Efficacy of Slow Repetitive Transcranial Magnetic Stimulation in the Treatment of Resistant Auditory Hallucinations in Schizophrenia: A Meta-Analysis

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Objective: Slow repetitive transcranial magnetic stimulation (rTMS), at a frequency of 1 Hz, has been proposed as a treatment for auditory hallucinations. Several studies have now been reported regarding the efficacy of TMS treatment, but results were inconsistent. Therefore, meta-analytic integration of the published trials is needed to evaluate the prospects of this new treatment.

Data sources: A literature search was conducted using PubMed and Web of Science for the years 1966 until February 2006. We used the search terms *transcranial magnetic stimulation*, *TMS*, *rTMS*, and *hallucination**.

Study selection: From 15 treatment studies published since 1999, ten were sham-controlled trials and provided sufficient valid information to be included. All studies targeted the left temporoparietal cortex using 1 Hz rTMS.

Data extraction: Standardized mean gain effect sizes of real rTMS versus sham rTMS were computed based on pretreatment-posttreatment comparisons (computed from mean and SD values or t or F statistics).

Data synthesis: After calculation of treatment gain on hallucination ratings using standardized mean differences (sham vs. active rTMS), a mean weighted effect size was computed in the random effects model. We observed a significant mean weighted effect size for rTMS versus sham across the 10 studies, involving 212 patients, d = 0.76 (95% CI = 0.36 to 1.17). When only studies were included that used continuous stimulation (9 studies), the mean effect size increased to d = 0.88 and heterogeneity disappeared. There was no significant effect of rTMS on a composite index of general psychotic symptoms.

Conclusions: The results of this meta-analysis provide evidence for the efficacy of rTMS as an intervention that selectively alters neurobiologic factors underlying auditory hallucinations.

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Transcranial magnetic stimulation (TMS) is a noninvasive technique that enables safe, relatively painless, focal brain stimulation in human subjects. In TMS, a time-varying magnetic field is generated by a current pulse through a stimulator coil placed over a certain scalp position. The rapid rise and fall of the magnetic field induces a flow of current in the underlying brain tissue (diameter of approximately 2–3 cm), resulting in membrane depolarization and neural activation.[1,2] Transcranial magnetic stimulation is increasingly being applied in cognitive neuroscience as a brain-mapping method[3,4] because it allows for causal inference due to the transient disruption of ongoing neural activity in a specific region that might be necessary for a given cognitive task.

Repetitive TMS (rTMS; i.e., at frequencies of 1 Hz or higher) has also been proposed as a treatment for psychiatric disorders,[5,6] particularly for depression and for hallucinations in schizophrenia. When used for treatment, rTMS is applied in daily sessions for several days or weeks. Most studies have focused on the effects of rTMS over the prefrontal cortex in depression (usually at a frequency of 10 Hz). Several reviews and meta-analyses of these studies have recently been published, with mixed conclusions.[7–9] Nonetheless, the weight of the evidence supports the suggestion that rTMS might have some antidepressant effects, although definite clinical efficacy remains to be established.[10]

With regard to hallucinations in schizophrenia, the first report using rTMS treatment was published by Hoffman, et al.[11] in 1999, which reported improvement of hallucination severity in 3 schizophrenia patients with medication-resistant hallucinations after a total of 40 minutes of 1 Hz rTMS given over 4 days. In a subsequent, larger (N = 12), double-blind, sham-controlled crossover study, Hoffman

et al.[12] replicated this effect. One Hz, or slow rTMS, was used because it reduces brain excitability (for review, see Hoffman and Cavus[13]), in contrast to the fast rTMS (> 5 Hz) used in depression studies, which enhances brain excitability. The reduction of brain excitability with 1 Hz rTMS resembles the experimentally-induced synaptic modification known as long-term depression, which is induced by low-frequency electrical stimulation directly applied to afferent fibers.[13] The initial reports of beneficial rTMS effects on hallucinations in schizophrenia have been followed by 12 other studies over the past years. Whereas some reported significant improvements, others failed to find changes in hallucination ratings due to the rTMS treatment (see Table 1). In the present review, our aim was to integrate the published findings regarding the efficacy of rTMS treatment of hallucinations using meta-analysis. We also review different study parameters that may have influenced the results. Finally, apart from methodological issues, we discuss putative neurobiologic mechanisms that may underlie the effect of rTMS on hallucinations.

METHOD

Selection of Studies

A literature search was conducted using PubMed and Web of Science for the years 1966 until February 2006. We used the search terms *transcranial magnetic stimulation*, *TMS*, *rTMS*, and *hallucination**. The main outcome measure was reduction of hallucinations as measured with appropriate psychometric rating scales. Studies were included in the meta-analysis when they reported a parallel or crossover design with sham or active control in patients with schizophrenia and used a hallucination rating scale or hallucination item from a standardized psychiatric interview (e.g., Positive and Negative Syndrome Scale [PANSS], Brief Psychiatric Rating Scale) to assess changes in hallucination severity. An example of a typical hallucination rating scale is the Auditory Hallucinations Rating Scale,[14] which is a 7-item scale measuring frequency, reality, loudness, number of voices, length, attentional salience, and distress level. Some studies reported one composite, patient-specific rating of hallucination intensity, such as the Hallucination Change Scale.[12] This scale is anchored at baseline using the narrative description of hallucinations by the patient for the prior 24 hours, which is assigned a score of 10. For subsequent assessments, the score can range from 0 to 20 (with a score of 20 corresponding to hallucinations twice as severe as baseline).

Studies were excluded from the meta-analysis when they reported open trials or did not provide data in adequate form to permit calculation of effect sizes (means and standard deviations or F or t values for rTMS main effect for change scores). The study by Saba et al.[15] provided sufficient information to calculate an effect size for the PANSS positive subscale but did not provide sufficient data to calculate the effect size for the hallucination item, and was therefore excluded from the main analysis, i.e., the treatment effect, but was included in the analysis on general positive symptoms. When studies reported on the same sample (or partly overlapped), only 1 study was included (the largest). For example, in the case of the 2 articles by Hoffman et al.,[14,16] only the latter[16] was included in the meta-analysis. When studies reported on multiple brain areas that were targeted with rTMS (e.g., Schönfeldt-Lecuona et al.[17]), only the left temporoparietal cortex was included. There were too few studies that reported on other areas to permit analysis of other brain areas. For all studies, active rTMS over the left temporoparietal cortex was compared to sham or placebo rTMS, with the exception of 1 study,[17] which did not have a sham control condition, but an active control condition consisting of rTMS over the occipital lobe. The left temporoparietal cortex was generally defined as the position halfway between the T3 and P3 electrode positions of the International 10–20 System, following Hoffman et al.[14]

Effect Size Calculation and Data Synthesis

Effect sizes concerned standardized mean differences (sham vs. real rTMS) of the pretreatment-posttreatment change in hallucination ratings. Standardized mean gain effect sizes were computed to account for the fact that the same sample is measured twice (pre-post contrast) and to take into account that not all studies used the same hallucination rating scale.[18] We computed the standardized mean gain for each study based on the procedure described by Becker[19] and the effect size–computation program developed by Wilson.[20] After computation of individual effect sizes for each study, meta-analytic methods were applied to obtain a combined effect size, which indicated the magnitude of the association across all studies.[21] Individual effect sizes were weighted for sample size to correct for upwardly biased estimation of the effect in small sample sizes. Additionally, a homogeneity statistic, Q, was calculated to test whether the studies could be taken to share a common population effect size. A significant Q statistic indicates heterogeneity of the individual study effect sizes, which poses a limitation to a reliable interpretation of the results. If significant heterogeneity is found, a moderator analysis can be performed to investigate the potential moderating factors.[22] The meta-analyses were carried out in a random effects model by using META 5.3.[23]

RESULTS

A total of 15 studies[11,12,14–17,24–32] were identified that reported empirical data regarding rTMS treatment of auditory hallucinations. Of these, 10 studies fulfilled inclusion

Table 1. Characteristics of Studies Investigating rTMS Effects on Hallucinations That Were Included in the Meta-Analysis

Study[a]	N[b]	Hallucination Scale	PANSS/ SAPS	Treatment Settings[c]	Days	Effect Size	Study Design[d]	Randomly Assigned
Brunelin et al (2006)[24]	24	Auditory Hallucination Rating Scale	+	90% MT, 2 × 17 min	5	1.22	Parallel	Yes
Chibbaro et al (2005)[25]	16	Scale for Auditory Hallucinations	+	90% MT, 15 min	4	0.95	Parallel	Not mentioned
Fitzgerald et al (2005)[26]	32	Hallucination Change Scale	+	90% MT, 15 min	10	0.47	Parallel	Yes
Hoffman et al (2000)[12]	12	Hallucination Change Scale	–	80% MT, 4–16 min	4	1.49	Crossover	Yes
Hoffman et al (2005)[16]	50	Hallucination Change Scale	ND[e]	90% MT, 8 or 16 min	9	0.77	Parallel	Yes
Jandl et al (2006)[27]	14	Hallucination subscale of PSYRATS	ND[e]	100% MT, 15 min	5	0.61	Crossover	Yes
Lee et al (2005)[28]	27	Auditory Hallucination Rating Scale	ND[e]	90% MT, 20 min	10	0.10	Parallel[f]	Yes
McIntosh et al (2004)[29]	16	10-point Likert scale (intensity of hallucinations)	+	80% MT; 4, 8, 12, 16 min respectively	4	–0.34	Crossover	Yes
Poulet et al (2005)[30]	10	Auditory Hallucination Rating Scale	+	90% MT, 2 × 17 min	5	1.96	Crossover	Yes
Saba et al (2006)[15]	18	PANSS	+	80% MT, 5 × 1 min	10	ND[e]		Yes
Schönfeldt-Lecuona et al (2004)[17]	11	Revised Haddock self-rating scale	–	90% MT, 16 min	5	1.46	Crossover	Yes

[a]Saba et al.[15] was only included in the PANSS analysis, not in the main analysis, i.e., the treatment effect, as no sufficient data were reported for that study.
[b]N refers to the number of patients included in comparisons between real and sham rTMS over the left temporoparietal cortex.
[c]All studies used 1 Hz.
[d]With exception of Schönfeldt-Lecuona et al.,[17] which had an active rTMS control condition, all studies are double-blind, sham-controlled. Double-blind indicates that neither patient nor evaluator was aware of the treatment condition; the clinician administering the rTMS usually was aware of the different treatment conditions.
[e]The scale was included, but no sufficient data were provided for meta-analysis.
[f]Sham-controlled left or right.
Abbreviations: MT = motor threshold, ND = no data, PANSS = Positive and Negative Syndrome Scale, PSYRATS = psychotic symptom rating scales, rTMS = repetitive transcranial magnetic stimulation, SAPS = Scale for the Assessment of Positive Symptoms.

Table 2. Characteristics of Studies Investigating rTMS Effects on Hallucinations That Were Excluded From the Meta-Analysis

Study	N[a]	Hallucination Scale	Treatment Settings[b]	Days	Reason for Exclusion	Study Design	Randomly Assigned
D'Alfonso et al (2002)[31]	8	Topography of Voices Rating Scale	80% MT, 20 min	10	No control condition	Open label	NA
Franck et al (2003)[32]	1	Scale for the Assessment of Positive Symptoms	90% 2 tesla, 17 min	10	No control condition	Open label	NA
Hoffman et al (2003)[14]	24	Hallucination Change Scale	90% MT, 8–16 min	9	Overlap with Hoffman et al (2005)[16]	Double-blind, sham-controlled	Yes
Hoffman et al (1999)[11]	3	Auditory Hallucination Rating Scale	80% MT, 4–16 min	4	Overlap with Hoffman et al (2005)[16]	Double-blind, sham-controlled, crossover	NA

[a]N refers to sample size.
[b]All studies used 1Hz.
Abbreviations: MT = motor threshold, NA = not applicable, rTMS = repetitive transcranial magnetic stimulation.

criteria and were included in the treatment effect analysis. Table 1 lists characteristics of studies that were included in the meta-analysis, whereas Table 2 contains information regarding the studies that were excluded. For the 10 studies that were included, total N was 212. Mean standardized gain effect size was 0.76 (95% CI = 0.36 to 1.17), z = 3.67, p = .0001. There was significant heterogeneity among individual effect sizes (Q = 21.4, p = .01). We hypothesized that mode of stimulation could be a moderator variable (i.e., continuous stimulation vs. insertion of multiple pauses between treatments). When we excluded the only study[29] that inserted multiple pauses during the stimulation session, the heterogeneity disappeared (Q = 12.2, p = .14). Mean standardized gain effect size then became 0.88 (95% CI = 0.52 to 1.23), z = 4.88, p < .0001.

To investigate whether number of stimulation sessions would be an important variable, we compared studies with less than 5 sessions (4 studies, mean number of sessions = 4.25) to studies applying more than 5 stimulation sessions (6 studies, mean = 9.83). This yielded similar mean effect sizes, ES = 0.79 (95% CI = –0.01 to 1.60) and ES = 0.80 (95% CI = 0.21 to 1.40), respectively. We also analyzed the effect of rTMS on severity of all positive symptoms, as reflected in PANSS positive subscale or Scale for the Assessment of Positive Symptoms

(SAPS) ratings. There was no significant improvement (N = 134 [6 studies], effect size = 0.21 [95% CI = –0.29 to 0.72], z = 0.83, p = .20). Two other studies included the PANSS (Lee et al. [2005][28]; Hoffman et al. [2005][16]) but did not report sufficient data to calculate effect sizes. Both report that there was no significant improvement of rTMS on the PANSS positive subscale. Jandl et al. (2006)[27] reported a lack of changes on the SAPS.

We also conducted separate analyses for studies using a parallel-group design (with one group receiving real TMS and the other group sham TMS) versus a crossover design (all patients consecutively receive both sham and rTMS treatments). For studies using a parallel-group design (5 studies, total N = 149), the mean weighted effect size was 0.63 (95% CI = 0.30 to 0.97), z = 3.70, p = .0001. There was no significant heterogeneity (Q = 4.0, p = .40). For studies using a crossover design (5 studies, total N = 63), the mean weighted effect size was 0.93 (95% CI = 0.17 to 1.69), z = 2.39, p = .009, with significant heterogeneity (Q = 17.2, p = .002). Again, when the study by McIntosh et al. (2004)[29] was left out, heterogeneity disappeared (Q = 4.3, p = .23) and the effect size increased to 1.22 (95% CI = 0.71 to 1.74), z = 4.69, p < .0001.

DISCUSSION

The results of our meta-analysis of 10 rTMS sham-controlled treatment studies of auditory hallucinations (including a total of 212 patients) provide support for the efficacy of this treatment in reducing the severity of hallucinations in schizophrenia. In contrast to the effects obtained on hallucinations, rTMS did not improve positive symptoms in general. Thus, the observed effect was specific to auditory hallucinations. Our results have clinical as well as more fundamental implications. On the clinical side, rTMS may prove to be a promising method for reducing frequency and intensity of auditory hallucinations in treatment-resistant patients. Large clinical trials are warranted to further establish the clinical significance of this novel treatment. Preliminary findings from the largest study to date,[16] in which 50 patients were randomly allocated to either rTMS or sham stimulation, revealed a mean duration of survivorship of 19.7 weeks among patients classified as responders (i.e., more than 20% improvement on the Hallucination Change Scale). In addition, no major complications (such as convulsions) occurred, and the treatment was well tolerated, with no evidence of neurocognitive impairment associated with rTMS. This lack of adverse events has also been confirmed in other studies.[26,31]

It would be instructive to compare the effect sizes we observe for TMS treatment of treatment-resistant hallucinations with those reported for pharmacologic treatment of such hallucinations. Unfortunately, meta-analyses of efficacy of medication treatments in treatment-resistant schizophrenia have not reported separately on hallucinations, and they concern comparisons between first- and second-generation antipsychotics. Nonetheless, such analyses can give an indication of effect size magnitude obtained with antipsychotic medication in treatment-resistant psychotic patients. More specifically, a meta-analysis[33] of clozapine versus typical antipsychotics in treatment-resistant schizophrenia yielded a mean effect size of 0.48 on Brief Psychiatric Rating Scale total score, with individual effect sizes ranging from 0.14 to 0.81 (5 studies).

On a more fundamental note, the evidence of reduction of hallucinations after magnetic stimulation over the left temporoparietal cortex may yield clues to the pathophysiology of auditory hallucinations. That is, the finding that reducing cortical excitability in speech perception areas may interfere with hallucinations suggests aberrant activation of language perception areas as a cause of auditory hallucinations. Increased activation of these areas[34] could in turn be due to disinhibition from frontal areas, e.g., as a consequence of reduced integrity of white matter tracts that connect frontal and temporoparietal regions.[35] The fact that receptive language areas seem to be crucially involved in auditory hallucinations is consistent with models implying derailments in speech perception or auditory imagery.[36–38] With the regard to the neurochemical basis of the rTMS effects on hallucinations, it is important to note that prefrontal, fast rTMS (as applied in the treatment studies of depression) has been shown to affect striatal dopamine release.[39] Using slow rTMS treatment to reduce cortical excitability, as is the case in the hallucination treatment studies, might inhibit subcortical dopamine release. Studies using positron emission tomography (PET) and single-photon emission computed tomography are needed to evaluate this putative mechanism.

The studies included in this meta-analysis used comparable TMS procedures, and all targeted the left temporoparietal cortex. Some exceptions should be noted, however. Specifically, McIntosh et al.[29] interrupted the stimulation trains by inserting 15 seconds of rest after each minute of stimulation to check coil position and allow the patient to move. This may not allow for sufficient buildup of the depressant effect of slow rTMS and thus interfere with the inhibitory effect of the stimulation. When this particular study was excluded from the analysis, between-study heterogeneity disappeared. Saba et al.[15] also reported a lack of effects of rTMS on symptom severity in patients with schizophrenia, but this study similarly used stimulation parameters that are presumably insufficient to induce the long-term depression–like effects of reduced excitability, which typically requires 15 minutes of continuous stimulation.[13] In contrast, each treatment session in the study by Saba et al.[15] consisted of 5 stimulation trains of 1 minute separated by a 1-minute

interval. With regard to the duration of the treatment, we did not observe larger effect sizes in studies that included more treatment sessions. On the other hand, the effect size for the studies with larger number of sessions was more reliable as evidenced from the confidence intervals. Caution is needed, however, in interpreting this moderator analysis, as the number of studies in each group was small, and studies may differ on other relevant characteristics. For example, the study by Schönfeldt-Lecuona et al.[17] reported the largest effect size (1.46) in the group of studies with few sessions (5 sessions or less). However, this was the only study in the meta-analysis that used functional magnetic resonance imaging (fMRI) during a language task to target the temporoparietal cortex in each patient individually. Thus, the large effect size might be due to a more precise localization of speech perception areas.

Half of the studies used a parallel-group design, and the other half used a crossover design. Studies using the latter design tended to yield larger effect sizes. This outcome might be due to the fact that in a crossover design a patient is his or her own control, as all patients consecutively receive both sham and rTMS treatments (the order was counterbalanced with equal numbers of patients starting with TMS as with sham). When patients are their own control, several potentially confounding factors (e.g., clinical and demographic variables) are eliminated. A limitation of the crossover design is the problem of carryover effects when active treatment is followed by sham.

Studies also differed in several other methodological aspects. For instance, different hallucination rating scales were used. Most scales measured several aspects of hallucinations, such as loudness, frequency, duration, and distress. The scales ranged from a 4-point scale[25] to a 20-point scale.[16] All scales incorporated more than 1 dimension of hallucinations (i.e., frequency, loudness, duration, number of voices, distress) in the final ratings. It has been suggested that rTMS mainly reduces the frequency of voices.[16] Because very few studies reported data for this dimension separately, we were not able to conduct a separate meta-analysis for frequency of hallucinations. However, the 2 studies[16,28] that do report separate data reported slightly larger effect sizes for frequency separately as compared to a composite measure of hallucination severity. In addition, different methods were applied for sham stimulation. The most frequently used method was tilting the coil by 45 or 90 degrees.[16,25] A problem with this method is that it has been shown that doing this can still affect brain activity, albeit to a substantially lesser degree as compared to real rTMS.[40] This problem can be overcome by using a placebo coil. Such a coil is identical in appearance to the real TMS coil and makes the same characteristic "click" sound. However, no magnetic field enters the brain. A limitation is that the placebo coil does not cause the characteristic twitch sensation on the scalp and thus differs in that respect from the real rTMS.

A number of studies were excluded from our meta-analysis due to the lack of a sham-controlled design. The results of these studies are nevertheless consistent with our meta-analysis of controlled studies, and of interest in their own right. For example, D'Alfonso et al.[31] studied effects of daily 1 Hz rTMS over the left auditory cortex in 8 medication-resistant hallucinating patients in an open trial. Thus, the location of stimulation was anterior to the usually targeted temporoparietal cortex. This approach was based on fMRI studies that reveal auditory cortex activation during auditory hallucinations.[41] A statistically significant improvement was observed on a hallucination scale after 10 days of TMS at the left auditory cortex.

Some limitations of our quantitative review should be noted. First, the limited number of published studies did not allow comparisons between different scalp regions of stimulation. For example, a few studies also stimulated the right hemisphere temporoparietal cortex,[27,28] with conflicting results. Furthermore, it was not possible to evaluate whether the use of neuronavigation (determining the scalp locations for stimulation on the basis of magnetic resonance imaging scans) will enhance the effects. Finally, it has been suggested[16] that certain patients may be nonresponders, but this issue remains to be investigated in more detail.

In summary, our meta-analysis of sham-controlled treatment studies of auditory hallucinations provides evidence for the potential efficacy of this novel treatment strategy. Large-scale (multicenter) trials are now needed to definitely establish clinical efficacy and tolerability. Studies should preferably use the same hallucination scale to index improvement. The Auditory Hallucinations Rating Scale[14] would be a suitable candidate, as it measures several relevant aspects of hallucination severity in a concise way, and it has been used most frequently in previous TMS trials.[14,16,24,30] Follow-up measurements should always be included, up to 6 months after the treatment. In order to enhance efficacy, brain-imaging methods may be applied to determine the functional locus of hallucination activity individually and to target these regions of interest with rTMS using a neuronavigator. Future studies should also investigate why certain patients respond to rTMS treatment, whereas others do not seem to improve. Using near-infrared spectroscopy to measure brain activation, Eschweiler et al.[42] observed that absence of prefrontal activation during a cognitive task predicted therapeutic effects of rTMS in depression. In a similar way, potential responders and nonresponders to rTMS treatment of hallucinations might be distinguished a priori on the basis of left temporoparietal cortex activation during a speech perception and imagery tasks (e.g., Aleman et al.[43]). For example, several patients have been demonstrated to show hallucination-related activity in predominantly right

hemisphere temporoparietal areas.[44] In these patients, rTMS directed at the left (or contralateral) hemisphere may be less effective. Studies might also explore the effect of bilateral TMS treatment, which has recently been successfully applied in depression.[45] Finally, studies using fMRI and PET before and after rTMS treatment in hallucinating patients are needed to establish the functional neuroanatomical mechanisms underlying this treatment.

Drug name: clozapine (FazaClo, Clozaril, and others).

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