Review of the Efficacy of Transcranial Magnetic Stimulation for Auditory Verbal Hallucinations

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With an increase of the number of studies exploring repetitive transcranial magnetic stimulation (rTMS) for the treatment of auditory verbal hallucinations (AVH), an update is provided on the efficacy of different paradigms. A literature search was performed from 1966 through April 2013. Twenty-five randomized controlled trials using the severity of AVH or psychosis as outcome measures were included. Standardized mean weighted effect sizes were computed; a qualitative review of the literature was performed to assess the effects of various rTMS paradigms. rTMS versus sham treatment for AVH yielded a mean weighted effect size of .44. No significant mean weighted effect size was found for the severity of psychosis (i.e., .21). For patients with medication-resistant AVH, the mean weighted effect size was .45. rTMS applied at the left temporoparietal area with a frequency of 1 Hz yielded a moderate mean weighted effect size of .63, indicating superiority of this paradigm. Various other paradigms failed to show superior effects. rTMS applied at the right temporoparietal area was not superior to sham treatment. rTMS, especially when applied at the left temporoparietal area with a frequency of 1 Hz, is effective for the treatment of AVH, including in patients with medication-resistant AVH. The results for other rTMS paradigms are disappointing thus far. A next step should be to explore the effects of rTMS in medication-free individuals, for example, during the initial phases of psychosis, and in patients with diagnoses other than schizophrenia who do not have comorbid psychotic symptoms.

Key Words: Auditory hallucinations, deep brain stimulation, meta-analysis, psychosis, review, transcranial magnetic stimulation

Auditory verbal hallucinations (AVH) are common in psychiatric disorders, notably in psychotic disorders. The ensuing distress is often high and may result in severe social dysfunction, violence, or suicide attempts (1,2). Antipsychotic medication is effective in most cases but may be accompanied by side effects such as weight gain, somnolence, hyperprolactinaemia, and dystonia and other movement disorders. As a result, patients may refuse antipsychotic medication. In addition, some 25% to 30% of patients diagnosed with schizophrenia experience AVH that are unresponsive to antipsychotic medication (3). Alternative treatment options are scarce. Cognitive-behavioral therapy, for example, can decrease the burden caused by AVH but is unable to affect their frequency or duration (4).

Noninvasive treatment methods have been proposed for the treatment of AVH, including repetitive transcranial magnetic stimulation (rTMS) and direct-current stimulation. In rTMS, a rapidly fluctuating electrical current induces a fluctuating magnetic field, which can effectively depolarize neurons up to a depth of approximately 2 cm beneath the skull. When applied during several days, rTMS is thought to yield longer-lasting effects by means of long-term depression/potentiation, although it should be noted that direct evidence for this mechanism is lacking (5). When applied in accordance with standard international safety guidelines, rTMS is associated with few side effects and is generally accepted as safe (6).

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Because AVH may co-occur with activity in the left temporoparietal area (7,8), this area was stimulated with a frequency of 1 Hz and showed that repeated stimulation induced a longer-lasting decrease of the frequency and severity of medication-resistant AVH (9). The left temporoparietal area is involved in the perception of speech (10,11). Increased activation of this area during AVH may arise from deficits in self-monitoring resulting in misinterpretation of inner speech (12,13). Various studies have subsequently been performed replicating the positive effects found by Hoffman *et al.* (14–22), but others failed to do so (23–33). This article provides an update on rTMS as a treatment method for auditory hallucinations, based on a quantitative, structured review. It adds novel information compared with our previous quantitative review (6) because it provides separate meta-analyses of rTMS paradigms other than low-frequency rTMS directed at the left temporoparietal area, investigates the effect on severity of psychosis in general, and includes the most recent studies.

Methods and Materials

A search of the literature was performed using the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, Embase Psychiatry 1997 through January 2013, Ovid Medline 1966 through January 2013, PubMed 1990 through January 2013, and PsycInfo 1990 through 2013, with the search terms *auditory verbal hallucination*, *auditory hallucination*, *psychosis*, *psychotic features*, *noninvasive treatment*, *transcranial magnetic stimulation*, *repetitive transcranial magnetic stimulation*, *TMS*, *rTMS*, and *repetitive TMS*. Whenever necessary, cross-references were checked.

Meta-Analyses

Meta-analyses were performed when the following criteria were fulfilled: 1) At least three articles on comparable rTMS paradigms; 2) outcome measures: the severity of AVH (assessed with the summed score of the Auditory Hallucination Rating Score, Hallucination Change Score, Severity of Hallucinations, or the AVH-related items of the Psychotic Symptom Rating

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Scales); severity of psychosis (assessed with the Positive and Negative Syndrome Scale or the Scale for the Assessment of Positive Symptoms); 3) a double-blind, randomized controlled design using a sham condition; 4) sufficient data for the computation of mean weighted effect sizes (i.e., sample size, means, SD, or exact *t* or *p* values for rTMS main effect for change scores); 5) only publications in English; 6) restriction of the analysis to the largest sample size in case of different publications with overlapping patient samples; and 7) a separate analysis for groups of patients with medication-resistant AVH, defined as insufficient response to at least two antipsychotic agents, administered at adequate dosages for at least 6 weeks.

Articles that failed to meet these criteria but were nevertheless considered relevant were reviewed qualitatively.

Data Extraction

The data acquired comprised the number of patients per treatment condition, pre- and posttreatment means and SDs for the severity of AVH at baseline and at the end of treatment, or exact *F*, *t*, or *p* values. In addition, we collected 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. When publications contained insufficient and/or incomplete results, the authors were approached personally with a request to grant insight into additional data.

Effect Size Calculation

The mean weighted effect size, Hedge's *g*, was computed with the aid of the Comprehensive Meta-Analysis, Version 2.0 (Biostat, Englewood, New Jersey) in a random-effects model. Hedge's *g* is a measure of standardized effect size that finesses the bias induced by using the sample SD of treatment responses. A standardized effect size is essentially the treatment response divided by its SD. The effect sizes (Hedge's *g*) were calculated for the mean change in symptom severity between pre- and posttreatment states for the separate conditions and weighted according to sample size. In studies with three treatment conditions, the two actual treatments were either compared separately with the sham condition or with each other. Finally, meta-analytic methods were used to obtain a combined, mean weighted effect size.

A homogeneity statistic, I^2, was computed to test whether the studies could be taken to share a common population effect size (34). 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. This moderator analysis can be regarded as a multiple linear regression or analysis of covariance in which we test for interactions between the various factors described earlier and treatment in mediating the observed response. These parameters were correlated with the mean weighted effect sizes using Pearson's correlations in Statistical Packages for the Social Sciences (SPSS, Chicago, Illinois), Version 18.

Because the effect size can be overestimated in cases of omissions of studies with negative results, a fail-safe number was computed, that is, an estimation of the number of missing studies necessary to change the results of the meta-analysis to nonsignificant (35). In addition, a funnel plot was made to explore publication bias with the aims of Comprehensive Meta-Analysis, version 2.0 (Biostat).

Results

A total of 134 studies were considered, and 115 were excluded. The reasons for exclusion are presented in Table 1. Details of the 19 randomized, sham-controlled studies that were included are presented in Table 2.

Meta-Analyses

Six meta-analyses could be conducted: 1) rTMS versus sham treatment for AVH; 2) rTMS versus sham treatment for psychotic symptoms in general; 3) rTMS for treatment-resistant AVH; 4) 1-Hz rTMS directed at the left temporoparietal area versus sham treatment for AVH; 5) 1-Hz rTMS directed at the right temporoparietal area versus sham treatment for AVHs; and 6) 1-Hz rTMS versus high-frequency rTMS for AVH.

Meta-Analysis 1: rTMS versus Sham Treatment for AVH

Nineteen studies with a total number of 548 patients were included for the first meta-analysis (see Figure 1). The mean weighted effect size was .44, $p < .001$, $I^2 = 27.06$, $p = .10$). The fail-safe number was 3,688 studies. A moderator analysis revealed no significant correlation between effect size and rTMS parameters.

Meta-Analysis 2: rTMS versus Sham Treatment for Psychotic Symptoms in General

Fourteen studies were included to assess the effects of rTMS on the severity of psychosis (i.e., the summed Positive and Negative Syndrome Scale positive score and the Scale for the Assessment of Positive Symptoms) with a total number of 353 patients. The mean weighted effect size was .21, $p = .11$, $I^2 = 22.92$, $p = .19$ (Figure 2).

Meta-Analysis 3: rTMS versus Sham Treatment for Medication-Resistant AVH

Ten studies with a total number of 357 patients fulfilled the criteria for inclusion. The results are presented in Figure 3. The mean weighted effect size was .45, $p < .001$, $I^2 = 29.72$, $p = .13$. The fail-safe number was 576 studies. No significant correlation was found between the mean weighted effect size and rTMS parameters.

Table 1. Reasons for Exclusion from the Meta-Analysis of Sham-Controlled rTMS Studies in the Treatment of AVH

Reasons for Exclusion	Number of Excluded Studies
$n < 3$	25
Open-Label Study	11
AVH Severity Not Included as an Outcome Measure	22
No Clinical Trial	41
No rTMS	2
No Sham Condition	3
Overlap with Other Patient Samples	3
Non-English Language	8
Total Number of Excluded Studies	115

AVH, auditory verbal hallucinations; rTMS, repetitive transcranial magnetic stimulation.