STUDY PROTOCOL
AND
STATISTICAL ANALYSIS PLAN

Study Title:
Efficacy of Low-frequency Repetitive Transcranial Magnetic Stimulation on Rehabilitation of Aphasia

Study Design : Randomized Controlled Trial

Research Center : İstanbul Medipol University, Speech, Language and Swallowing Therapy and Research Center (MEDKOM)

Document Date : 28.06.2022

RESEARCH TEAM

Principal Investigator

Name : Talat BULUT
Title / Expertise : Assist. Prof. / Cognitive Neuroscience
Area of expertise : Cognitive Neuroscience
Institution : Istanbul Medipol University
Email : tbulut@medipol.edu.tr; buluttalat@gmail.com

Investigator

Name : Meryem Bilge TOPRAK
Title / Expertise : Speech and Language Therapist / Speech and Language Therapy
Institution : Istanbul Medipol University
Email : mrymblgtprk@gmail.com

Investigator

Name : N. Evra GÜNHAN ŞENOL
Title / Expertise : Assist. Prof. / Speech and Language Therapy
Institution : Istanbul Medipol University
Email : negunhan@medipol.edu.tr

Investigator

Name : Lütfü HANOĞLU
Title / Expertise : Prof. Dr. / Neurology
Institution : Istanbul Medipol University
Email : lhanoglu@medipol.edu.tr

STUDY PROTOCOL
AND
STATISTICAL ANALYSIS PLAN

1. PURPOSE

The purpose of the study is to compare effectiveness of two repetitive transcranial magnetic stimulation (rTMS) protocols in rehabilitation of aphasia:

1. Inhibitory, low-frequency stimulation of right inferior frontal gyrus,
2. Inhibitory, low-frequency stimulation of right posterior superior temporal gyrus.

2. METHODS

Research Design

Randomized controlled trial

Population

People with aphasia aged between 18-80 whose native language is Turkish

Sample, Inclusion and Exclusion Criteria

20 participants

Inclusion Criteria:

- Right-handedness,
- Normal or corrected-to-normal vision and hearing,
- Aphasia following cerebrovascular accident,
- Cerebrovascular accident at least 6 months prior to enrolment in the study,
- Satisfying current TMS safety guidelines (Rossi et al., 2021, 2009), which are:
    - No previous history of epilepsy,
    - No implants (e.g., cochlear implant) or stimulators (e.g., deep brain stimulation) in the head which may interact with the magnetic field,
    - No use of central nervous system (CNS) active drugs that lower seizure threshold (as listed in the aforementioned guidelines)

Exclusion Criteria:

- Left-handedness, ambidexterity,
- Impaired and uncorrected vision or hearing,
- No aphasia symptoms following cerebrovascular accident,
- Time since cerebrovascular accident less than 6 months,
- Violating current TMS safety guidelines (Rossi et al., 2021, 2009). In other words:
    - Having a previous history of epilepsy,

- Having an implant (e.g., cochlear implant) or a stimulator (e.g., deep brain stimulation) in the head which may interact with the magnetic field,
- Taking central nervous system (CNS) active drugs that lower seizure threshold (as listed in the aforementioned guidelines)

rTMS Interventions

Intervention 1: Right frontal (inferior frontal gyrus) 1 Hz rTMS

Low-frequency (1 Hz) inhibitory rTMS will be administered to right inferior frontal gyrus with the following parameters:

- Frequency: 1 Hz
- Stimulation site: Right IFG (as determined using EEG 10-20 system)
- Intensity: 100% of motor threshold
- Dosage: 20 minutes per day
- Duration: 10 days over 2 weeks (no stimulation during weekends)

Intervention 2: Right temporal (posterior superior temporal gyrus) 1 Hz rTMS

Low-frequency (1 Hz) inhibitory rTMS will be administered to right posterior superior temporal gyrus with the following parameters:

- Frequency: 1 Hz
- Stimulation site: Right posterior superior temporal gyrus (as determined using EEG 10-20 system)
- Intensity: 100% of motor threshold
- Dosage: 20 minutes per day
- Duration: 10 days over 2 weeks (no stimulation during weekends)

Outcome Measurements

1. ADD Scores

Baseline and post-treatment scores obtained from the Turkish Aphasia Language Assessment Test (ADD)

Time Frame: Immediately before and immediately after the intervention

2. Naming Scores

Naming performance (% accurately named pictures & naming latency for correctly named pictures) on the IPNP picture sets

Time Frame: Immediately before, during and immediately after the intervention

3. Eye movements

An eye tracking-while-listening paradigm will be used to determine proportions of dwell time on the correct picture (out of two alternatives) corresponding to auditorily presented Turkish sentences which vary in morphosyntactic complexity.

Time Frame: Immediately before and immediately after the intervention

3. STATISTICAL ANALYSES

The statistical analyses will be conducted in R (R Core Team, 2013) using the lme4 package (Bates, Mächler, Bolker, & Walker, 2015). Numeric dependent variables (tests scores, naming latency, dwell time) will be analyzed using linear mixed-effects models (LMM), and binary data (accuracy) will be analyzed using generalized linear mixed-effects models (GLMM) with a binomial link function.

The following fixed effects will be entered into the models:

- rTMS interventions (right frontal, right temporal),
- Assessment time (pre, intermediate, post),
- Interaction between rTMS protocol and assessment time.

Participants and items will be included in the models as random effects.

The lmerTest package (Kuznetsova, Brockhoff, & Christensen, 2017) in R will be used to calculate the *p* values (alpha level at .05).

4. REFERENCES

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, *67*(1). https://doi.org/10.18637/jss.v067.i01

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*, *82*(13). https://doi.org/10.18637/JSS.V082.I13

R Core Team. (2013). R: A language and environment for statistical computing. *R Foundation for Statistical Computing, Vienna, Austria*.

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., … Hallett, M. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clinical Neurophysiology*, *132*(1), 269–306. https://doi.org/10.1016/j.clinph.2020.10.003

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., Avanzini, G., Bestmann, S., … Ziemann, U. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*(12), 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016