NCT04762368

Official Title: Improving Vision in Adults with Macular Degeneration, Study 2: The Effect of Concurrent Perceptual Learning and Brain Stimulation

Date: Dec 03, 2024

Statistical Analysis Plan

Primary objective: The primary objective of this study is to compare the changes in the rate of reading (i.e. log RSVP maximum reading speed) between patients who received active tDCS combined with perceptual learning and those receiving sham tDCS combined with perceptual learning.

***Secondary objectives*:**

1. To determine the effect of active vs. sham tDCS combined with perceptual learning on the following changes before and after training:
    - RSVP CPS (critical print size)
    - Sentence reading performance
    - Crowded and uncrowded visual acuity
    - Contrast sensitivity
2. To assess if a range of covariates (age, baseline RSVP log MRS, and CPS) have any moderating effects.
3. To assess if tDCS combined with perceptual learning has different effects on participants reading different languages.[1]

Exploratory objectives:

1. To investigate the changes in participants' visual acuity over the duration of the study.
2. To investigate the rate of learning in participants receiving active vs. sham tDCS across different training sessions.

[1] Because tDCS influences English and Chinese differently (Silva et al., 2022), language will be analyzed separately to ensure its potential impact is accounted for.

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1. Planned Study Components

1.1. Completed number of participants:

a. Hong Kong: 20 (2 JMD + 18 AMD)
b. Waterloo: 5

1.2. Independent variables:

a. Stimulation type (active vs. sham stimulation)
b. Test time: Assessments were conducted at three time points: baseline (before training), post-training (immediately after training), and 30 days post-training.

For statistical analysis, test time will be transformed into two levels to account for the large inter-subject variabilities in baseline measures:

i. Post training - baseline
ii. 30 days post-training – baseline

1.3. Covariates:

a. Age (will be dichotomized)[2]
b. RSVP baseline critical print size (will be dichotomized)[2]
c. RSVP baseline log maximum reading speed (will be dichotomized)[2]

1.4. Analysis framework and primary outcome measures:

a. 2 (Stim type) x 2 (Test time) analysis: Outcome is change in RSVP maximum reading speed in log words/characters per minute (log MRS).

1.5. Analysis framework and secondary outcome measures

1.5.1 Outcomes analysis

a. 2 (Stim type) x 2 (Test time) analysis for change in each of the following outcomes:
    - RSVP critical print size (CPS) in logMAR.
    - MNRead MRS in log words/characters per minute (log MRS_{MNRead})
    - MNRead CPS in logMAR (CPS_{MNRead})
    - Uncrowded VA in logMAR (FrACT)
    - Crowded VA in logMAR (FrACT)
    - Crowded - uncrowded VA in logMAR (FrACT)
    - Contrast sensitivity in logCS (FrACT).

** Interactions: An interaction between Stimulation type and Test time indicates that active and sham tDCS have different enhancement effects on perceptual learning, but these effects are not consistent across all Test times. Therefore, the planned contrast for such an interaction is to perform individual comparisons between active vs. sham tDCS at each Test time.*

[2] The listed covariates will be dichotomized using a median split. The "low" group will include participants with a score at or below the median, while the "high" group will consist of participants with a score above the median.

1.5.2 Integration of covariates into analysis

a. 2 (Stim type) x 2 (Test time) analysis with age as covariate: Outcome is change in RSVP log MRS and the above secondary outcome measures.
b. 2 (Stim type) x 2 (Test time) analysis with baseline RSVP log MRS as covariate: Outcome is change in RSVP log MRS and the above secondary outcome measures.
c. 2 (Stim type) x 2 (Test time) analysis with baseline RSVP CPS as covariate: Outcome is change in RSVP log MRS and the above secondary outcome measures.

1.5.3 Sensitivity analysis for language effects

a. Bootstrapping approach: To address the limited sample size of the English-reading participants and evaluate the tDCS effect across different languages, a bootstrapping method will be employed. A total of 1,000 bootstrap samples will be generated by random sampling with replacements from the existing subject pool. For each resampled dataset, the differential outcome changes between active vs. sham tDCS will be computed for Chinese- and English-reading participants. The distribution of differences will be analyzed to estimate the confidence intervals of the language effects.
b. Subgroup analysis: The changes in outcomes for active vs. sham tDCS will be compared within the Chinese reading participants. The results from this subgroup analysis will be compared to the overall outcome measures of the entire study population.

1.6. Analysis framework and exploratory outcome measures

1.6.1 Changes in visual acuity

a. (Stim type) x 2 (Test time) analysis: Outcome is change in distance visual acuity in logMAR.

1.6.2 Analysis of learning rate:

a. Slope fitting: A linear regression model will be fitted to the session-by-session data for RSVP log MRS and CPS (averaged across on- and off-stimulation). The slope obtained from the regression analysis will be compared between active vs. sham stimulation.

1.7. Additional details:

a. Participants with incomplete data will be excluded from the analysis.
b. All statistical tests will be performed as two-tailed tests, using a significance level of alpha = 0.05.

2. Analysis Procedure

2.1. Assess whether the assumptions for ANOVA are violated.

a. Sphericity of variances: Use Mauchly's Test of Sphericity to check for significant violations of sphericity.
    i. If the sphericity assumption is violated, apply the Greenhouse-Geisser correction for all main effects and interactions.
b. Homogeneity of variances: Use Levene's test to check for significant violations of homogeneity.
    i. If the homogeneity assumption is violated, employ the Mann-Whitney U test to do the pairwise comparison between active and sham stimulation.
c. Normality of residuals: Use Kolmogorov-Smirnov test to check for significant deviations from normality.
    i. If the normality assumption is not violated, proceed with parametric analysis (*Section 2.2*)
    ii. If the normality assumption is violated, proceed with nonparametric analysis (*Section 2.3*)

2.2 Parametric statistics

2.2.1 Primary analysis:

a. Perform repeated-measure ANOVA with Test time as a within-subject factor and Stimulation type as a between-subject factor for change in RSVP log MRS.
    i. If there is a significant interaction, apply pairwise comparisons to examine differential effects of stimulation.

2.2.2 Secondary analysis

a. Perform repeated-measures ANOVA with Test time as a within-subject factor and Stimulation type as a between-subject factor for changes in the outcomes listed in *Section 1.5.1.*
    i. If there is a significant interaction, apply pairwise comparisons to examine differential effects of stimulation.

b. Performed repeated-measures ANCOVA with Test time as a within-subject factor and Stimulation type as a between-subject factor, incorporating each of the covariates listed in *Section 1.5.2.*
    i. If any listed covariate effect is significant or significantly interacts with another factor, perform separate repeated-measure ANOVAs for each level of the covariate.

c. Perform sensitivity analysis using Bootstrapping approach and subgroup analysis as described in Section *1.5.3.*

*2.2.3 **Exploratory analysis***

a. Perform repeated-measure ANOVA with Test time as a within-subject factor and Stimulation type as a between-subject factor for change in distance visual acuity.
    i. If there is a significant interaction, apply pairwise comparisons to examine differential effects of stimulation

b. Perform Student's t-test with Stimulation type as a between-subject factor for the fitted slope coefficients.

2.3 Nonparametric statistics

*2.3.1 **Primary analysis:***

a. Perform Aligned Rank Transform (ART) for nonparametric ANOVA with Test time as a within-subject factor and Stimulation type as a between-subject factor for change in RSVP log MRS.
    i. If there is a significant interaction, apply pairwise comparisons to examine differential effects of stimulation.

*2.3.2 **Secondary analysis:***

a. Perform ART nonparametric ANOVA with Test time as a within-subject factor and Stimulation type as a between-subject factor for changes in the outcomes listed in *Section 1.5.1*.
    i. If there is a significant interaction, apply pairwise comparisons to examine differential effects of stimulation.

b. Perform ART nonparametric ANOVA with Test time as a within-subject factor and Stimulation type as a between-subject factor, incorporating each of the covariates listed in *Section 1.5.2*.
    i. If any listed covariate effect is significant or significantly interacts with another factor, perform separate ART nonparametric ANOVAs for each level of the covariate.

c. Perform sensitivity analysis using Bootstrapping approach and subgroup analysis as described in Section *1.5.3.*

*2.3.3 **Exploratory analysis***

a. Perform ART nonparametric ANOVA with Test time as a within-subject factor and Stimulation type as a between-subject factor for change in distance visual acuity.
    ii. If there is a significant interaction, apply pairwise comparisons to examine differential effects of stimulation

b. Perform Mann-Whitney U Test with Stimulation type as a between-subject factor for the fitted slope coefficients.

3. Data and demographics summary table

A. A summary table will be generated with separate columns for each stimulation type (active and sham), combining both languages. The rows will include:

1. Age (mean with SD)
2. Sex (in percentage)
3. Language (in percentage)
4. Macular degeneration type (AMD or JMD)
5. Disease duration
6. Best corrected visual acuity (distance and near)
7. Baseline RSVP maximum reading speed
8. Baseline RSVP critical print size
9. Baseline MNRead maximum reading speed
10. Baseline MNRead critical print size
11. Baseline contrast sensitivity

B. Supplementary demographic table

A demographic table will be generated, one row per participant. The columns will include:

1. Age
2. Sex
3. Macular degeneration type (AMD or JMD)
4. Disease duration
5. Language (Chinese or English)
6. Stimulation type (active or sham)
7. Distance and near visual acuity (better eye and worse eye)
8. Tested eye
9. Baseline RSVP maximum reading speed
10. Baseline RSVP critical print size
11. Baseline MNRead maximum reading speed
12. Baseline MNRead critical print size
13. Baseline contrast sensitivity

Reference:

Silva, A. E., Lyu, A., Leat, S. J., Khan, S., Labreche, T., Chan, J. C. H., . . . Thompson, B. (2022). A differential effect of visual cortex tDCS on reading of English and Chinese in patients with central vision loss. *Brain Stimul, 15*(5), 1215-1217.