Treatment of mild cognitive impairment with transcutaneous vagal nerve stimulation
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Protocol

1. **Title:** Treatment of mild cognitive impairment with transcutaneous vagal nerve stimulation

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4. **Abstract:**

Patients with amnestic mild cognitive impairment (MCI) often have compromised quality of life. Cognitive impairment is a major contributor to decrements in quality of life and progression of MCI often leads to loss of independence and withdrawal from social participation. MCI, in many patients, is an early expression of neurodegenerative disease. Patients with MCI frequently convert to Alzheimer's disease (AD) (12-16 percent by some estimates per year). Treatments for MCI are of limited scope and availability and of limited effectiveness. Thus, there is great need for treatments that can improve cognition and extend quality of life in patients with MCI. Early intervention (prior to the development of dementia) is more likely to successfully treat this population. We propose to investigate the effect of a non-invasive and safe intervention that should have direct influence on brain systems underlying AD, transcutaneous vagal nerve stimulation (tVNS). This promising approach has not yet been studied in patients with MCI.

The hippocampus is a structure that deteriorates in AD. Further, studies have suggested that the locus coeruleus (LC), the brainstem nucleus that is the brain's sole source of norepinephrine (NE), may be one of the first structures that deteriorate in patients with AD. The release of NE in the hippocampus and frontal lobes has an important role in cognition and is critical in mediating memory and attention. The ascending portions of the vagus nerve form synapses within the nucleus of the solitary tract, which projects to the LC and to the hippocampus. The LC also projects directly to the hippocampus. Thus, vagal nerve stimulation (VNS) may ameliorate symptoms of MCI. We have demonstrated, in patients with epilepsy, that VNS improves memory; however, VNS has not been used to treat patients with MCI. VNS can now be performed without surgery by transcutaneous stimulation of the auricular branch with electrodes on the external ear. tVNS has the potential to improve cognition and may even alter the course of decline in patients with MCI. We will employ a multimodal MRI-based neuroimaging approach combined with comprehensive and targeted cognitive testing to assess changes with tVNS in cognition in patients with MCI.

We will evaluate the effects of tVNS on patients who have been diagnosed with MCI. To maximize statistical power, we will employ a cross-over design with tVNS and control stimulation conditions (stimulating an area on the external ear that does not have nerve endings that connect to the vagus). Very little in the way of mechanistic data or understanding of individual differences in response to tVNS in MCI/AD has been published. Thus, this is a necessary study to evaluate the potential utility of tVNS to enhance cognitive performance in patients with MCI. These data may serve as a platform for supporting the development of a clinical trial with this technology.

5. Background:

A1.1 Public health significance 1) The Alzheimer's Association predicts there will be >16 million Americans with AD by the year 2050. 2) AD associated cognitive impairment directly contributes to a decline in quality of life and is thus a major public health concern. 3) Interrupting brain deterioration early in the degenerative process to reduce future disability is a major target of intervention. 4) MCI can be caused by several processes including AD pathology[4-6]. Because of heterogeneity and inconsistencies in the identification of MCI, estimates of prevalence and incidence vary. In a recent meta-analysis of people who are 55 years old or older, the prevalence percentage for patients with MCI in the US ranged from 18.8% - 28.3%[7]. Further, in patients with MCI, approximately 12%-16% convert to dementia each year. 5) Since MCI is associated with neuropsychiatric symptoms and functional decline[8], MCI is associated with declines in quality of life[9]. 6) tVNS is a promising potential 1st line treatment with minimal side effects and multiple vectors of impact on systems that affect cognition including on primary areas of deterioration in MCI/AD. 7) Data from this study will provide mechanistic data on alterations in cognition induced by tVNS and will support the development of more extensive evaluation of this promising intervention.

A1.2 The locus coeruleus Studies of patients with AD have provided experimental evidence that the LC may be one of the earliest sites of AD pathology[1]. Activation of the neurons of the LC modulates several processes that are altered in brains of patients at risk for AD including synaptic plasticity, inflammation, metabolism, and blood-brain-barrier permeability. Further, NE deficiency increases beta-amyloid deposition in the brain[11]. Regardless of whether the LC deteriorates early, it projects to the hippocampus and, along with its role in NE production, may influence memory processes. Thus, enhancing LC function may be helpful in MCI.

A1.3 Mechanisms of cognitive dysfunction in MCI may be modifiable via tVNS About 30 years ago, it became possible to effectively stimulate the vagus nerve in humans. Vagal nerve stimulation (VNS) initially was used to treat patients with poorly controlled seizures[12]. Because of its potential impact on hippocampal and prefrontal systems, VNS may impact memory encoding, retrieval, and working memory. *See figure 1.*

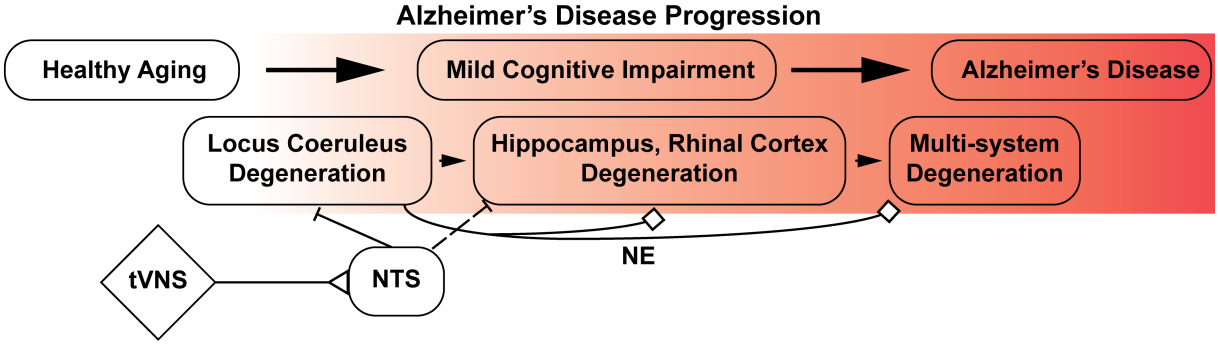

Figure 1. Simplified cognitive enhancement path for tVNS

A1.4 Methods of stimulating the vagus VNS is FDA approved, but requires surgical implantation of a device in the chest and electrodes placed around the vagal nerve in the neck. tVNS is a non-invasive and promising means of modifying brain function. tVNS stimulates the auricular branch of the vagus (located medially at entry of the acoustic meatus[13]). Because it does not directly stimulate descending cardiac fibers, it does not appear to affect mean heart rate or blood pressure and does not carry the cardiac risks of implanted VNS.

6. Specific Aims:

tVNS has the potential to improve cognition in patients with MCI and may even alter the course of decline. We will employ a multimodal approach including neuropsychological testing, structural and functional MRI to assess changes with tVNS in cognition in patients with MCI in support of the development of a therapeutic role for tVNS in the treatment of this disabling disorder.

Aim 1) Evaluate the influence of tVNS on memory performance in participants with MCI. tVNS may alter the activity of the areas of the brain that are critical for encoding or recalling memories and which are often impaired in patients with MCI. Therefore, tVNS may improve behaviors supported by these networks.

Hypothesis 1: During tVNS, participants with MCI will improve in verbal and visuo-spatial memory compared to off-tVNS performance (sham-stimulation).

Aim 2) Determine mechanisms of treatment response variability. Differences in the etiology and expression of MCI may result in different cognitive responses to tVNS. For example, patients with memory loss may have degeneration of the entorhinal cortex and hippocampus or injury to the frontal subcortical networks. These differences in neuroanatomical involvement produce different kinds of memory impairments. We will examine the relationships between the response to tVNS as a function of differences in baseline cognitive and structural presentation. *Further, in secondary analyses, we will examine the effects of biological variables such as sex and also common changes in the brain associated with aging including changes in healthy appearing white matter (DTI assessed) and white matter hyperintensities (leukoaraiosis as assessed though FLAIR MRI).*

Hypothesis 1: Those patients with amnestic MCI who have baseline memory impairment including flat learning curve, poor free recall, and reduced recognition memory will improve with tVNS treatment.

Hypothesis 2: Research has demonstrated that neurodegeneration of medial temporal structures is the best antecedent MRI marker of imminent conversion to AD, with decreased hippocampal volume (left > right) being the most robust. Since the hippocampus receives direct input from the NTS as well as norepinephrine from the LC, those participants with MRI evidence of degeneration of the hippocampus/entorhinal cortex (its direct path connections (using diffusion tensor imaging [DTI]) *will improve during tVNS and the degree of improvement may be related to the degree of atrophy.*

Hypothesis 3: Those patients with MCI who have baseline memory impairment including reduced working memory and poor retrieval with intact recognition will improve with tVNS.

Hypothesis 4: Since norepinephrine is important for the function of the prefrontal-executive systems, patients with deterioration of prefrontal cortex as evidenced by atrophy and/or white matter integrity loss will show improvements in retrieval and working memory with tVNS as assessed by cognitive testing (digit span, free retrieval memory after a delay) and *the degree of improvement may be related to the degree of structural abnormality.*

7. Research Plan: Experimental design The design of the study is a hybrid, crossover trial structure with randomized and counterbalanced order of tVNS or sham tVNS (to control for ability to detect stimulation/placebo effects) administration *(see table 1 for basic design elements)*. This will allow us the benefits of both a parallel and crossover design in that we will have equal numbers of subjects who have received sham or tVNS at time point 1 allowing a between subject analysis, while also allowing a crossover analysis. This design also enables the assessment of potential carryover and practice effects. Participants will attend four contact periods: 1) consent, inclusion screening, MRI eligibility and screening, structured history interview; 2) MRI scan; 3) and 4) stimulus sessions separated by at least 7 days, each consisting of the experimental protocol described below.

Intervention	***Predictor***	***Outcome***
tVNS versus sham stimulation (counterbalanced)	***Baseline/sham cognitive performance***	***Cognitive performance*** - ***Memory, executive function***
	Hippocampal/entorhinal volume	
	White matter variables	

Table 1: Intervention, predictors, and outcomes

C2.1 Study participants will be patients who meet the diagnostic criteria for MCI (see 2.2 and 2.3 for criteria). In addition, we will recruit an additional group of healthy aged adults without MCI. All patients will have undergone neurological or neuropsychological evaluation. Participants will sign an informed consent or delayed consent prior to initiation of research activity. Each participant will also receive neuropsychological testing. To further improve our ability to identify mechanisms of memory change, we will also measure autonomic nervous system (ANS) activity and other measures of neuropsychological domains including executive functions and attention (see neuropsychological battery).

C2.2 Inclusion criteria The participants included in this study will be native speakers of English between the ages of 60-89. Potential MCI participants without an existing clinical diagnosis will perform a phone screen, potentially including the T-MMSE (if they verbally consent). The T-MMSE has high correspondence with the MMSE, a common first screening tool for clinicians. Participants who are not ruled out through the phone-screen and/or the T-MMSE will be invited for an intake interview. Intake criteria will be based on established NIA-AA/DSM-V criteria including patient/informant/clinician concern regarding a relative decline in cognition, and/or a global CDR of .5 with objective evidence of relative impairment in another domain that is based on neuropsychological testing for deficits[22-24]. To be included, participants will have a preservation of independence in functional abilities including performing activities of daily living and instrumental activities (i.e., not demented). Test performance will be judged as “impaired” if it is significantly (> or = 1.5SD) below the expected level (based on demographic information and educational level) based on normative data.

C2.3 Exclusion criteria For MCI, we will exclude participants who reveal dementia based on NIA-AA/DSM-V criteria. The diagnosis of dementia will be primarily based on the Functional Activities Questionnaire, which recommends a cutoff point of 9 in order to identify potential cognitive impairment. We will also use the Clinical Dementia Rating Scale [26] which has been shown to be capable of distinguishing patients with dementia from those with MCI[27]. We will also exclude subjects with significant deficits in multiple cognitive domains. For both MCI and healthy aged groups, other neurological diseases or related conditions other than MCI will be

excluded (e.g., large vessel stroke, Parkinson's Disease, or significant seizures). We will exclude patients with other medical conditions that may be associated with impaired cognition in such a manner that may interfere with interpretation of results. Patients with significant depression as determined by the Beck Depression Inventory-2, or with uncorrected hearing or visual loss, will also be excluded. If participants indicate suicidal ideation on the BDI-2 and scores moderate or severe on the Columbia Suicide Severity Rating Scale, a brief risk assessment will be performed by one of the study clinicians (Williamson, Cohen or DeKosky). This assessment will include questions typical of a clinical evaluation of immediate risk. This will go something akin to this (list of questions that might be asked):

Psychologist – "You indicated that you have had thoughts of harming yourself on one of our test forms. Note that the form says within the past two weeks. Are you currently feeling like you want to hurt yourself?" Depending on how the patient responds, we will proceed to a different set of questions. The purpose of the questions to establish major risk factors and vulnerabilities for suicide including intent, plan, access to resources to carry out plan, and lack of social support. We will ask about current mental health treatment status. Do they currently see a psychologist or psychiatrist? We will ask if they have recently seen a mental health professional and discussed these thoughts. We will determine if the participant needs immediate help, in which case we will either walk them to the emergency room or call 911. We will offer to provide information to the patient for mental health services.

C2.4 Neurological and neuropsychological testing MCI testing Premorbid intelligence will be estimated with the Wechsler Test of Adult Reading[28]. Dementia and MCI presence, in addition to activities of daily living (ADL) assessment using the Functional Activities Questionnaire[25], will be verified with the CDR[26] and the Montreal Cognitive Assessment (MOCA)[29]. The MoCA is a brief test, and has a high sensitivity (90%) and specificity (87%) for detecting individuals with MCI and distinguishing them from individuals with normal cognition. In 114 participants with MCI that progressed to dementia and 51 that did not, 90.5% of participants with MCI with a MoCA score less than 20/30 at baseline converted to AD within the average follow-up period of 18 months, compared with 52.7% of participants with MCI above the cutoffs on both scores[30].

Patients who have been diagnosed as MCI, and who score <27 on the MOCA and have a CDR sum of boxes score of 0.5 – 4.0 along with verified neuropsychological performance on memory testing (e.g., Hopkins Verbal Learning Test – Revised [HVLT-R]) at or below 1.5 SD below the expected normative level will continue in the study[33]. In some cases, MOCA scores at 27 will be considered for inclusion based on clinical consensus if the deficit in performance is specific to memory and there is evidence of MCI determined through other available metrics including HVLT-R, CDR and clinical record review. To verify amnestic MCI, in addition to review of recent neuropsychological/neurological testing data, the CDR, and administration of the MoCA in the current study protocol, we will administer a form of the HVLT-R[34]. The short-form of the Boston Naming Test will be used to assess verbal/visual function. We will use the WMS-III digit span to determine effort during testing.

Healthy aged participants must score >=26 on the MOCA, have a CDR sum of boxes score of 0, and not be below 1.5SD of normative levels on the HVLT-R.

C2.6 Recruitment We will meet our recruitment objectives for participants based on the availability of cases from UF clinical medicine programs. UF informatics showed that 1139 patients with MCI were seen over the past four years at UF. Both PIs have clinics that see patients that are within the target differential (older patients with reported memory problems) and our department and two other departments with which we are affiliated (Aging and

Clinical and Health Psychology) that also evaluate patients that will meet our inclusion criteria. We may use certain UF services including I2B2 and Healthstreet.

Additionally, we will request a copy of the State of Florida Voter Registration registry. We will narrow down this list by voters that meet our age range (60-89) and send them an IRB approved flyer. This flyer would provide a brief overview of the study; as well as, study contact information for interested individuals.

C3.1 Procedural sequence The sequence and flow of the assessments to be conducted are as follows. Recruited participants will be screened over the phone after giving verbal consent. Participants will be mailed or emailed a map with directions to our study spaces if they request it. Participants who pass the initial phone screen will then be formally consented with a written ICF and then screened for inclusion/exclusion factors via interview, screening questionnaires, and review of medical records. Individuals who live farther away and are interested in the study but not wanting to make the drive without knowing they qualify for the study will have the option of having the intake administered by study staff at their (the potential participants) home. Any information and forms completed during this intake will be locked in a small filing cabinet and driven back to the University of Florida by study staff. All remaining study visits will be conducted at the University of Florida as usual.

Included participants will then undergo the MCI classification portion of the study, which characterizes the sample, collects covariates for mixed model analysis, and verifies group inclusion. Participants will be randomized between the two arms of the crossover sessions (initial tVNS vs. Sham). Behavioral portions of the testing will then be carried out twice, with at least one week between sessions (to avoid carryover effects). MRI scan will occur at least 72 hours from behavioral sessions.

C4.1 Intervention: tVNS Transcutaneous stimulation of the auricular branch of the vagus nerve will be applied. The auricular branch of the vagus projects to the brain stem and is accessible via electrical stimulation through surface electrodes. Stimulation produces vagus sensory evoked potentials, whereas stimulation of nearby regions does not. tVNS will be performed during the cognitive battery. tVNS will also be performed during fMRI. We may use two different stimulator devices. For the tasks outside of the scanner, we may use the Digitimer SD7A or a stimulator from Biopac. The Biopac stimulator is also MRI safe and thus, in the scanner, we will use the stimulator designed for MRI use from Biopac. This stimulator model is already in use at AMRIS. Both devices are capable of the same specs in terms of stimulation parameters.

C4.2 Electrode placement and stimulation The same type of electrodes will be used for both the MRI and lab based stimulation sessions. These are MRI safe electrodes and will be placed over the auricular branch of the vagus, held in place with adhesive gel. For the control condition, electrodes will be placed on the earlobe using the same electrodes. The ground electrode for tVNS will be placed just anterior to the tragus to minimize off-target stimulation per local pilot protocol, and the sham ground will be on the opposite side of the earlobe. Previous research has demonstrated that with tVNS versus stimulation of the ear lobe, fMRI showed BOLD-signal changes in the hippocampus, parahippocampal gyrus and the middle and superior temporal gyrus, as well as in the insula, precentral gyrus and the thalamus. In contrast, ear lobe stimulation did not show similar changes on fMRI[35]. Stimulus will be set at 5-10V pulses and will be delivered at 20Hz, 100 μs pulse width consistent with our pilot stimulus protocol and within the range of published stimulus parameters[13,35-43]. Stimulus intensity for sham and tVNS will be ramped from 0 to the threshold of discomfort, then reduced to 80% of threshold, a level which is tolerable, as per local pilot protocol and prior investigations[13,37-39,42]. Intensity level is expected to be between 4mA-15mA based on our pilot

data and prior reports, though subjects who express no discomfort may go beyond these levels, and subjects who express discomfort early may go below.

C5.1 MRI protocol We will use a research dedicated scanner in the UF Advanced MRI and Spectroscopy (AMRIS) facility. The scanning sequences will take ~1-1.5 hours to acquire and may include: 1) Structural MRI, 2) Diffusion Tensor Imaging (DTI). 3) fMRI 4) Magnetic Resonance Spectroscopy

Subjects will be provided a de-identified DVD with their structural scans if they request it. We will also mail copies of the DVD to subjects if they request it.

Task fMRI We will present the fMRI task (2-Back) using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) viewed through a double-mirror attached to the head coil. An MRI-compatible response box attached to the stimulus presentation computer will collect performance data.

2-Back. Verbal working memory will be assessed on a 2-Back and 0-back task, as in past studies[19,47]. In both conditions, consonants are visually presented. In the 0-back condition, participants determine if each stimulus is the same or different from the previous stimuli, responding by binary button press. In the 2-back condition, participants respond yes if a stimulus is the same as the consonant two letters earlier, both the 0 and 2-back contain 33% targets. 8 blocks of both the 0-back and 2-Back conditions are pseudo-randomized across two 6-minute runs. Accuracy and reaction times are recorded.

C5.5 _tVNS cognitive testing We will test the impact of tVNS with the following cognitive tests using:

- Repeatable Battery for the Assessment of Neuropsychological Status story learning and recall,
- Wechsler Memory Scale-IV Paired Associates I & II
- Phonemic and semantic fluency tests
- Paced auditory serial addition test (PASAT)
- WAIS-IV Digit Span (working memory) and Digit-symbol Coding [48]
- Rey Auditory Verbal Learning Test (RAVLT)
- ARCPT
- Trails
- tVNS or sham will be active throughout testing.

Possible Discomforts and Risks:

Non serious adverse events:

Non serious adverse events are defined as conditions that may be unpleasant and bothersome to the participant that do not require discontinuing the study. Study staff will be directly observing or participating in the execution of the research protocol and will contact the principal investigator or hospital staff as necessary should any adverse event occur. Should participants experience an adverse event outside of the contact periods, such as after the culmination of the research, they will be able to contact the principal investigator through the contact sheet provided during the consenting process.
Neuropsychological and behavioral testing will be conducted during the course of this study. Participants may experience fatigue and feelings of frustration while completing the cognitive tests. They may also feel of inadequacy if they do not complete all items on tests or can not recall all items on memory test. As part of the enrollment process and during each testing session, participants are reminded that the tests in this research project were chosen to be challenging and the most people do not complete all items of each test.

Transcutaneous Vagal Nerve Stimulation (tVNS) is considered to be safe application of the well established transcutaneous electrical nerve stimulation technology. tVNS has few potential risks, skin irritation at the site of stimulation due to skin prep or to sustained exposure to the conductive gels used to maintain electrical conductivity and conduct.

Adverse events:

Adverse events are unlikely to occur during the proposed research protocol, however precautions are in place in case of an unexpected adverse event. An adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the intervention irrespective of whether it is considered related to the intervention.

Serious adverse events (SAEs):

SAEs are defined as events that may be harmful to the participant and/or may be serious enough to warrant either temporary or permanent discontinuation of the study intervention, either because they are intolerable or because they are judged to be potentially harmful. All serious adverse events require immediate reporting and an assessment of the implications for the continuation of the study and/or modification of the consent form. SAEs include events which: are acute or life threatening; result in prolonged, permanent or severe disability; induce another severe illness including worsening of a pre-existing condition, injury or accidents; require an inpatient hospitalization or surgical procedure, or a treatment to prevent a serious event; result in death. During each visit, participants will log any health-related problems or symptoms they are experiencing during structured interviews. Should participants experience a serious adverse event outside of the contact periods, including after the culmination of the research, they will be asked to contact the principal investigator through the contact sheet provided during the consenting process. These reports will be reviewed by study staff before allowing the participant to continue if research has not completed. All adverse events will also be categorized according to the likelihood that they are related to the study intervention. Events will be labeled either definitely, probably, possibly or unrelated to the study intervention and will be reported to the IRB and UF research service in accordance with regulatory requirements. Minor adverse events will be reported at the time of annual review. Both the principal investigator and the study staff will review the study regularly to examine reports of adverse incidents and evaluate study participant recruitment and study follow-through. Throughout the course of the study, information regarding issues deemed critical to the study or to the safety of research participants will be provided to the principal investigator and other study staff as needed. As a result of receiving this critical information, a meeting to discuss this information may be convened including the mentoring team. Information deemed critical would include: serious and non-serious adverse events that may occur; suspicion of scientific fraud or misconduct; incidental findings; any other issues which may warrant protocol changes or modifications.

Documentation of training on protection of human participants:
will be maintained by the University of Florida IRB. All key personnel on the study have successfully completed and will maintain certification from the University of Florida for mandatory education in human research subjects' protection, protection of personally identifiable information, and HIPAA compliance. This includes Collaborative Institutional Training Initiative (CITI) and Institutional Review Board IRB training

Potential benefits to participants and others:

There is no direct benefit to the participants in the study beyond compensation for travel and participation and, if requested, a copy of their assessments. These neuropsychological results may prove to be clinically valuable, but are not available because of any specific anticipated clinical purpose. The major potential benefit to patients with MCI as a group is through advances in our understanding of specific behavioral and neurophysiological outcomes of tVNS, especially with regard to its impact on cognition. This may lead to therapeutic clinical trials in subsequent studies. Improved treatments for MCI will help patients by improving quality of life via extension of independence and social participation capabilities.

Conflict of interest statement:

There are no real or potential conflicts of interest with regard to this research project. The research was conducted in the absence of any commercial or financial relationships that could be explained as a potential conflict of interest.