Treatment of mild cognitive impairment with transcutaneous vagal nerve stimulation
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C6.1 Data analytic strategy *Dr. Liang (Co-I, biostatistician) will conduct the statistical analyses, which will be performed using statistical software, R or SAS. First, standard summary statistics will be provided for all measures (including behavioral and demographic [e.g., sex] measures, volumetrics from T1 weighted images, white matter integrity on DTI and white matter hyperintensities from FLAIR, and baseline neuropsychological test performance) by treatment (sham or active during the first stimulus session). Second, hypotheses will be tested with formal inferential techniques. Third, exploratory analysis for baseline neuropsychological test performance, brain regional volume, and other regional indices from DTI for predicting treatment response will be conducted. We will adjust for multiple comparisons by controlling the false discovery rate and determine statistical significance for each aim. The crossover design will increase the precision, where each subject serves as his or her own control and within subject comparison can be used. The increased power with greater precision to estimate the treatment differences reduces the necessary sample size. Despite this advantage, a potential problem in a crossover design is that carryover effects may bias the direct treatment effects. To account for the potential carryover effects, we will consider the following mixed-effect model. Let* y_{ijk} *denote the memory score measured at time period k from the jth subject in sequence i,*

$$y_{ijk} = \mu + \beta_{j(i)} + \gamma_k + \tau_{d(i,k)} + \lambda_{c(i,k)} + \epsilon_{ijk},$$

where i=sequence (tVNS-sham or sham-tVNS), j=subject, k=period, μ is the overall mean, δ_i *is the fixed effect of sequence i,* $\beta_{j(i)}$ *is the random effect for patient j with sequence i,* γ_k *is the effect of period k,* $\tau_{d(i,k)}$ *is the direct effect of the treatment applied during period k in sequence i,* $\lambda_{c(i,k)}$ *is the carryover effect of the treatment applied during period k in sequence i, and* ϵ_{ijk} *is the random error effect. Note that there is randomization of the subjects to the sequences. If the outcome measures do not follow a normal distribution, certain transformation, e.g., a Box-Cox transformation, will be applied before modeling. With this mixed-effect model, various hypotheses on the treatment effects, period effects and carryover effects can be separated and tested. If the carryover effect is not significant between the two sequences, then the data from two periods can be combined and analyzed. In the case that the carryover effect is significant, the overall conclusion about the treatment effect would be in question, however, the data from the first time period can still be used in testing for treatment effects because there would be no carryover from any previous applications of the treatments. Further, we will conduct secondary analysis for investigating the effect of tVNS on the other cognitive domains including language (phonemic and semantic fluency) and executive functions. To identify the factors that mediate the effects of tVNS, i.e., testing the hypothesis in Aim 2, the memory scores will be regressed on the selected factors, such as baseline memory performance (flat learning curve, poor free recall, reduced recognition memory; reduced working memory and poor retrieval with intact recognition), and hippocampal/entorhinal cortex volume (normalized by intracranial volume). Important covariates such as sex, age and education will be adjusted in the regression model if they relate significantly to the outcome variables. Variable selection can be conducted for the model under the standard Bayesian or frequentist framework. For example, a L1-penalty[49] might be used in variable selection under the frequentist framework. In addition to the plain linear regression model, the generalized additive model[50] will also be tried for the problem, which is expected to fit the data better and have a better power to detect the factors that are truly associated with the effects of tVNS.*

C6.2 Power and sample size considerations *The enrollment sample of 60 participants is intended to provide data on the impact of tVNS on the cognitive performance in participants with MCI and predictors of improvement with treatment including brain volume changes associated with AD pathology. Further, these data will be used to indicate feasibility of a larger trial and to provide descriptive estimates of acute effects. To get a rough idea for the effectiveness of the trial, we made the following calculation. Assuming α = 0.05, two-sided test, and 60 participants in total. If the carryover effect is negligible, we will have 90% power to detect an effect size of 0.604 for memory improvement in hypothesis 1 in aim 1 based on within subject comparisons. In the case that the carryover effect is significant and we use the first period data only (similar as in a parallel design), we will have 90% power to detect an effect size of d=0.854 for aim 1. For the regression analysis in predicting treatment response in aim 2), we will have 90% power to detect a factor that has a marginal correlation of r=0.43 with the response variable.*

Overall, our methodology and analyses offer a comprehensive approach to understanding the mechanism of action of tVNS as a potential enhancer of cognition affected by decline in the continuum of AD. Our strategy should establish feasibility and our personalized medicine approach will allow us to interrogate treatment responsiveness and examine predictors of said responsiveness. Subsequent larger scale clinical trials including biomarkers such as amyloid imaging, CSF tau, and genetic subtypes (APOE) and longitudinal evaluation of sustainability of effects and whether decline in functional status can be achieved will follow.