Transcranial Magnetic Stimulation of Left Temporoparietal Cortex in Three Patients Reporting Hallucinated "Voices"

Ralph E. Hoffman, Nashaat N. Boutros, Robert M. Berman, Elizabeth Roessler, Aysenil Belger, John H. Krystal, and Dennis S. Charney

Background: *Prior studies suggest that auditory hallucinations of "voices" arise from activation of speech perception areas of the cerebral cortex. Low frequency transcranial magnetic stimulation (TMS) can reduce cortical activation.*

Methods: *We have studied three schizophrenic patients reporting persistent auditory hallucinations to determine if low frequency TMS could curtail these experiences. One hertz stimulation of left temporoparietal cortex was compared with sham stimulation using a double-blind, cross-over design.*

Results: *All three patients demonstrated greater improvement in hallucination severity following active stimulation compared to sham stimulation. Two of the three patients reported near total cessation of hallucinations for ⩾ 2 weeks.*

Conclusions: *TMS may advance our understanding of the mechanism and treatment of auditory hallucinations.*
Biol Psychiatry 1999;46:130–132 © *1999 Society of Biological Psychiatry*

Key Words: Auditory hallucinations, transcranial magnetic stimulation, schizophrenia, speech processing, cerebral cortex, psychosis

Introduction

Brain regions underlying speech perception may contribute to the pathophysiology of auditory hallucinations of "voices." This hypothesis is supported by a speech processing study comparing schizophrenic patients with and without this symptom (Hoffman et al 1999), as well as a hemodynamic study demonstrating activation of various left-sided auditory/linguistic association cortical regions simultaneous with these experiences (Silbersweig et al 1995).

Extended duration (≥ 15 minutes) low frequency (~ 1 Hz) transcranial magnetic stimulation (TMS) has been shown to reduce cortical activation (Chen et al 1997; Wassermann et al 1997). One previous report suggested that TMS administered using similar parameters to right prefrontal cortex reduced symptoms of post-traumatic stress syndrome (McCann et al 1998). Our prediction was that extended duration, low frequency TMS to brain regions responsible for speech processing could curtail or interrupt auditory hallucinations (AHs).

Methods and Materials

We report below results of the first 3 patients with AHs studied using TMS in a double-blind, cross-over design. Patients provided informed consent to participate in the study and were paid $300. Patients were maintained on their psychotropic medication with no change in dose. Each patient was right-handed and had routine laboratory studies, electrocardiogram (ECG) and electroencephalogram (EEG), which were normal. DSM-IV diagnoses were established using the CASH (Andreasen 1987).

Patients were initially randomized to active or sham stimulation. Active stimulation at one hertz was administered using a CADWELL system and figure-eight coil positioned midway between the left temporal (T_3) and left parietal (P_3) EEG electrode sites. Left temporoparietal cortex plays an important role in speech perception (Fiez et al 1996). Stimulation was at 80% motor threshold. Patients were admitted to the hospital on a Friday and received 4 minutes TMS on Monday, with increases of 4 minutes each day to reach a maximum of 16 minutes on Thursday. If active TMS was administered during week I sham treatment was administered during week II and vice-versa. Stimulation for week II was initiated the following Monday through Thursday. Sham stimulation was administered at the same location, strength, and frequency with the magnet angled 45° away from the skull to induce scalp stimulation without brain stimulation. Both types of stimulation produced the sensation of "knocking" on the head, and occasionally, contractions of scalp musculature which was described as uncomfortable but not painful. Patients and clinical raters were blind regarding stimulation condition. Clinical EEGs were assessed prior to and immediately after each TMS session by a board-certified electroencephalographer (NB).

AHs were assessed using a rating scale individualized for each patient. Ten corresponded to a narrative description of the

From the Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (REH, NNB, RMB, ER, AB, JHK, DSC).
Address reprint requests to Ralph E. Hoffman, MD, Yale Psychiatric Institute, P.O. Box 208038, New Haven, CT 06520-8038.
Received July 15, 1998; revised October 20, 1998; accepted November 5, 1998.

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0006-3223/99/$20.00
PII S0006-3223(98)00358-8

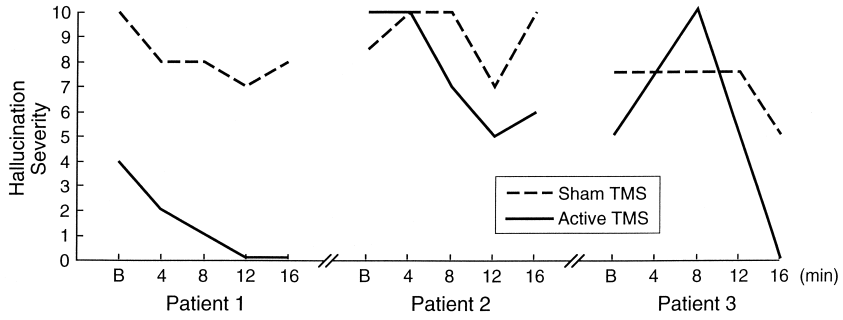

Figure 1. Hallucination severity assessed the morning following active versus sham TMS. X–axis indicates the duration of TMS, which is administered on successive days. B = baseline.

patient's voices at the time of admission to the hospital and zero corresponded to no hallucinations. Reassessments were conducted by eliciting a narrative description of current hallucinations and generating, in collaboration with the patient, a severity rating with anchor points described above. Ratings corresponded to a composite score that incorporated loudness, frequency, content, and level of distress. Following baseline assessment, patients were reassessed each morning to reflect symptom severity subsequent to the last TMS session. The PANSS was used to assess psychiatric symptoms overall.

Results

Patient #1

38-year-old African-American male with a diagnosis of paranoid schizophrenia. Patient reported a 15-year history of AHs and was poorly responsive to typical and atypical antipsychotic drugs. At the time of study entry, he had experienced AHs continuously for many months. He also reported tactile hallucinations and grandiose delusions. He had been treated with olanzapine for 9 months and at his dose at study entry was 20 mg/day.

The patient received active TMS during the first week. After 12 minutes of stimulation, the patient reported that AHs had been reduced to a meaningless "mumble." During the second sham stimulation week, and three weeks thereafter, AHs remained at this level with subsequent gradual return to baseline. The patient re–entered the study 4 months later with sham stimulation administered during the first week which was associated with some reduction in AHs (Figure 1). Further reductions in AHs to a meaningless mumble were observed after receiving 12 minutes of active stimulation (Figure 1). AHs remained at this level for 2 weeks.

Patient #2

30-year-old Caucasian female with a diagnosis of schizoaffective disorder, depressed type. She reported a 5-year history of AHs, which occurred 10–15 times/day and consisted of male and female "voices." Depressive symptoms included low mood, low energy, hopelessness and suicidal ideation. Besides depressive symptoms, the patient reported ideas of reference. Her medication regimen was risperidone 4 mg BID and sertraline 100 mg Qday.

AHs were reduced during the active stimulation week (Figure 1). Upon debriefing, the patient reported that hallucinations had largely disappeared. However, the patient continued to rate hallucination severity as moderate because she continued to talk out loud to herself, a behavior which she had previously associated with AHs. AH ratings returned roughly to baseline levels during the second, sham stimulation week (Figure 1).

Patient #3

54-year-old African-American male. His diagnosis was paranoid schizophrenia. Onset of psychosis was at age 45 with persistent AHs since that time. At study entry AHs occurred 30–50 times/day with critical and command content. He also reported visual hallucinations, grandiose delusions and episodic anxiety. His medication was haloperidol 30 mg/day. During the first sham stimulation week, AHs remained essentially unchanged (Figure 1). During the second, active stimulation week, AHs initially worsened but then ceased entirely following 16 minutes of stimulation with the exception of a meaningless acoustic "hum." AHs returned to baseline levels after 7 weeks (Figure 1).

No significant complications due to TMS were observed. EEGs were normal at baseline and after each TMS. Modest improvements in PANSS scores were observed for other symptoms following both active and sham stimulation.

Discussion

To summarize, AH improvement was greater following active stimulation compared to sham stimulation for all 3 patients; 2 of these patients demonstrated near total elimination of this symptom for $\geq$ 2 weeks following active stimulation.

It is noteworthy that some improvement was detected

following sham stimulation. Placebo and effects of hospitalization are likely to have contributed, at least in part, to these clinical changes. Moreover, it is possible that sham treatment was in fact partially active due to residual magnetic field penetration arising from the 45° angle of the coil.

Active stimulation may have produced more intense physical sensations relative to sham stimulation which reduced effectiveness of sham control stimulation. When questioned at the end of the study, all 3 patients successfully "guessed" which stimulation was active, although "guessing" was based not on physical sensation of stimulation but the degree to which hallucinations improved. One approach for dealing with this difficulty would have been to use an active stimulation control condition directed at another part of the brain. This approach, however, would have added another level of complexity since it is not clear which cortical circuits could be stimulated which are not involved in schizophrenia. Moreover, an additional risk would have been incurred due to exposure of active TMS at another site. For this preliminary study, we therefore, chose to use sham stimulation as the "placebo control," which is currently the standard for assessing TMS treatments.

One possible reason for the variable response to TMS for the three subjects is suggested by the Silbersweig et al (1995) study. They reported considerable inter-subject variability in the location of neocortical activation associated with AHs, whereas deeper brain regions (e.g., thalamus and limbic cortex) demonstrated more uniform activation. The latter brain regions are not accessible to TMS except indirectly via stimulation by association cortex. Consequently, TMS, which was administered at a single site based on EEG coordinates alone, probably varied in the degree to which brain regions activated during AHs were accessed.

Although our findings are very preliminary, they suggest that TMS offers new tools for understanding the mechanism and treatment of positive symptoms in schizophrenia.

Research supported by NIMH grant MH–50557, NIH/NCRR/GCRC Program Grant RR00125, the Chrysalis Fund, and the State of Connecticut.

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