Cathodal Transcranial Direct Current Stimulation (tDCS) in Mild Cognitive Impairment (MCI): A Randomized, Double-Blind, Sham-Controlled Pilot Study

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Cathodal Transcranial Direct Current Stimulation (tDCS) in Mild Cognitive Impairment (MCI): A Randomized, Double-Blind, Sham-Controlled Pilot Study

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Title	Cathodal Transcranial Direct Current Stimulation (tDCS) in Mild Cognitive Impairment (MCI): A Randomized, Double-Blind, Sham-Controlled Pilot Study
IRB Protocol Number	16-007478
Phase	Pilot
Study Design	Randomized (1:1), double-blind, sham-controlled
Overall Study Duration	12 months
Participant Participation Duration	8 weeks
Objectives	(1) To compare the effects of cathodal tDCS applied to the right dorsolateral prefrontal cortex (DLPFC) on cognitive outcomes as measured by the NIH Toolbox Cognition Battery 1-month post treatment as compared to baseline in participants with MCI. (2) To compare the effects of cathodal tDCS applied to the right dorsolateral prefrontal cortex (DLPFC) on cognitive outcomes as measured by the NIH Toolbox after 1 session of tDCS in participants who are cognitively unimpaired (CU). (3) To compare the effects of cathodal tDCS applied to the right dorsolateral prefrontal cortex (DLPFC) on cognitive outcomes as measured by the NIH Toolbox after 1 session of tDCS in participants who have MCI.
Number of Participants	44 MCI participants in 5 day intervention: 22 in each arm (active vs sham); 44 CU participants in the 1 day intervention: 22 in each arm (active vs sham); 44 MCI participants in the 1 day intervention: 22 in each arm (active vs sham)
Diagnosis and Main Inclusion Criteria	Diagnosis of mild cognitive impairment or cognitively unimpaired healthy elderly (verified by the Montreal Cognitive Assessment), male/female aged 55-85, right handed
Study Device	Soterix Medical 1x1 Low Intensity Transcranial Electric Stimulator (tES) Model 2001: Stimulates cerebral cortex at low intensity (up to 2mA) resulting in changes in cortical excitability and neural plasticity
Duration of Exposure	5 Day MCI: Cathodal stimulation over the right DLPFC (with reference electrode on left DLPFC) will occur at 1.5mA intensity for 15 minutes over 5 consecutive treatment sessions (completed within 1 week) in participants with MCI. Cathodal stimulation over the right DLPFC (with reference electrode on left DLPFC) will occur at 1.5mA intensity for 15 minutes over 1 treatment session in participants who are cognitively unimpaired (CU) or for participants with MCI who are enrolled in the 1 Day intervention.

Statistical Methodology	Continuous variables will be summarized as a mean ± SD or median (range). Categorical variables will be summarized using number and percentage. Univariate descriptive statistics and frequency distributions will be calculated as appropriate for all variables. Stratified analysis for age in deciles will also be performed. Comparisons between sham and active tDCS (between group comparisons) will be made by one-way Analysis of Covariance (ANCOVA) method to compare the post-intervention test scores adjusting for baseline (pre-intervention) scores for the NIH Toolbox Cognition Battery (NTCB). Paired t-tests will be used for within group comparisons for NTCB scores. The NIH Toolbox Cognition Battery has six subdomains: Executive Function (NIH Toolbox Flanker Inhibitory Control and Attention Test, NIH Toolbox Dimensional Change Card Sort Test), Attention (NIH Toolbox Flanker Inhibitory Control and Attention Test), Episodic Memory (NIH Toolbox Picture Sequence Memory Test, NIH Toolbox Auditory Verbal Learning Test), Language (NIH Toolbox Picture Vocabulary Test, NIH Toolbox Oral Reading Recognition Test), Processing Speed (NIH Toolbox Pattern Comparison Processing Speed Test, NIH Toolbox Oral Symbol Digit Test), Working Memory (NIH Toolbox List Sorting Working Memory Test). Each subdomain separately, in addition to the NIH Toolbox Cognitive Function Composite Score, will be computed using the Fully Adjusted Scale score adjusted to normative data. Statistical significance will be accepted for two-sided p-values less than 0.05. To control for multiple comparison issues, p-values from pairwise comparisons will be adjusted using the false discovery rate method.

Abstract:

Mild cognitive impairment (MCI) is an intermediate stage between normal cognition (cognitively unimpaired) and dementia. MCI represents a critical window of opportunity for intervening and potentially altering the trajectory of cognitive decline. In addition, aging is associated with functional decline in a wide range of cognitive domains, and healthy elderly who are cognitively unimpaired (CU) may have pre-symptomatic cognitive impairment (with underlying brain pathology changes occurring). Transcranial direct current stimulation (tDCS), a non-pharmacological method, provides a non-invasive way to electrically stimulate the brain by altering the excitability of cortical areas by its polarizing effects on neuronal resting membrane potentials. The trajectory of connectivity changes over the disease course of MCI and Alzheimer's disease (AD) is largely unclear. Cross-sectional and longitudinal studies in symptomatic individuals suggest that AD pathology spreads along brain connections, leading to the hypothesis that neurodegenerative diseases might be 'networkopathies.' Studies reveal that many older adults who were cognitively unimpaired (CU) and those with MCI perform worse on cognitive tasks and "over-recruit" brain regions that are not activated in younger cohorts performing the same task. However, this paradigm is still controversial and understudied [1]. Some posit that it supplements the functioning of a failing network, while others propose it is potentially detrimental either through general breakdown in the functional specialization of the cortex, or an inability to shut down activity not related to the cognitive task at hand. Cathodal transcranial direct current stimulation (tDCS) is generally considered to be inhibitory, which may be able to modulate neuroplasticity-related functions, suppress maladaptive patterns, and influence learning by network reorganization [2]. We propose to use low intensity (1.5mA) cathodal/sham tDCS on patients with MCI to stimulate (inhibit) the right DLPFC in five consecutive sessions to address the potential maladaptive over activity seen in early cognitive impairment and to measure cognitive outcomes. We will also use the same tDCS montage on participants who are cognitively unimpaired (CU) who will receive 1 treatment session. In addition, there will be another MCI arm that will receive the same treatment as the CU arm for comparison on the 1 treatment session.

Specific Aims:

1) To compare the effects of 1.5mA cathodal tDCS applied for 5 consecutive days to the right DLPFC on cognitive outcomes in participants with MCI as measured by the NIH Toolbox Cognition Battery at 1 month post treatment compared to baseline.

1) We will assess whether 5 consecutive sessions of cathodal tDCS (1.5mA, 15 minute stimulation) applied over the right DLPFC is associated with improved cognitive outcomes after one month. Participants will be randomized 1:1 to active or sham treatment.

2) To compare the short term effects of 1 session of 1.5mA cathodal tDCS applied to the right DLPFC on cognitive outcomes in healthy elderly who are cognitively unimpaired (CU) and MCI as measured by the NIH Toolbox.

2) We will assess whether 1 session of cathodal tDCS (1.5mA, 15 minute stimulation) applied over the right DLPFC is associated with improved cognitive outcomes after 1 treatment session. Participants will be randomized 1:1 to active or sham treatment. We will have two arms- one CU and one MCI.

Hypothesis: Studies indicate that older adults who are cognitively unimpaired who perform worse on cognitive tasks and those with MCI "over-recruit" brain regions that are not activated in younger individuals performing the same task [1]. Here, we hypothesize that inhibition of the right DLPFC counteracts maladaptive recruitment of the bilateral DLPFC, which will affect cognitive outcomes and neurophysiological measurements.

Background/Significance: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation similar to rTMS. The mechanism of action in tDCS is a subthreshold modulation of neuronal membrane potentials, which alters cortical excitability and activity dependent on the current flow direction of the target neurons [3]. tDCS changes the likelihood of neuron action potential discharge. It involves the application of a weak electrical current (1-2mA) through the scalp. Unlike rTMS, tDCS is not focal or localized through MRI, but relies on the International 10-20 electrode placement system. tDCS has the ability to do sham stimulation and can keep the double-blind on the study through pre-programmed settings. tDCS is for investigational use only and is not currently FDA approved.

The trajectory of connectivity changes over the disease course of healthy aging/cognitively unimpaired participants and those with MCI and AD is largely unclear. Cross-sectional and longitudinal studies in symptomatic individuals suggest that pathology spreads along brain connections, leading to the hypothesis that neurodegenerative diseases might be 'networkopathies' [4]. An important study by Guedj et al 2009 investigated the relationship between entorhinal and hippocampal MR volumes and whole-brain SPECT perfusion and connectivity in patients with amnestic MCI with a memory profile suggestive of early AD dementia [5]. They report a strong negative correlation between medial temporal lobe volumes and right dorsolateral prefrontal perfusion at a basal state [5]. This study contrasts the findings of patients with AD where hippocampal atrophy is correlated with a decrease in metabolism in the DLPFC, and suggests that the mechanisms of reorganization, where the right DLPFC may be overactive, affects patients at the stage of MCI [5]. It is unknown whether this relationship, specifically an overactive right DLPFC, compensates for cognitive impairment in an appropriate way or rather, illustrates a maladaptive mechanism related to the lack of normal connectivity. We propose to use cathodal tDCS on patients with MCI and those who are cognitively unimpaired (CU) to stimulate the right DLPFC to address the potential maladaptive over activity seen in early cognitive impairment and measure cognitive outcomes. Other studies have reported enhancement of cognitive function in patients who are CU or have AD or MCI with five or fewer rTMS treatment sessions [6-11]. To our knowledge, the only study employing tDCS in MCI patients employed a single-session protocol, but numerous AD tDCS studies also support enhancement with five or fewer session [12-15]. The importance and clinical relevance of this project is to expand the use of non-invasive brain stimulation (tDCS) in Arizona, with the hopes of translating this into clinical practice. The results of this project will improve AZ practice of medicine and advance the body of scientific knowledge in the field of MCI. This project will be the first in AZ to utilize the Soterix tES device, which serves as important leverage to establish project feasibility and to increase awareness and visibility of this technology at MCA and its availability to all investigators in all departments. The advantages of tDCS include portability (can be used anywhere in MCA), inherent NSR determination, and ease of use for interested investigators.

Experimental Approach:

Accrual plan: Participants will be identified though medical records, a flyer posted internally at Mayo Clinic Scottsdale and Phoenix, and by referrals from other Mayo physicians. The HABIT program led by Dr. Dona Locke is very visible in the MCI community, and there exists a database of past MCI participants who may be interested in joining. Approval from the Mayo Clinic Institutional Review Board is necessary and all participants will provide written informed consent prior to participation in this study.

Power and Sample Size Calculation**:** A systematic review and meta-analysis examining effects of tDCS on cognitive function in AD shows an estimate effect size of 0.76 on outcomes similar to that of the NIH Toolbox Cognition Battery [16]; for our pilot study, a conservative estimate effect size (d=0.60) was used due to time of

intervention. A calculated sample size of 38 (19 for each group) was derived from an ANCOVA method adjusting for pre-intervention scores with an alpha of 0.05 error, which will have 70% power to reject the null hypothesis. Thus, 38 participants (19 in each arm) will provide sufficient power. For the 5 day intervention, **we aim to enroll 44 participants with MCI total (22 in each arm), with an anticipated drop out or loss-to-follow up accounted for 10-15% in the statistical analysis to realistically achieve 19 participants per group. For the 1 day intervention, both the cognitively unimpaired group and MCI group will be identical: we aim to enroll 44 CU participants (22 in each arm) and 44 MCI participants (22 in each arm), with an anticipated drop out or loss-to-follow up accounted for 10-15% in the statistical analysis to realistically achieve 19 participants per group.**

Sex/minority mix: Although studies have found a higher incidence and prevalence of MCI in men, this study will strive to include 50% women [17, 18]. No discrimination or exclusion of female or minority participants will occur. Adherence to the inclusion and exclusion criteria of the study will be free of bias from race, gender, culture or religious background.

Inclusion Criteria:

- Male or female outpatients with confirmed MCI diagnosis or who are cognitively unimpaired (CU) as verified by the Montreal Cognitive Assessment (MoCA) scoring ≥26.
- Age 55-85
- Right handed (tested using the Edinburgh handedness inventory [19])
- Total PHQ-8 of ≤ 9 which signifies no moderate or severe depression [20]
- All participants and/or caregivers must be able to provide informed consent

Exclusion Criteria:

- Neurodegenerative disease (e.g. Parkinson's, Huntington's, Multiple Sclerosis) other than MCI
- Previous brain lesion
- Intracranial abnormality such as prior stroke
- History of seizure disorder or epilepsy
- A "true" positive response, after patient clarification, to any question on the modified TMS/tDCS Adult Safety Screen questionnaire that would impact patient safety [21] (Refer to **Appendix A**)
- Any history of brain stimulation treatment (e.g., electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagal nerve therapy (VNS), deep brain stimulation (DBS))
- Use of any investigational drug within 4 weeks
- Cardiac pacemakers, implanted medication pumps, intracardiac lines; acute or unstable cardiac disease; intracranial implants (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head (exception: mouth/dental work) that cannot be safely removed
- Known or suspected pregnancy (extremely unlikely as the age range for this study is 55-85 years)

Intervention (independent variable): 5 Day intervention (MCI): Five consecutive weekday tDCS sessions with the Soterix tES system; 1 Day intervention (CU and MCI): 1 tDCS session. Each tDCS session will include cathode electrode placement over the right DLPFC (using the International 10-20 system) at 1.5mA intensity for 15 minutes with anode reference electrode placement over the left DLPFC. The CogState Brief Battery (One Card Learning and One Back Test) is a computerized cognitive battery that will be administered while participants undergo either active or sham tDCS stimulation. Patients who meet the inclusion criteria for the study will be randomized in a 1:1 fashion between sham and active TMS treatment. For this study, we will stratify age in deciles (55-65 years, 66-75 years, 76-85 years), as age is the number one risk factor for neurodegenerative disease. Following randomization, the patients and investigator will be blinded to the treatment group assignment and staff administering treatment will be unblinded. Refer to **Appendix B** for more information regarding device description.

Study Schedule: 5-Day MCI	Pre-Intervention		5 Day Intervention					Follow-Up
	Estimated Time	Screening & Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	1 Month Follow up
Informed Consent	*1 hour*	x						
Eligibility Checklist[1]	*10 minutes*	x						
Adverse Event Monitoring	*5 minutes*		x	x	x	x	x	
NIH Toolbox: Cognitive Battery[2]	*30 minutes*	x					x[3]	x
CogState Brief Battery[4] (Simultaneous with intervention)	*15 minutes*		x	x	x	x	x	
Intervention: 1.5mA tDCS	*15 minutes*		x	x	x	x	x	

1. Eligibility checklist includes review of inclusion/exclusion criteria, the modified TMS/tDCS Adult Safety Screen questionnaire, Edinburgh handedness inventory, and PHQ-8 questionnaire

2. NIH Toolbox Cognitive Battery includes: NIH Toolbox Picture Vocabulary Test, Flanker Inhibitory Control and Attention Test, List Sorting Working Memory Test, Dimensional Card Sort Test, Pattern Comparison Processing Speed Test, Picture Sequence Memory Test, Oral Reading Recognition Test

3. NIH Toolbox: Cognitive Battery will be administered 5 minutes after stimulation on Day 5

4. CogState Brief Battery will be administered while active or sham stimulation occurs

The study will be performed over 7 sessions **for MCI participants in the 5 Day Intervention (Figure 1):**

- **Visit 1 (Screening and Baseline visit):** This will occur ~1-2 weeks before the Five Day Intervention. The purpose of this visit is to obtain informed consent for the study, to screen participants for inclusion and exclusion criteria, and obtain baseline performance of the participant's NIH Toolbox Cognition Battery and CogState Brief Battery (One Card Learning and One Back Test).The TMS/tDCS Adult Safety Screen questionnaire, Edinburgh handedness assessment, and the PHQ-8 will also be administered.
- **Visits 2-6 (Five Day Intervention Days 1-5):** During these visits the participant will receive either active tDCS or sham stimulation. The CogState Brief Battery (One Card Learning and One Back Test) will be administered during stimulation. The visits will take place during a 1-week period (Day 1-5 corresponds to visits 2-6), as five consecutive visits (Monday-Friday). An Adverse Event questionnaire will be administered after each visit. On Visit 5 (last day of intervention), all participants will complete the NIH Toolbox Cognition Battery testing after stimulation.
- **Visit 7 (One month after completion of intervention) follow up visit:** Participants will undergo final NIH Toolbox Cognition Battery. A questionnaire for blind assessment will also be completed.

Study Schedule: 1-Day MCI and CU	*Estimated Time*	Pre-Intervention	Intervention	Post-Intervention
Informed Consent	*1 hour*	x		
Eligibility Checklist[1]	*10 minutes*	x		
Adverse Event Monitoring	*5 minutes*		x	
NIH Toolbox: Cognitive Battery[2]	*30 minutes*	x		x[3]
CogState Brief Battery[4] (Simultaneous with intervention)	*15 minutes*		x	
Intervention: 1.5mA tDCS	*15 minutes*		x	

1. Eligibility checklist includes review of inclusion/exclusion criteria, the Montreal Cognitive Assessment (MoCA) >26 (for CU group only), the modified TMS/tDCS Adult Safety Screen questionnaire, Edinburgh handedness inventory, and PHQ-8 questionnaire

2. NIH Toolbox Cognitive Battery includes: NIH Toolbox Picture Vocabulary Test, Flanker Inhibitory Control and Attention Test, List Sorting Working Memory Test, Dimensional Card Sort Test, Pattern Comparison Processing Speed Test, Picture Sequence Memory Test, Oral Reading Recognition Test

3. NIH Toolbox: Cognitive Battery will be administered 5 minutes after stimulation

4. CogState Brief Battery will be administered while active or sham stimulation occurs

For participants in the 1 day session (MCI and CU) (**Figure 2)**, one visit will include a screening/baseline assessment to screen participants who inclusion and exclusion criteria, and to obtain baseline performance with the NIH Toolbox. The TMS/tDCS Adult Safety Screen questionnaire, Edinburgh handedness assessment, and the PHQ-8 will also be administered, as well as the Montreal Cognitive Assessment (MoCA) >26 for CU participants. Following that, a 15 minute tDCS treatment (active or sham) will be administered and after a rest break, the same assessment using the NIH Toolbox will be repeated. During the tDCS treatment, the participant will do the CogState Brief Battery (One Card Learning and One Back Test). An adverse event questionnaire will be administered after the stimulation.

Risks and Adverse Events: For a full list of risks, see **Appendix C** for more information on anticipated risks**.** A symptom-based questionnaire will be used to measure adverse events and will be administered at each visit after the screening visit. The frequency and percentage of adverse events will be compared between the 2 treatment arms. Comparisons between arms will be made by using either the Chi-square or the Fisher's exact test.

Safety Evaluation: A literature review showed that all tDCS trials between 1998-2010 [22] showed that of the 209 studies, similar rates in frequency of adverse events in the active vs. sham arms were observed. The most common AE were headache, itching, burning, discomfort and tingling, occurring in 10-40% of patients regardless of treatment group. Refer to **Appendix D** for the Data and Safety Monitoring Plan.

Efficacy Evaluation**:** The primary outcome measurement is the NIH Toolbox Cognition Battery either at 1 month after intervention (MCI) or after 1 tDCS session (CU and MCI) as compared to baseline scores.

Expected outcomes: We anticipate a change in the NIH Toolbox Cognition Battery scores in the 1-month follow up scores (MCI) or after 1 tDCS session (CU and MCI) as compared to baseline and do not anticipate any change in the sham group.

Statistical analysis: Continuous variables will be summarized as a mean ± SD or median. Categorical variables will be summarized using number and percentage. Univariate descriptive statistics and frequency distributions

will be calculated as appropriate for all variables. Stratified analysis for age in deciles and sex will also be performed. Comparisons between sham and active tDCS (between group comparisons) will be made by one-way Analysis of Covariance (ANCOVA) method to compare the post-intervention test scores between active tDCS group and sham group and adjusting for their baseline (pre-intervetion) scores for the NIH Toolbox Cognition Battery. Paired t-tests will be used for within groups for ADAS-cog scores. For analysis of the NIH Cognition Battery, the same method (ANCOVA, paired t-test) will be used. NIH Toolbox Cognition Battery has six subdomains: Executive Function (NIH Toolbox Flanker Inhibitory Control and Attention Test, NIH Toolbox Dimensional Change Card Sort Test), Attention (NIH Toolbox Flanker Inhibitory Control and Attention Test), Episodic Memory (NIH Toolbox Picture Sequence Memory Test, NIH Toolbox Auditory Verbal Learning test), Language (NIH Toolbox Picture Vocabulary Test, NIH Toolbox Oral Reading Recognition Test), Processing Speed (NIH Toolbox Pattern Comparison Processing Speed Test, NIH Toolbox Oral Symbol Digit Test), Working Memory (NIH Toolbox List Sorting Working Memory Test). Each subdomain separately, in addition to the NIH Toolbox Cognitive Function Composite Score, will be computed using the Fully Adjusted Scale score adjusted to normative data. CogState Brief Battery (One Card Learning and One Back Test) will not be included in statistical analysis. Statistical significance will be accepted for two-sided p-values less than 0.05. To control for multiple comparison issues, pairwise comparisons p-values between the groups will be adjusted using the false discovery rate method.

Potential pitfalls & alternative approaches: *Enrollment:* We may be unable to fulfill the planned enrollment schedule of 44 MCI participants within 1 year. If we see enrollment not achieved by Year 1, we will extend the study to Year 2 and consider alternative recruitment strategies (addition of remuneration, etc). *MCI evolution:* Not everyone diagnosed with MCI will go on to develop dementia, and not everyone who develops dementia will develop AD dementia. It is possible brain pathology will have different underlying components (beta amyloid, tau, alpha-synuclein) in participants. Therefore, the MCI group is heterogeneous at best. It should be recognized that there might be a direct interaction between pathology and the subsequent treatment response. *Feasibility:* This is a pilot study to determine feasibility and collect requisite pilot data for grant applications.

Data management: All participant material will be de-identified and stored in a locked cabinet. Any electronically recorded data will be stored on a password-protected hard-drive on a secured, study-specific computer. A Microsoft Excel database will be developed to record data. All data will be double entered. A comparison will be run between the primary and secondary entries to detect inconsistencies and data entry errors. The data will be checked item-by-item against the raw data, and random errors will be corrected. When systematic errors are found, data entry will stop and the data management system will be evaluated. All investigators have completed required training by IRB. Confidentiality will be protected through the use of study identification numbers that will be kept separate from personal identifiers. All study documents will be kept in locked file cabinets in the Collaborative Research Building at Mayo Clinic in Arizona. All study materials will identify participants solely by the assigned code numbers. We will take all necessary steps to protect the confidentiality of all data and computer records.

Feasibility and Time Frame:

	Months 1-2	Months 3-4	Months 5-6	Months 7-8	Months 9-10	Months 11-12
Training of staff, IRB approval						
Recruitment of participants						
Data collection						
Data Analysis						
Manuscript						

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Appendix A: tDCS/**TMS Adult Safety Screen (TASS) Questionnaire:**

1. Have you ever had an adverse reaction to TMS/tDCS?
2. Have you ever had a seizure?
3. Have you ever had a stroke?
4. Have you ever had a head injury (including neurosurgery)?
5. Do you have any metal in your head (outside of your mouth), such as shrapnel, surgical clips, or fragments from welding or metalwork?
6. Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines?
7. Do you suffer from frequent or severe headaches?
8. Have you ever had any other brain-related condition?
9. Have you ever had any illness that caused brain injury?
10. Are you taking medications?
11. If you are a woman of childbearing age, are you sexually active, and if so, are you not using a reliable method of birth control?
12. Does anyone in your family have epilepsy?
13. Do you need further explanation of TMS/tDCS and its associated risks?

*If any question is answered in the “yes” direction, further investigate the question and seek clarification.

(Adapted from [21] Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol. 2001;112(4):720.)

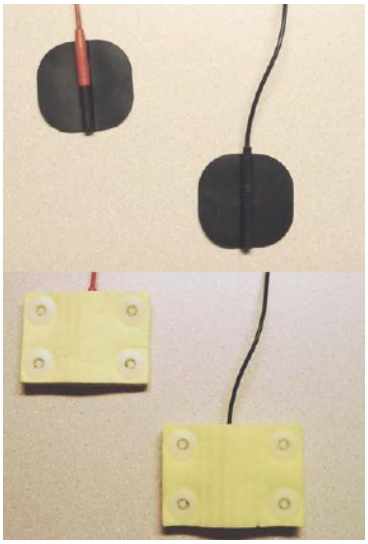
Appendix B: **Soterix tES Device Description**

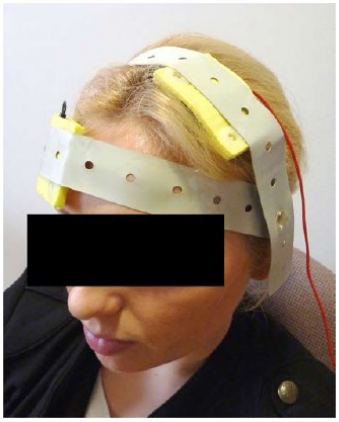
Device Description
The Soterix Medical 1x1 Low Intensity Transcranial Electrical Stimulator (tES) Model 2001 is a device that delivers low-intensity electrical current to the scalp and brain with the aim of modulating brain function non-invasively. Stimulation is applied via 2 electrodes (anode and cathode) covered by saline-soaked sponges that are held against the scalp by a pair of large, adjustable head straps. During stimulation, a small current (2mA or less) is applied to the scalp, resulting in a smaller about of current reaching the underlying cerebral cortex. The device is powered by two 9-volt alkaline batteries.

No tDCS devices are currently FDA-approved for transcranial stimulation. tDCS devices are often determined by the FDA to constitute nonsignificant risk in research protocols.

The stimulator is comprised of a small control box (length 7.91 in., width 5.9 in., height 2.83 in.) that contains the power source (2 9-volt alkaline batteries), displays (actual current delivered, impedance/contact quality, stimulation time remaining, low battery indicator), and controls (power, current intensity, stimulation duration, stimulation “start,” and emergency abort). The device’s maximum output voltage is 40V +/- 5%, and maximum output current is 2mA DC +/- 1%.

Pictures below depict the tDCS devive (1x1 tES), electrodes and sponges, and representative illustration of participant wearing the device.





Appendix C: Anticipated Risks

There is ample literature supporting the safety of tDCS, including several systematic reviews. Brunoni et al. (2011)[22] reviewed 209 tDCS studies, the majority of which involved healthy control adult participants and single-session tDCS; of these, 74 studies (with 1851 participants) included reporting of AEs. The authors noted that tDCS appeared well-tolerated overall, with relatively mild AEs (scalp itching in 39.3%; tingling sensations, 22.2%; headache, 14.8%; scalp discomfort, 10.4%; burning sensations, 8.7%) in those receiving active tDCS, and with no difference in AE rates between those receiving active and sham treatments. Aparício et al. (2016)[23] presented an updated systematic review of 64 randomized controlled trials (2262 participants) whose protocols involved five or more treatment sessions. By contrast, the majority of studies included in this review consisted of samples with neurologic and psychiatric conditions. Participants receiving active tDCS did not drop out of studies at higher rates that those receiving sham, and nearly half of studies reported no dropouts, indicating good acceptability of tDCS over multiple sessions. Another recent review by Bikson and colleagues (2016)[24] notes that over 33,200 sessions of tDCS have been performed in human participants across a range of treatment parameters, without any serious adverse events (SAEs) or evidence of irreversible injury reported.

Seizures: **No reports have been published of seizures following tDCS at the rate and strength of the stimulation in this study.** However, individuals who have a history of epilepsy or have had a seizure during the last 12 months will be excluded from this research study.

Seizure management plan and precautions to ensure safety of participants

A "help" pull cord is available in the treatment room, and access to life-support equipment and antiepileptic drugs are accessible. Furthermore, a clinician trained in seizure management will be on the same floor as the treatment room, and are readily available. In management of seizures, attention must be taken to minimize the risk of aspiration, and when possible, guiding the patient into the left lateral decubitus position is desirable. Because most seizures are brief (typically <60 seconds) and without serious physical sequelae, efforts will be focused on preventing complications of the seizure rather than initiating any specific medication that is not required unless a seizure is prolonged. If a prolonged seizure (>60 seconds) is identified, appropriate response measures will be initiated which may include notifying a hospital-based rapid response team and/or escorting patient to the nearest emergency department upon stabilization. If a seizure occurs during the active treatment phase of the study, active treatment as part of the study will be discontinued. Ongoing monitoring of neurocognitive symptoms per the study protocol will be offered.

Other potential side effects of tDCS that may be experienced *during* treatment

- Skin Irritation: There is a risk of mild skin irritation at the location where the electrode sensors have been placed, but this usually consists of minor redness that will go away quickly after they are removed. Localized tingling sensation, itching, skin erythema, scalp discomfort, and burning sensations have also been reported equally in active and sham tDCS and resolve after treatment.
- Headache: A mild headache can occur following tDCS treatment that usually resolves soon after the procedure. We will try to reduce the risk of headache by assuring the participant's comfort before and during the procedures.

Treatment plan for other side effects of rTMS experienced *during* treatment

Prophylactic use of acetaminophen or ibuprofen will be recommended, but not provided, to participants reporting painful sensations at stimulation site or discomfort. Any report of scalp burning sensation by a participant will result in discontinuation of treatment for the day. Treatment would be offered the following day or as tolerated within the study timeframe.

Other potential side effects that may be experienced *following* rTMS treatment

Transient redness under the electrode, local pain, headache including migraine, transient dizziness, brief changes in attention and thinking). Severe depression: If a participant states they are severely depressed during the trial, we will promptly refer them to Arizona's Psychiatry and Psychology department. This will be facilitated through Dr. Geda (PI) and Dr. Locke, who are members of the department of psychiatry and psychology and part of the research team.

Treatment plan for other potential side effects experienced *following* treatment:
Participants reporting headaches during or following study treatment will be encouraged to take acetaminophen or ibuprofen prior to the daily treatment. All patients will be monitored, and appropriate treatment will be recommended including the possibility of stopping tDCS. All symptomatic interventions will be recorded in participant's case file.

Device-Related Adverse Event
A device related adverse event is defined as any adverse event for which, at least, a reasonable possibility exists between the event and the investigational device (e.g., the relationship between the device and event cannot be ruled out).

Device Failure, Malfunctions and Near Incidents
Investigators will report all possible device failures, malfunctions or near incidents observed during the course of the trial. These incidents will be documented as follows:
Device Failure: A device failure has occurred when the device is used in compliance with the study protocol, but does not perform as described in device manual and also negatively impacts treatment of the study participant.
Device Malfunction: A device malfunction occurs when an unexpected change to the device that is contradictory to the device manual is observed, which may or may not affect device performance.
Device Misuse: Any use of the investigational device by an investigator that is contradictory to the application described in the study protocol will be categorized as device misuse.

Suicide Risk: It should be recognized that suicidal ideation may occur in about 40% of older adults with major depression and of cognitive impairment, ranging from mild cognitive deficits to moderate dementia [25]. We do not anticipate this being an issue in our study as we are screening for depression using the PHQ-8. In addition, we will closely monitor the participant during the course of the treatment, and assess any situation where the participant has any changes in behavior or mood.

Overall Risk Analysis Statement
It is felt that the potential benefits of this study outweigh the risks. The protocol procedures are felt to be safe, are well within previously established tDCS guidelines.

Appendix D – Data and Safety Monitoring Plan

Data and Safety Monitoring Plan

Principal Investigator: Yonas E. Geda, MD, MSc

Study Title: ***Cathodal Transcranial Direct Current Stimulation (tDCS) in Mild Cognitive Impairment (MCI): A Randomized, Double-Blind, Sham Controlled Pilot Study***

IRB Number: 16-007478

1. **Participant Safety**

a) Safety will be monitored by the Investigator and study team
b) Participants will be seen by an appropriately trained health professional at every visit and the evaluation will be documented.
c) Participants will be monitored for adverse events (AEs) throughout every visit.

1.1 Participant Removal from Study

a) Participants may be removed from study participation for any of the following reasons:
    a. Failure to meet inclusion/exclusion criteria
    b. Withdrawal of consent
    c. Lost to follow-up
    d. Other reasons, such as specified administrative reasons
b) The Principal Investigator will make the final decision about termination of study participation

1.2 Reporting Mechanisms

a) IRB Reports
    a. Investigator will determine if event is an UPIRTSO or non-UPIRTSO
    b. UPIRTSOs must be reported to the IRB within 5 working days of knowledge of problem or event (per IRB procedure)
    c. If Investigator determines event to be a non-UPIRTSO, event will be reported at continuing review

2. Data Integrity

a) Data is entered into an excel spreadsheet
b) Study data will be reviewed regularly by the Investigator and Co-Investigators for the following:
    a. Participant inclusion criteria has been met
    b. Transcription of data is accurate and complete
    c. Units of measure are recorded appropriately

3. **Participant Privacy**

a) Study visits will take place in a confidential setting

4. **Data Confidentiality**

a) Non-electronic source document data will be stored in a locked cabinet in a secure office. Only authorized study staff will have access.
b) Electronic data will be stored on a secure database. Only authorized users will have access. All users will have unique identifiers and passwords. Sharing of log-in information is not permitted.

5. **Product Accountability**

a) Not applicable

6. **Study Documentation**

a) Quality assurance will be conducted on a regular basis by the study team to assure that required documentation and reports are on file, accurate, and completed

7. **Study Coordination**
   a) Study staff will be thoroughly educated about the protocol and requirements of the study
   b) All study activities will be conducted by study staff within their appropriate scope of education
   c) Study staff will have regular meetings to ensure that the study is conducted in a systematic manner by all who contribute
   d) Study team will have open communication to assure that ideas and concerns are addressed in a timely manner