Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis

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CRD summary
This review compared auditory hallucination rates in schizophrenia after slow repetitive transcranial magnetic stimulation and sham treatment. The authors concluded that the intervention was effective in reducing hallucination rates. These conclusions may not be reliable as the review methodology was poorly reported, the searches were limited, and the included studies had small sample sizes, varying intervention schedules and outcomes and were of uncertain quality.

Authors' objectives
To evaluate the effects of slow repetitive transcranial magnetic stimulation (rTMS) at a frequency of 1 Hz on auditory hallucinations in patients with schizophrenia.

Searching
PubMed and Web of Science were searched from 1966 to February 2006; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Studies were eligible for inclusion if they used a placebo or active control parallel or crossover trial design. In the case of multiple publications the largest study was included. The included studies had between 10 and 50 participants.

Specific interventions included in the review
Studies were eligible if they assessed the effects of rTMS at a frequency of 1 Hz to the left temporoparietal cortex compared with sham or an active control treatment. Most of the included studies compared rTMS with sham or placebo rTMS, except for one study which only had an active control condition consisting of rTMS over the occipital lobe. Motor thresholds varied between 80 and 100%, durations of stimulation ranged from one session of 4 to 16 minutes to two sessions of 17 minutes, and treatment duration was between 4 and 10 days.

Participants included in the review
Studies were eligible if they included patients with schizophrenia. No further information on the patients in the included studies was reported.

Outcomes assessed in the review
The main outcome was reduction in hallucinations, as measured by a psychometric rating scale. Studies were eligible if they used a hallucination rating scale or a hallucination item from a standardised psychiatric interview. The severity of all positive symptoms was also reported; studies used the Positive and Negative Syndrome Scale (PANSS) positive subscale or the Scale for the Assessment of Positive Symptoms (SAPS). Studies that did not provide enough data to calculate effect sizes were excluded.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity, although they stated that open trials were not eligible.
Data extraction
Standardised mean differences for pre- to post-treatment changes were computed from mean and standard deviations or t and F statistics. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The results were pooled using a random-effects model, weighted by sample size. The resultant effect sizes were reported together with 95% confidence intervals (CIs).

How were differences between studies investigated?
Heterogeneity was assessed using the Q statistic. Further analyses assessed mode of stimulation, number of stimulation sessions, and parallel versus crossover design as effect modulators.

Results of the review
Eleven studies (n=230) were included in the review; all but one were randomised controlled trials (n=212).

All but one of the included studies were double-blind (i.e. neither the patient nor the evaluator was aware of the treatment condition) and sham-controlled. All studies except one (for which no information was available) were described as randomised.

The mean standardised gain effect size for change in hallucination severity after rTMS was 0.76 (95% CI: 0.36, 1.17, p=0.0001; 10 studies) compared with sham treatment. There was significant heterogeneity between the studies (p=0.01) which disappeared after excluding a study inserting multiples pauses during stimulation sessions. After the exclusion of that study, the mean standardised gain effect size was 0.88 (95% CI: 0.52, 1.23, p<0.0001). The results in studies with less than five stimulation sessions versus more than five sessions were similar. Studies with a parallel-group design had a mean weighted effect size of 0.63 (95% CI: 0.30, 0.97, p=0.0001), while those with a crossover design had a mean weighted effect size of 0.93 (95% CI: 0.17, 1.69, p=0.009). The authors did not report whether this difference was statistically significant.

There was no significant improvement in the severity of all positive symptoms (PANSS positive subscale or SAPS); the effect size was 0.21 (95% CI: -0.29, 0.72, p=0.20; 6 studies).

Authors' conclusions
The results provide evidence for the effectiveness of slow rTMS at a frequency of 1 Hz as a treatment that selectively alters neurobiologic factors underlying auditory hallucinations.

CRD commentary
This review had clearly stated inclusion criteria with respect to the study design, participants, interventions and outcomes. The search was limited to PubMed and the Web of Science; no efforts were made to search more specific databases or to search for unpublished studies, making it likely that pertinent studies have been missed and that publication bias might have been introduced in the review. Methods such as the study selection, validity assessment and data extraction procedures were not reported, making it difficult to evaluate the review. The quality of the included studies was not assessed and patient characteristics were not reported, thus the comparability of the studies is not clear. The included studies varied greatly in their treatment schedules.

The limited search strategy and the lack of information on review methodology, alongside some methodological problems of the included studies (small sample sizes, uncertain quality, variation in intervention schedules, different rating scales used) cast some doubt on the reliability of the conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that large multicentre clinical trials are needed to establish the clinical significance and tolerability of rTMS. Studies should use the same hallucination scale to measure improvement; a suitable scale would be the Auditory Hallucinations Rating Scale. Follow-up measurements should be included up to 6 months following treatment. Brain-imaging methods should be used to identify the functional locus of hallucination activity and to target these regions with rTMS using a neuronavigator. Future studies should also investigate why some patients do not seem to improve with this treatment. Specific comparisons between rTMS and pharmacological treatment could also be useful.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.