

A double blind study showing that two weeks of daily repetitive TMS over the left or right temporoparietal cortex reduces symptoms in patients with schizophrenia who are having treatment-refractory auditory hallucinations

Seung-Hwan Lee^a, Won Kim^b, Young-Cho Chung^a, Kyung-Hee Jung^c, Won-Myong Bahk^b, Tae-Yun Jun^b, Kwang-Soo Kim^b, Mark S. George^d, Jeong-Ho Chae^{b,*}

^a Department of Psychiatry, Ilsanpaik Hospital, Inje University of Korea, Koyang, South Korea

^b Department of Psychiatry, St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Yoido-dong, Youngdeungpo-gu, Seoul, 150-713, South Korea

^c Department of Psychiatry, Keyo Hospital, Uiwang, South Korea

^d Department of Psychiatry, Radiology and Neurology, Center for Advanced Imaging Research, Brain Stimulation Laboratory, Medical University of South Carolina, Charleston, USA

Received 22 June 2004; received in revised form 16 November 2004; accepted 17 November 2004

Abstract

The aim of this study was to evaluate the effect of repetitive transcranial magnetic stimulation (rTMS) on the left and right temporoparietal cortex compared with sham stimulation in schizophrenic patients with treatment-refractory auditory hallucinations (AH). Thirty-nine patients with schizophrenia with treatment-refractory AH were allocated randomly to one of three groups: daily left, right, and sham rTMS groups. rTMS was applied to the TP3 or 4 regions with the aid of the electroencephalography 10–20 international system at 1 Hz for 20 min per day for 10 treatment days. Symptoms were evaluated using the Auditory Hallucination Rating Scale (AHRS), the Positive and Negative Symptoms Scale (PANSS), the Clinical Global Impression—Severity (CGI-S), and Clinical Global Impression—Improvement (CGI-I) scale. For the time effect (within-subject comparison), there were significant changes in the frequency of AHs, positive symptoms of PANSS, and CGI-I. A between-group comparison revealed significant differences in the positive symptoms of PANSS, and CGI-I scores. Post hoc analysis revealed that both the right- and left-side rTMS treatment groups exhibited better CGI-I scores compared to the sham-stimulated group. This study suggests that 10 days of low-frequency rTMS applied daily for 20 min to either temporoparietal cortex significantly reduces the symptoms in patients with schizophrenia who are having refractory AH, but the left sided rTMS is not superior to right or sham rTMS.

© 2004 Elsevier Ireland Ltd. All rights reserved.

Keywords: Repetitive transcranial magnetic stimulation; Schizophrenia; Auditory hallucination

Auditory hallucinations (AH) are a distressing symptom reported by 50–80% of patients with schizophrenia [1]. Some researchers have suggested that the hallucinated voice might actually be inner speech that is misperceived as stimulation from the outside [6]. Another hypothesis is that the hallucinated voice occurs due to a malfunction of the speech percep-

tion system. That is, the system itself creates speech perception without any inputs from the outside. The neuroanatomical basis of AH is thought to involve increasing blood flow of the speech perception areas of the brain, such as the superior temporal cortex of the dominant hemisphere [21]. In addition, several positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have suggested AH involved a distributed extensive bilateral network of cortical and subcortical areas [17,18].

* Corresponding author. Tel.: +82 2 37792019; fax: +82 2 7806577.
E-mail address: alberto@catholic.ac.kr (J.-H. Chae).

Repetitive transcranial magnetic stimulation (rTMS) is a new non-invasive technique that has been explored as a possible treatment for a variety of neuropsychiatric disorders. It has been shown that extended-duration (>15 min), low-frequency (~1 Hz) TMS reduces cortical activation [4], and rTMS, when applied to the left temporoparietal area at a frequency of 1 Hz, reduces the frequency of occurrence of AHs [8]. However, there is some evidence to show that the pathology of AH involves not only the left, but also the right hemisphere [17]. Thus, would daily rTMS over the right hemisphere also reduce AH? The purpose of the double-blind study presented here was to evaluate whether daily rTMS for 10 days over the left or right temporoparietal cortex reduced AH in treatment-resistant patients with schizophrenia.

Thirty-nine patients with schizophrenia and treatment-refractory AH were recruited into the study. Diagnostic assessments were made using the Structural Clinical Interview for DSM-IV [2]. The presence of medication resistance was confirmed using Lublin's definition [12]: patients who have had at least two periods of treatment with two different classes of antipsychotic drugs at an adequate dosage for the minimum period of 4 weeks each, without experiencing significant symptomatic relief, and clinically significant psychopathology with reduced social functioning or reduced quality of life (QOL). The lower and upper age cutoffs were 18 and 60 years, inclusive. Patients were excluded if they had a history of neurologic illness, or substance abuse or if their estimated intelligence quotient was less than 80. They were also excluded if they were pregnant or left-handed.

All patients were randomly allocated to a left (13), right (12), or sham rTMS group (seven left and seven right) (Table 1). Patients gave written voluntary informed consent for this study which was approved by the hospital's ethics committee. Then, rTMS was performed using a Neotonus stimulator with a figure eight solid core coil (Neotonus, Atlanta, GA, USA). rTMS at a frequency of 1 Hz administered to the left or right temporoparietal cortex halfway between T3/T4 and P3/P4, as per the International 10–20 System. The stimulus intensity was 100% of the patient's resting motor threshold. While receiving rTMS (or sham stimulation) treatment, which lasted 20 min per day for a 10-day period, patients were seated in a reclined, head-supported examination

chair. The sham group received identical rTMS treatment as the group receiving real rTMS, but we raised the lateral wing of the coil 90° off the head with the edge of the medial wing of the coil still touching the scalp. rTMS was administered each day by a trained psychiatrist (K.H.J.) who purposefully had very limited verbal interaction with the subject.

The Auditory Hallucination Rating Scale (AHRS), which was developed by Hoffman et al. [8], was used to evaluate the severity of AH (Table 2). The Positive and Negative Syndrome Scale (PANSS) [9], Clinical Global Impression—Severity (CGI-S), and Clinical Global Impression—Improvement (CGI-I) [15] scale were used to evaluate clinical status. Clinical assessments were conducted by an independent investigator who was blind to the stimulation condition at baseline, on day 5, and on day 10 (at the end of the trial). Assessments reflected the state of the patient during the prior 24 h.

Two-factor repeated-measures analyses of variance (ANOVA) (subject group, time of evaluation) were performed for all AHRS items, PANSS subscales (positive, negative and general subscales), CGI-S and CGI-I scores. To prevent the effects of multiple tests, Bonferroni's methods of correction were used. Post hoc analysis was performed using Scheffe's method between the three groups. For all experiments, data are given as means, standard deviation (S.D.). All significance levels reported were two-tailed and the criterion for statistical significance was 0.05.

Three study groups did not show any statistically significant differences in baseline scores of AHRS, PANSS subscale (positive, negative and general) and CGI-S.

For the time effect (within-subject comparison), there were significant improvements in the frequency of AHs ($F = 10.13$, d.f. = 2, $P < 0.001$), positive symptoms of PANSS ($F = 10.93$, d.f. = 2, $P < 0.001$), and CGI-I ($F = 17.64$, d.f. = 2, $P < 0.001$; Table 2 and Fig. 1).

For the time by treatment interaction (between-subject comparison), there were significant differences in positive symptoms of PANSS ($F = 7.41$, d.f. = 2, $P = 0.002$), and the CGI-I ($F = 9.63$, d.f. = 2, $P < 0.001$) score. Post hoc analysis revealed that rTMS applied to the right ($P = 0.002$) and left ($P = 0.004$) sides resulted in a better change of CGI-I score compared to sham rTMS (Fig. 1). A trend for a time

Table 1
Descriptive features of the patients groups

	Left TMS (N = 13)	Right TMS (N = 12)	Sham TMS (N = 14)
Age (years)	41.3 (10.3)	39.7 (6.9)	39.9 (8.9)
Education (grade)	10.2 (2.7)	11.8 (3.1)	11.9 (2.8)
Numbers of prior hospitalizations	4.0 (3.2)	3.0 (1.4)	4.1 (2.1)
Male/female	8/5	7/5	8/6
Diagnosis			
SPR, paranoid type	11	9	11
SPR, undifferentiated type	2	3	3
Numbers of prior ECT	5	3	4
Duration of current hospitalization (days)	33.2 (5.2)	36.5 (3.5)	34.4 (4.2)

Data are given as mean (S.D.). TMS: transcranial magnetic stimulation, SPR: schizophrenia, ECT: electro-convulsive therapy.

Table 2

Changes of Auditory Hallucinations Rating Scale across the three assessment periods of the left rTMS, right rTMS and sham rTMS trial for 10 days in patients with schizophrenia

Auditory Hallucinations Rating Scale	Left TMS (N=13)			Right TMS (N=12)			Sham TMS (N=14)		
	Baseline	Day 5	Day 10	Baseline	Day 5	Day 10	Baseline	Day 5	Day 10
Frequency ^a	6.8 (3.0)	5.4 (3.2)	4.6 (2.9)	5.3 (3.4)	3.8 (3.4)	3.1 (2.5)	4.9 (3.4)	4.6 (3.0)	4.3 (3.3)
Reality	3.6 (1.6)	2.7 (2.0)	2.8 (2.2)	2.8 (1.7)	3.4 (1.6)	2.4 (1.4)	2.6 (1.7)	2.5 (2.2)	2.4 (2.1)
Loudness	2.5 (1.1)	2.6 (1.3)	3.4 (0.8)	2.7 (1.3)	2.1 (1.4)	2.3 (0.9)	2.8 (1.3)	2.4 (1.4)	2.1 (1.5)
Numbers of voices	3.7 (2.2)	2.9 (1.9)	3.5 (2.0)	3.3 (2.2)	3.1 (1.7)	2.6 (1.4)	3.5 (1.7)	3.1 (1.4)	3.4 (1.7)
Length	3.4 (1.0)	3.3 (1.2)	3.8 (0.4)	2.8 (1.1)	2.8 (1.0)	2.4 (1.1)	3.0 (1.2)	2.6 (1.2)	2.4 (1.3)
Attentional salience ^b	5.8 (1.8)	4.8 (2.0)	4.8 (1.6)	4.4 (1.7)	3.4 (1.7)	3.8 (1.5)	4.4 (2.1)	5.2 (1.3)	4.6 (2.0)
Distress level	3.2 (1.7)	3.1 (1.6)	3.2 (1.5)	3.4 (1.6)	2.5 (1.1)	2.6 (1.2)	2.3 (1.0)	2.4 (1.4)	2.6 (1.6)

Data are given as mean (S.D.). rTMS: repetitive transcranial magnetic stimulation, two-factor repeated-measures analyses of variance (ANOVA).

^a Significant time effect ($F = 10.13$, d.f. = 2, $P < 0.001$).

^b A trend for a time by treatment effect ($F = 4.88$, d.f. = 2, $P = 0.07$).

by treatment effect was found for the attentional salience of AHs ($F = 4.88$, d.f. = 2, $P = 0.07$). The right rTMS group showed a significantly different changing pattern compared to the sham-stimulated group, suggesting more improvement by post hoc analysis.

Adverse effects reported by the subjects during the real trial were headache ($N = 5$), dizziness ($N = 2$), and amnesia ($N = 1$), while sham trial were headache ($N = 2$), dizziness ($N = 1$), and difficulty in concentrating ($N = 1$). These adverse effects disappeared within 10 min of the completion of each rTMS treatment and were seen with both left and right hemisphere treatment.

Our study has demonstrated significant improvements in symptoms of patients with schizophrenia who are having treatment-resistant AH following the administration of daily rTMS for 10 days over the right or left temporoparietal cortex (i.e., T3/T4–P3/P4). These improvements were particularly marked for the frequency of AHs, the positive symptoms of the PANSS, and CGI-I scores.

The initial study with this method by Hoffman et al. [8] found that left temporoparietal rTMS for 9 days at 90% of motor threshold was effective in improving the symptoms of AH in patients with schizophrenia. However, the present study was not able to replicate Hoffman's findings [8] of robust improvement in AHs in patients with schizophrenia. They used a composite, patient-specific targeted symptoms scale (Hallucination Change Scale) as primary outcome measure [8], but we used descriptive measures of specific characteristics of AHs (AHRs) for the evaluation of AHs. A possible limitation is that it would be difficult to accurately measure the hallucinatory experience, is reliant on the accuracy of self-report. There may be differences between the measurement for the specific characteristics and the global estimation of AHs. In this line of thoughts, although no significant effects of rTMS on the AHRs scores in the present study, the global state by CGI appeared significantly better in patients when receiving rTMS as opposed to sham TMS.

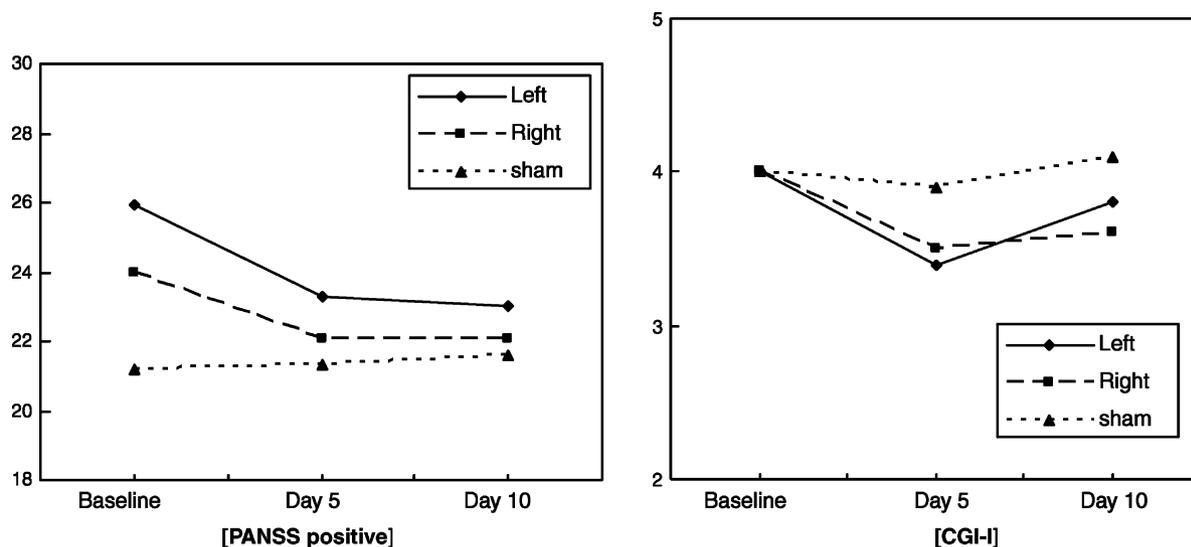


Fig. 1. The Positive and Negative Syndrome Scale (PANSS) positive symptoms score and Clinical Global Impression—Improvement (CGI-I) scale showing a significant time effect and time by treatment interaction after repetitive transcranial magnetic stimulation (rTMS) application for 10 days. Post hoc analysis showed that right rTMS applied to the right ($P = 0.002$) and left ($P = 0.004$) sides resulted in a better change of CGI-I compared to sham rTMS.

Interestingly, Hoffman et al. [8] reported that attentional salience and hallucination frequency were two aspects of AHs that showed greatest improvement by rTMS [8]. Similarly, we had also found a significant time effect in the frequency of AHs and a trend for a time by treatment effect for the attentional salience of AHs.

In contrast, McIntosh et al. [14] recently reported that AHs in 16 patients with schizophrenia improved from baseline with both real and sham TMS at 1 Hz and 80% of motor threshold over left temporoparietal cortex, and there was no significant difference between real and sham treatments. However, mean or median improvement of symptoms consistently appeared somewhat better in patients when receiving TMS as opposed to sham TMS. They have speculated that the pathological anatomy of AHs in schizophrenia differs between subjects.

The results of our study, which had used higher powered (80% versus 100% of motor threshold) stimuli than McIntosh's study [14], imply that rTMS applied to the right side may also significantly reduce symptoms of schizophrenia with AHs. Interestingly, McIntosh et al. [14] reported that the PANSS positive symptoms were significantly reduced after rTMS, which were similar to our results. If the mechanism for these TMS induced auditory hallucinatory improvements involves interaction with auditory cortex, then these findings might suggest that the auditory circuit responsible for AH involves both the right and left hemispheres. Alternatively, right hemisphere stimulation might affect the left auditory cortex through trans-callosal fibers, much like stimulation of one cortical region can induce a mirror focus in the opposite hemisphere [7]. Brain imaging studies of patients with AH have revealed an active area in the right and left superior temporal cortex [21], Broca's area [13], and the left temporoparietal cortex [10]. Shergill et al. [17] reported the presence of active areas in the anterior cingulate cortex, right thalamus, left hippocampus, and parahippocampal cortex when subjects were experiencing AHs. These imaging studies imply that several cortical and subcortical areas in both the left and right hemispheres are involved in the brain circuitry responsible for AHs.

In a related case study, Schreiber et al. [16] showed that daily right prefrontal rTMS for 20 days at 10-Hz frequency with 90% motor threshold may induce a general clinical improvement in brain function of patients with schizophrenia. They designed their theory based on the theory that AHs are associated with increased activity bilaterally in the basal ganglia and the hippocampus as well as decreased activity in the bilateral lateral frontal lobe [13]. However, they did not find a significant reduction of AH. Since they evaluated a single patient and used different protocols—high frequency stimulation delivered to prefrontal cortex, it is difficult to compare their study with ours.

The data available regarding the physiological effects of 1 Hz rTMS are still accumulating. Over left prefrontal cortex, 1 Hz stimulation has been shown to produce significant decreases in blood flow of right prefrontal cortex, left medial

temporal cortex and left subcortical areas [19]. On the contrary, some have reported increased activation of the brain cortex after short bursts of 1 Hz rTMS [3,5]. For example, Bohning et al. [3] reported a fMRI study showing increased activity both locally and remotely (trans-synaptically) immediately after high intensity 1 Hz stimulation. Fox et al. [5] observed 1 Hz TMS on primary motor cortex increased blood flow in the stimulated site and caused various remote effects by excitatory or inhibitory connectivity. This phenomenon implies that the effect of rTMS can spread to the opposite hemisphere through interhemispheric connections. Recently Li et al. [11] have shown that cortical TMS at 1 Hz causes changes subcortically as well. Finally, Strafella et al. [20] have elegantly shown that 10 Hz prefrontal rTMS can cause changes in basal ganglia dopamine release using positron emission tomography. Thus, there are many potential explanations for our findings of reduced symptoms of schizophrenia following temporoparietal TMS, including local or distributed changes in excitability or resting neurotransmitters.

The number of subjects in the current study was small. Patients were maintained on medications. There was no active TMS over another non-temporoparietal site. Thus, these effects might occur non-specifically over any brain region and the specificity to the temporoparietal cortex remains to be established. Although we have used 90° tilting of the coil as the sham condition, it is impossible to completely exclude the partial magnetic field effects in cortex.

Despite this small sample with limited power, this study found that low-frequency rTMS applied to either the right or left temporoparietal cortex reduced symptoms in patients with schizophrenia. It seems that the brain circuits involved in the production of AHs and symptoms of schizophrenia are widespread and not confined in the left temporoparietal cortex.

Acknowledgements

This work was supported by grant No. R01-2003-000-10432-0 from the Basic Research Program of the Korea Science & Engineering Foundation.

References

- [1] M. Alpert, Language processes and hallucination phenomenology, *Behav. Brain Sci.* 9 (1986) 518–519.
- [2] American Psychiatric Association, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth ed., American Psychiatric Association, Washington, DC, 1994.
- [3] D.E. Bohning, A. Shastri, K.A. McConnell, Z. Nahas, J.P. Lorberbaum, D.R. Roberts, C. Temeback, D.J. Vincent, M.S. George, A combined TMS/fMRI study of intensity-dependent TMS over motor cortex, *Biol. Psychiatry* 45 (1999) 385–394.
- [4] R. Chen, J. Classen, C. Gerloff, P. Celnik, E.M. Wassermann, M. Hallett, L.G. Cohen, Depression of motor cortex excitability by low-

- frequency transcranial magnetic stimulation, *Neurology* 48 (1997) 1398–1403.
- [5] P. Fox, R. Ingham, M.S. George, H. Mayberg, J. Ingham, J. Roby, C. Martin, P. Jerabek, Imaging human intra-cerebral connectivity by PET during TMS, *NeuroReport* 8 (1997) 2787–2791.
- [6] C. Frith, The role of the prefrontal cortex in self-consciousness: the case of auditory hallucinations, *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 351 (1996) 1505–1512.
- [7] R. Hanajima, Y. Ugawa, K. Machii, H. Mochizuki, Y. Terao, H. Enomoto, T. Furubayashi, Y. Shio, H. Uesugi, I. Kanazawa, Inter-hemispheric facilitation of the hand motor area in humans, *J. Physiol.* 531 (2001) 849–859.
- [8] R.E. Hoffman, K.A. Hawkins, R. Gueorguieva, N.N. Boutros, F. Rachid, K. Carroll, J.H. Krystal, Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations, *Arch. Gen. Psychiatry* 60 (2003) 49–56.
- [9] S.R. Kay, L.A. Opler, J.P. Lindenmayer, Reliability and validity of the positive and negative syndrome scale for schizophrenics, *Psychiatry Res.* 23 (1988) 99–110.
- [10] B.R. Lennox, S.B.G. Park, I. Medley, P.G. Morris, P.B. Jones, The functional anatomy of auditory hallucinations in schizophrenia, *Psychiatry Res.* 100 (2000) 13–20.
- [11] X. Li, Z. Nahas, F.A. Kozel, B. Anderson, D.E. Bohning, M.S. George, Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions, *Biol. Psychiatry* 55 (2004) 882–890.
- [12] H.K. Lublin, Psychopharmacological treatment of treatment-resistant schizophrenia, *Ugeskr Laeger.* 159 (1997) 7128–7133.
- [13] P.K. McGuire, G.M.S. Shah, R.M. Murray, Increased blood flow in Broca's area during auditory hallucinations in schizophrenia, *Lancet* 342 (1993) 703–706.
- [14] A.M. McIntosh, D. Semple, K. Tasker, L.K. Harrison, D.G. Owens, E.C. Johnstone, K.P. Ebmeier, Transcranial magnetic stimulation for auditory hallucinations in schizophrenia, *Psychiatry Res.* 127 (2004) 9–17.
- [15] National Institute of Mental Health, Special features: rating scales and assessment instruments to use in pediatric psychopharmacology research, *Psychopharmacol. Bull.* 21 (1985) 839–843.
- [16] S. Schreiber, P.N. Dannon, E. Goshen, R. Amiaz, T.S. Zwas, L. Grunhaus, Right prefrontal rTMS treatment for refractory auditory command hallucinations—a neuroSPECT assisted case study, *Psychiatry Res.* 116 (2002) 113–117.
- [17] S.S. Shergill, M.J. Brammer, S.C. Williams, R.M. Murray, P.K. McGuire, Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging, *Arch. Gen. Psychiatry* 57 (2000) 1033–1038.
- [18] D.A. Silbersweig, E. Stern, C. Frith, C. Cahill, A. Holmes, S. Grootoank, J. Seaward, P. McKenna, S.E. Chua, I. Schnorr, T. Jones, S.J. Frackowiak, A functional neuroanatomy of hallucinations in schizophrenia, *Nature* 378 (1995) 176–179.
- [19] A.M. Speer, T.A. Kimbrell, E.M. Wassermann, J.D. Repella, M.W. Willis, P. Herscovitch, R.M. Post, Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients, *Biol. Psychiatry* 48 (2000) 1133–1141.
- [20] A.P. Strafella, T. Paus, J. Barrett, A. Dagher, Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus, *J. Neurosci.* 21 (2001) 1–4, RC157.
- [21] M. Suzuki, S. Yuasa, Y. Minabe, M. Murata, M. Kurachi, Left superior temporal blood flow increases in schizophrenic and schizophreniform patients with auditory hallucination: a longitudinal case study using ¹²³I-IMP SPECT, *Eur. Arch. Psychiatry Clin. Neurosci.* 242 (1993) 257–261.