Meta-analysis of repetitive transcranial magnetic stimulation in the treatment of auditory verbal hallucinations: update and effects after one month

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CRD summary
The review concluded that, with the inclusion of studies with larger patient samples, the effect size of repetitive transcranial magnetic stimulation directed at the left temporoparietal area for auditory verbal hallucinations decreased over time, although the effect was still significant. The review had several methodological limitations that mean the authors' conclusions should not be considered as being reliable.

Authors' objectives
To evaluate the efficacy of repetitive transcranial magnetic stimulation (rTMS) for auditory verbal hallucinations, including assessment of long-term effects (one month after the end of treatment).

Searching
The Cochrane Library, EMBASE Psychiatry, MEDLINE and PsycINFO were searched to August 2012 for studies in English; search terms were reported. Reference lists of obtained articles were screened.

Study selection
Randomised double-blind sham-controlled trials of rTMS used at 1Hz were eligible. Auditory Hallucination Rating Scale scores or scores of another relevant visual analogue scale were the main outcomes of interest. Studies had to report sufficient data to compute Hedges' g.

Most studies directed treatment at the left temporoparietal area and most included some patients with therapy-resistant auditory verbal hallucinations. The number of treatment sessions ranged from three to 20. The parameters of sham treatments varied. A wide range of questionnaires were used to assess outcomes.

One reviewer screened studies.

Assessment of study quality
The authors did not state that they assessed study quality, although they did report that the number of drop-outs was extracted for each study.

Data extraction
Pre- and post-treatment (immediately after treatment cessation and one month after) auditory verbal hallucination severity data were extracted in order to calculate mean differences with 95% confidence intervals (CI). Where these data were not available, data for severity of psychosis were extracted. Authors were contacted for missing data where necessary.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Meta-analyses were performed to calculate pooled standardised mean differences, expressed as Hedges' g, using a random-effects model. Fail-safe N was calculated. Heterogeneity was assessed using $I^2$. Crossover studies were excluded in a sensitivity analysis.

Results of the review
Seventeen studies (337 participants) were included.

Treatment with rTMS directed at the left temporoparietal area significantly reduced auditory hallucinations when compared with sham treatment (Hedge's $g = 0.44$, 95% CI 0.19 to 0.68; 15 trials; $I^2=36$; fail-safe N=996). When four crossover studies were excluded a similar result was seen. When studies that directed treatment at other brain regions...
were included the difference was smaller (Hedge's g 0.33, 95% CI 0.17 to 0.50; 17 studies; I²=13%).

There were no significant differences between groups at one month of follow-up (Hedge's g 0.40, 95% CI 0.23 to 0.102; five studies; I²=64%; fail-safe N=10).

Side effects were reported as being mild. The number of drop-outs did not differ significantly between groups.

No associations were found between treatment parameters or other study variables and effect size. Studies published before 2007 had significantly larger effect sizes than more recent studies.

**Authors’ conclusions**
With the inclusion of studies with larger patient samples, the effect size of rTMS directed at the left temporoparietal area for auditory verbal hallucinations decreased, although the effect was still significant. Duration of the effect of rTMS may be less than one month. More research was needed to optimise parameters and further evaluate the clinical relevance of this intervention.

**CRD commentary**
The review question was supported by reproducible eligibility criteria; it appeared that any population types were eligible. Attempts to identify relevant studies were undertaken by searching electronic databases and checking references. Language restrictions and the absence of a specific search for unpublished trials meant that some relevant studies may have been missed.

The authors did not report that they used suitable methods (such independent duplicate processes) to reduce the risks of reviewer error and bias during the review. Study quality was not assessed formally and this made it very difficult to evaluate the reliability of the trial results. Basic study details were provided and appropriate methods were used to pool data and assess and investigate heterogeneity, although the reliability and relevance of estimates derived from such a varied range of outcome measures was questionable.

The review had several methodological limitations that mean the authors’ conclusions should not be considered as being reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that larger studies were needed to optimise treatment parameters and further evaluate clinical relevance.

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