Methods: We conducted a meta-analysis of randomized sham-controlled, double-blind trials. Instead of a systematic search for the primary studies and new risk-of-bias assessment, we used 13 systematic reviews and meta-analyses that were published by February 25, 2022. We used a random-effects model, and analyzed the standardized effect sizes, and instead of only calculating the confidence intervals, as was done in literally all 13 meta-analyzes, we calculated the 95% prediction intervals to respect the uncertainty in estimating between-study variance.

Results: Total number of eligible studies was 42, of witch large number did not define the primary outcome. In the final analysis, we included 26 studies with 549 patients in active and 537 in passive sham arms. The overall effect of rTMS on severity of tinnitus was Hedges g= -0.39 (95% CI -0.57; -0.21; 95% prediction interval -1.00; 0.22) (Figure 1).

Conclusion: Too many randomized sham-controlled trials on the efficacy of rTMS on tinnitus and reporting of their results are of unsatisfactory quality. The whole body of literature is fragmented into small, too often poorly designed trials with exclusive/new protocols and presumably low reproducibility. The whole field would probably benefit from larger, better theoretically founded studies, replications of the most promising experiments, and the empirically founded patient-oriented approach that will respect the tinnitus phenotype heterogeneity and the existence of distinct patient subpopulations. In this area of research, the race for the ad-hoc discovery of the Holy Grail of rTMS *perfect* protocol should be stopped, and the traditional scientific paradigm of theoretically grounded gradual improvement on previous studies and theories should be adhered to.

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EFFICACY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION WITH H7-COIL IN THE TREATMENT OF TINNITUS: PROTOCOL FOR PHASE IIA, PROOF OF CONCEPT, RANDOMIZED, SHAM-CONTROLLED, DOUBLE BLIND CLINICAL TRIAL

Natko Gereš[1,2], Sandra Zečević Penić[1], Željko Milovac[1], Strahimir Sučić[1], Tomislav Gajšak[1], Barbara Koret[1], Josefina Gerlach[1], Diana Prskalo-Čule[1], Darjan Svetinović[1], Nikolina Tunjić-Vukadinović[1], Ivana Orgulan[1], Vladimir Požgaj[1], Andro Košec[3], Goran Geber[3,4], Goran Ivkić[5], Sandra Vuk Pisk[1,2] & Igor Filipčić[1,2,6]

[1]University Psychiatric Hospital Sveti Ivan, Zagreb, Croatia
[2]Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
[3]Department of Otorhinolaryngology & Head and Neck Surgery, University Hospital Center Sestre Milosrdnice, Zagreb, Croatia
[4]University School of Dental Medicine, Zagreb, Croatia
[5]Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Zagreb, Croatia
[6]School of Medicine, University of Zagreb, Zagreb, Croatia

Background: There is no gold standard for treating tinnitus. A relatively large number of studies of the efficacy of rTMS on tinnitus have been conducted. Generally, low-frequency (LF) stimulation of the auditory cortex in combination with high-frequency (HF) stimulation of the DLPFC, has shown efficacy in reducing symptoms (especially loudness and anxiety). A possible alternative target for HF rTMS of the DLPFC, is the medial prefrontal cortex (mPFC), using the H7 coil. There is no study of the acceptable quality on the effects of H7-coil in stimulating the auditory cortex and mPFC.

Objectives: To examine the efficacy of H7 coil LF/HF rTMS, with H7-coil applied in the treatment of idiopathic, chronic, tinnitus disorder with normoacusis.

Hypothesis: The LF rTMS (1Hz) placed over auditory cortex combined with HF (10Hz) H7-coil placed over mPFC, applied for 15 days, has superior efficacy on tinnitus symptoms measured by the overall Tinnitus Handicap Inventory (THI) score, than the SHAM passive coil.

Study design: We plan an industry-independent, single-center, prospective, randomized sham-controlled, two-arms, double-blind superiority clinical trial with concealed allocation and masked independent outcome assessment.

Population: Outpatients diagnosed for ≥ 12 months and ≤ 5 years with persistent, subjective, normoacoustic tinnitus disorder of at least moderate severity defined by the THI score ≥ 38, both unilateral and bilateral, both genders, and with no hearing loss, age 18-65 years, with the tinnitus treatment unchanged for at least one months. Exclusion criteria: organically caused tinnitus and organic brain lesion, objective

tinnitus, severe hearing loss or Menier's disease, middle ear disease, diagnosed mental disorder, suicidality, alcohol or drugs addictions, clinically relevant neurological disorder, and standard rTMS exclusion criteria.

Sample size: 52 in HR rTMS H7-coil arm, and 52 in sham control arm.

Primary outcome: Adjusted median of differences in total THI score. We will adjust the means for the distribution of age, gender, tinnitus severity, duration, and treatment.

Secondary outcomes: Change in TQ score, change in VAS score, the proportion of patients with clinically relevant lowering of total THI score ≥ 7 points, percentage of the awake time aware of tinnitus, percentage of awake time annoyed, distressed or irritated by tinnitus, change in BDI-II score, change in BAI score, change in PSQI score.

Data analysis: Within-between subjects ANCOVA or multivariable quantile regression of outcome measure score after the therapy to the treatment group, adjusted for baseline outcome measure score and all preplanned possible confounding variables in the intention-to-treat population.

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INTERIM ANALYSIS OF EFFICACY AND SAFETY OF HIGH-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION WITH H7-COIL IN TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA SPECTRUM DISORDERS: A RANDOMIZED, SHAM-CONTROLLED TRIAL

Igor Filipčić[1,2,3], Ivona Šimunović Filipčić[2,4], Katarina Matić[1], Strahimir Sučić[1], Željko Milovac[1], Natko Gereš[1,2], Mirela Čelić-Ružić[1], Sandra Zečević Penić[1] & Ivana Orgulan[1]

[1]Psychiatric Clinic "Sveti Ivan", Zagreb, Croatia
[2]Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
[3]School of Medicine, University of Zagreb, Zagreb, Croatia
[4]Department of psychiatry and psychological medicine, University Hospital Center Zagreb, Zagreb, Croatia

Background: At present, the main treatment for schizophrenia relies on antipsychotic medication. Antipsychotics, although relatively effective on positive symptoms, have no consistent, reliable, and satisfactory effect on negative and cognitive symptoms. High frequency repetitive transcranial magnetic stimulation (HF rTMS) with H7-coil represents a safe, non-invasive technique that has been hypothesized to improve negative symptoms in this population.

Objectives: The purpose of this randomized sham-controlled, two-arms, double-blind superiority clinical trial with concealed allocation and masked independent outcome assessment study is to examine the efficacy and safety of HF rTMS with H7-coil applied once daily during the twenty days, augmentative to the standard antipsychotic and other pharmacotherapy of negative symptoms in schizophrenia.

Methods: This is a report of the interim analysis after completing 50% of the planned sample size. The target population was outpatients diagnosed with SSD (ICD-10: F20-F29), both genders, age 18-55 years, with PANSS negative symptoms subscale score > 24, and PANSS positive symptoms subscale score < 20, stable during at least three months and with the antipsychotic therapy unchanged for at least three months. The primary outcome was adjusted mean of total score on The Scale for the Assessment of Negative Symptoms (SANS).

Results: We randomized 25 patients in active, H7-coil arm, 44% of them women, and 26 in inactive, sham-coil arm, 38% of them women. The median (interquartile range) of age was 38 (27-48) years in H7 and 34 (24-44) years in sham arm. During the intervention total SANS score was lowered in both study groups [-45% (95% CI -55; -35%) lowering of SANS score in H7, and -33% (95% CI -43; -23%) in sham arm]. Time x group interaction was significant p=0.035; η^2=0.11; false discovery rate <5%). We observed significant effects on blunting and alogia SANS subscales, and no significant effects on avolition/apathy, anhedonia, and attention subscales.

Conclusion: This interim analysis indicated a possible effect of HF rTMS with H7-coil on the overall severity of negative symptoms and acceptable safety and tolerability in the population of patients diagnosed with schizophrenia and pronounced negative symptoms.

Key words: *transcranial magnetic stimulation - schizophrenia spectrum and other psychotic disorder - psychotic disorder - negative symptoms*

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