = 15°. For resting state fMRI, participants were instructed to focus their gaze on the fixation cross on the screen and to not fall asleep. Resting state data was acquired through an echo planar imaging (EPI) multi-band sequence and parameters were: FOV = 240, Matrix = 74 × 74, 45 slices per volume, 3.4 × 3.4 × 3 mm voxel size, TR = 900 ms, TE = 30 ms, flip angle = 70°. For the functional task portion, participants were instructed to view the spacial navigation videos and remember key landmarks or series of turns depending whether it was allocentric or egocentric task. Functional task data was also acquired through an echo planar imaging (EPI) multi-band sequence with the following parameters: FOV = 220, Matrix = 88 × 88, 51 slices per volume, 2.5 × 2.5 × 2.5 mm voxel size, TR = 1200 ms, TE = 30 ms, flip angle = 70°.

Memory Testing**:** After scanning, participants perform a spatial navigation memory test that uses a touchscreen monitor to evaluate responding. Allocentric accuracy is measured as the distance (in CM) between the actual and selected location (lower values indicate greater accuracy) of a given landmark within a given map. Egocentric memory accuracy is evaluated by showing participants an image of a given environment after which they recall the sequence of turns through the environment. The dependent variable is the number of turns correctly recalled.

Statistical Design:

The primary analytic technique for the behavioral measures will be a repeated measures ANOVA (via the current version of SPSS). The effects of HD-tDCS for allocentric and egocentric performance will be examined separately. These analyses may include potential confounding factors as covariates.

fMRI data analysis MRI images were preprocessed and analyzed through SPM8 (SPM8; Wellcome Trust Centre for Neuroimaging). Slice timing correction was performed for functional volumes. Functional volumes were realigned to the first volume in the experiment to correct for head motion, co-registered with the high-resolution sagittal images. The structural images were spatially normalized to a standard MNI template using the voxel-based morphometry toolbox (VBM8 http://dbm.neuro.uni-jena.de/vbm) and DARTEL high-dimensional warping and resampled to a 3x3x3 mm voxel size. Estimated deformation fields from warping were applied to normalize images to MNI space, and smoothed using an 5-mm FWHM Gaussian kernel. Motion scrubbing (removal of volumes) was performed based on a framewise displacement threshold of 0.3. The time course data for each voxel was band-pass filtered (0.01 to 0.10 Hz band) to capture the low-frequency spontaneous BOLD oscillations in resting state signals.

Task analysis

For the spatial navigation task, preprocessed MRI data were analyzed with the general linear model framework in SPM8. Two block regressors were modeled: allocentric and egocentric. The onsets and durations of blocks were convolved with a canonical hemodynamic response function (HRF) to create the block regressors, in addition to covariates of six image realignment parameters to reduce movement induced artifacts. In the first-level analysis for each participant, the parameter estimates of block regressors were computed at each voxel. Appropriate linear contrasts were applied to the parameter estimates to produce contrast images and statistical parametric maps (SPM t map). To evaluate activations associated with task, session, and group effects, we've

constructed a mixed ANOVA model to test the influence of the aforementioned variables. Second-level maps were initially thresholded at whole-brain $p < .01$ to .001, uncorrected (extent threshold, $k = 10$). In addition to whole brain analysis, we also created a mask from activations seen in the whole brain analysis of task main effects (voxel-wise FWE $p < .05$) for use in group analyses of session effects. Specific regions of interests (ROIs) were also utilized, selected based on prior work (Hampstead et al., 2014) in regards to spatial navigation and derived from the Anatomical Automatic Labeling software (Tzourio-Mazoyer et al, 2002). These ROIs included hippocampus, superior parietal lobule, and caudate (all small volume corrected at voxel-wise FWE $p < .05$). Beta values of surviving brain activations were extracted and analyzed with ANOVA with significance threshold set at $p < .05$.

Resting state analysis

Resting state functional connectivity was first examined using a region of interest (ROI) "seed" at the stimulation site, right superior parietal lobule (rSPL), using a 10 mm radius spheres centered at MNI: (24, -60, 60). Pearson product–moment correlation coefficients were calculated between the average BOLD time course in the seed region and all other voxels in the brain. Each correlation resulted in a 3D correlation coefficient image (r-image). R-images were then transformed to z scores using a Fisher r to z transformation. Z score images from the individual functional connectivity analyses were entered into second-level random effects analyses (factorial ANOVA and t-tests) implemented in SPM8.

We have further applied a 'data-driven' approach based on Graph Theory to analyze the functional connectivity network before and after the intervention. We've used Power's 264 anatomical coordinates to segment the brain into 264 ROIs. We included additional medial temporal and subcortical ROIs. Each ROI was defined as a 5 mm sphere centered around these coordinates. A binary grey matter mask was created through the segmentation procedure in VBM8 and the threshold probability of 0.6 (as suggested by Zalesky et. al.) was used to overlay on the normalized resting state images. The average time course signal of the grey matter voxels in each ROI was measured. Pearson's correlation between the signal time course of all possible pairs of ROIs was conducted. Correlation weights that failed the false discovery rate (FDR) threshold at $p < 0.05$ were discarded. Graph parameters, including total functional connections, network strength, and network cost were calculated.

Within each group (HC and MCI), we will use the active > sham contrast to identify regions that differ as a result of HD-tDCS. Correlations between behavioral performance (e.g., accuracy in CM) and BOLD signal will also be calculated to determine whether the altered BOLD signal is behaviorally meaningful. Because we expect functional reorganization throughout the brain within both groups as a result of HD-tDCS, we intend to use connectivity analyses to examine changes in the connectivity between the parietal cortex and the remainder of the brain.

Exploratory between group analysis will use two primary contrasts. 1) HC sham > MCI sham – which will identify disease-related differences in activation between the groups; 2) HC active > MCI active – which will examine whether the tDCS-related changes are greater in one group than the other. Taken together, these contrasts will also clarify whether tDCS restores functioning in brain regions involved in "normal" (i.e., age appropriate) navigation or whether it allows MCI patients to recruit alternative brain regions in a compensatory manner.

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

tDCS Safety: tDCS has been used with literally thousands of patients world-wide. Brunonni et al., (2011) demonstrated that the rate of side effects is comparable between those receiving active and sham stimulation. We will follow current safety guidelines for dosing and will use a current strength of up to 2mA and duration of 20 minutes per session. Few, if any, side effects are reported with these parameters and those that are reported are mild in nature (e.g., tingling, itching, burning sensation, (Nitsche & Paulus, 2011). Importantly, we will collect data on tDCS-related adverse effects using the questionnaire provided by Brunoni and colleagues (2011). This questionnaire is provided below.

tDCS Adverse Effects Questionnaire – Session _____

Do you experience any of the following symptoms or side-effects?	Enter a value (1–4) in the space below (1, absent; 2, mild; 3, moderate; 4, severe)	If present: Is this related to tDCS? (1, none; 2, remote; 3, possible; 4, probable; 5, definite)	Notes
Headache			
Neck pain			
Scalp pain			
Tingling			
Itching			
Burning sensation			
Skin redness			
Sleepiness			
Trouble concentrating			
Acute mood change			
Others (specify)			