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

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ABSTRACT

*Objective:* Several meta-analyses considering repetitive transcranial magnetic stimulation (rTMS) for auditory verbal hallucinations (AVH) have been performed with moderate to high mean weighted effect sizes. Since then several negative findings were reported in relatively large samples. The aim of this study was to provide an update of the literature on the efficacy of rTMS for AVH and to investigate the effect of rTMS one month after the end of treatment.
*Data sources:* A literature search was performed from 1966 through August 2012 using Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Embase Psychiatry, Ovid Medline, PsycINFO and PubMed. Randomized, double blind, sham-controlled studies with severity of AVH or severity of psychosis as an outcome measure were included.
*Study selection:* Data were obtained from 17 randomized studies of rTMS for AVH. Five studies fulfilled the criteria for the meta-analysis on the effect of rTMS one month after the end of treatment.
*Data extraction:* Standardized mean weighted effect sizes of rTMS versus sham were computed on pre- and posttreatment comparisons.
*Data synthesis:* The mean weighted effect size of rTMS directed at the left temporoparietal area was 0.44 (95% CI 0.19–0.68). A separate meta-analysis including studies directing rTMS at other brain regions revealed a mean weighted effect size of 0.33 (95% CI 0.17–0.50) in favor of real TMS.
The effect of rTMS was no longer significant at one month of follow-up (mean weighted effect size = 0.40, 95% CI −0.23–0.102). Side effects were mild and the number of dropouts in the real TMS group was not significantly higher than in the sham group.
*Conclusions:* With the inclusion of studies with larger patient samples, the mean weighted effect size of rTMS directed at the left temporoparietal area for AVH has decreased, although the effect is still significant. The duration of the effect of rTMS may be less than one month. More research is needed in order to optimize parameters and further evaluate the clinical relevance of this intervention.



## 1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a safe treatment method with only mild side effects such as transient headache and scalp discomfort during stimulation. Hoffman et al. (1999) were the first to investigate the effect of rTMS in the treatment of medication-resistant auditory verbal hallucinations (AVH). In their initial study, rTMS was directed at the left temporoparietal cortex at a frequency of 1 Hz. This site of stimulation is believed to overlay Brodmann area 40 (Homan et al., 1987) and was selected in light of results of a previous positron emission tomography (PET) study demonstrating activation in this brain area during AVH (Silbersweig et al., 1995). Furthermore, this region has a central role in speech perception (Ojemann, 1978; Fiez et al., 1996; Benson et al., 2001). Since that first study several randomized sham-controlled studies on this subject have been published, some with positive, others with negative findings. These publications have been summarized in four meta-analyses revealing moderate to high mean weighted effect sizes ranging from 0.54 to 1.0 (Aleman et al., 2007; Tranulis et al., 2008; Freitas et al., 2009; Slotema et al., 2010). Since the publication of these meta-analyses several negative studies have become available which included relatively large sample sizes. In addition, these previous meta-analyses focussed on the direct effects of rTMS at the end of the treatment trial, and did

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not explore effects of rTMS at follow-up after some weeks or months. The aim of this study is therefore twofold:

1. to conduct a new meta-analysis considering the effect of rTMS for AVH
2. to investigate the long term effects of rTMS for AVH.

## 2. Experimental/materials and methods

A search of the literature was performed using Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Embase Psychiatry 1997 through August 2012, Ovid Medline through August 2012, PubMed 1990 through August 2012 and PsycINFO 1990 through 2012. All articles were searched for cross-references.

The search terms *auditory verbal hallucinations*, *auditory hallucinations*, *psychosis*, *psychotic features*, *transcranial magnetic stimulation*, *repetitive transcranial magnetic stimulation*, *TMS* and *repetitive TMS* were used.

Criteria for inclusion were:

1. Treatment with rTMS using the frequency of 1 Hz.
2. The summed score of the Auditory Hallucination Rating Scale (AHRS) (Hoffman et al., 2003) was used as an outcome measure; if the summed score could not be obtained, the item 'frequency' of the AHRS or a Visual Analogue Scale such as the Hallucination Change Scale was used as a second or third choice respectively. In case the severity of AVH was not included as an outcome measure, the scores for a scale assessing positive symptoms (of schizophrenia) were obtained.
3. The study was performed in a double-blind, randomized controlled design using a sham condition. In a separate analysis cross-over studies were excluded as patients might not remain blinded during this design, which may influence the results.
4. Sufficient data were needed to compute Hedges' g (i.e., sample size, means, standard deviations or exact t or p values for rTMS main effect for change scores).
5. The article was written in English.
6. When different publications had an overlap in patient samples, the article with the largest sample size was included.

The studies were screened conforming to the criteria for inclusion. The first author performed the screening.

### 2.1. Data extraction

The following data were acquired: number of treated patients per treatment condition, pre- and posttreatment (defined as immediately after the end of treatment and one month after cessation of treatment) means and standard deviations of the severity of AVH at baseline and at end of treatment, or exact F, t or p values. Furthermore, the study design and treatment parameters, such as frequency, percentage of the individual motor threshold, number of TMS pulses, number of sessions, focus of treatment and type of coil, were acquired. Finally, information considering dropouts and side effects was obtained.

Authors were contacted and invited to send additional data in case publications contained insufficient or incomplete results.

### 2.2. Effect size calculation

The mean weighted effect size, Hedges' g, was computed with the aims of Comprehensive Meta-Analysis Version 2.0 (Biostat, Englewood, New Jersey) in a random effects model. First, the effect sizes were calculated for the mean change in symptom severity between pre- and posttreatment for the separate conditions and weighted according to sample size. In studies with three treatment conditions, the two actual treatments were compared separately with the sham condition. Then, meta-analytic methods were used to obtain a combined, weighted effect size. In order to investigate the effect of rTMS on the severity of psychosis, a separate analysis was conducted by using the changes assessed with the summed score of the positive items of the Positive And Negative Syndrome Scale. Separate analyses were confined to rTMS directed at the left temporoparietal area, rTMS targeted at all brain regions and interview-based clinician-rated versus self-report measures.

A homogeneity statistic, $I^2$, was computed to test whether the studies could be taken to share a common population effect size (Higgins et al., 2003). A percentage of 50% or higher indicates heterogeneity of the individual study effect sizes, which poses a limitation to a reliable interpretation of the results. Whenever significant heterogeneity was found, a moderator analysis was performed to investigate the potential moderating factors, such as localization of target area for stimulation, intensity of the individual motor threshold and number of TMS pulses. These parameters were correlated with Hedges' g using Pearson's correlations in Statistical Packages for the Social Sciences (SPSS, Chicago, Illinois) version 18.

The effect size can be overestimated in case of an omission of studies with negative results in the literature. Therefore, a fail-safe number was computed, which is an estimation of the number of missing studies that is needed to change the results of the meta-analysis to non-significant (Rosenthal, 1979). To visualize a putative decline of effect sizes over the last years, the mean weighted effect sizes were plotted against year of publication.

## 3. Results

Fifteen studies were included in the meta-analysis considering rTMS directed at the left temporoparietal area. Two additional studies were included for the meta-analysis for all rTMS foci. In Table 1 the number of studies that was excluded and the reason for exclusion are presented.

Three hundred and thirty-seven patients were included (Hoffman et al., 2000; McIntosh et al., 2004; Schonfeldt-Lecuona et al., 2004; Chibbaro et al., 2005; Fitzgerald et al., 2005; Hoffman et al., 2005; Lee et al., 2005; Poulet et al., 2005; Brunelin et al., 2006; Jandl et al., 2006; Rosa et al., 2007; Saba et al., 2006; Vercammen et al., 2009; Loo et al., 2010; Slotema et al., 2011; De Jesus et al., 2011; Blumberger et al., in press; Bais et al., in preparation); 209 and 197 patients received real rTMS targeted at the left temporoparietal area and sham-treatment respectively. Details of the treatment-paradigms of all studies are presented in Table 2. Ten out of fifteen studies included patients with therapy-resistant AVH and Hoffman et al. (2005) included 42 out of 50 patients with therapy-resistant AVH.

**Table 1**
Number of excluded studies and reason for exclusion.

| | No. of retrieved studies | No. of excluded studies | Reasons for exclusion |
|---|---|---|---|
| Gateway ovid | | No clinical trial | 19 |
| | | No RCT with placebo | 17 |
| | | No English | 12 |
| | | Severity of AVH no outcome measure | 6 |
| | | Overlap | 3 |
| Total | 76 | | 61 |
| PubMed | | No clinical trial | 83 |
| | | No English | 11 |
| | | No RCT with placebo | 5 |
| | | Overlap | 3 |
| | | Severity of AVH no outcome measure | 2 |
| Total | 121 | | 104 |

RCT = randomized controlled trial.
AVH = auditory verbal hallucinations.