Effects of Repetitive Transcranial Magnetic Stimulation on Auditory Hallucinations Refractory to Clozapine

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Objective: To study the therapeutic effects on auditory hallucinations refractory to clozapine with 1-Hz repetitive transcranial magnetic stimulation (rTMS) applied on the left temporoparietal cortex.

Method: Eleven patients with schizophrenia (DSM-IV) experiencing auditory hallucinations (unresponsive to clozapine) were randomly assigned to receive either active of rTMS (N = 6) or sham stimulation (N = 5) (with concomitant use of clozapine) using a double-masked, sham-controlled, parallel design. A total of 160 minutes of rTMS (9600 pulses) was administered over 10 days at 90% motor threshold. The study was conducted from January 2003 to December 2005.

Results: There was a reduction in hallucination scores in both groups, which persisted during follow-up in the active group for the items reality (p = .0493) and attentional salience (p = .0360). Both groups showed similar patterns of symptomatic changes on subscales (negative symptoms, general psychopathology) and total scores of the Positive and Negative Syndrome Scale, Clinical Global Impressions scale, and Visual Analog Scale.

Conclusion: Active rTMS in association with clozapine can be administered safely to treat auditory hallucinations, although its clinical utility is still questionable. No significant clinical effects were observed in the sample studied, possibly because it was too small and/or due to its high refractoriness.

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Schizophrenia is a chronic and debilitating disorder with a prevalence of 1% in the general population.[1] A key feature of the disorder is the presence of auditory hallucinations,[2] generally consisting of spoken speech or "voices," reported by 50% to 70% of patients with schizophrenia.[3]

Since the introduction of chlorpromazine (and later of haloperidol and thioridazine), several authors[4–7] observed that about 30% of the patients in their studies did not respond adequately to the treatment. This rate did not change until the atypical antipsychotics were introduced.[4] Refractory criteria were developed,[5–7] although there is hardly an agreement between the different authors.[8] Clozapine provided a change in this panorama, with a rate of response of 30% to 60% for patients previously refractory to conventional antipsychotics.[9] In addition to the limited efficacy of the drugs, side effects are a main concern for patients and doctors as well.[10] Although pharmacotherapy is largely effective in treating acute psychosis and in preventing relapse, a proportion of patients experience persistent symptoms even while adhering to optimal treatment.[11]

Repetitive transcranial magnetic stimulation (rTMS) in the left temporoparietal cortex has been used to modulate neuronal activity and reduce auditory hallucinations (mainly in schizophrenia and schizoaffective disorder).[12–14] The specific mechanisms are unknown, but imaging studies have suggested a hyperactivity on the left temporoparietal cortex related to the genesis of the hallucinatory phenomenon,[15–18] and rTMS has inhibitory effects when given at slow frequencies (≤ 1 Hz).[19]

Several studies have been conducted in order to alleviate hallucinations with inhibitory (1 Hz) rTMS. D'Alfonso et al.[20] performed an open trial with an intensity of 80% of motor threshold for 10 days with 20 minutes each train on the left temporal cortex. Seven of 9 patients demonstrated reduction of hallucinations (they were taking clozapine and olanzapine). Hoffman et al.[13] randomized 24 patients with schizophrenia or schizoaffective disorder presenting persistent auditory hallucinations

refractory to treatment with medications to receive either active rTMS or "sham" stimulation on the left temporoparietal cortex. A reduction of greater than or equal to 50% was observed for the auditory hallucinations in 9 of 12 patients in the active group versus 2 of 12 patients in the sham group (p = .004). Hoffman et al.[21] published the same study with an expanded sample of 50 patients (26 were added) and found reductions in hallucination frequency and Clincal Global Impressions scale (CGI) scores. Lee et al.[22] randomly allocated 39 patients with schizophrenia and treatment-refractory auditory hallucinations to receive active rTMS or sham stimulation on the left or right temporoparietal cortex. They found an effect in positive symptoms of the Positive and Negative Syndrome Scale (PANSS) (p = .002) and the CGI scores (p < .001) for the active group.

Negative results were also reported in some studies. McIntosh et al.[23] described negative results when left temporoparietal rTMS was compared with sham stimulation in patients with auditory hallucinations. Mirroring an earlier trial,[12] they administered a total of 40 minutes of stimulation over 4 days with an intertrain interval of 15 seconds every minute, which may have curtailed physiologic effects. Also, Saba et al.[24] failed to show efficacy in the treatment of 18 schizophrenia patients. They used rTMS on the left temporoparietal cortex (1 Hz, 80% motor threshold) with each session of 5 trains of 1 minute with a 1-minute interval. An important point is that all of these previous studies were heterogeneous in terms of diagnosis and antipsychotic medication regimen.

In the current work, we performed a randomized, double-blind study to assess the efficacy on refractory auditory hallucinations of slow rTMS (1 Hz) applied to the left temporoparietal region of patients with paranoid schizophrenia according to DSM-IV criteria[25] (when patients' selection began, the Portuguese version of the DSM-IV-TR was not yet available). Only super refractory patients were included, i.e., those with persistent hallucinations even while taking clozapine (350 mg or more) for at least 6 months.

METHOD

Subjects

Eleven patients with a diagnosis of schizophrenia, confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders,[26] with auditory hallucinations entered the study after giving written informed consent. All patients were required to be taking at least 350 mg of clozapine per day for 6 months or more and had to have failed at least 2 adequate trials with standard antipsychotic medication from 2 different pharmacologic groups with a minimum dose of 1000 mg of chlorpromazine equivalents. Age range was 18 to 50 years inclusively. Additional patient characteristics are given in Table 1.

Table 1. Characteristics of Patient Sample

Characteristic	Active rTMS	Sham rTMS	p
Age, mean (SD), y	29.83 (8.40)	33.00 (12.08)	.621*
Gender, N (male/female)	4/2	2/3	.0567**
Education, N			> .999**
0–8 y	1	2	
9–11 y	4	3	
12 y or more	1	0	
Baseline PANSS score, mean (SD)	97.33 (15.31)	99.80 (7.85)	.9946*
No. of hospitalizations, mean (SD) (> 24 h)	2.17 (2.93)	1.20 (1.10)	.924***
Duration of illness, mean (SD), mo	76.67 (69.31)	93.60 (41.91)	.645*
Dosage of clozapine, mean (SD), mg/d	475.00 (88.03)	475.00 (204.94)	.599*

*Student t test.
**Fisher exact test.
***Mann-Whitney test.
Abbreviations: PANSS = Positive and Negative Syndrome Scale, rTMS = repetitive transcranial magnetic stimulation.

Exclusion criteria for the study were a history of seizures, neurologic or medical illness, pregnancy, suicide risk, and concurrent substance or alcohol abuse. The local institutional ethical committee approved the study. The study was conducted from January 2003 to December 2005.

Patients were randomly assigned to receive either active (N = 6) or sham (N = 5) stimulation. They continued to take clozapine during treatment, and no dose adjustment or use of other psychotropic medication was allowed during the trial. None of the patients were undergoing psychotherapy during the study.

rTMS Procedures

Transcranial magnetic stimulation was performed using a high-speed magnetic stimulator (Magpro, Medtronic, Minneapolis, Minn.) and a figure-of-8 coil. The applied parameters were 90% of the motor threshold, on the left temporoparietal cortex (located between sites T3 and P3 of the International 10-20 EEG System). A marked swimming cap was used to determine the EEG points. No stereotaxic system was used to place the coil. Stimulus frequency of 1 Hz was delivered during 16 minutes in each session[12,13,21,27] for 10 days (total number of pulses: 9600). Sessions were performed from Monday to Friday with an interval of 2 days after the first 5 sessions.

Sham stimulation followed the same schedule using a placebo coil (produced by the manufacturer). The coil was constructed with normal wound-up iron, instead of the standard μ-metal (a nickel-iron alloy that has a very high magnetic permeability). The magnetic field was reduced by 95%.

Patient Assessments

Descriptive measures of specific characteristics of the auditory hallucinations were assessed with a Portuguese version (simple translation, not validated) of the 7-item

Table 2. Effect of rTMS on PANSS and CGI Scores Over Time[a]

Measure	Baseline	Week 1	Week 2	Week 6
PANSS score				
Total				
Active	97.33 ± 15.31	104.33 ± 34.09	78.00 ± 15.52	83.00 ± 16.55
Sham	99.80 ± 7.85	91.80 ± 5.63	81.20 ± 5.17	85.75 ± 3.86
Positive symptoms				
Active	23.67 ± 2.42	20.33 ± 3.83	18.50 ± 5.82	19.80 ± 5.63
Sham	25.60 ± 2.19	24.40 ± 1.34	20.00 ± 2.65	22.25 ± 3.50
Negative symptoms				
Active	21.50 ± 4.51	19.00 ± 5.14	18.00 ± 4.94	18.00 ± 4.80
Sham	22.00 ± 2.92	19.80 ± 2.59	17.20 ± 2.17	18.75 ± 0.50
General psychopathology				
Active	52.17 ± 9.37	46.33 ± 9.97	41.50 ± 8.17	45.20 ± 8.23
Sham	52.20 ± 5.89	47.60 ± 4.88	44.00 ± 4.85	44.75 ± 1.50
CGI score[b]				
Active	3.00 ± 0.89	2.17 ± 0.41	2.67 ± 0.52	…
Sham	3.40 ± 0.89	2.40 ± 0.55	2.40 ± 0.55	…

[a]Data reported as mean ± SD.
[b]The CGI was performed at baseline and after 5 and 10 days of treatment (week 1 and week 2).
Abbreviations: CGI = Clinical Global Impressions scale, PANSS = Positive and Negative Syndrome Scale, rTMS = repetitive transcranial magnetic stimulation.
Symbol: … = not performed.

Table 3. Effect of rTMS on AHRS Scores Over Time (within-subject comparison)

AHRS Item	Week 1	Week 2	Week 6
Reality	Active: p = .0412	Active: p = .0039	Active: p = .0076
Attentional salience	Active: p = .0383	Active: p = .0013	Active: p = .0130
	…	Sham: p = .0130	…
Frequency	Active: p = .0128	Active: p = .0294	…
Length	Active: p = .0270	Active: p = .0040	Active: p = .0367
No. of voices	…	Active: p = .0280	…
	…	Sham: p = .0015	…
Distress level	…	Active: p = .0011	Active: p = .0057
	…	Sham: p = .0057	…
Loudness	…	Sham: p = .0003	…

Abbreviations: AHRS = Auditory Hallucinations Rating Scale, rTMS = repetitive transcranial magnetic stimulation.
Symbol: … = no significant difference found.

Auditory Hallucinations Rating Scale[13] (AHRS) (frequency, reality, loudness, number of voices, length, attentional salience, and distress level).

Other measures included the composite PANSS,[28] CGI, and Visual Analog Scale (VAS).[29] All scales were administered by one of the authors (M.M.), a trained and certified rater.

Auditory Hallucinations Rating Scale and PANSS assessments were conducted at baseline (24 hours before the first treatment) and at weekly intervals (after 5 and 10 days, week 1 and week 2, respectively) of treatment. A follow-up evaluation was performed weekly until 4 weeks after the end of the treatment. The CGI and VAS were performed at baseline and after 5 and 10 days of treatment (week 1 and week 2). Both patients and rater were blinded to treatment received.

Statistical Analysis

Demographic and clinical characteristics of the 2 groups were compared using Student t test or Mann-Whitney and Fisher exact test. To compare the overall effect of treatment over time in the 2 groups, a repeated-measures analysis of variance (ANOVA) approach was employed with treatment as the between-group factor and time as the within-subject factor. The significance level was set at p = .05.

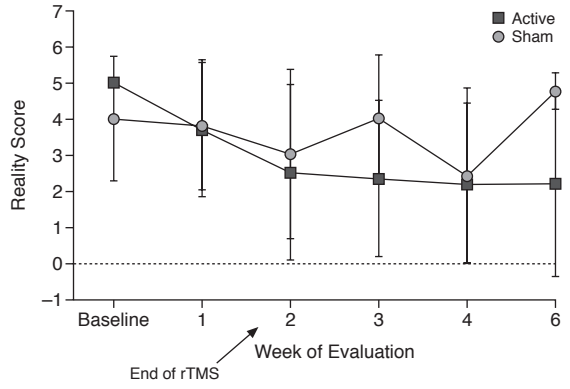
RESULTS

No differences between groups were observed on baseline psychopathology (AHRS, CGI, VAS, PANSS). Positive and Negative Syndrome Scale and CGI scores are presented in Table 2. Treatment was well tolerated, and only 1 patient in the active group complained of headache after each rTMS session (with spontaneous remission). No other adverse effects were reported.

The active group demonstrated a time effect (within-subject comparison), with a significant linear decrease in 6 of the 7 items of the AHRS, some of which persisted during follow-up (Table 3).

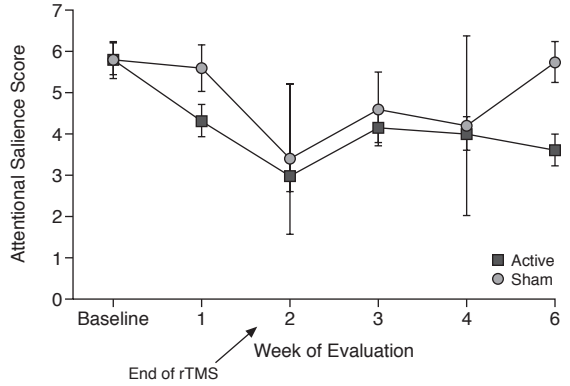
The sham group did not show a significant decrease in reality, frequency, and length but showed a significant

Figure 1. AHRS Mean (± SD) Scores for "Reality" Over Time[a]



[a]A significant difference (p = .0493) was found at week 6.
Abbreviations: AHRS = Auditory Hallucinations Rating Scale, rTMS = repetitive transcranial magnetic stimulation.

Figure 2. AHRS Mean (± SD) Scores for "Attentional Salience" Over Time[a]



[a]A significant difference (p = .036) was found at week 6.
Abbreviations: AHRS = Auditory Hallucinations Rating Scale, rTMS = repetitive transcranial magnetic stimulation.

linear decrease on the items attentional salience, distress level, number of voices, and loudness, especially in week 2 (end of rTMS treatment) (Table 3).

During the follow-up (week 6), there was a significant group effect (between-subject comparison) in the reality (Figure 1) and attentional salience (Figure 2) scales of the AHRS ($F = 4.11$, $df = 1,41$; $p = .0493$ and $F = 4.40$, $df = 1,11$; $p = .0360$, respectively).

Both groups showed a similar pattern of symptomatic changes on subscales (negative symptoms, positive symptoms, and general psychopathology) and the total score of the PANSS. No differences across treatment modalities were observed in CGI and VAS scores at any time.

DISCUSSION

This is the first study of the effects of 1-Hz rTMS on the left temporoparietal cortex using a sample of patients with auditory hallucinations exclusively refractory to clozapine. Although it is a very specific sample of patients, clinicians treat them in their daily practice and many times have little to offer these patients. The use of 2 or more antipsychotics in conjunction[30] or the use of ECT[31] usually does not add much to the efficacy and only causes more side effects than benefits. Even a slight amelioration of some characteristics of the "voices" may be meaningful.

The use of slow rTMS is based on a possible reduction of excitability in cortical speech processing circuits. It has been postulated that rTMS 1 Hz may have therapeutic effects by curtailing excitability of the left temporoparietal auditory-linguistic association cortex. This hypothesis is based on the potential importance of the temporoparietal cortex in the production of hallucinations suggested by previous imaging studies[16,32] and other studies demonstrating long-lasting reductions in cortical excitability following stimulation of cortical regions.[19]

Our results are limited due to the small sample size. Inclusion criteria were very tight, and the sample was composed of people with schizophrenia with very severe symptoms who met strict treatment-resistant criteria including clozapine resistance. In addition, these patients were young (usually with a poorer prognosis), with a long duration of illness and with adequate doses of clozapine. The study is probably underpowered, and it is quite possible that the negative results of the trial reflect the lack of power to detect significant differences between active and sham treatment groups, although a power analysis was not performed.

Also, caution is needed before a conclusion can be made. For instance, if an adjustment is performed for multiple comparisons (e.g., Bonferroni's correction), a total of 12 dependent, quantitative variables were to be taken into account, with the level of significance dropping to .004 (.05/12). With this significance level, no group differences could be found, and only a time effect could still be seen in both groups. On the other hand, with the correction, type II error could also be too large. Another difficulty of this kind of study is accurate measurement of hallucinatory experiences, because it is reliant on self-reports of a subjective phenomenon.[20]

Both groups showed similar patterns of improvement, with a significant difference between groups only observed during follow-up 4 weeks after the end of the trial, suggesting a possible delayed action of the slow stimulation. A time effect in auditory hallucinations in the active group began during the trial and lasted during the follow-up until the endpoint. In the sham group, this effect was not sustained, and all patients returned to baseline scores, suggesting a temporal weakness of the placebo effect.

Our findings suggest that 1-Hz rTMS in association with clozapine can be administered safely to patients with schizophrenia to treat auditory hallucinations. On the other hand, group differences were not observed in negative symptoms, general psychopathology and total scores of the PANSS, or CGI or VAS scores. These results lead us to question the clinical utility of rTMS for patients with this clinical profile.

This study found a weak reduction in auditory hallucinations as reported previously by Lee et al.,[22] which used a methodology similar to Hoffman et al.[13,21] If efficacy cannot be conclusively proven (making this a negative study), the safety profile of the study can be considered a very positive result. No important side effects and no complications (including seizure risks) were observed. Further studies with an expanded sample using 1-Hz rTMS for treatment-resistant hallucinating patients to confirm possible benefits are encouraged.

Drug names: chlorpromazine (Thorazine and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa).

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