NCT04111068

Official Title: Improving Vision in Adults With Macular Degeneration, Study 1: the Effect of Brain Stimulation

Date Last Updated: February 4, 2022

Statistics Analysis Plan

Planned Study Components

A. *Independent Variables:*
   1. Stimulation Type (active vs sham)
   2. Test Time (effect during, effect 5 mins post, effect 30 mins post)

      For statistical testing, Test time will contain 3 levels, defined as:
      - i. During stimulation – baseline
      - ii. 5 mins post stimulation – baseline
      - iii. 30 mins post stimulation – baseline

B. *Experimental Design and Outcome Measures:*
   1. 2 (Stim type) x 3 (Test time) analysis: Outcome is Crowded VA in logMAR (FrACT)
   2. 2 (Stim type) x 3 (Test time) analysis: Outcome is Uncrowded VA in logMAR (FrACT)
   3. 2 (Stim type) x 3 (Test time) analysis: Outcome is RSVP reading analysis

C. *Interactions:* An interaction between stim type and test time indicates that active stimulation was effective, but not at every timepoint. Therefore, the planned contrast in the event of an interaction:
   1. Active vs. sham: individually compare active vs sham at the three timepoints.

D. *Covariates to examine:*
   1. Language, primary analysis (dichotomous)
   2. Age (continuous)
   3. Distance visual acuity (will be dichotomized) [a]
   4. RSVP critical print size (will be dichotomized) [a]
   5. RSVP maximum reading speed (will be dichotomized) [a]
   6. Cognitive Screening: MoCA-blind (UW) and (HKPU) (will be dichotomized) [b]
   7. Type of AMD: wet, dry (dichotomous) [c]

   a. Because the different languages likely elicit different mean performances, covariates listed will be dichotomized with a median split separately for each language to allow combined data analysis with the included covariate. The "low" group will include any participants scoring the median. The "high" group will include only participants scoring better than the median.
   b. Cognitive Screening will be dichotomized separately for each language along standard thresholds for clinical significance. This covariate will only be tested if at least 5 total participants are allocated to both groups.
   c. Type of AMD will only be tested if at least 5 total participants are allocated both groups.

E. *Additional Details:*
   1. The analysis will be run individually for each planned outcome measure.
   2. Participants with incomplete data will be excluded from the analysis
   3. All tests will be 2-tailed with alpha = 0.05

Analysis Procedure

1. *Normality check:* Check if ANOVA assumptions are violated (languages combined)
   1. Sphericity of variances – use Mauchly's Test of Sphericity to check for significant violations of sphericity.
   2. Normality of Residuals – visually inspect pp plot and qq residual plots evaluate the degree of violation.

   - If sphericity assumption is violated: Use Greenhouse – Giesser correction for all main effects and interactions, following *Parametric Statistics*, section 2a
     - If interaction between independent variables is significant: Use Wilcoxon-signed-rank tests for planned pairwise comparisons instead of ttests.
   - If normality assumption is violated: follow *Nonparametric Statistics*, section 2b.

2a. Parametric Statistics

1. Primary Analysis:
   i. Perform repeated-measures ANCOVA, with Language as covariate.

   If interaction between stimulation type and test time is significant:
   ii. Examine planned comparisons with within-subject ttests

   If language covariate is significant or significantly interacts with another factor:
   iii. Run separate repeated-measures ANOVAs for each language

   If either ANOVA reveals an interaction:
   iv. Examine planned pairwise comparisons with within-subject ttests

2. Secondary Analysis:
   i. Perform repeated-measures ANCOVA, iteratively with each secondary covariate to be tested.

   If interaction between stimulation type and test time is significant:
   ii. Examine planned comparisons with within-subject ttests

   If any dichotomous covariate is significant or significantly interacts with another factor:
   iii. Run separate repeated-measures ANOVAs for each level of the covariate

   If either ANOVA reveals an interaction:
   iv. Examine planned pairwise comparisons with within-subject ttests

2b. Nonparametric Statistics

1. Primary Analysis:
   i. Perform aligned rank transform for nonparametric ANOVA with 3 independent factors.
   - 2 (Stim type) x 3 (test time) x 2 (language) mixed effects ANOVA

   If stim type and test time interact, but language is not significant and no interaction involving language occurs:
   ii. Run planned pairwise comparisons using Wilcoxon-signed-rank tests

   If language is significant or if language significantly interacts with any other factor:
   iii. Discard previous analysis and run two separate ART-transformed 2 (stim type) x 3 (test time) nonparametric ANOVAs, one for each level of language.

   If either ANOVA reveals an interaction:
   iv. Run planned pairwise comparisons with Wilcoxon-signed-rank tests

2. Secondary Analysis:
   i. Perform the same procedure as the primary analysis iteratively for each covariate to be tested.

Aligned-rank transform reference:
Wobbrock et al. (2011). The aligned rank transform for nonparametric factorial analyses using only ANOVA procedures. Proceedings of the SIGCHI conference on human factors in computing systems.
https://dl.acm.org/doi/10.1145/1978942.1978963

Data and demographics summary table:

1. A summary table will be generated, one row per participant. Columns will include:
    - Age
    - Sex
    - macular degeneration type (wet AMD, dry AMD, JMD
    - language
    - distance VA
    - MNREAD CPS (equivalent to near VA)
    - MNREAD speed
    - RSVP CPS
    - RSVP speed