Theta Burst Transcranial Magnetic Stimulation for Auditory Verbal Hallucinations: Negative Findings From a Double-Blind-Randomized Trial

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Background. Auditory verbal hallucinations (AVH) in schizophrenia are resistant to antipsychotic medication in approximately 25% of patients. Treatment with repetitive transcranial magnetic stimulation (rTMS) for refractory AVH has shown varying results. A stimulation protocol using continuous theta burst rTMS (TB-rTMS) showed high efficacy in open label studies. We tested TB-rTMS as a treatment strategy for refractory AVH in a double-blind, placebo-controlled trial. Methods. Seventy-one patients with AVH were randomly allocated to TB-rTMS or placebo treatment. They received 10 TB-rTMS or sham treatments over the left temporoparietal cortex in consecutive days. AVH severity was assessed at baseline, end of treatment, and follow-up using the Psychotic Symptom Rating Scale (PSYRATS) and the Auditory Hallucinations Rating Scale (AHRS). Other schizophrenia-related symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS). Results. Seven patients dropped out before completing the study. In the remaining 64, AVH improved significantly after treatment in both groups as measured with both PSYRATS and AHRS. PANSS positive and general subscores also decreased, but the negative subscores did not. However, improvement did not differ significantly between the TB-rTMS and the placebo group on any outcome measure. Conclusions. Symptom reduction could be achieved in patients with medication-resistant hallucinations, even within 1 week time. However, as both groups showed similar improvement, effects were general (ie, placebo-effects) rather than specific to treatment with continuous TB-rTMS. Our findings highlight the importance of double-blind trials including a sham-control condition to assess efficacy of new treatments such as TMS.

Key words: TMS/RCT/psychotic disorder/local stimulation/voices

Introduction

Auditory verbal hallucinations (AVH) are a core symptom of schizophrenia. Approximately 60%–80% of patients daily experience AVH1 with mostly negative and abusive content.2 In some 25% of patients, AVH are irresponsive to antipsychotic medication.3 As schizophrenia is a common and life-long disorder, many patients face chronic hallucinations which severely decrease their quality of life and increase risk for suicide and violence.4 Alternative treatment options are limited. Cognitive behavioral therapies show effects on associated distress and fear, but frequency and loudness usually remain unchanged.5 A treatment that reduces the severity and frequency of medication-resistant hallucinations would be of great value.

Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe and non-invasive method to alter neuronal excitability by using rapidly changing magnetic fields. Hoffman and colleagues6 were the first to explore rTMS as a treatment for AVH. When directed at the left temporoparietal cortex, the treatment ameliorated medication-resistant AVH. The efficacy of low frequency rTMS may be explained by its potential to induce long-term neuronal depression (LTD).8 Several smaller studies replicated this effect.10–13 Recent larger studies, however, could not.14–17 This has led to a decreased effect size (Hedge’s g = 0.44) in the most recent meta-analysis on rTMS in AVH.18 The diminishing efficacy of 1-Hz rTMS for AVH over time has prompted the field to search for more responsive stimulation paradigms. One of the most promising candidates is theta burst TMS (TB-rTMS), a 3-pulse burst at 50 Hz, given every 200 ms.19 This stimulation pattern is based on the physiologic pattern of neuronal firing in the hippocampus.20 In animal studies, TB-rTMS induced strong long term potentiation (LTP) and depression.
Intermittent TB-rTMS induces an LTP effect whereas continuous TB-rTMS, consisting of a noninterrupted TB-rTMS train, has a strong inhibitory effect. Larson and colleagues showed this method was more effective on LTP than other stimulation frequencies such as 1-Hz rTMS. A limited number of studies tested continuous TB-rTMS as a treatment for AVH. In a case-report, Poulet and colleagues reported a 50% decrease in AVH severity after a 5-day TB-rTMS treatment targeted at the left temporoparietal cortex. Another case report showed reduced AVH severity after 5 treatments and complete remission after 6 weeks of bilateral continuous TB-rTMS at 50 Hz. Although exciting, these results must be interpreted with caution, as a control condition was lacking. Kindler and colleagues compared TB-rTMS with 1-Hz rTMS in 24 patients, and found that TB-rTMS and 1-Hz rTMS were equally effective. However, this study also lacked a placebo arm. Plewnia and colleagues recently found a trend toward reduced AVH in a sham-controlled trial of bilateral TB-rTMS in 16 patients.

The effect of TB-rTMS on AVH has never been compared with placebo treatment in a sufficiently large sample, making it impossible to establish whether TB-rTMS deserves a place in the treatment guidelines for AVH. The current study aimed to investigate the efficacy of continuous TB-rTMS compared with placebo treatment to reduce AVH and other psychotic symptoms, in a relatively large sample.

Methods

Subjects

71 patients with a psychotic disorder were recruited at the University Medical Center Utrecht, the Netherlands, for this randomized placebo-controlled double-blind trial (2012–2014). Patients were diagnosed by an independent psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. They were selected for participation if they met the following inclusion criteria:

1. Diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or psychosis not otherwise specified,
2. Frequent AVH (at least 5 times per hour),
3. A stable dose of antipsychotic medication for >2 weeks.

Exclusion criteria were:

1. Age <18,
2. Nonremovable metal objects in or around the head,
3. History of seizures,
4. Increased intracranial pressure due to infarcts or trauma,
5. Professional metal workers or a history of eye trauma with a metal object.
6. Coercive treatment at a psychiatric ward (based on a judicial ruling),
7. Representation by a legal ward or under legal custody,

Patient demographics are shown in table 1.

All participants gave their written informed consent. The study was approved by the human ethics committee of the University Medical Center Utrecht, and registered on www.clinicaltrials.gov with number NCT01512290.

Procedures

Using computer-generated randomization on www.randomization.com, patients were randomized with a 1:1 ratio over active TB-rTMS or placebo treatment. Participants, study staff, and clinical staff were blind to the allocated treatment except for the TB-rTMS administrators. Only TB-rTMS administrators had access to the randomization list; they had minimal contact with the patients, and no role in assessing AVH.

Participation entailed 6 study visits and a follow-up measurement by phone. On the first visit, the Auditory Hallucination Rating Scale (AHRS), Psychotic Symptom Rating Scale (PSYRATS), and the Positive and Negative Syndrome Scale (PANSS) were obtained by a trained investigator to assess baseline severity of AVH and other symptoms.

On the second visit, the participant’s resting individual motor threshold (MT) was assessed according to the 5-step procedure described by Schutter & van Honk. The descending staircase method was used. Afterwards, participants received TB-rTMS or placebo treatment twice a day for 5 consecutive days, with a 30 min break in between treatments. The treatment was targeted at the left temporoparietal cortexie, midway between the T3 and P3 site according to the international 10/20 system of electroencephalography (EEG) electrode placement. The temporoparietal cortex is thought to overlay one of the main areas where activation is found during AVH.

After the last treatment, the AHRS, PSYRATS, and PANSS were obtained, as well as the Global Index of Safety (GIS) to assess adverse events of the treatment. Patients were instructed to focus their answers on the past few days.

A month after the last treatment, participants were interviewed by phone to obtain the AHRS, PSYRATS, and GIS. They were instructed to focus their answers on the past week. Participants were asked to guess their treatment allocation, to check if the study remained well blinded. Their answer was noted in the case report form. Afterwards, they were unblinded by the study coordinator. Participants in the placebo group were given the opportunity to receive active treatment. All but one participant in the placebo group chose to receive active treatment after deblinding.
Table 1. Patient Demographics per Treatment Group

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>TB-rTMS</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>24/13</td>
<td>16/18</td>
</tr>
<tr>
<td>Age (M, SD)</td>
<td>38 (15)</td>
<td>42 (13)</td>
</tr>
<tr>
<td>AHRS total (M, SD)</td>
<td>24 (5)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>PSYRATS total (M, SD)</td>
<td>28 (6)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>PANSS total (M, SD)</td>
<td>73 (20)</td>
<td>70 (20)</td>
</tr>
<tr>
<td>Diagnosis Schizophrenia (paranoid)</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Diagnosis Schizophrenia NOS</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Diagnosis Schizoaffective disorder</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Diagnosis Schizophrenia (disorganized)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosis Schizophrenia (undifferentiated)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diagnosis Schizophreniform disorder</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Antipsychotic Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>20 (370)</td>
<td>12 (341.67)</td>
</tr>
<tr>
<td>Aripiprazol</td>
<td>2 (25)</td>
<td>7 (17.86)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3 (308)</td>
<td>4 (675)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>8 (18.44)</td>
<td>3 (11.67)</td>
</tr>
<tr>
<td>Zuclopentixol</td>
<td>1 (200)</td>
<td>—</td>
</tr>
<tr>
<td>Flupentixol</td>
<td>1 (15)</td>
<td>—</td>
</tr>
<tr>
<td>Pimozide</td>
<td>—</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>—</td>
<td>1 (600)</td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: AHRS, Auditory Hallucinations Rating Scale; M, mean; PANSS, Positive and Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scale; SD, standard deviation; TB-rTMS, theta burst rTMS.

a There were no significant differences between groups on any variable.
bRepresents number of participants on that type of medication. The number between brackets denote the mean dosage in milligram.

Theta Burst rTMS

A MagStim Rapid2 stimulator (Magstim Company Ltd.) was used with a 70-mm air-cooled figure-of-eight coil for continuous TB-rTMS treatment. An identical-looking coil was used for the placebo treatment, which produced identical sounds but no magnetic pulses. Treatment was based on a protocol by Huang and colleagues, consisting of a 60-s stimulation train with a 3 pulse burst at 50 Hz repeated every 200ms. Stimulation was performed at 80% of the individual MT, or at the highest intensity the stimulator could apply for this protocol (51% of the maximal stimulator output). As a result, stimulation was performed at 64%–78% of the individual MT in 8 out of 32 patients in the active treatment group.

During treatment, patients were placed in a lying position on a bed and the TMS coil was fixated to the head with a Magstim Articulated Coil Stand (Magstim Company Ltd.). Participants wore sound attenuating earplugs to prevent hearing damage.

Outcome Measures

The primary outcome measure was AVH change after TB-rTMS and at follow-up as measured by the AHRS and PSYRATS. The secondary outcome measures were changes in other psychotic symptoms as measured by the PANSS, the number of responders to treatment defined as participants who showed a decrease of 25% or more on the AHRS or PSYRATS severity score, adverse events of TB-rTMS treatment as measured by the GIS, and the percentage of correct and incorrect guesses of treatment allocation.

Statistical Analysis

All statistical analyses were performed with SPSS (version 20). Baseline comparisons were done over the intention-to-treat group of 71 participants. Age, pretreatment AHRS, PSYRATS, and PANSS scores between the 2 treatment groups were compared with an independent sample t test. Gender comparison between the 2 groups was done with a chi-square test. Medication use comparison between the 2 groups was done with Fisher's exact test. For analysis of the primary and secondary outcomes, all dropouts were excluded. Hallucination severity and PANSS scores were analyzed using a mixed design ANOVA, with hallucination severity over time and PANSS scores over time as within subject factors and treatment condition as between subject factors. The Greenhouse-Geisser correction was used to adjust the degrees of freedom if the assumption of sphericity was violated. The difference in amount and severity of adverse effects between the 2 treatment groups was analyzed with an independent samples t test. Fisher's exact test was used to analyze differences in the number of responders on the AHRS and PSYRATS. As some patients were stimulated below 80% MT, the mixed design ANOVA analyzing changes in hallucination severity was repeated using only patients stimulated at 80% MT (N = 44). Eight missing MT values were not included in this analysis. Blinding effectiveness was measured using Fisher's exact test. Two missing values in the PSYRATS questionnaire were imputed by carrying the last observation forward. Additional analyses considering patients belief in the allocated treatment, clozapine use, age, and gender are in supplementary material 1.

Results

Dropout

From the initial 71 participants, 64 completed the study. Of the 7 patients who dropped out, 2 were randomized to placebo and 5 to TB-rTMS. Supplementary table 1 provides an overview for reasons for drop-out and time point during the study.

Baseline Comparison

There were no significant differences between the two treatment groups in age (t(69) = -1.25, P = .22, 95% CI = -11.0 to 2.54) gender (χ^2(1) = 2.28, P = .16)
and baseline scores such as the AHRS severity score ($t(69) = -0.51$, $P = .61$, 95% CI = -2.91 to 1.72), PSYRATS severity score ($t(69) = -0.48$, $P = .64$, 95% CI = -3.21 to 1.97), PANSS total ($t(69) = .64$, $P = .53$, 95% CI = -6.44 to 12.51), PANSS positive ($t(69) = .26$, $P = .80$, 95% CI = -2.42 to 3.15), PANSS negative ($t(69) = .74$, $P = .46$, 95% CI = -1.88 to 4.09) and PANSS general score ($t(69) = 1.1$, $P = .29$, 95% CI = -2.33 to 7.71). Type of medication differed between the groups on trend level ($P = .06$, Fisher’s exact test).

Hallucination Severity

Hallucination severity as measured by the AHRS decreased significantly over time, $F(2,124) = 9.413$, $P < .001$, $\eta^2_p = .13$, as well as hallucination severity as measured by the PSYRATS, $F(2,124) = 6.724$, $P = .002$, $\eta^2_p = .10$. However, there was no significant interaction effect with treatment group for both the AHRS ($F(2,124) = .19$, $P = .83$) and the PSYRATS ($F(2,124) = .19$, $P = .83$). Thus, the decrease of hallucination severity was the same in the active treatment group and in the placebo group (figures 1 and 2).

The mean total PANSS score was 70 ($SD = 20$) at baseline for the placebo group and 73 ($SD = 20$) for the TB-rTMS group. Total PANSS score decreased significantly over time, $F(1,62) = 4.25$, $P = .04$, $\eta^2_p = .06$, but there was no significant time by group interaction ($F(1,62) = .08$, $P = .79$). Scores on the positive PANSS scale decreased significantly over time, $F(1,62) = 4.93$, $P = .03$, $\eta^2_p = .07$, as well as scores on the general scale, $F(1,62) = 6.4$, $P = .01$, $\eta^2_p = .09$, but not on the negative scale, $F(1,62) = .04$, $P = .85$. There were no significant time by group interactions for the positive scale, $F(1,62) = .00$, $P = 1$, or the general scale, $F(1,62) = .90$, $P = .35$. Table 2 displays means and standard deviations for each group at each timepoint for AHRS, PSYRATS, and PANSS.

Responders

Responders were defined as participants who showed a decrease of 25% or more on AHRS or PSYRATS severity score. No group differences were found in the number of responders for the AHRS (4 responders in both groups; $P = 1$, 2-tailed Fisher’s exact test), and the PSYRATS (3 responders in the TB-rTMS group and 1 in the placebo group; $P = .61$, two-tailed Fisher’s exact test).

Stimulator Output

Restricting data to patients who were stimulated at 80% MT, AHRS score decreased significantly over time, $F(2,84) = 3.05$, $P = .05$, $\eta^2_p = .07$, as well PSYRATS score, $F(1.7,71.7) = 3.85$, $P = .03$, $\eta^2_p = .08$. There was no significant time by group interaction (AHRS: $F(2,84) = .14$, $P = .87$, PSYRATS: $F(1.7,71.7) = .08$, $P = .90$).

Adverse Events

In both treatment groups, participants reported adverse events using the GIS. An overview of all GIS items and the frequency of occurrence can be seen in table 3. None of these events needed medical attention. There was no significant difference between the active and the placebo treatment group in the number and severity of adverse events ($t(62) = -0.57$, $P = .57$).

Study Blinding

In total, 36 participants (56.3%) guessed their allocated treatment condition correctly, 26 (40.6%) guessed...
incorrectly, and 2 participants (3.1%) refused to guess as they had no idea what treatment they received.

In the active treatment group, 16 participants (50%) correctly guessed they received active treatment, 15 participants (46.9%) incorrectly guessed they received the placebo treatment, and 1 participant refused to guess.

In the placebo group, 20 participants (62.5%) correctly guessed they received the placebo treatment, 11 participants (34.4%) incorrectly guessed they received the active treatment, and 1 participant refused to guess.

There was no significant effect of allocated treatment group on blinding ($P = .30$, Fisher’s exact test).

Discussion

This study indicates no specific benefit of active treatment over placebo treatment on intractable AVH in patients with a psychotic disorder. Although AVH severity decreased significantly, this decrease was the same in both treatment arms. AHRS change scores defined 4 responders in each treatment group. PSYRATS change scores defined 1 responder in the placebo group and 3 responders in the active treatment group, but this difference did not reach significance. Furthermore, both positive and general symptoms as measured by the PANSS decreased significantly after treatment, but to an equal extent in both groups. AVH improvement was not mediated by the patients’ perception of the allocated treatment.
Although it is encouraging that patients with intractable hallucinations can improve significantly in only 1 week of experimental treatment, these findings indicate the efficacy of TB-rTMS is largely (possibly completely) caused by nonspecific (ie, placebo) effects. As preclinical studies show TB-rTMS is a more powerful intervention than 1-Hz TMS, these findings are disappointing. A previous study by Kindler and colleagues found no significant difference between TB-rTMS and 1-Hz TMS after 10 days of treatment. Both groups did show a significant reduction in AVH, but no placebo group was included to control for aspecific effects. A recent pilot study by Plewnia and colleagues including only 16 patients with AVH in a sham-controlled trial of bilateral TB-rTMS found a trend toward reduced AVH after 15 treatment sessions. This study did not report any data on blinding. As TMS produces a sensation over the skull in addition to the characteristic sounds, it is essential to use a sham condition that is indistinguishable from real treatment, as patients have experienced real TMS during MT assessment. In our study, we asked all patients to guess their treatment allocation before unblinding. Results showed our study remained well blinded. Differences in the sham condition, especially differences in tactile stimulation, may lead to undesired unblinding of patients (especially those in the placebo group, who miss the skull sensation), which may explain differences between studies from our lab and those from other groups.

Importantly, the vast reductions of AVH observed in initial case studies of TB-rTMS were not replicated in any study investigating this treatment in a larger sample size, including the present study which showed a responder percentage of only 12.5%. Focusing on larger randomized double-blind placebo-controlled trials applying any type of rTMS, only 2 of 8 trials showed clinical benefit of active rTMS versus placebo on the severity of hallucinations but not as robust as initially observed. The remaining 6 studies failed to find significant benefits of rTMS over placebo, among which the 2 largest 1-Hz rTMS studies to date. When new treatment strategies are introduced, initial reports tend to feature relatively small sample sizes with favorable results, whereas small studies with negative findings tend not to become published. When larger studies appear, negative findings become published as well. In other areas of research, such trends have led effect sizes to decrease per year of publication. This was also noticeable in meta analyses on 1-Hz TMS. The most recent meta-analysis showed a decrease in effect size after inclusion of studies with larger sample sizes and negative findings. With regard to TB-rTMS, this is an important consideration, as this is the first double-blind RCT with a relatively large sample size again showing negative results.

Despite the absence of a specific effect of TMS, both groups did show significant improvement of intractable AVH, which was still present 1 month after the last treatment. It is of interest to investigate which nonspecific factors contribute to this overall clinical benefit. Several potential factors come to mind, such as extensive time spent with a researcher talking about hallucinations and ways to cure them, or the fact that treatment is focused at the brain, which is a strong cognitive intervention suggesting voices come from the brain rather than from external factors (ie, devils or ghosts). Or perhaps it is the suggestion that other treatments are still available to offer relief of chronic symptoms. Such factors can be implemented into existing treatment strategies, to increase their effectiveness.

**Strengths and Limitations**

This is the second largest study comparing (any type of) rTMS with placebo in patients with AVH to date and the largest study applying TB-rTMS. Seventy-one patients with a schizophrenia spectrum disorder who experienced intractable frequent AVH participated in this trial, of whom 64 completed all procedures. A placebo condition was included which remained well blinded throughout the study. Some limitations should be noted. Site positioning was done according to the international 10/20 system of EEG electrode placement. Although this method was sufficient to elicit all previous positive effects, the use of a stereotactic neuronavigation technique based on an individual's structural MRI scan may be superior to positioning the coil at the target site. However, our group has previously performed 2 neuro-navigated rTMS trials which found no difference between active and sham treatment. In addition, although the left temporoparietal area is used as a target site for stimulation in the majority of rTMS designs for AVH, many other brain regions are also associated with AVH experience including right-sided language-related areas. Bilateral TB-rTMS to both the left and right temporoparietal cortex only showed a statistical trend toward being superior to sham treatment in one previous study, but the total decrease in PSYRATS scores was more substantial than in the current study. It may be of value to investigate this method in a larger sample. Furthermore, the used questionnaires ask participants to introspect over the past week or month. As the second measurement takes place after 1 week of treatment, the suitability of the questionnaires may be limited. However, the AVH decrease measured after a week of treatment was unchanged after 1 month follow-up, suggesting the questionnaires were successful in capturing AVH decrease. Finally, in the current study a total of 10 TB-rTMS treatments were administered over 1 week time, whereas some studies administered more treatments over a more extended period. Although the current study did find a decrease in AVH symptoms in both treatment groups, it has been suggested that amelioration of AVH might only occur gradually after prolonged treatment. This suggestion remains to be verified by empirical findings in a large sample. The latest meta-analysis
on TMS in AVH found no correlation between the total number of TMS stimuli and the effect size of TMS studies, suggesting prolonged treatment is not superior to shorter treatment durations.

Conclusions
Our results indicate that the efficacy of TB-rTMS for AVH is not better than placebo treatment. An alternative treatment for this group of patients is still highly needed, but results on rTMS in the previous years have so far been disappointing. As both groups improved, this study also indicates that significant clinical improvement is still possible in this group of patients with treatment resistant AVH even within 1 week time, suggesting that extra time and energy spent for these patients pays off.

Supplementary Material
Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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References


