REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN TREATMENT OF TINNITUS: META-ANALYSIS OF RANDOMIZED SHAM-CONTROLLED TRIALS

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Background: Tinnitus etiology and clinical presentations are highly variable. There is no stringent and universally accepted definition of the disorder, and objective diagnostic biomarkers are missing. There is no gold treatment standard, and the results of studies on various treatment effects are inconsistent. Clinical practice guidelines from 2014 stated that rTMS may not be recommended for the routine treatment of tinnitus neither, because of methodological heterogeneity/weaknesses, and inconsistencies of results of rTMS randomized controlled trials. Since 2014, more studies of rTMS efficacy on tinnitus have been published, but the results are still highly heterogenous, poorly reported, with low reproducibility, and non-conclusive. To access the efficacy of rTMS on idiopathic, chronic tinnitus disorder.

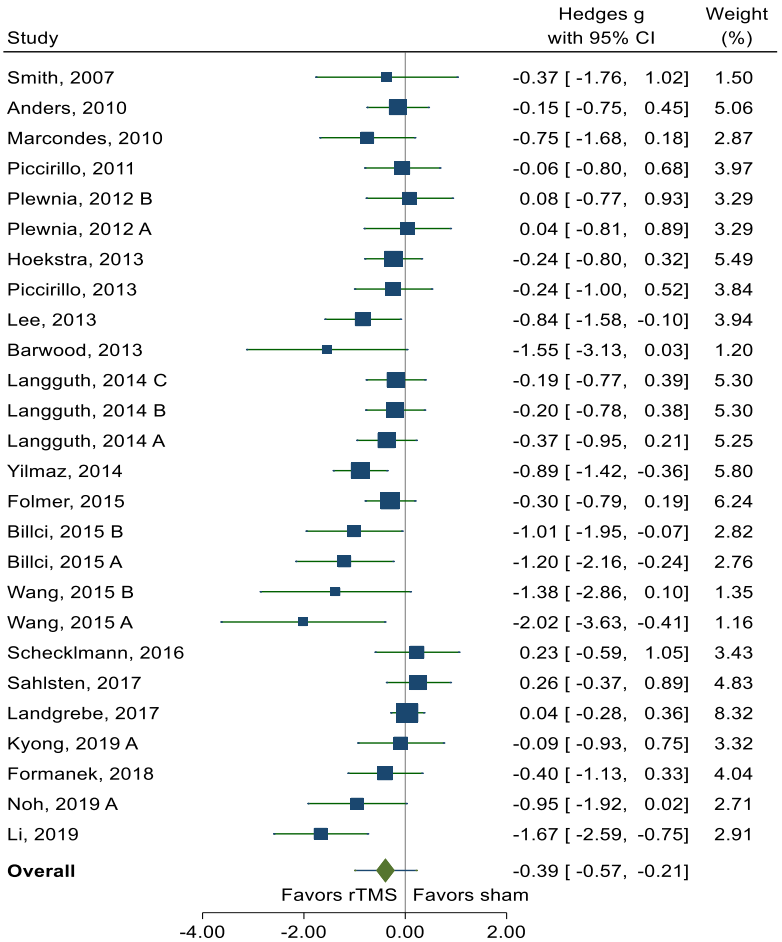

Figure 1. Forest plot of standardized mean differences (Hedges g) between active rTMS and passive sham coil in the effect on tinnitus severity measured immediately after the intervention; error lines in the summary measure represent 95% prediction interval (-1.00; 0.22); (n = 26 studies; 549 patients in active rTMS arms, 537 in passive sham arms); studies are sorted by the year of publishing of the first results in order starting with the oldest one

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

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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