ORIGINAL ARTICLE

Transcranial Magnetic Stimulation of Left Temporoparietal Cortex and Medication-Resistant Auditory Hallucinations

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Background: Neuroimaging studies suggest that auditory hallucinations (AHs) of speech arise, at least in part, from activation of brain areas underlying speech perception. One-hertz repetitive transcranial magnetic stimulation (rTMS) produces sustained reductions in cortical activation. Recent results of 4-day administration of 1-Hz rTMS to left temporoparietal cortex were superior to those of sham stimulation in reducing AHs. We sought to determine if a more extended trial of rTMS could significantly reduce AHs that were resistant to antipsychotic medication.

Methods: Twenty-four patients with schizophrenia or schizoaffective disorder and medication-resistant AHs were randomly allocated to receive rTMS or sham stimulation for 9 days at 90% of motor threshold. Patients receiving sham stimulation were subsequently offered an open-label trial of rTMS. Neuropsychological assessments were administered at baseline and during and following each arm of the trial.

Results: Auditory hallucinations were robustly improved with rTMS relative to sham stimulation. Frequency and attentional salience were the 2 aspects of hallucinatory experience that showed greatest improvement. Duration of putative treatment effects ranged widely, with 52% of patients maintaining improvement for at least 15 weeks. Repetitive transcranial magnetic stimulation was well tolerated, without evidence of neuropsychological impairment.

Conclusions: These data suggest that the mechanism of AHs involves activation of the left temporoparietal cortex. One-hertz rTMS deserves additional study as a possible treatment for this syndrome.

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AUDITORY HALLUCINATIONS (AHs) are reported by 50% to 70% of patients with schizophrenia[1,2] and generally consist of spoken speech or "voices." A large percentage of these patients experience AHs as highly distressing, especially when verbal content is negative or intrusive.[3-5] Auditory hallucinations disrupt social functioning and are associated with acts of violence and suicide.[6-8] In about 25% of cases, AHs respond only partially to drug therapy.[9] Effective treatment alternatives for AHs would benefit patients and their communities.

The study described herein is based on 2 sets of findings. First, neuroimaging studies of patients during AH periods have identified activation in brain regions involving speech perception, including right and left superior temporal cortex,[10-13] Broca's area,[13,14] and left temporoparietal cortex.[11,15] These findings are consistent with results of neuroimaging studies[16,17] of visual and somatic hallucinations that also demonstrate activation of brain areas underlying modality-specific perceptual processes. Second, 1-Hz, extended duration (approximately 15 minutes) repetitive transcranial magnetic stimulation (rTMS) has been shown to produce sustained reductions in brain activation in the brain area directly stimulated,[18-20] as well as in other brain areas functionally connected to the former.[21-23] Reduced activation induced by 1-Hz rTMS is evidenced by results of studies of motor function,[18,20,21] perception,[19] event-related potentials,[22] and functional neuroimaging.[23,24] The physiological basis of these effects is not well understood but may reflect reduced pyramidal neuron excitability[25] or neuroplasticity changes analogous to those associated with long-term depression.[26,27] These findings, considered together, suggest that 1-Hz rTMS delivered to brain regions critical to auditory speech perception may curtail AHs.

Consequently, a pilot study[28] was undertaken of 12 patients with schizophrenia-spectrum disorder and persistent AHs us-

Table 1. Descriptive Characteristics of the Patient Groups*

Characteristic	Active (n = 12)	Sham (n = 12)
Age, y	35.8 ± 12.1	35.0 ± 9.6
Education, grades	13.5 ± 1.7	13.8 ± 1.5
No. of prior hospitalizations	4.6 ± 3.8	6.9 ± 5.9
Duration of current episode of hallucinations, mo	117 ± 98	126 ± 111
M/F, No. of patients	7/5	6/6
Diagnosis, No. of patients		
Paranoid schizophrenia	4	3
Schizoaffective, bipolar type	1	3
Schizoaffective, depressed type	6	6
Schizophrenia, undifferentiated type	1	0
No. of patients with prior alcohol or other drug abuse	7	5
No. of patients receiving >1 antipsychotic medication at study entry	7	6

*Data are given as mean ± SD unless otherwise indicated.

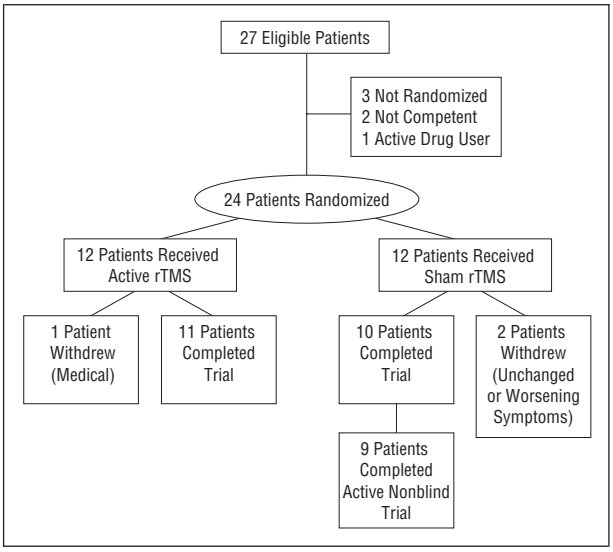

Figure 1. Profile of the trial. rTMS indicates repetitive transcranial magnetic stimulation.

ing a double-blind, crossover design. Left temporoparietal cortex was selected as the site of stimulation in light of results of a previous positron emission tomographic study[15] demonstrating activation in this brain area during AHs, the central role of this region for speech perception,[29-31] and its ready accessibility to scalp-administered rTMS. Hallucination severity was significantly improved following active rTMS relative to sham stimulation. Duration of symptom improvement generally was 2 weeks or less.

The study described herein used a more extended course of 1-Hz rTMS at higher stimulation strength to determine if more robust and sustained clinical improvements could be obtained. Patients in this study reported AHs that were medication-resistant. Positive findings in this group would underscore the potential clinical usefulness of rTMS for treating AHs.

METHODS

PARTICIPANTS

Patients were recruited into the study if they reported medication-resistant AHs on average at least 5 times per day based on prospective assessment using a diary or handheld counter. Medication resistance was defined as daily AHs occurring in the face of at least 2 adequate trials of antipsychotic medications, including at least 1 atypical antipsychotic medication. An adequate medication trial was defined as a minimum of at least 6 weeks at a daily dosage of 1000 chlorpromazine equivalents for patients with standard neuroleptics[32] and the following dosages for atypical neuroleptics: daily minimum of 6 mg risperidone, 15 mg olanzapine, 500 mg quetiapine, or 400 mg clozapine. Lower and upper age cutoffs were 18 and 60 years, inclusively. Patients were excluded if they had a history of seizures or neurological illness, a first-degree relative with epilepsy, a complicated medical history, left-handedness, pregnancy, or subnormal intelligence (ie, estimated IQ <80). Histories of substance abuse or alcoholism were not exclusion criteria, provided that patients had not abused alcohol or other drugs within 4 weeks of study entry. All patients were maintained on their psychotropic medication at steady dosages for at least 4 weeks before study entry and for the duration of the trial.

The study herein presents results from the first 24 patients with medication-resistant AHs enrolled in the trial. This group does not include any participants from the previous study.[28,33] Enrollment was from February 8, 2000, to May 18, 2001. Patient characteristics are provided in **Table 1**. There were no statistically significant differences in age, sex, number of prior hospitalizations, or duration of current hallucination episode, defined as the number of months since the patient last had a remission of AHs of 4 weeks or longer. The duration of unremitting hallucinations was extended (mean, 10 years in each group). Four patients in the active group had histories of electroconvulsive therapy treatment, and 1 patient in the sham group had a history of this treatment. Two patients in each group were studied as outpatients. The remaining patients were admitted to an inpatient research unit for the trial. Competence to give informed consent was assessed based on the patient's ability to provide a spontaneous narrative description of key elements of the study. Two patients recruited into the study were not permitted to enroll based on lack of competence, while a third recruited patient was excluded before initiation of the trial because of relapse of substance abuse (**Figure 1**). Enrollment in every case was reviewed and approved by one of us (R.E.H.).

rTMS PROTOCOL

Participants were randomly allocated to sham vs active stimulation based on a coin toss by one of us (R.E.H.). Allocation of the last 2 patients was coupled to ensure equal sample size. The projected sample size for reporting these data was based on pilot data demonstrating robust effect sizes for the primary outcome variable. Allocation of all patients, including the last 2, was made subsequent to enrollment. A double-blind, parallel design was used with a sham stimulation control condition. Knowledge of intervention type was exclusive to the psychiatrists administering rTMS (R.E.H. and F.R.) and a research technician assisting in the procedure. Their interactions with the patients once the trial was under way were limited to administration of rTMS and assessment of safety and tolerability of the procedure. Study participants, clinical raters, and all personnel responsible for the clinical care of the participants remained blind to allocated condition and allocation parameters.

A Magstim Super system (Magstim Company Ltd, Whitland, Wales) with an air-cooled, figure-eight 70-mm coil was used.

This system generates a magnetic field up to 2 T, with a sharp peak at the center of the coil that drops off by approximately 50% at a 2-cm radius.[34] Magnetic field pulses pass undistorted through scalp and skull, inducing electrical currents that produce neuronal depolarization beneath the coil[35,36] with propagated effects in functionally connected regions.[21-23,36,37] Stimulation for our trial was administered at 90% of motor threshold. Motor threshold was assessed to be the lowest stimulation strength able to elicit visible movement of any of the digits of the right hand in 4 of 8 tries, with a 10-second delay between test stimulations. Motor threshold was probed each day of the trial by stimulation of the primary motor cortex in the neighborhood of C3 (based on the International 10-20 System of electroencephalographic electrode placement[38]) (**Figure 2**), with the site adjusted to maximize motor response. Visual monitoring of muscle activity has been shown to produce motor threshold readings similar to those of electromyographic monitoring.[39]

Trial stimulation was administered to left temporoparietal cortex halfway between T3 and P3, per the International 10-20 System (Figure 2). Stimulation was given at 1 Hz while patients were seated in a reclined, head-supported examination chair (Lumex Inc, Bay Shore, NY). Sham stimulation was administered at the same location, strength, and frequency with the coil angled 45° away from the skull in a single-wing tilt position. This method reproduces sound and some somatic sensations (eg, contraction of scalp muscles) similar to those of active stimulation with minimal direct brain effects. For the last 6 patients in the study, the stimulation coil was positioned using a mechanical arm, whereas for earlier participants in the study, the stimulation coil was handheld. Clinical improvements tended to favor the mechanical arm method, although differences in outcome were not statistically different.

Patients received 8 minutes of stimulation on day 1, 12 minutes on day 2, and 16 minutes for the next 7 days (excluding weekends). For patients enrolling into the study as inpatients, the hospital environment can have a symptom-reducing effect. For inpatients, therefore, the trial was not initiated until hallucination severity had restabilized over a 48-hour period. For patients randomized to the sham condition, a subsequent nonblind active rTMS trial using the same parameters as the blind trial was offered. Nine of 12 patients allocated to the sham group received subsequent active rTMS.

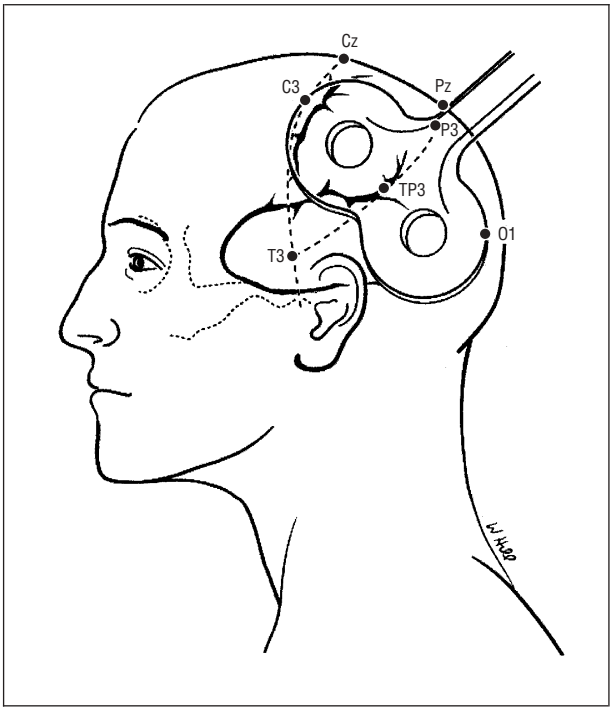

Figure 2. Location of the stimulation sites used in this study. Motor threshold was ascertained in the neighborhood of C3 and corresponded to the site of stimulation generating maximum finger movement. TP3 was the site of the intervention trial and was defined as being midway between T3 and P3. This region falls along the posterior border of Wernicke area. Cz, C3, Pz, T3, O1, and P3 are electrode sites defined according to the International 10-20 System.[38] TP3 is located halfway between T3 and P3.

PATIENT ASSESSMENTS

All patients underwent a medical evaluation that included physical examination, routine laboratory studies, drug toxicology screening, electrocardiogram, and a serum pregnancy test if female of childbearing age. Diagnostic assessments were made using the Structured Clinical Interview for *DSM-IV* (version 2.0).

Pilot work had found that severity of AHs depended on several factors, including frequency, loudness, verbal content, affective charge, and attentional salience. Moreover, dimensions critical for determining symptom severity were different for different patients and often did not covary between or within patients. Therefore, a composite, patient-specific targeted symptom scale[40] (Hallucination Change Scale) was used as our primary outcome measure. The scale was anchored at baseline using the narrative description of AHs provided by the patient for the prior 24 hours, which was assigned a score of 10. For subsequent assessments, the Hallucination Change Scale ranged from 0 to 20 (with a score of 20 corresponding to hallucinations twice as severe as baseline). Secondary descriptive measures of specific characteristics of AHs were based on a 7-item Auditory Hallucinations Rating Scale developed by our group (**Table 2**). Internal consistency was acceptable (Cronbach $\alpha = .60$), as was interrater reliability (**Table 3**). Whenever possible, frequency of AHs was also assessed by requesting the patient to carry a handheld counter that was clicked each time an AH occurred. Other secondary measures included composite positive and negative symptom clusters assessed using the Positive and Negative Syndrome Scale (PANSS)[41] and the Clinical Global Improvement (CGI) scale.[42] Clinical assessments were conducted at baseline, on days 4 and 7, and at the end of the trial. Assessments reflected the prior 24 hours.

Although no studies have demonstrated neuropsychological impairment associated with 1-Hz rTMS,[43,44] direct electrical stimulation of left temporoparietal cortex can disrupt short-term verbal memory.[30] Patients with schizophrenia have demonstrated impairments in this cognitive domain[45-48] and may therefore be more vulnerable to verbal memory alterations following rTMS to this brain area. Patients consequently received a neuropsychological test battery at baseline and after each arm of the trial. One component was the California Verbal Learning Test. This task has demonstrated excellent sensitivity in detecting various types of verbal learning and memory difficulties[49,50] and has demonstrated impairments in patients with schizophrenia.[47] Other tasks included the Controlled Oral Word Association Test, Semantic Fluency, Digit Distraction Task, Reading: Wide Range Achievement Test–Revised, Trails A and B, Grooved Pegboard, Digit Symbol Task, and Temporal Orientation. In addition, 2 neuropsychological screening tasks were administered serially during the trial to detect signs of verbal memory impairment that warranted discontinuation of the rTMS trial. The first was the Hopkins Verbal Learning Test, which assesses short-term verbal memory and has the advantage of having 6 alternative forms.[51,52] The second was the letters-numbers span test.[53] Alternative forms for this task can be generated readily. These 2 tasks were administered at baseline and 24 hours after day 3, day 6, and the last stimulation session of the trial. Our algorithm for withholding rTMS was based on the SE of measurement ($SEM = SD \times [1 - R]^{1/2}$, where R corre-

Table 2. Auditory Hallucinations Rating Scale

1. *Frequency*. How often do the voices occur?
   0 = Stopped
   1 = Rare (1-5 times per 24 h)
   2 = Occasional (6-10 times per 24 h)
   3 = Occasional (approximately 1-2 times per hour)
   4 = Frequent (approximately 3-6 times per hour)
   5 = Frequent (7-10 times per hour)
   6 = Very frequent (11-20 times per hour)
   7 = Very frequent (21-50 times per hour)
   8 = Rapid (1 per minute)
   9 = Relatively uninterrupted
2. *Reality*. How real do the voices seem to you?
   0 = Indistinguishable from own thoughts
   1 = Imaginary
   2 = Vague
   3 = Dreamlike
   4 = Somewhat real
   5 = Very real
3. *Loudness*. On average, how loud is the predominant voice?
   0 = Too faint to be heard properly
   1 = Whispered but clear
   2 = Soft
   3 = Normal speaking voice
   4 = Loud
   5 = Yelling or screaming
4. *Number of voices*. How many different voices do you hear whose words you can make out?
   0
   1
   2
   3
   4
   5
   6 = >5
5. *Length*. How extensive is the content of the predominant voice?
   0 = No words heard
   1 = Single words
   2 = Phrases
   3 = Whole sentences
   4 = Multiple sentences
6. *Attentional Salience*. To what degree do the voices alter what you think, feel, and do?
   1 = Doesn't affect me at all
   2 = Distracts me occasionally
   3 = I am briefly distracted by the voice when it occurs
   4 = I mostly have to pay attention to the voice when I hear it
   5 = When I hear a voice it often alters what I do, say, and think
   6 = When I hear a voice it completely alters what I do, say, and think (talking back, laughing, etc)
   7 = The only thing that is important and I pay attention to is my voices
7. *Distress Level*. How distressing are the voices?
   1 = Not distressing at all
   2 = Mildly distressing
   3 = Moderately distressing
   4 = Sometimes produces significant anxiety
   5 = Often produces significant fear or anxiety

sponds to the test-retest reliability). *R* was estimated to be 0.75 for the Hopkins task and 0.70 for the letters-numbers task, based on pilot study and previously published data.[52,54] Our "stop criteria" for rTMS were the following: (1) a score decline (from one administration to the next or from baseline) greater than 3 SEMs on the Hopkins task *or* the letters-numbers task or (2) a score decline (from one administration to the next or from baseline) greater than 2 SEMs on the Hopkins task *and* the letters-numbers task.

Table 3. Interrater Reliability of Auditory Hallucination Measures

Measure	*R*
Hallucination Change Score	0.81
Frequency of hallucination	0.98
How real do voices seem?	0.80
Loudness	0.98
No. of distinct voices	0.91
Attentional saliance of voices	0.87
Length (words, phrases, sentences, etc)	0.97
Distress level induced by voice	0.98

Abbreviation: *R*, intraclass correlation coefficient based on assessment of 10 participants by psychologist rater and one of us (R.E.H.).

All adverse events spontaneously reported or observed were recorded. Before each rTMS session, the patient was specifically questioned regarding difficulties in concentration and memory, problems in perceiving speech, and other alterations in consciousness since the last stimulation session.

All patients reporting more than 20% improvement in Hallucination Change Scale score following active rTMS were followed up by telephone at least monthly. Nonsurvivorship was defined as a return to a Hallucination Change Scale score of 8 or higher, an increase in the patient's antipsychotic medication dosage, or a switch from one antipsychotic medication to another.

STATISTICAL ANALYSES

Data from the full intention-to-treat sample were analyzed in 2 stages. Repeated-measures analyses of between- and within-group differences in the double-blind phase of the study were performed first. Within-group comparisons between the double-blind and the follow-up nonblind active phase in the sham group were performed second. Two separate random-effects models[55] were fitted for each continuous outcome variable that accommodated randomly missing data. The treatment by time effect was always tested first and was followed by estimation of individual slopes for the 2 groups and associated 95% confidence intervals (CIs). No intercepts were estimated in the models for Hallucination Change Scale score, given that baseline values for all individuals were fixed at 10. All outcomes were checked for normality before analysis. Log transformation was applied to the countermeasure of hallucination frequency and to the overall rating of negative symptoms on the PANSS to eliminate skewness. Positive and Negative Syndrome Scale ratings for hallucinations, PANSS ratings for delusions, and the distress caused by AHs scale were analyzed using cumulative-logit generalized estimating equation models for ordinal data.[56] Change scores for neuropsychological tests of the full battery and CGI scores were compared using *t* tests. All significance levels reported were 2-tailed. Slope estimates expressed variable change per 24 hours.

RESULTS

SAFETY AND TOLERABILITY OF rTMS

A patient in the sham group withdrew from the study because of absence of clinical improvement, and a second patient in the sham group was removed by clinical staff because of clinical worsening. A patient in the active double-blind group was removed from the study because of ischemic chest pain. This patient had a history of hypertension, smoking, and diabetes mellitus. Ad-

Table 4. Adverse Effects*

Effect	Headache	Lightheadedness	Concentration Difficulties	Memory Difficulties	Hearing and Speech Perception Difficulties	Increased Auditory Hallucinations During rTMS	Other
Active-DB (n = 12)	4	3	2	0	0	1	Racing thoughts (n = 1)
Sham-DB (n = 12)	1	1	2	1	0	2	Pain in shoulder (n = 1)
Active-NB (n = 9)	2	1	1	1	0	2	Visual hallucination (n = 1)

Abbreviations: Active-DB, active stimulation, double-blind phase; active-NB, active stimulation, nonblind phase; rTMS, repetitive transcranial magnetic stimulation; sham-DB, sham stimulation, double-blind phase.
*Data are given as numbers of patients.

verse effects reported during the trial are outlined in **Table 4**. Concentration and memory difficulties were transient, lasting 5 to 10 minutes following rTMS, and did not appear more frequently in the 2 active arms of the trial relative to the sham arm.

There were no statistically significant changes on any component of our full neuropsychological test battery when comparing patients receiving active vs sham stimulation in the double-blind phase. Analyzing serial Hopkins Verbal Learning Test and letters-numbers working memory data via a random-effects model did not demonstrate any significant time by treatment effect for the double-blind phase ($P=.72$ for the Hopkins Verbal Learning Test and $P=.94$ for the letters-numbers task). A follow-up analysis comparing the sham and nonblind active phase also did not demonstrate a treatment group effect for the letters-numbers task ($P=.61$). A marginally significant time by treatment group effect for the Hopkins Verbal Learning Test was detected in the follow-up phase ($F_{1,57.9}=4.14$, $P=.05$). The estimated slope was positive ($t_{57.7}=2.35$; 95% CI, 0.04-0.47) for the active phase, suggesting improvement in function. One patient receiving active rTMS demonstrated a decline in function on the Hopkins task exceeding our threshold criterion, but this impairment emerged only after the last stimulation and was not accompanied by subjective complaints of altered memory or concentration.

In general, patients experienced subjective relief following reduced AHs, although this was not inevitably the case. One patient reported worsening depressive mood after losing "the voice of God," while relieved to be rid of the "satanic voices." Another patient became briefly depressed after the trial, reporting that she was more lonely in the absence of AHs.

HALLUCINATION CHANGE SCALE

There was a significant time effect ($F_{1,18.4}=48.29$, $P<.001$) and a significant time by treatment interaction ($F_{1,18.4}=11.27$, $P=.003$) for Hallucination Change Scale scores in the double-blind phase of the trial (**Figure 3**). The active group demonstrated a significant linear decrease in the Hallucination Change Scale scores over time ($t_{11}=-10.02$, $P<.001$; 95% CI for slope, –0.65 to –0.42), while the sham group did not show a significant decrease over time ($t_{11.3}=-2.09$, $P=.06$; 95% CI for slope, –0.38 to 0.01). Defining 50% or greater improvement in the Hallucination Change Scale score as a positive response, 9 (75%) of 12 patients demonstrated a positive response following the active phase vs 2 (17%) of 12 for the sham phase ($\chi^2_1=8.22$, $P=.004$). There was a significant time by phase interaction ($F_{1,8.27}=7.63$, $P=.02$) in the crossover arm of the trial, indicating clinical improvement during the nonblind active phase relative to the sham phase. Similar to the slope of the active group in the double-blind portion of the trial, the slope in the nonblind active phase was significantly negative ($t_{8.53}=-4.29$, $P=.002$; 95% CI, –0.72 to –0.22).

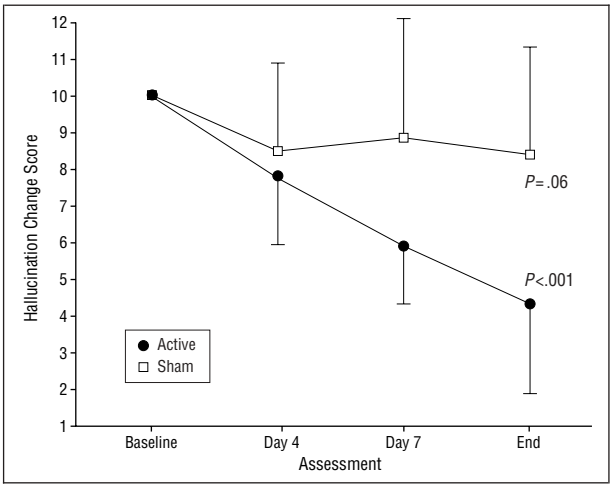

Figure 3. Hallucination Change Scale scores across the 4 assessment periods of the double-blind phase of the study. Day 4 and day 7 assessments took place just before stimulation on these days and reflected in each case the prior 24 hours. "End" assessment reflected the 24 hours immediately following the last repetitive transcranial magnetic stimulation administration. Error bars are SDs. Significance levels reflect probability that slopes are different from 0.

ATTENTIONAL SALIENCE OF HALLUCINATIONS

The attentional salience measure reflected the tendency of the patient to shift attention or respond (in thought or action) to AHs (Table 2). For this variable, there was a significant time effect ($F_{1,30.4}=8.93$, $P<.006$) and a significant time by treatment interaction ($F_{1,30.4}=8.83$, $P=.03$) in the double-blind phase of the trial. The active group demonstrated a significant linear decrease in attentional salience over time ($t_{29.7}=-3.90$, $P<.001$; 95% CI for slope, –0.26 to –0.08), while the sham group did not show a significant decrease in this scale over time ($t_{31.1}=-0.43$, $P=.66$; 95% CI for slope, –0.12 to 0.08). There was a significant time by phase interaction ($F_{1,54.1}=5.83$, $P=.02$) in the crossover arm of the trial, indicating reduced attentional salience during the nonblind active phase rela-

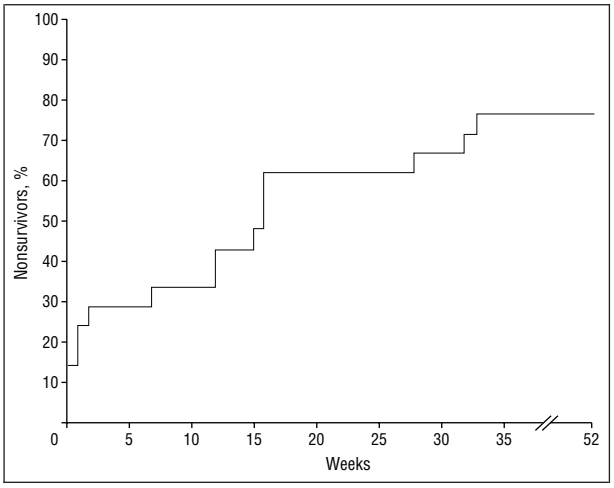

Figure 4. Survival curve is for all patients receiving active repetitive transcranial magnetic stimulation during the double-blind phase or during the open-label crossover phase (n=21) during a nonblind follow-up of 1 year. The timeline of the x-axis begins immediately after completion of the active trial for each participant. Nonsurvival was defined as a return of auditory hallucinations to at least 80% of baseline severity (ie, Hallucination Change Scale score ≥8), any increased dosage of antipsychotic medication, or any switch to another antipsychotic medication. Three of 21 patients were nonresponders and hence classified as nonsurvivors at time 0 of the follow-up, and 5 of 21 patients maintained survivor status at 1 year following the trial.

tive to the sham phase. Similar to the slope of the active group in the double-blind portion of the trial, the slope in the nonblind active phase for this measure was significantly negative ($t_{53.9}$=–3.69, P=.005; 95% CI, –0.33 to –0.10).

HALLUCINATION FREQUENCY

Hallucination frequency was assessed via 2 methods: a counter carried by the patient and a rater assessment. For the counter measure of frequency, there was a significant time effect ($F_{1,19.5}$=18.3, P<.001) and a significant time by treatment effect ($F_{1,19.5}$=5.4, P=.03) for the double-blind phase of the trial. The active group demonstrated a significant linear decrease in hallucination count over time ($t_{18.7}$=–4.69, P<.001; 95% CI for slope, –0.18 to –0.07), while the sham group did not show a significant decrease in slope over time for this measure ($t_{20.3}$=–1.37, P=.18; 95% CI for slope, –0.09 to 0.02). The time by treatment phase interaction of hallucination count also was significant for sham patients receiving subsequent nonblind active rTMS ($F_{1,54.6}$=4.1, P=.047). Similar to the slope of the active group in the double-blind portion of the trial, the slope in the nonblind active phase was significantly negative ($t_{54.9}$=–4.01, P=.002; 95% CI, –0.18 to –0.06).

For rater assessments of hallucination frequency, there was a significant time by treatment effect for hallucination frequency in the double-blind phase of the trial ($F_{1,21.6}$=7.0, P=.02) but not for the within-subject comparison of blind sham and nonblind active groups ($F_{1,30.4}$=1.35, P=.25). The active group showed a significant decrease in hallucination frequency over time ($t_{20.7}$=–4.35, P<.001; 95% CI, –0.29 to –0.10), while the control group did not show significant change over time for this variable ($t_{22.3}$=–0.47, P=.64; 95% CI, –0.11 to 0.08). The nonblind active group also showed a significant decrease over time ($t_{64.1}$=–2.06, P=.04; 95% CI, –0.15 to –0.002), although it was not significantly different from that of the sham phase.

Comparisons of other hallucination ratings (ie, loudness, number of different voices, duration of voices, or level of distress) during double-blind active rTMS vs sham stimulation did not achieve statistical significance.

PANSS RATINGS FOR DELUSIONS, NEGATIVE SYMPTOMS, AND GENERAL PSYCHOPATHOLOGIC SYMPTOMS

No significant treatment differences relative to outcome measures were observed for delusions, negative symptoms, or general psychopathologic symptoms (P>.15 for all).

CGI SCORES

Mean±SD CGI scores were 2.83±0.83 for the active double-blind group and 3.75±0.62 for the sham group, a difference that was statistically significant ($t_{20.3}$=–3.05, P=.006). The mean±SD CGI score following the open-label active phase was 2.66±1.41 (n=9). Differences between CGI scores following the sham phase vs the open-label active phase were not statistically significant (t_8=–1.90, P=.09).

INTEGRITY OF PATIENT BLIND

To assess the integrity of the blind, all patients were asked to guess the type of stimulation received after completion of the double-blind phase of the trial and to report the basis for their guess. Six patients (3 receiving active and 3 receiving sham stimulation) stated that they had no basis for guessing which type of stimulation was received. One patient receiving active guessed sham because of the absence of somatic sensation. Three patients receiving active guessed sham because of continued residual AHs. One patient receiving sham guessed active, based on improvement in AHs. Five patients correctly guessed that they received active stimulation, based on improved AHs. Eight patients correctly guessed that they received sham stimulation because of the absence of improvement in hallucinations. In no case did a patient attribute correct guessing of stimulation type to somatic sensation, adverse effects, or cues other than change in clinical symptoms.

FOLLOW-UP ASSESSMENTS

Results of follow-up assessments for up to 1 year of all patients receiving active rTMS are provided in **Figure 4**. Fifty-two percent of patients had sustained improvement at 15 weeks.

COMMENT

Our rTMS protocol seemed to be well tolerated. Headaches were mild and readily improved spontaneously or with acetaminophen. Lightheadedness lasted at most 5

to 15 minutes following rTMS. A single episode of ischemic chest pain was reported hours after rTMS was administered and was likely related to long-standing risk factors. A small number of patients reported increased AHs during the trial, but this effect seemed to be unrelated to active stimulation insofar as sham stimulation also produced these effects. It is possible that the sound of rTMS (a loud click) contributed to transient worsening of AHs. Increases in AHs and other symptoms (eg, racing thoughts) were transient and returned to baseline as soon as the rTMS session ended. In terms of pooled neuropsychological test data, there was no indication of negative effects of active rTMS on cognition. This is consistent with results of a previous study[57] of patients with focal dystonia in which 1-Hz rTMS selectively curtailed pathogenic motor cortical activation, while leaving normal motor function intact. The one exception was a patient who demonstrated a significant drop in Hopkins score following the active trial. This patient may have been exceptional insofar as the rTMS trial followed immediately a course of electroconvulsive therapy. It is possible that the latter induced cognitive impairment that rendered the patient more vulnerable to rTMS effects.

Patients as a group demonstrated robust reductions in AH severity following active rTMS relative to sham rTMS during the double-blind phase of the protocol. Patient guessing suggested that somatic experience or other events did not provide cues regarding the type of stimulation received during the double-blind phase. Improvements were detected primarily in frequency and attentional salience of hallucinations. Treatment effects endured at least 15 weeks or more for half of the patients (Figure 4). These findings extend results of the earlier study[28] to include AHs determined to be medication-resistant by specific criteria and suggest that a protocol of longer duration produced more sustained clinical improvements. Broad-spectrum clinical improvement was not detected, based on comparison of composite PANSS scores for active relative to sham stimulation. However, CGI scores suggested that active rTMS was associated with modest overall clinical improvement. Improvements during the subsequent crossover phase for patients randomized initially to sham rTMS were less robust, although in the same direction as treatment effects associated with the active stimulation during the double-blind phase. A reason for more limited crossover findings may be the lower number of patients; 3 of 12 patients did not remain in the nonblind active arm of the trial.

As indicated earlier, neuroimaging studies of patients with AHs have detected activation in different brain regions underlying speech perception.[10-15] These neuroimaging data are not necessarily inconsistent with the findings of our study (in which rTMS was delivered to a single site), because 1-Hz rTMS effects can be detected at regions distant from the direct site of stimulation, presumably mediated by functional connections.[21-23] Along these lines, left temporoparietal cortex (our site of stimulation) exchanges functional connections with temporal cortex and Broca's area during speech perception.[58] Reductions in AHs secondary to rTMS directed to temporoparietal cortex may therefore reflect effects propagated to this distributed network (see also Wassermann et al[59]).

Our study was motivated by the hypothesis that 1-Hz rTMS reduces neural excitability. Of note is that not all changes in brain activation have identical effects on AHs and other psychotic symptoms. Anticonvulsant drugs, although reducing brain activation, appear ineffective in treating AHs. Clozapine, the most potent antipsychotic available to date, is especially prone to seizure induction, thereby suggesting increased neural excitability. Additional research is needed to differentiate activation or deactivation effects of alternative somatic interventions.

This study has obvious limitations. The sample size is small, and we used sham stimulation as the control condition rather than active stimulation to another brain area. Intersubject variability in the location of language functions in the brain is known to be significant.[60] Analogously, there may be considerable intersubject variability in brain regions underlying AHs that was not considered when positioning rTMS.

In summary, our findings support the hypothesis that left temporoparietal cortex, a region critical to speech perception, participates in the generation of AHs. Data suggest that 1-Hz rTMS can be administered safely to patients with active schizophrenia and schizoaffective disorder and deserves further study as a possible treatment for patients with AHs. Future studies should examine interactions of psychotropic drugs with rTMS[28] and efficacy of extended protocols that include maintenance rTMS administration.

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