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Featured Article

Combined mnemonic strategy training and high-definition transcranial direct current stimulation for memory deficits in mild cognitive impairment

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Abstract

Introduction: Memory deficits characterize Alzheimer's dementia and the clinical precursor stage known as mild cognitive impairment. Nonpharmacologic interventions hold promise for enhancing functioning in these patients, potentially delaying functional impairment that denotes transition to dementia. Previous findings revealed that mnemonic strategy training (MST) enhances long-term retention of trained stimuli and is accompanied by increased blood oxygen level–dependent signal in the lateral frontal and parietal cortices as well as in the hippocampus. The present study was designed to enhance MST generalization, and the range of patients who benefit, via concurrent delivery of transcranial direct current stimulation (tDCS).

Methods: This protocol describes a prospective, randomized controlled, four-arm, double-blind study targeting memory deficits in those with mild cognitive impairment. Once randomized, participants complete five consecutive daily sessions in which they receive either active or sham high definition tDCS over the left lateral prefrontal cortex, a region known to be important for successful memory encoding and that has been engaged by MST. High definition tDCS (active or sham) will be combined with either MST or autobiographical memory recall (comparable to reminiscence therapy). Participants undergo memory testing using ecologically relevant measures and functional magnetic resonance imaging before and after these treatment sessions as well as at a 3-month follow-up. Primary outcome measures include face-name and object-location association tasks. Secondary outcome measures include self-report of memory abilities as well as a spatial navigation task (near transfer) and prose memory (medication instructions; far transfer). Changes in functional magnetic resonance imaging will be evaluated during both task performance and the resting-state using activation and connectivity analyses.

Discussion: The results will provide important information about the efficacy of cognitive and neuromodulatory techniques as well as the synergistic interaction between these promising approaches. Exploratory results will examine patient characteristics that affect treatment efficacy, thereby identifying those most appropriate for intervention.

Trial status: The study is actively enrolling participants.

Trial Registration: www.clinicaltrials.gov: NCT02155946 (Registered on May 29, 2014).

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1. Introduction

It is well known that the proportion of older adults is increasing within both the United States and globally. Alzheimer's disease is the most common cause of dementia (i.e., Alzheimer's dementia—AD) with a rate of about 9.5% in those for more than age 70 years; this rate is expected to increase twofold to threefold in the coming decades [1,2]. Delaying conversion to AD will not only improve patient quality of life but may also reduce the financial costs of the disease. The diagnosis of mild cognitive impairment (MCI) captures those who are cognitively symptomatic and at high risk of conversion to AD, yet demonstrate relatively preserved everyday functioning [3–5]. Learning and memory deficits are the most common presenting problem [3,5] and are associated with medial temporal lobe atrophy and dysfunction [5–7]. Associative memory paradigms may be especially sensitive to early decline given their reliance on medial temporal lobe structures [8]. In fact, patients with MCI demonstrate deficits on ecologically relevant associative tasks such as face-name [9] and object-location associations [10], which are accompanied by hypoactivation of key lateral frontoparietal and medial temporal regions relative to control subjects [10]. The lateral frontoparietal network (i.e., middle and inferior frontal gyri, inferior frontal sulcus, and intraparietal sulcus) is known to be important in successful memory formation [11], possibly because of its role in mediating working memory [12–14]. We further supported the importance of this network using effective connectivity analyses, which revealed that cognitively intact older adults engaged the left frontoparietal network during the successful encoding of new object-location associations [15]. In contrast, MCI patients engaged the right frontal eye field, a region known to mediate basic attentional saccades. Together, these findings suggest that memory deficits in patients with MCI may emerge through a combined "loss" of medial temporal and frontoparietal functioning.

The critical question is how to enhance or otherwise maximize memory in those with MCI, especially considering the limited cognitive effects of existing pharmacologic agents [16–18]. The current, ongoing, double-blind, randomized controlled trial addresses this question using two promising nonpharmacologic approaches: mnemonic strategy training (MST) and transcranial direct current stimulation (tDCS).

As we previously described [19,20], MST teaches participants to use cognitive "tools" that enhance the organization of information while also requiring patients to process information more deeply, factors known to enhance memory [21,22]. We demonstrated that MST enhances memory for face-name [23] and object-location associations [19] and others have found comparable benefits for tasks such as word lists [24]. These behavioral improvements were accompanied by increased activation in regions of the lateral frontoparietal network [24,25] and the hippocampus [26]. Together, these findings suggest that MST may enhance memory by re-engaging these previously dysfunctional brain regions/networks. However, our prior data indicate two potential limitations. First, MST appears less effective in patients with "late" MCI (i.e., those closer to developing AD) than "early" MCI (i.e., those closer to "normal") [19,23]. Second, patients have difficulty spontaneously transferring MST to novel types of information, a common problem in this area of research.

We selected tDCS as a potential method for overcoming these limitations. tDCS modulates neuronal excitability by passing a weak electric current between electrodes that are placed on the scalp. Traditionally, tDCS uses two electrodes (usually 25–35 cm^2): an anode that "introduces" the electrical current and a cathode that "collects" the current. Evidence suggests that neuronal somata under the anode become depolarized [27]. Thus, tDCS does not directly induce neuronal firing but, rather, produces conditions that make firing more or less likely to occur. To enhance focality, we are using high definition (HD) tDCS. This method uses a 4 $\times$ 1 ring configuration in which the central electrode is surrounded by four electrodes of the opposite polarity [28,29]. Practically, this means that the "ring" electrodes each use about ¼ of the electrical current, whereas the central electrode uses the full amount. This approach limits the cortical modulation effects to the area of the four-electrode ring (see [29]) and presumably minimizes the confounding physiological effects of the ring electrodes. Applied to the motor cortex, HD-tDCS induces greater and more persistent neuromodulatory effects than the traditional approach [30] while remaining well tolerated and without significant side effects (see [28,31]).

We believe the combined use of MST and HD-tDCS is especially appropriate because there is evidence that concurrent tDCS and training enhances consolidation of the trained skill (see [32]). We target the left lateral prefrontal cortex (PFC) given its importance in successful learning and in mnemonic strategy use (as described previously). Thus, we are particularly interested in the synergistic effects of combined MST and HD-tDCS. The current trial randomizes participants to one of four treatment groups that consist of MST or an autobiographical memory recall (ABR) in combination with active or sham HD-tDCS.

The primary objectives of the study are as follows:

(1) Examine the cognitive benefits of the interventions using ecologically relevant outcome measures. We predict main effects of group where MST is more effective than ABR and active HD-tDCS is more effective than sham HD-tDCS. Our primary interest, however, is in the cognitive by stimulation group interaction where we expect the greatest benefits of combined MST + active HD-tDCS and least (if any) improvement in ABR + sham HD-tDCS. Persistent gains are predicted to be most likely in the combined MST + active HD-tDCS group.
(2) Use functional magnetic resonance imaging (fMRI) to evaluate the neuroplastic/neurophysiological changes associated with intervention. We predict main effects of group where the MST and active HD-tDCS groups will demonstrate greater (ventro)lateral PFC activation than the ABR and sham HD-tDCS groups. The cognitive by stimulation group interaction is again of particular interest and should mirror the behavioral changes in Aim 1. An intriguing alternative outcome of reduced activation within the context of improved behavioral performance (analogous to a repetition suppression fMRI effect) would suggest increased processing efficiency.

Exploratory analyses will examine treatment effects on working memory and semantic processing. The targeted left ventrolateral PFC plays an important role in working memory, semantic processing, and successful memory encoding, all of which may be enhanced by active HD-tDCS over this region. These effects will be evaluated via behavioral performance and fMRI with the expectation of a main effect of stimulation (active > sham) but not necessarily a cognitive training group (given the targeted nature of MST) or interaction effect.

2. Methods

This is a double-blind, randomized controlled trial with parallel groups allocated 1:1:1:1 using a superiority framework. After an initial consent/screening session, participants complete seven sessions within approximately 2 weeks and an eighth session at the 3-month time point. Participants undergo fMRI during sessions 1, 7, and 8 as well as intervening training during five consecutive daily sessions (Sessions 2–6). Behavioral outcome measures are evaluated at baseline/Session 1, Session 6 (after training), and Session 8. The study timeline is shown in Fig. 1.

2.1. Participants

We intend to recruit 100 right-handed participants, age 50 years and older, who hold a diagnosis of MCI. Participants are drawn from the VA Ann Arbor Healthcare System, the University of Michigan Alzheimer's Disease Core Center and associated participant registries, and the surrounding community. *Inclusion criteria:* patients will have a diagnosis of MCI based on the Albert et al. [5] criteria. Specifically, patients will (1) report a subjective decline in memory (report can also be provided by an informant or clinician), (2) demonstrate objective impairment in memory (based on neuropsychological testing), and (3) remain generally independent in activities of daily living. All patients will be stable on medications for at least 1 month before study initiation. *Exclusion criteria*: a history of (1) other neurologic (e.g., epilepsy, moderate to severe traumatic brain injury) or medical conditions that are known to affect cognitive functioning and that are considered primary to cognitive decline; (2) significant psychiatric conditions (e.g., moderate to severe depression, bipolar disorder, schizophrenia); (3) sensory impairments that limit the ability to take part in the study; and (4) current alcohol or other drug abuse/dependence. Participants are also screened to ensure MRI and HD-tDCS compatibility. Eligible participants who cannot undergo MRI will be enrolled in the study and will complete only the stimulation and behavioral portions of the study (including outcome evaluations) within a quiet office setting. Enrollment is open to participants regardless of race, gender, or social status.

2.2. Baseline evaluations

After providing informed, written consent obtained by a study team member, participants undergo a brief neuropsychological protocol that includes the Montreal Cognitive Assessment [33], Wechsler Test of Adult Reading [34], Repeatable Battery for the Assessment of Neuropsychological Status [35], Emory short version of the Wisconsin Card Sorting Test [36], Trail Making Test [37], Geriatric Depression Scale [38], and Functional Activities Questionnaire [39]. This protocol ensures patients continue to meet criteria for MCI and also characterizes their cognitive functioning at the time of enrollment, which are important given the lag that may occur between diagnosis and study entry. Primary and secondary outcome measures are collected during this initial session but are not used to determine inclusion.

2.3. Primary outcome measures

Primary outcome measures include two internally developed memory tests that are meant to emulate real-world difficulties that patients with MCI experience. We designed these measures to adhere to common parameters used in clinically based tests to facilitate comparison with the wider area of research. Both these tasks have three versions that are comparable based on a number of critical features. Mnemonic strategies require time to implement (see discussion of important methodological factors in [22]), so both tasks provide 15-second exposures for each of 15 associations. Memory for these stimuli is evaluated after a 15-minute delay. Recognition foils are actual target stimuli (i.e., targets that were incorrectly paired with the face or

STUDY PERIOD							
			Post-allocation				
	Baseline	S1	S2	S3-5	S6	*S7*	*S8 (3-month f/u)*
ENROLLMENT:	X						
Eligibility screen	X						
Informed consent	X						
Neuropsychological Testing	X						
fMRI Scanning & associated tests		X				X	X
Primary outcome measures **FNGT** **OLTT**	X				X		X
Secondary outcome measures **MMQ** **EMS-Route Recall** **EMS Medical Instructions**	X				X		X
Allocation/Randomization			X				
MST+ active HD-tDCS			X	X	X		
MST + sham HD-tDCS			X	X	X		
ABR + active HD-tDCS			X	X	X		
ABR + sham HD-tDCS			X	X	X		

Fig. 1. Schedule of enrollment, interventions, and assessments. Abbreviations: ABR, autobiographical memory recall; EMS, ecological memory simulations; fMRI, functional magnetic resonance imaging; FNGT, face-name generalization task; OLTT, Object Location Touchscreen Test; HD-tDCS, high definition transcranial direct current stimulation; MMQ, Multifactorial Memory Questionnaire; MST, mnemonic strategy training.

object), thereby reducing reliance on familiarity and increasing reliance on recollection of the actual association. Key features and dependent variables for these tasks are listed subsequently. These measures are collected during the baseline/screening session, Session 6 ($\sim$60 minutes after the end of training), and Session 8.

2.3.1. Face-name generalization task

Memory for each association is first assessed using *cued recall* where the patient sees a face and is asked to recall the name. Participants then complete the *recognition* phase in which they select the correct name from three options. The dependent variable is the number of correctly recalled or selected names and analyses will focus on change from baseline.

2.3.2. Object-location touch screen test (see [40])

Memory is assessed under three unique conditions. *Free recall*: First, participants see a target object followed by a blank screen and are instructed to touch the location of the object on a 19 in. ELO touch screen monitor (ELO Touch Solutions, Milpitas, CA, USA). *Cued recall:* Next, participants see the object and then its associated room (without the object present) and are instructed to touch its location. The primary dependent variable for both of these conditions is the distance (in centimeters) between the selected and target location. This approach allows us to quantify the severity of memory failure as opposed to relying on the traditional dichotomous view of memory as correct or incorrect. *Recognition:* Finally, participants complete a recognition trial in which they select the location of the object from three potential locations. Including this trial allows us to place the results within the context of traditional dichotomous views of memory. The dependent variable is the number of correctly selected locations. Analyses will focus on change from baseline for each of these measures.

2.4. Secondary outcome measures

2.4.1. Multifactorial Memory Questionnaire [41]

This questionnaire is a self-report measure that was developed to specifically assess dimensions of memory that are applicable to clinical assessment and intervention. Participants indicate the degree to which they agree with a

statement along a 5-point scale. Three scales are provided: (1) the Ability scale (20 items), which assesses self-report of difficulty with everyday memory situations; (2) the Contentment scale (18 items), which assesses the emotions and perceptions that individuals have about their current memory ability; and (3) the Strategy scale (19 items), which examines the respondent's use of memory aids and strategies. The Multifactorial Memory Questionnaire has strong psychometric properties (see [41] for a full description) and has been used in several intervention studies in both healthy older adults [42] and MCI patients [43,44]. Dependent variables are the number of items endorsed on each scale. Analyses will evaluate change from baseline.

2.4.2. Ecological memory simulations

Two subtests from the ecological memory simulations [45,46] will be used to evaluate transfer effects. There are two versions of each subtest, and we are using Form 1 at baseline, Form 2 during the post-training evaluation (Session 6), and repeating Form 1 during the 3-month evaluation (Session 8).

2.4.2.1. Route Recall Simulation

This simulation asks patients to learn and remember an indoor route presented as a series of two- and three-choice intersections where a model chooses to go left, right, or straight an equal number of times. Memory for this route is assessed immediately and after a 15-minute delay by showing participants an intersection and asking them to recall the direction in which the model traveled. Recall of the route is assessed in both serial and random order. The dependent variable is the number of turns correctly recalled. Analyses will evaluate change from baseline. We included this task as a measure of near transfer because the design is amenable to mnemonic strategy use (e.g., identifying a salient feature at each intersection, developing a reason linking that feature with the targeted direction—see description of MST mentioned previously).

2.4.2.2. Medical instructions simulation

This simulation is a prose memory task in which the patient is read medication instructions and then asked to recall this information immediately, after a second presentation of the instructions, and after a 15-minute delay. We included this task as a measure of far transfer because the task measures memory, yet the particular mnemonic strategies we teach are unlikely to help the patient process such information. Thus, task improvement would be expected because of general "strengthening" of the key frontoparietal network as a result HD-tDCS. The dependent variable is the amount of information recalled. Analyses will evaluate change from baseline.

2.5. Session 1: fMRI scanning

Activation will be assessed using memory encoding, working memory, and semantic processing paradigms. Participants will complete scanning during Sessions 1, 7, and 8. Although the study focuses on task-based fMRI, resting-state data are collected at the start of each of these sessions and will be interrogated for exploratory purposes.

2.5.1. Memory encoding

Because we are interested in the general network underlying successful MST use, participants complete functional runs during which they encode novel stimuli from both the face-name and object-location association paradigms. Importantly, these stimuli are independent of those used for our primary outcome measures. Two repeated stimuli within each paradigm are presented multiple times and will serve as the control condition. We reconfigured our existing paradigms [10,25] to create three lists (Lists A, B, and C) of 30 stimuli. As shown in Tables 1 and 2, these lists are comparable on a number of key features. A different list is used in Sessions 1, 7, and 8, thereby mitigating stimulus-specific effects. We elected to hold the list constant (i.e., List A in Session 1; List B in Session 7; and List C in Session 8) so that only the treatment condition differs between the groups.

Participants complete a total of four functional runs, two in each condition (each 6 minutes, 20 seconds in duration). We selected a mixed event-related block design based on simulation data because it maximized power and provided optimal flexibility (e.g., retrospectively coding each stimulus as remembered vs. forgotten for an

Table 1
Properties of the face-name task used in fMRI

	SET A	SET B	SET C	$F_{2,87}$
Popularity $\bar{x}$ (SD)*	90.06 (129.63)	87.34 (107.09)	87.22 (86.91)	0.007, $P = .993$
Letters $\bar{x}$ (SD)†	5.50 (0.51)	5.50 (0.51)	5.53 (0.51)	0.040, $P = .960$
Ethnicity				$\chi^2(2)$
Minority	$n = 16$	$n = 11$	$n = 11$	2.155, $P = .34$
Mean rank	53.5	46	46	
Gender				
Male	$n = 14$	$n = 15$	$n = 16$	0.248, $P = .88$
Mean rank	50	48.5	47	

*Popularity of ranking is based on Social Security data and assessed by approximate age (by decade) of face.
†Number of letters in each name.

Table 2
Properties of the object-location task used in fMRI

	List A $\bar{x}$ (SD)	List B $\bar{x}$ (SD)	List C (3) $\bar{x}$ (SD)	$F_{2,87}$
Frequency*	49.62 (128.45)	20.86 (35.47)	37.66 (86.02)	0.747, P= .477
Percentage†	9.99 (17.58)	6.71 (8.71)	9.32 (16.45)	0.412, P = .664
Letters‡	5.63 (2.25)	6.10 (1.77)	5.70 (1.60)	0.533, P = .589

*Frequency per million words based on corpus developed by Brysbaert and New (2009). Moving beyond Kucera and Francis: a critical evaluation of current word frequency norms and the introduction of a new and improved word frequency measure for American English. *Behavior Research Methods*, *41(4)*, 977–990.

†Percentage of times word appears in a film (within the corpus).

‡Number of letters in the word.

event-related analysis). Each run consists of six active blocks (three novel and three repeated stimuli) and seven rest blocks (20 seconds each). During active blocks, five stimuli are presented for 5 seconds each and are separated by an interstimulus interval (ISI) of 1, 2, 3, 4, or 5 seconds. The ISI was randomized so that the across-block average within a given run was 15 seconds, which led to variability in the length of individual active blocks (from 34 to 46 seconds). Participants are instructed to push a button with their right index finger each time a new stimulus appears, a requirement meant to ensure they are attending to the task at hand. Run order is randomized for each patient. The interaction contrast of list and time is of primary interest (Novel [post-training > pretraining] > Repeated [post-training > pretraining]). We refer to this as the encoding contrast hereafter. Exploratory analyses will evaluate activation changes within each paradigm individually (i.e., face-name or object-location). Participants complete a memory test using these stimuli outside of the scanner.

2.5.2. *Working memory and semantic processing*

Participants complete a standard *n*-back working memory paradigm. In the 0-back (control) condition, participants push a button on an fMRI compatible response pad using their right index finger when a target stimulus appears. The 2-back condition requires participants to push the button when a given stimulus was also seen two stimuli ago. The primary contrast of interest examines the interaction between condition and time: (post-training [2-back > 0-back] > pretraining [2-back > 0-back]). We refer to this as the contrast for item working memory hereafter.

To evaluate whether MST or HD-tDCS also affects semantic processing, we developed a semantic 2-back task that requires participants to determine if a given stimulus is of the same semantic category (e.g., an animal) as the one presented two stimuli ago. Similar paradigms have effectively engaged the left lateral PFC [47]. 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 blood oxygen level dependent (BOLD) signal associated with working memory from the semantic task via the interaction contrast of task and time: (semantic [2-back post-training > 2-back pretraining] > item [2-back post-training > 2-back pretraining]). We refer to this as the contrast for semantic processing hereafter.

These paradigms allow us to directly examine the cognitive processes and associated brain regions underlying mnemonic strategy use (Aim 2) as well as any HD-tDCS–related improvements in other cognitive abilities (Aim 3). In developing these tasks, we selected a total of 45 stimuli using color versions of the classic Snodgrass and Vanderwart set (obtained at http://spell.psychology.wustl.edu/Rossion_stimuli/) and, specifically, five stimuli from each of nine semantic categories. We created three groups of 15 stimuli (three semantic categories with five stimuli per category in each list) (Group 1: body parts, animals, and furniture; Group 2: tools, fruits, and clothing; Group 3: musical instruments, vegetables, and vehicles). These same three groups of stimuli are used in each scan session to mitigate any stimulus-specific effects; however, the stimuli used for a given cognitive task (0-back, 2-back, semantic 2-back) are rotated for each session. For example, group 1 could be used for 0-back during Session 1, 2-back for Session 7, and semantic 2-back for Session 8. Stimuli are presented using a block design (4 minutes, 30 seconds) that consists of five active and six (20 second) rest blocks. Within each 30″ active block, 15 stimuli are presented for 1″ and separated by a 1″ ISI. Four to six target stimuli are shown in each active block, a design meant to reduce predictability. Participants respond by pushing a button with the right index finger.

2.5.3. *MRI image acquisition*

All imaging is performed using a 3 T GE Signa MRI with a 32-channel head coil. Stimuli are presented on a rear-mounted liquid crystal display screen. High-resolution anatomic images are acquired using a three-dimensional BRAVO sequence with repetition time (TR) 12.2 ms, echo time (TE) 5.2 ms, inversion time 500 ms, flip angle (FA) 15°, 160 sagittal slices of 1 mm thickness, in-plane resolution (IPR) 1 × 1 mm, in-plane matrix (IPM) 256 × 256, and field of view (FOV) 256 mm. All *fMRI data* are collected using T2*-weighted functional images acquired with a multiband slice accelerated gradient-recalled echo planar imaging sequence with BOLD contrast and the following parameters: resting-state scans: TR, 900 ms; TE, 30 ms; FOV, 240 mm; FA, 70°; 45 axial slices of 3 mm thickness; IPR, 3.0 × 3.0 mm; IPM, 74 × 74; 3.24 × 3.24 × 3 mm voxels. All task-related scans use the following parameters: TR, 1200 ms; TE, 30 ms; FOV,

220 mm; FA, 70°; 51 axial slices of 2.5 mm thickness; IPR, 2.5 × 2.5 mm; IPM, 88 × 88; voxel size, 2.5 mm isotropic.

2.6. Interventions

Administered in Sessions 2 to 6.

2.6.1. Randomization

During the consent process, participants are informed that the study evaluates cognitively based interventions; however, participants are not given specific information about the interventions to keep them blinded to the alternative cognitive condition. Participants are also informed that sham HD-tDCS may be used but are not told the difference between active and sham parameters. All participants receive a study ID that is used on all study materials (i.e., no personal identifiers are used). All data are double scored and entered into a secure database to which only study team has access.

A series of random 6-digit computer-generated codes were created and preprogrammed into the Soterix Medical, Inc Clinical Trial tDCS unit. We use the sealed envelope method in which group assignment (i.e., the cognitive training condition and the numeric code for the tDCS unit) is placed within a sealed envelope at the beginning of the study. This numeric code is participant unique and allows for double blinding of HD-tDCS condition. A blocked randomization schedule is used with 1:1:1:1 allocation to each of the four groups that are run in parallel (i.e., active HD-tDCS + MST, sham HD-tDCS + MST, active HD-tDCS + ABR, or sham HD-tDCS + ABR). Soterix Medical Inc generated the codes. The study principal investigator (B.M.H.) generated the allocation sequence and shuffled the sealed envelopes. Study staff enroll participants and assign study conditions.

At the beginning of Session 2 (i.e., the first training session), a study staff member opens the envelope, thereby revealing the participant's cognitive training group and unique HD-tDCS code. Thus, participants are double-blinded (i.e., to the other cognitive intervention and to HD-tDCS status) and study staff are single-blinded (i.e., to HD-tDCS status). A study team member who did not administer the intervention(s) performs the outcome evaluations. A separate study team member who is double-blinded analyzes first level fMRI data. Second-level fMRI analyses will be performed at the end of the study after breaking the blind. Unblinding will occur during the study period only if a patient experiences an unexpected adverse event.

2.6.2. Intervention by group

All groups undergo five training sessions on consecutive days. Each session lasts approximately 80 to 120 minutes depending on the speed with which the patient completes the training. The first 10 to 15 minutes of each session are used to measure and place the HD-tDCS electrodes. The cognitive intervention (i.e., MST or ABR) occurs during the next 60 to 110 minutes (the first 30 minutes are concurrent with HD-tDCS) and the final 10 minutes are used to answer any questions and remove the HD-tDCS electrodes. Participants are allowed to miss up to two training sessions and still remain active in the study.

2.6.2.1. Mnemonic Strategy Training

A brief didactic period is provided during the first session in which the rationale and methods are explained. MST begins at the same time as HD-tDCS stimulation and persists for approximately 30 to 90 minutes after stimulation has ended. This approach intends to capitalize on the neuroplastic changes induced by HD-tDCS and to adaptively shape them using MST, thereby reinforcing the interactions necessary for successful strategy use. Patients will use the same three-step process as in our prior studies [19,23]. We refer to this process as "FRI", for feature (F), reason (R), and image (I). In the first step, a salient *feature* is identified. Participants are encouraged to select something that is especially unique or unusual about the stimulus. Next, a verbally based *reason* for selecting that specific feature is developed. This reason should integrate the feature with the targeted information (e.g., the name). Finally, participants *imagine* and integrate these previous steps using mental imagery (i.e., by creating a mental "picture" or "movie"). On each subsequent trial, we require participants to recall the feature, the reason, the image, and then the targeted information (e.g., the name) in that specific order. To reinforce the use of the FRI approach, patients are given nine trials per stimulus. This process is designed to promote a specific series of steps that participants will use when encountering information in the future, thereby altering the manner in which they learn and recall information. We previously discussed the benefits of a trial-based format [20], which ensures comparable exposure to the study methods relative to a session or time-based design where individual sessions may differ substantially both within and between participants. Participants are required to independently develop the feature, reason, and image cues for each stimulus. A member of our research team monitors and records each step of the process to ensure compliance. We provide assistance and model appropriate cues as needed to promote successful strategy use. Participants practice this MST approach using a total of 12 stimuli (six faces and names; six objects and locations) in each session (108 trials per session; 540 total trials across all sessions).

2.6.2.2. Autobiographical memory recall

We selected ABR as an active control condition for MST because it focuses on memory and engages patients in general conversation with our research team, thereby matching nonspecific factors and total session time. This approach is similar to reminiscence therapy, which has shown some positive effects in patients with AD [48] and, as a result, can be considered an active comparator.

This condition begins at the same time as HD-tDCS and persists for approximately 30 to 90 minutes after stimulation has ended. During each session, participants are asked to identify and write a brief description of five emotionally positive memories from each of five distinct periods of life (Session 1, 0–15 years old; Session 2, 16–30 years old; Session 3, 31–45 years old; Session 4, 45 years old to 5 years ago; Session 5, last 5 years). Participants are then asked to describe each memory in their own words. The entire session is audio recorded for later transcription and analysis. After this free recall period, our staff asks the participant to rate how pleasant, significant, intense, novel, and vivid each memory is using a 7-point scale (with anchored values; 1 being lowest/worst and 7 being highest/best). Participants are also asked how frequently they think about or recall the memory. We then ask a series of questions that are meant to further probe the episodic aspects of each memory including how the participant felt during the event, what sights were around them, what kind of smells they experienced, and why the participant thinks they still recall the particular memory. These questions are meant to ensure comparable engagement and experience as with the MST group. In addition, however, we intend to analyze the transcribed data for linguistic qualities by Linguistic Inquiry and Word Count or other related methods. This approach may be especially informative given that HD-tDCS is being performed over the left lateral PFC (including "Broca's area"), which is known to be vital for speech production. Thus, it is possible that active HD-tDCS versus sham HD-tDCS could facilitate speech output over the course of the five sessions (this possibility will be evaluated in exploratory analyses). Such findings may be especially powerful given evidence that MCI patients recall fewer episodic details and use less complex language relative to control subjects [49,50].

2.6.2.3. *High definition transcranial direct current stimulation*

Stimulation is performed using a Soterix Medical Inc tDCS unit (Clinical Trial system and connected 4 × 1 HD stimulation unit) within a quiet room. Fig. 2 shows our HD-tDCS montage and finite element models of electrical current flow (comparable results can be obtained using HD-Explore software from Soterix Medical, Inc). As can be seen, our montage selectively targets the left lateral PFC, especially the inferior frontal sulcus and gyrus. Participant-specific codes are entered and the unit automatically discontinues stimulation after the specified time has elapsed, which is based on active versus sham grouping. At the end of the session, participants complete a brief questionnaire about the nature and severity of any side effects, as recommended by Brunoni et al. [51]. An independent tDCS expert reviews safety and tolerability data on a biannual basis and submits findings to the institutional review board.

2.6.2.3.1. *Active tDCS protocol*

This protocol provides a 30-second ramp-up period in which the electrical current is gradually increased, followed by 29 minutes of stimulation at 2 mA, and finally a 30-second ramp down period during which the electrical current is gradually removed. This "dose" was based on two previous tDCS studies in patients with AD [52,53].

2.6.2.3.2. *Sham tDCS protocol*

This protocol follows standard designs [54] and provides a 30-second ramp-up period to the full 2 mA, followed immediately by a 30-second ramp down. We repeat this process during the final minute of the session to provide patients with both "primacy" and "recency" experiences of stimulation. This is an appropriate comparator for active HD-tDCS because it provides comparable sensory experiences absent the physiological effect, thereby resulting in effective blinding [28,31,51].

2.7. *Session 7*

Approximately 2 to 4 days after the final training session (depending on participant and scanner availability), participants complete fMRI scanning using a novel list of stimuli for each task (List B). Memory for the face-name and object-locations is assessed outside the scanner as described previously.

2.8. *Session 8*

Approximately 3 months after Session 7 (typically ±7 days), participants return for a follow-up session. Primary and secondary outcome measures are collected. Participants are then escorted to the MRI scanner, where they complete scanning using a novel list of stimuli for each task (List C).

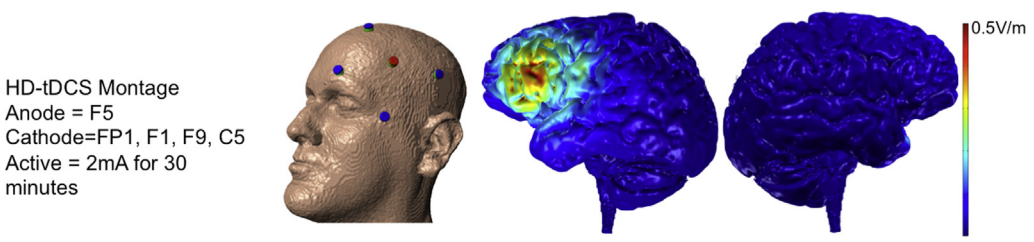

Fig. 2. Finite element models of electric current flow using our HD-tDCS montage. Abbreviation: HD-tDCS, high definition transcranial direct current stimulation.

2.9. Power and statistical analysis

Previously published results [55] of neurostimulation studies suggest mean cognitive effect sizes (in Cohen's *d*) of 0.42 for single sessions and 0.89 for multiple sessions in healthy older adults and even larger effects in patients with AD, ranges generally consonant with those recently suggested for tDCS studies [56]. Our prior studies with MST indicated large effect sizes ($p\eta^2 = 0.16$) relative to tightly matched active control conditions [21]. fMRI power analysis is complex owing to the large number of potential variables (and brain regions). Two independent studies have recommended group sizes of 20 to 25 assuming a 0.5% BOLD signal change, 80% power, and α of 0.05 to 0.002 [57,58]. Fig. 3 (via G*Power 3.1, power = 0.8, $\alpha = 0.05$) shows the within-between interaction sensitivity to effect sizes based on total sample size and indicates that the present study will be sensitive to medium ($f(V) \sim 0.4$) to large ($f(V) \sim 0.5$) effect size even with 20% attrition. These same parameters yield sensitivity to medium between-groups ($f(V) = 0.336$) and within-groups ($f(V) = 0.348$) effect sizes.

To protect confidentiality, participants are assigned a subject ID that is used for all materials. Only select team members have access to the code. No identifiers are included in study folders or digital files. Digital data are stored on a secure server to which only select study team members have access. Neuropsychological and outcome data are collected by trained study team members, double scored, and then entered into a secure database. Range checks and double entry will be used to ensure data accuracy. MRI data are transferred to a secure server and analyzed using an "attached" virtual machine. The primary analytic technique for behavioral data will be regression using the SAS mixed procedure (PROC MIXED or another comparable approach), 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, and so forth), although a large amount of missing data is considered unlikely because of the nature of the study and the efforts that will be made to ensure consistent follow-up participation. Each mixed linear model equation will model the change from baseline for one of the outcome measures 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 $P = .05$) even despite randomization (there should be few, if any, given the sample size). Results of primary and secondary outcome measures will be considered significant if $P \leq .05$.

2.9.1. fMRI analyses

Given the anatomic specificity of our hypothesis, our primary fMRI analyses will use a region of interest (ROI) approach following the anatomic boundaries of the left ventrolateral PFC. After single-session preprocessing, we will calculate voxelwise area under the curve in which the hemodynamic response is averaged across all voxels and time points for the previously described contrasts during each of the fMRI session (Sessions 1, 7, and 8). 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 ROI-based data using the same PROC MIXED (or related) procedures. Exploratory whole brain analyses will also be performed to evaluate treatment-induced changes that would suggest compensatory and/or restorative mechanisms. Connectivity analyses will be performed using the ROI as the seed area. 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 object-location touch screen test and face-name generalization task. These behavioral measures are completely independent of the fMRI data and, therefore, will provide an unbiased measure of the relationship between these variables. Exploratory behavioral and fMRI analyses for the working memory and semantic processing tasks will follow the aforementioned analytic plan.

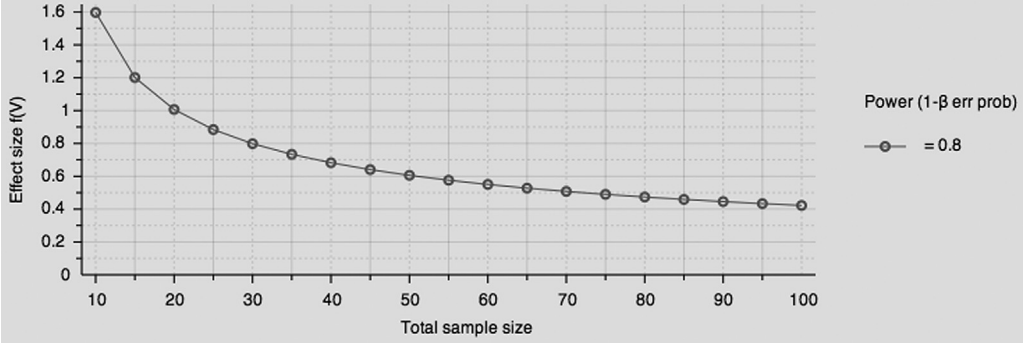

Fig. 3. Sensitivity (80% power) to effect size (y-axis) by total sample size (x-axis) for the present study (figure provided by G*Power 3.1).

3. Discussion

This ongoing double-blind, randomized controlled trial with four parallel groups evaluates the behavioral and neurophysiological changes associated with MST and HD-tDCS in patients with MCI. As discussed previously, prior research indicated that MST enhanced long-term retention of new information but that these benefits were attenuated in more advanced patients. In addition, patients have difficulty spontaneously transferring MST to new types of information—a limitation that makes this type of training task-specific. HD-tDCS was included a method that may enhance functioning on its own, facilitate the acquisition and long-term use of MST, and, perhaps, increase the range of patients who benefit from MST. This approach builds on prior evidence from the motor literature that stimulation may enhance and/or prolong effects of behavioral training [32]. Thus, the difference in outcome measures in Session 6/7 (post-treatment) relative to baseline will provide evidence of near-term efficacy, whereas the difference between post-training and the 3-month follow-up will provide vital information about the persistence of changes and inform the timing of any necessary booster sessions.

Several methodological challenges exist with this type of study and we have adopted a number of procedures to proactively deal with such issues. First, we use a range of methods to enhance retention including didactics about why dropout is so detrimental to longitudinal research, encouraging participants to take part only if they are certain they will complete the study, and providing session reminders (via participant's preferred method of contact). Second, scheduling is tailored to the participants' availability, thereby minimizing conflicts. Third, additional travel funds were allocated to ensure equal access for all interested and eligible participants. Fourth, participants are allowed to take part in all standard clinical care activities. Importantly, however, there are no cognitive or physically based clinical programs for those with MCI that could confound results in the geographical region. Participants are required to be stable on medications for at least 4 weeks before the study and are asked not to alter their medications, unless recommended by their physician, until the end of the study. Any changes in medications or other health conditions are recorded at the time of the next study visit.

Our outcome measures were designed to be ecologically relevant to enhance participant motivation and transfer to everyday life. Although group-level effects are important, the study will yield rich clinical and neuroanatomic data that will be used to identify individual patient factors that affect treatment response. Such factors include cognitive functioning (e.g., scores on standardized neuropsychological testing) as well as the structural (e.g., brain volume/cortical thickness) and functional integrity of the brain at baseline (e.g., resting-state functional connectivity). Together, we expect our findings will provide critical information about these nonpharmacologic approaches that will guide future research and, ideally, meaningfully inform clinical practice in this growing population.

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Author contributions: All authors played a role in study design. B.M.H. drafted and finalized the manuscript with input of all authors.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Ethics approval and consent to participate: The VA Ann Arbor Healthcare System's Institutional Research Board approved this study. All participants provided informed and written consent. Any protocol amendments will be approved by the VA AAHS IRB and necessary modifications made to www.clinicaltrials.gov.

RESEARCH IN CONTEXT

1. Systematic review: Previous studies have demonstrated that mnemonic strategy training can (re) engage key lateral frontoparietal and medial temporal regions thereby enhancing learning and memory, at least under some conditions. It is unclear whether forms of noninvasive brain stimulation can enhance and prolong this effect, thereby improving subjective and objective memory performance in those with memory impairment.
2. Interpretation: The results of the intervention(s) described in this protocol will (1) extend our understanding of the conditions under which cognitively oriented treatments are effective, especially in respect to the transfer of trained skills and (2) evaluate the independent and synergistic effects of noninvasive brain stimulation on learning and memory.
3. Future directions: Study results will identify the extent, magnitude, and persistence of change in memory-related abilities as well as participant-specific predictors of response, thereby enhancing future trial design and facilitating the clinical translation of such methods.

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