Should we treat auditory hallucinations with repetitive transcranial magnetic stimulation? A metaanalysis

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CRD summary
This review concluded that low-frequency repetitive transcranial magnetic stimulation had a medium effect on patients suffering from schizophrenia with medication-resistant auditory hallucinations. The authors' conclusions appear to be reliable.

Authors' objectives
To review the efficacy of repetitive transcranial magnetic stimulation in the treatment of auditory hallucinations experienced by patients with schizophrenia spectrum disorders.

Searching
The authors searched a range of resources from 1985 (first description of transcranial magnetic stimulation use in humans) to May 2006. These included MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and the Current Controlled Trials website. The controlled trials databases were cross-referenced with published papers. Investigators were contacted to provide additional data when necessary.

Study selection
To be eligible, studies were required to be experimental studies of repetitive transcranial magnetic stimulation treatment for auditory hallucinations in patients who had been diagnosis of schizophrenia spectrum disorders. Studies had to be randomised and include a placebo control group. Eligible studies had to have three treatment sessions or more, and use a valid psychometric assessment scale. Eligible studies had to focus on the left temporoparietal cortex and administer repetitive transcranial magnetic stimulation at low frequency (1Hz or less).

The primary outcome was the reduction of auditory hallucinations. The secondary outcome was the reduction of positive psychotic symptoms.

A variety of different measurement scales was used in the included studies. All included studies evaluated 1Hz repetitive transcranial magnetic stimulation as an adjuvant treatment for medication-resistant auditory hallucinations. The duration of treatment ranged from four to 10 days, with an average intensity of 89% of the motor threshold.

All papers were screened independently and disagreements were resolved by discussion.

Assessment of study quality
Trial quality was assessed based on the Cochrane checklist and involved six criteria: allocation of concealment, blinding of participant, blinding of investigator, blinding of outcome assessor, completeness of follow-up and intention-to-treat analysis. The intention-to-treat variable was excluded from the checklist when there was less than 10% attrition rate.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Where appropriate, data from subscales were pooled to provide one mean and standard deviation. Several scales were identified for each of the trial outcomes and information was extracted from these scales in two different orders of preference (as detailed in the paper). Data from each trial were transformed into z scores. The effect size was calculated by comparison of the active repetitive transcranial magnetic stimulation treatment with the sham treatment using a variety of methods in decreasing preference (described in the paper). For follow-up losses of more than 10% of the initial population, the intention-to-treat and last observation carried forward corrections were used. The authors of
clinical trials were contacted to obtain the most detailed information available.

More than one reviewer was involved in data extraction and differences were resolved by discussion.

**Methods of synthesis**
Each trial could only contribute once to the overall effect size estimate. Trials were combined in a random-effects meta-analysis. Publication bias was assessed using file drawer analysis. Heterogeneity was examined through the Q statistic. A set of variables were defined a priori to be investigated through meta-regression.

**Results of the review**
Ten randomised controlled trials (RCTs) were included in the review (n=232 participants). This included six parallel-arm double-blind placebo-controlled randomised trials and four cross-over RCTs. Results of quality assessment were not presented in full.

Overall, the effect of treatment with repetitive transcranial magnetic stimulation on auditory hallucinations in patients with schizophrenia was 0.514 (95% CI 0.225 to 0.804). No statistical heterogeneity was found. File drawer analysis suggested that 38 additional studies, showing no benefit from repetitive transcranial magnetic stimulation treatment, would be needed to reverse these findings.

Fixed-effect meta-regression analyses of the effect size as a function of total number of stimulations, repetitive transcranial magnetic stimulation intensity and duration of treatment were not statistically significant. Further analyses revealed a significant time x treatment interaction (F=7.55, df=1.31, p<0.01), which showed that over time there was a significant change in auditory hallucination scores for patients with schizophrenia treated with repetitive transcranial magnetic stimulation.

**Authors’ conclusions**
Low-frequency repetitive transcranial magnetic stimulation over the left temporoparietal cortex had a medium effect on patients suffering from schizophrenia with medication-resistant auditory hallucinations.

**CRD commentary**
This review had defined inclusion criteria for participants, intervention, outcomes and study design. A range of information sources were consulted and authors contacted for supplementary data. It was difficult to assess the risk of language bias, as the authors did not state whether language restrictions were applied during searching. Methods of study selection and data extraction were described, and attempts were made to reduce bias and error in these processes by the involvement of more than one reviewer.

Reporting of the methods and results of trial quality assessment was more limited. Meta-analysis appeared to be appropriate given that it was undertaken in conjunction with heterogeneity assessment. The investigation of the role of clinical and trial variables was pre-specified.

The authors’ conclusions are based on the results and appear to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the review supported the use of repetitive transcranial magnetic stimulation as a complementary treatment approach in patients suffering from schizophrenia with treatment-resistant auditory hallucinations

**Research:** The authors stated that repetitive transcranial magnetic stimulation use in unmedicated patients would be a promising line of future research. They suggested that cross-over studies should be avoided in further research due to potential bias from carry-over effects.

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Record Status
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.