Official Title: Application of Transcranial Alternating Current Stimulation for Modulation of Sleep and Cognitive Performance

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I. OBJECTIVES

Impaired sleep, in particular fragmented sleep and loss of slow wave activity (SWA) during non-rapid-eye-movement (NREM) sleep, is known to occur during the physiologic process of aging (1-3). Disrupted sleep is particularly pronounced among patients with diagnoses of Mild Cognitive Impairment (MCI) and those who progress to Alzheimer's Disease (AD), and is associated with worsening of cognitive impairment with progression of brain pathophysiology (4, 5). Recent advances in non-invasive neuromodulation via transcranial electric stimulation (tES) offer a chance for immediate impact on sleep and cognition, with a safe and readily available technology (6, 7). Neurophysiologic mechanisms of tES have been elucidated in both animal and human brains, and include local changes in cortical excitability (8, 9) and synaptic plasticity (10), with global modulation of cortical networks and functional connectivity (11, 12). Transcranial alternating current stimulation (tACS), a type of tES, has been demonstrated to modulate sleep architecture and cognitive performance when applied during SWA (7, 13). *Thus, we propose that application of tACS has the potential to improve sleep quality among patients with MCI, and to additionally improve measures of cognitive performance, mood, and quality of life.*

Hypotheses and Specific Aims: The purpose of this research is to investigate the utility of transcranial alternating current stimulation (tACS) to modulate sleep, cognition, mood, and quality of life among normal healthy adults, older adults, as well as individuals with mild cognitive impairment (MCI). We will do this with the following Specific Aims:

1). Optimize tACS parameters for duration, intensity and frequencies via utilization of EEG data recorded during tACS stimulation.

2). Determine whether recording artifacts introduced by tACS can confidently be removed from EEG signals.

3). Determine effects of tACS delivered with nested frequencies(multi-frequency signal) vs single frequency tACS, with regard to intrinsic EEG signal, for modulation of SWA coherence and power, as recorded in our overnight EEG sleep data.

4). Determine the cumulative effects of tACS delivered in multiple, consecutive nights on underlying EEG signals, sleep architecture, sleep quality and cognitive function among patients with MCI.

5). Determine if tACS is a viable treatment for disturbances of sleep and cognitive performance among patients with MCI.

6). Generate pilot data and manuscripts to support applications for larger randomized placebo-controlled clinical trials.

We hypothesize that through multiple and consecutive sessions, there are cumulative effects of tACS on sleep architecture, with subsequent impacts on cognitive performance, mood and quality of life among normal health adults, older adults, as well as individuals with MCI.

II. BACKGROUND AND SIGNIFICANCE

Transcranial alternating current stimulation (tACS) is a form of transcranial electrical stimulation (tES), similar to transcranial direct current stimulation (tDCS), each of which utilizes scalp electrodes to deliver current at low amperage through brain cortex. In the case the tACS this current is set to alternate in a specific frequency (14). This transcranial current flow has been demonstrated to alter cellular membrane potentials, with subsequent alteration of cortical excitability and synaptic potentiation (10). The use of tES in human trials has increased markedly within the last 15 years, and to date hundreds of trials with thousands of subjects have been reported without any serious side effects (10, 15). The benefits of tES have been demonstrated in treating the cognitive symptoms of many neurological illnesses including Alzheimer's disease, Parkinson's disease, stroke, depression and epilepsy; notably with exceptional tolerability and without any major safety concerns reported (16-22).

Unique to tACS is the ability to entrain underlying EEG rhythms with subsequent effects on spectral power and coherence of specific EEG frequencies (23). tACS has been demonstrated to modulate multiple domains of cognition and underlying brain networks, in a mechanism that is dependent on both frequency and location of cortical stimulation sites (reviewed in (24)). With respect to sleep modulation, tACS has been demonstrated to enhance slow wave sleep duration and quality in healthy adults, with subsequent improvement of cognitive performance in memory encoding (7, 13, 25). The use of tACS for such studies has until now relied on conventional sleep lab polysomnography for assessment of EEG and delivery of tACS. Recent innovations in EEG and tES technology, however, have now enabled both tES studies (26, 27), and EEG sleep studies (28) to be performed unsupervised in an at-home protocol. Our proposed study will utilize at-home tACS with simultaneous EEG monitoring to demonstrate feasibility in treating and assessing sleep impairment and accompanying cognitive impairment. Data and manuscripts from this work will be used to support applications for funding larger scale studies using remote treatment and assessment, and thus provide a paradigm which is more feasible to translate and implement in clinical settings.

Sleep impairment is common among patients with MCI and AD, and has been associated with worsening cognitive function and progression of the neurodegenerative process (reviewed in (29)). The pathological process of Aβ and tau accumulation has been associated with disruption of normal sleep physiology (4, 30, 31), and has been more specifically linked with the loss of SWA during NREM that is the hallmark of disease progression in MCI and AD (32). The process of memory consolidation occurs during SWA, and the loss of SWA in the context of disrupted sleep physiology has been demonstrated to produce symptoms of cognitive impairment (3, 32, 33). Further, a causal relationship between disruption of sleep and progression of neurodegenerative process has been demonstrated in animal models of AD (34, 35), and it has been suggested that a bi-directional relationship exists between sleep disruption and worsening AD pathology, with one of the functions of sleep being to clear toxic compounds from the brain (reviewed in (36)). Thus, targeted interventions to improve sleep physiology offer opportunities for clinical intervention, which may not only treat symptoms of cognitive impairment, but may also slow or reverse the progression of neurodegeneration from MCI to AD.

Our objectives are to assess the effects of tACS on sleep architecture in EEG recording, as well as effects on sleep quality and cognitive function, for the purpose of developing large scale, randomized, placebo-controlled clinical trials. We propose that this technology is fundamentally safe, and relatively cost effective. Demonstration of successful tACS pilot studies will allow for development of subsequent studies with broad application to studies of brain and sleep neurophysiology, as well as to more rapid

development of therapeutics for treatment of patients with neurodegenerative disease including MCI and AD and potentially neuroprotective trials.

III. PRELIMINARY STUDIES

The PI has assisted both planning and execution of tDCS and transcranial magnetic stimulation (TMS) experiments with his primary mentor. The mentor has significant experience in the application of TMS, has ongoing tDCS experiments (COMIRB 15-1035), and has completed training in the safety and use of tDCS in healthy adults and clinical populations at the Berenson-Allen Center for Noninvasive Brain Stimulation (Harvard Medical School) and has trained numerous graduate students and clinicians in the safe application of noninvasive brain stimulation in clinical and research contexts.

IV. RESEARCH STUDY DESIGN

1. **Optimization of tACS settings during sleep:** In this branch of our study we will optimize our tACS delivery in normal healthy research subjects by assessing response to EEG signal during stimulation. Recent developments in tACS technique allow for analysis of data acquired during tACS,(37) and this branch of our study will utilize this novel capability to determine optimal tACS stimulation intensity, duration, and frequencies for enhancement of slow wave sleep. This will be a single night tACS treatment, and multiple variables of tACS stimulation (different intensities, durations, and frequencies) will be applied for each subject. The outcome measures will be slow wave activity power, as well as synchronization of EEG signals in our recordings before, during and after tACS.

The subjects will initially be assigned to receive tACS with frequency, intensity and duration parameters in ranges similar to published trials utilizing tACS during sleep (0.75 Hz, five minutes duration, 0.318 mA/cm^2) (7, 25). Each of these tACS variables will be stepwise modulated, with multiple sets of parameters used sequentially for each subject night of sleep. EEG data will be analyzed for each stimulation condition to determine optimal response to tACS with regard to frequencies, intensity, and duration. Sequential subjects will receive iterations of optimization to allow for refinement of tACS response in EEG recorded data. We predict that measurable changes in EEG slow wave power, measured between 0.5-2 Hz, can be determined within single subjects via processing EEG data obtained during stimulation. This proposal seeks to enroll up to 52 subjects to allow for multiple cycles of optimization and repetition of parameters across multiple individuals. Optimal tACS parameters will then be applied for subsequent steps of the experiments outlined below.

2. Optimization of tACS and EEG recording settings while awake: In this branch of our study we will optimize our tACS delivery and EEG recording parameters during the awake state in normal healthy research subjects. The ability to record and analyze EEG signals during tACS requires successful removal of recording artifacts from the EEG signals. In this branch of the study we will record EEG in the MEG laboratory setting while subjects are awake to assist optimization of EEG recording and artifact removal.

The subjects will be assigned to receive tACS with frequency, intensity and duration parameters in ranges similar to our sleep optimization steps. The tACS variables will be stepwise modulated, with multiple sets of parameters used sequentially for each subject while subjects are awake. EEG data will be recorded with subjects in rest-state, and EEG artifacts will be introduced into the recording electrodes to assist in examination of artifacts that are encountered with application of tACS. We predict that tACS artifacts can be successfully removed from EEG recordings with a high degree of confidence with our optimized recording and stimulating techniques.

This proposal seeks to enroll up to 15 subjects to allow for multiple cycles of optimization and repetition of parameters across multiple individuals.

3. Assessment of multi-frequency nesting effects in tACS among Healthy 18-50 subjects: In this branch of our study we will test healthy 18-50 year old research subjects' response to tACS applied during NREM sleep, with addition of frequency nesting in multiple frequencies which recapitulate

intrinsic sleep EEG signals. Our outcomes will include EEG data, cognitive performance, and assessment of sleep quality. This will be a randomized-controlled cross-over trial with three study arms: a tACS treatment group nesting, a tACS single frequency treatment group, and a sham treatment group.

The subjects will be assigned to one of three treatment groups (tACS nested, tACS single frequency, or sham) using block randomization. Computer-generated randomization will place each subject into one of the study groups initially, then cross each subject the each other condition subsequent sessions. The primary outcome measure is induced EEG power of slow wave sleep of 0.5-2 Hz measured immediately before and after each train of stimulation. To detect a significant change ($p<0.05$) of EEG power increase ≥ 20% above sham, with a power of 0.80, a sample size of 15 subjects will be necessary, based on effect sizes from prior studies (7). Subjects will receive 1 session for each stimulation type, in a cross-over design with at least 1 week between each stimulation condition for wash-out. This will total to 3 sessions for each subject, with a total of 45 sessions for all subjects. Subjects will have up to 24 weeks to complete all study sessions and complete the trial. The proposed study seeks to enroll 30 participants to account for participants that may fail our screening criteria, have unusable data or drop-out of the study before completion. Secondary outcomes will include analysis of slow wave EEG coherence, sleep spindle signal, duration of slow wave sleep, total duration of sleep, word-paired associates task and finger tapping task (7, 25), as well as subjective sleep quality reported on the Consensus Sleep Diary and Pittsburgh Sleep Quality Index (38, 39). Data collection for this study is expected to take 6 months.

4. Assessment of tACS in Older Adult Subjects: In this branch of our study, we will test older adults for response to tACS applied during NREM sleep, with outcomes of EEG data, cognitive performance assessments, as well as assessment of sleep quality, mood, and quality of life measures. In addition, subjects will be screened for decisional capacity via the UCSD Brief Assessment of Capacity to Consent (UBACC), and subjects who are found to have impaired capacity will require a legally authorized representative for consent (40).

In this branch of our study we will test older adults' response to tACS applied during NREM sleep, with addition of frequency nesting in multiple frequencies which recapitulate intrinsic sleep EEG signals. Nested tACS will be applied in-phase in reference to underlying EEG signal using closed-loop stimulation. Our outcomes will include EEG data, cognitive performance, and assessment of sleep quality. This will be a randomized-controlled cross-over trial with two study arms: a tACS treatment group nesting, , and a sham treatment group. Additionally, prior to the two treatment arms, subjects will undergo an adaptation night which gives them the chance to practice using and sleeping with the equipment. There will be no tACS during the adaptation night but EEG will be recorded. Subjects can begin the treatment arms between three days and three weeks after completing the adaptation night.

The subjects will be assigned to one of two treatment groups (tACS nested , or sham) using block randomization. Computer-generated randomization will place each subject into one of the study groups initially, then cross each subject the each other condition for subsequent sessions. The primary outcome measure is induced EEG power of slow wave sleep of 0.5-2 Hz measured immediately before and after each train of stimulation. To detect a significant change ($p<0.05$) of EEG power increase ≥ 20% above sham, with a power of 0.80, a sample size of 15 subjects will be necessary, based on effect sizes from prior studies (7). Subjects will receive 1 session for each stimulation type, in a cross-over design with at least 1 week between each stimulation condition for wash-out. This will total to 2 sessions for each subject, with a total of 30 sessions for all subjects. Subjects will have up to 24 weeks to complete all study sessions and complete the trial. The proposed study seeks to enroll 35 participants to account for participants that may fail our screening criteria, have unusable data or drop-out of the study before completion. Subjects will also be required to have a study partner assist them at home during the adaptation night and treatment sessions. We are NOT collecting any information about the study partner, they are simply required to assist the subjects. Secondary outcomes will include analysis of slow wave EEG coherence, sleep spindle signal, duration of slow wave sleep, total duration of sleep, word-paired associates task and finger tapping task (7, 25), as well as subjective sleep quality reported

on the Consensus Sleep Diary and Pittsburgh Sleep Quality Index (38, 39). Data collection for this study is expected to take 6 months.

5. Assessment of tACS in MCI Subjects: In this branch of our study, we will test individuals with MCI for response to tACS applied during NREM sleep, with outcomes of EEG data, cognitive performance assessments, as well as assessment of sleep quality, mood, and quality of life measures. In addition, subjects will be screened for decisional capacity via the UCSD Brief Assessment of Capacity to Consent (UBACC), and subjects who are found to have impaired capacity will require a legally authorized representative for consent (40).

This will be a randomized-controlled trial with two study arms: a tACS treatment phase and a sham treatment phase. The subjects will be assigned to one of two treatment groups (tACS vs sham) in a 1:1 ratio using block randomization. Stimulation will be applied in-phase, single frequency or nested, if indicated based on the results of experiments 1 and 2. Computer-generated randomization will place each subject into one of the study groups. The primary outcome measured is EEG power of slow wave sleep of 0.5-2 Hz, measured immediately before and after each train of stimulation. To detect a significant change ($p<0.05$) of EEG power increase ≥ 20% above sham, with a power of 0.80, a sample size of 30 subjects will be necessary. Subjects will receive either stimulation type, tACS or sham, each night for the one week study period, for up to 7 stimulation sessions pending results of Experiment 2. Subjects will have up to 24 weeks to complete all study sessions and complete the trial. The proposed study seeks to enroll 35 participants to account for participants that may fail our screening criteria, have unusable data or drop-out of the study before completion.

Secondary outcomes will include analysis of slow wave EEG coherence, slow and fast spindle activity, duration of slow wave sleep, total duration of sleep, and subjective sleep quality reported on the Consensus Sleep Diary (CSD), Pittsburgh Sleep Quality Index (PSQI), mood assessment by the Hospital Anxiety and Depression Scale (HADS), overall function in the Clinical Global Impression of Change (CGIC).

Consensus Sleep Diary (CSD)

The CSD is a sleep journal instrument that is designed to measure sleep and has been validated for intervention trials in insomnia (38, 41).

Word Paired-Associate Task

Our computerized paired-associate task consists of 48 semantically related words selected from a normative database with assessment of memory encoding on recollection performance (25, 42)

Finger Tapping Task

This is a finger sequence tapping task of procedural memory. Subjects repeatedly finger-tap with their non-dominant hand a five-element sequence presented on a computer monitor, e.g. 4-2-3-1-4, as fast and accurately as possible on a key board (7).

Pittsburgh Sleep Quality Index (PSQI)

This is a 10 question questionnaire consisting of questions related to usual sleep habits (39).

The Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14 item self-assessment scale for rapid detection of anxiety and depression (43, 44).

Clinical Global Impression of change (CGIC; for patient, caregiver and clinician)

The CGIC is a three question assessment that consists of global measures to score severity of illness, global improvement, and efficacy index (45).

V. FUNDING

The American Academy of Neurology and Rocky Mountain Alzheimer's Disease Center are paying for this study.

VI. ABOUT THE SUBJECTS

Subject Population(s)	*Number to be enrolled*
Optimization-Asleep	52
Optimization-Wake	15
Healthy 18-50 Year Olds	30
Older Adult Subjects	35
MCI subjects	35

Optimization-Asleep:
Inclusion Criteria- The subject population will be individuals between the ages of 18-70 who are fluent in English
Exclusion Criteria-

- brain tumors
- skull defects
- epilepsy
- metal implants/devices above the neck
- eczema or sensitive skin
- severe insomnia that interferes with subject's ability to sleep
- currently taking sedatives and/or sleeping medications
- sleep apnea that requires CPAP
- REM-sleep behavior disorder
- currently pregnant or trying to become pregnant during the study period
- diagnosis of cognitive impairment.

Optimization-Wake:
Inclusion Criteria- The subject population will be individuals between the ages of 18-65 who are fluent in English
Exclusion Criteria-

- brain tumors
- skull defects
- epilepsy
- metal implants/devices above the neck
- eczema or sensitive skin
- severe insomnia that limits ability to sleep
- currently taking sedatives and/or sleeping medications
- sleep apnea that requires CPAP
- REM-sleep behavior disorder
- currently pregnant or trying to become pregnant during the study period
- diagnosis of cognitive impairment.

Healthy 18-50 year olds:

Inclusion Criteria- The subject population will be individuals between the ages of 18-50 who are native English speakers

Exclusion Criteria-

- brain tumors
- skull defects
- epilepsy
- metal implants/devices above the neck
- eczema or sensitive skin
- severe insomnia that limits ability to sleep at night
- currently taking sedatives and/or sleeping medications
- sleep apnea that requires CPAP
- REM-sleep behavior disorder
- currently pregnant or trying to become pregnant during the study period
- diagnosis of cognitive impairment.

Older adult subjects:

Inclusion Criteria- The subject population will be individuals between the ages of 51-85 who are native English speakers. We will further require older adult subjects to enroll in the study with a study partner to help them with the technological aspects of applying equipment and performing home-based cognitive assessments.

Exclusion Criteria-

- brain tumors
- skull defects
- epilepsy
- metal implants/devices above the neck
- eczema or sensitive skin
- severe insomnia that limits ability to sleep at night
- currently taking sedatives and/or sleeping medications
- sleep apnea that requires CPAP
- REM-sleep behavior disorder
- currently pregnant or trying to become pregnant during the study period
- diagnosis of cognitive impairment.

MCI subjects:

Inclusion Criteria- The subject population will be individuals between the ages of 45-90 who meet clinical criteria for diagnosis of amnestic MCI and are native English speakers. We will further require MCI patients enroll in the study with a study partner to help them with technological aspects of applying equipment and performing home-based cognitive assessments.

Exclusion Criteria-

- brain tumors
- skull defects
- epilepsy
- metal implants/devices above the neck
- eczema or sensitive skin
- severe insomnia that limits ability to sleep at night
- currently taking sedatives and/or sleeping medications
- sleep apnea that requires CPAP
- REM-sleep behavior disorder
- currently pregnant or trying to become pregnant during the study period

VII. VULNERABLE POPULATIONS

MCI individuals are considered a vulnerable population due to their cognitive impairment. They are the subject of this research study, and thus MCI individuals must be included. Subjects with diagnosis of MCI will be screened for decisional capacity via the UCSD Brief Assessment of Capacity to Consent (UBACC), and subjects who are found to have impaired capacity will require a legally authorized representative for consent (40).

VIII. RECRUITMENT METHODS

Recruitment of subjects will be done through e-mail notifications and through paper flyers placed in elevators and on bulletin boards throughout Anschutz Medical Campus. Additionally, community outreach will be conducted through paper flyers, Rocky Mountain Alzheimer's Disease Center community newsletters, and/ or email notifications. Flyers will direct participants to contact Nicola Haakonsen (Department of Neurology recruitment specialist) via email or telephone if they are interested and meet the inclusion and exclusion criteria. Pre-screening will be done via phone or email correspondence and will be determined by verifying that they satisfy the eligibility criteria. At this time, we will inform the subjects that they cannot consume alcoholic, caffeinated or nicotine products during the nighttime portion of the study period.

List recruitment methods/materials and attach a copy of each in eRA

1. *Recruitment flyer*

IX. COMPENSATION

Subjects will be paid $25 per home visit (or $25 per awake optimization visit) to participate in this study. Maximum payment amounts for each study arm are listed below.

Sleep Optimization= $25

Awake Optimization= $25

Healthy 18-50= $75

Older Adults= $75

MCI= $175

X. CONSENT PROCESS

Consent will be gathered from the subjects prior to the start of the study testing night, in the MEG facility of Building 500. Participants will be walked through the form with the experimenter upon arrival. All questions from the participant will be answered by the experimenter at this time. Additionally, participants will be provided with a copy of the consent form to keep for their records.

XI. PROCESS TO DOCUMENT CONSENT IN WRITING

Written consent will be obtained and a copy of the form will be given to the study participant. Since English as a primary language is an inclusion criteria, consent forms will only be presented in English.

XII. PROCEDURES

1. tACS FREQUENCY, INTENSITY AND DURATION OPTIMIZATION EXPERIMENTS

INITIAL VISIT

Name of Instrument/tool/procedure	**Purpose (i.e. what data is being collected)**	**Time to complete**

Gather informed consent	Gather consent	15 minutes
EEG/tACS Equipment Trial	Teach subjects proper equipment use/adjust for comfort	45 minutes
Total time		60 minutes

HOME PORTIONS

Name of Instrument/tool/procedure	**Purpose (i.e. what data is being collected)**	**Time to complete**
tDCS/EEG Stimulation and Recording	Gather EEG data before, during and after stimulation	overnight
Total time		Overnight x 1 nights

VISIT TWO

Name of Instrument/tool/procedure	**Purpose (i.e. what data is being collected)**	**Time to complete**
Post-procedure questionnaire	Assess for tolerability of device and address any safety concerns	15 minutes
Collection of Equipment	Collect and Inventory Instruments and Hardware	15 minutes
Total time		30 minutes

2. tACS and EEG ARTIFACT REMOVAL OPTIMIZATION-AWAKE

STUDY VISIT

Name of Instrument/tool/procedure	**Purpose (i.e. what data is being collected)**	**Time to complete**
Gather informed consent	Gather consent	15 minutes
EEG/tACS recordings	Generate EEG data while tACS is applied during awake state for optimization of artifact removal	60 minutes
Total time		75 minutes

3. tACS NESTING EFFECTS EXPERIMENT IN HEALTHY 18-50

INITIAL VISIT

Name of Instrument/tool/procedure	Purpose (i.e. what data is being collected)	Time to complete
Gather informed consent	Gather consent	15 minutes
EEG/tACS Equipment Trial	Teach subjects proper equipment use/adjust for comfort	45 minutes
Total time		60 minutes

HOME PORTIONS

Name of Instrument/tool/procedure	Purpose (i.e. what data is being collected)	Time to complete
tACS/EEG Stimulation and Recording	Gather EEG data before and after stimulation	overnight
Complete Consensus Sleep Diary	Assess Sleep Quality (after each night of study)	10 minutes
Word Paired-Associate Task	Assess Memory Encoding (before and after sleep)	20 minutes
Finger Tapping Task	Assess Procedural Memory (before and after sleep)	15 minutes
Total time		Overnight x 3 nights (1 week apart for washout)

VISITS TWO, FOUR and SIX

Name of Instrument/tool/procedure	Purpose (i.e. what data is being collected)	Time to complete
Post-procedure questionnaire	Assess for tolerability of device and address any safety concerns	15 minutes
Collection of Sleep Diary and Equipment	Collect and Inventory Instruments and Hardware	15 minutes
Total time		30 minutes

VISITS THREE and FIVE

Name of Instrument/tool/procedure	Purpose (i.e. what data is being collected)	Time to complete
EEG/tACS Equipment Distribution	Ensure subjects remember proper equipment use	20 minutes

Total time		20 minutes

4. tACS NESTING EFFECTS EXPERIMENT IN OLDER ADULTS

INITIAL VISIT

Name of Instrument/tool/procedure	**Purpose (i.e. what data is being collected)**	**Time to complete**
Gather informed consent	Gather consent	15 minutes
EEG/tACS Equipment Trial	Teach subjects proper equipment use/adjust for comfort	45 minutes
Total time		60 minutes

HOME PORTION- ADAPTATION NIGHT

Name of Instrument/tool/procedure	**Purpose (i.e. what data is being collected)**	**Time to complete**
EEG Recording	Gather EEG data before and after stimulation	overnight
Complete Consensus Sleep Diary	Assess Sleep Quality (after each night of study)	10 minutes
Total time		Overnight

HOME PORTIONS-tACS TREATMENT NIGHTS

Name of Instrument/tool/procedure	**Purpose (i.e. what data is being collected)**	**Time to complete**
tACS/EEG Stimulation and Recording	Gather EEG data before and after stimulation	overnight
Complete Consensus Sleep Diary	Assess Sleep Quality (after each night of study)	10 minutes
Word Paired-Associate Task	Assess Memory Encoding (before and after sleep)	20 minutes
Finger Tapping Task	Assess Procedural Memory (before and after sleep)	15 minutes
Total time		Overnight x 3 nights (1 week apart for washout)

VISITS TWO, FOUR, and SIX

Name of Instrument/tool/procedure	Purpose (i.e. what data is being collected)	Time to complete
Post-procedure questionnaire	Assess for tolerability of device and address any safety concerns	15 minutes
Collection of Sleep Diary and Equipment	Collect and Inventory Instruments and Hardware	15 minutes
Total time		30 minutes

VISITS THREE, and FIVE

Name of Instrument/tool/procedure	Purpose (i.e. what data is being collected)	Time to complete
EEG/tACS Equipment Distribution	Ensure subjects remember proper equipment use	20 minutes
Total time		20 minutes

5. tACS SLEEP MODULATION MCI EXPERIMENT

INITIAL VISIT

Name of Instrument/tool/procedure	Purpose (i.e. what data is being collected)	Time to complete
Gather informed consent/UBACC	Gather consent/Screen for capacity	15 minutes
EEG/tACS Equipment Trial	Teach subjects proper equipment use/adjust for comfort	45 minutes
HADS	Assess anxiety and depression (to be administered for MCI trial)	5 minutes
CGIC	Assess Global Impression (to be administered for MCI trial)	5 minutes
Total time		60-70 minutes

HOME PORTIONS

Name of Instrument/tool/procedure	Purpose (i.e. what data is being collected)	Time to complete
tDCS/EEG Stimulation and Recording	Gather EEG data before and after stimulation	overnight
Complete Consensus Sleep Diary	Assess Sleep Quality (after each night of study)	10 minutes

Word Paired-Associate Task	Assess Memory Encoding (before and after sleep each night)	20 minutes
Finger Tapping Task	Assess Procedural Memory (before and after sleep)	15 minutes
Total time		Overnight x 7 nights

VISITS TWO, FOUR and SIX

Name of Instrument/tool/procedure	**Purpose (i.e. what data is being collected)**	**Time to complete**
Post-procedure questionnaire	Assess for tolerability of device and address any safety concerns	15 minutes
HADS	Assess anxiety and depression (to be administered for MCI trial)	5 minutes
CGIC	Assess Global Impression (to be administered for MCI trial)	5 minutes
Collection of Sleep Diary and Equipment	Collect and Inventory Instruments and Hardware	15 minutes
Total time		30-40 minutes

VISITS THREE and FIVE

Name of Instrument/tool/procedure	**Purpose (i.e. what data is being collected)**	**Time to complete**
EEG/tACS Equipment Distribution	Ensure subjects remember proper equipment use	20 minutes
Total time		20 minutes

Location

Pre- and post-test sessions will occur in Building 500 of the Anschutz Medical Campus. Testing will occur at the subjects' homes.

tACS Procedure

tACS or sham will be administered using the StarStim stimulator. Anodes of the tACS stimulator will be placed bilaterally at frontal positions on a 10-20 EEG Electrode Placement System and the cathodes will be placed bilaterally on the posterior regions. Oscillating stimulation, ranging between 0 mA to 2.0 mA (maximum current density 0.515 mA/cm^2) will be applied through electrodes in trains up to ten minutes, at frequencies between 0 to 500 Hz in the tACS treatment groups while subjects are in stable stage 2 or deeper NREM sleep on EEG recording (total stimulation time not to exceed 60 minutes). This is similar to prior tACS sleep studies which have safely utilized stimulation protocols within this frequency range (7, 46-48). Our maximum current density is within guidelines of established protocols, and is well below safety thresholds of 14.29 mA/cm^2 from data obtained in animal models (49). All stimulation

parameters are well below currently accepted safety guidelines for tACS (50). Sham condition will be application of electrodes, without activation of current stimulation. The StarStim tACS device is designed to turn on and off automatically, without need for subject control.

XIII. SPECIMEN MANAGEMENT

There will be no specimens taken in this study.

XIV. DATA MANAGEMENT

All efforts will be made to protect the confidentiality of research subjects. All electronic data will be collected via REDCap, de-identified by the research team, and stored on their servers. Only study personnel will have access to the data. The dataset will be stored on a computer that is password-protected, virus-protected, and automatically logs the user off after a period of inactivity. The computer is located in a locked office. The computer will be password protected when not in use. All written data will be stored in a locked file cabinet in a private office, the research office of the Department of Neurology. All personnel involved in the study have completed HIPAA training. Any PHI will be stripped from data files (or shredded from written records) within 6 months of the end of the data collection period such that all PHI will be deleted prior to completion of the final data set. Any publication of data will be reported in aggregate.

XV. WITHDRAWAL OF PARTICIPANTS

Subjects will be withdrawn if they experience adverse effects due to tACS application or are unable to tolerate wearing of equipment. Data from subjects that withdraw will be collected and protected, but not utilized in the data analysis. Follow up will only be performed in the case of adverse events to ensure the safety of the patient.

XVI. RISKS TO PARTICIPANTS

tACS

Over 10,000 research subjects had received tES, including tACS, as of 2014, without any serious side effects reported (51). There has been no evidence of seizures, neuronal pathology, edema or neuropsychological damage (15). At-home, unsupervised, application of tES has been demonstrated to be safe and well-tolerated, without any major adverse events or safety concerns (26, 27). During administration of tES, subjects have reported a mild tingling sensation (70.6%), moderate subjective fatigue (35.3%) and a light itching sensation (30.4%). After administration of tES, subjects have reported mild transient headaches (11.8%), nausea (2.9%) and insomnia (0.98%) (52). Our stimulation parameters (maximum current density 0.515 mA/cm^2) are far below established safety thresholds of 14.29 mA/cm^2 (49). All stimulation parameters within this proposal are well below currently accepted safety guidelines for tACS (50).

Independently-constructed and direct-to-consumer tES devices have been utilized in the home setting, and in scientific study, without any reported significant adverse events and are considered to be safe for use without food and drug administration (FDA) oversight (53, 54). Direct-to-consumer tES devices include the Thynk (http://www.thynk.com/ ;©THYNK) and Foc.us (http://www.foc.us/ ;©FOC.US), which are marketed for multiple purposes including mood regulation, athletic performance, and cognitive enhancement. The Foc.us device is further marketed for sleep enhancement, and is available with a sleep kit to apply tACS at home by consumers. Additional consumer applications include the Halo Sport (http://www.haloneuro.com/ ;©HALO NEUROSCIENCE) tES device, which is available direct-to-consumer without physician or FDA oversight, has been trialed for athletic training by several athletic organizations, including the US Ski and Snowboarding Association (USSA) national Olympic governing body (http://ussa.org/) (55).

The Starstim device, as detailed below, is considered a non-significant risk device, as defined under 21 C.F.R. § 812.3(m). Safety features include integrated limited of current intensity, voltage, and impedance to assure stimulation is kept well below accepted safety guidelines. This device has been designed to allow safe at-home use.

EEG

EEG is a passive recording technology and has been utilized with simultaneous tES devices without any reported major side effects or complications (23, 56). Participants will be assessed for discomfort of the EEG cap prior to its use.

XVII. MANAGEMENT OF RISKS

There are no major risks associated with this study. Regarding the mild tACS side effects listed above, we will minimize these by use of a device with automatic limits of current intensity, voltage, and impedance. Additionally, we will review of tACS session logs, verification of tACS delivery by EEG recording, and patient report inquiry for any side effects.

XVIII. POTENTIAL BENEFITS

Subjects are not expected to benefit from this study. However the risks to participants are minimal given the following: 1) tACS is well tolerated and not associated with any serious adverse side effects 2) The data is not sensitive.

With regard to societal benefits, this study will provide data that may benefit patient populations that suffer from primary sleep disorders, as well as poor sleep due to neurologic and psychiatric illness. This study may indicate that home application of tACS during sleep is a practical and affordable treatment for patients. tACS is an inexpensive, noninvasive, and safe intervention, so providing data that supports its efficacy may substantiate its utility in reducing healthcare costs.

XIX. PROVISIONS TO MONITOR THE DATA FOR THE SAFETY OF PARTICIPANTS

Identification and documentation of adverse events will be the responsibility of the PIs and co-investigators, who will also be performing data collection. Reporting of adverse events will be the responsibility of the principal investigator, Dr. Brice McConnell. A review of summarized safety information will be performed by Dr. McConnell and will occur after 1 subject has participated in the study as well as midway through data collection. The study will be stopped if any serious adverse event occurs. A statistical interim analysis will not be performed given that this study is minimal risk.

XX. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

All efforts will be made to protect the privacy of research subjects. However, since this study does not involve sensitive data, no privacy measures will be taken other than the data management steps outlined in section XIV.

XXI. MEDICAL CARE AND COMPENSATION FOR INJURY

Medical care and compensation for injury are not applicable given that this is a minimal risk study.

XXII. COST TO PARTICIPANTS

There are no costs to subjects.

XXIII. DRUG ADMINISTRATION

Not applicable.

XXIV. INVESTIGATIONAL DEVICES

The StarStim (http://www.neuroelectrics.com) stimulator qualifies as an investigational device. It will deliver the tACS to the patient. The device is battery powered and controlled by a microprocessor for

safety monitoring and to ensure precise current delivery. The device consists of a stimulator, a programmer, and EEG recorder and a set of electrodes. The device is programed with safety features to limit current intensity, voltage, and impedance to assure stimulation is kept well below accepted safety guidelines, and has been designed to allow safe at-home use. There are no anticipated changes to the device during the course of this study. Starstim is considered a non-significant risk device, as defined under 21 C.F.R. § 812.3(m).

XXV. MULTI-SITE STUDIES

Not applicable.

XXVI. SHARING OF RESULTS WITH PARTICIPANTS

Participants interested in the results of the study will receive a summary of findings via mail following completion of data analysis and dissemination of results.

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