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TRANSCRANIAL MAGNETIC STIMULATION OF WERNICKE'S AND RIGHT HOMOLOGOUS SITES TO CURTAIL "VOICES:" A RANDOMIZED TRIAL

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Abstract

BACKGROUND—Auditory/verbal hallucinations (AVHs) are accompanied by activation in Wernicke's and right homologous regions. Efficacy in curtailing AVHs via 1-hertz repetitive magnetic stimulation (rTMS) targeting a site in each region ("W" and "rW") was therefore studied.

METHODS—Patients with schizophrenia and AVHs (N=83) were randomly allocated to double-masked rTMS versus sham stimulation, with blocks of 5 sessions given to W and rW in random order, followed by 5 sessions to the site yielding greater improvement. The primary outcome measure was Hallucination Change Score (HCS). Hallucination frequency, total auditory hallucination rating scale score, and clinical global improvement (CGI) were secondary outcome measures. Attentional salience of AVHs and neuropsychological measures of laterality were studied as predictors of site-specific response.

RESULTS—After 15 sessions, rTMS produced significant improvements relative to sham stimulation for hallucination frequency and CGI, but not for HCS. After limiting analyses to patients whose motor threshold was detected consistently: (i) endpoint HCS demonstrated significantly greater improvement for rTMS compared to sham stimulation; (ii) for high salience AVHs, rTMS to rW after the first five sessions yielded significantly improved HCS scores relative to sham stimulation, while, for low salience AVHs, rTMS to W produced this finding. Nondominant motor impairment correlated positively with hallucination improvement following rW rTMS.

CONCLUSIONS—One-hertz rTMS per our site-optimization protocol produced some clinical benefit in patients with persistent AVHs as a group, especially when motor threshold was

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consistently detected. Level of hallucination salience may usefully guide selection of W versus rW as intervention sites.

Keywords

auditory verbal hallucinations; schizophrenia; transcranial magnetic stimulation; Wernicke's area; salience; sham stimulation

INTRODUCTION

Auditory/verbal hallucinations (AVHs) occur in 60–80% of persons with schizophrenia and often produce high levels of distress, functional disability and behavioral dyscontrol (1–3). Insofar as these hallucinations respond poorly to treatment in approximately 25% of cases (4), more effective interventions are needed.

One-hertz (1-Hz) repetitive transcranial magnetic stimulation (rTMS) reduces excitability in the brain region stimulated (5). Two studies by our group demonstrated efficacy of 1-Hz rTMS compared to sham stimulation for persistent AVHs delivered to a left temporoparietal site (6,7) implicated in their genesis by an early positron emission tomography study (8). Other trials utilizing similar rTMS protocols for AVHs yielded mixed results with two recent negative trials (9–18). The latest meta-analyses of these trials found significant efficacy relative to sham stimulation, even when factoring in negative publication bias, but in a range suggesting that further optimization of this intervention is needed (19–21).

The majority of rTMS trials for AVHs have used the left temporoparietal (TP3) site derived from the International Federation 10/20 electrode system to position the stimulation coil. This positioning method relies on head surface landmarks only (22), yielding diverse cortical locations across subjects (23). Functional magnetic resonance imaging (fMRI) studies have linked AVHs with activation in Wernicke's area anterior to the TP3 site, and in homologous right temporal sites (24–27). Both these regions activate during external speech processing (28). Right temporal regions have been implicated in acoustic processing of voice characteristics (29), detecting speaker identity based on acoustic signature (30) and ascertaining speaker intentionality (31). Insofar as AVHs in schizophrenia typically are experienced as having acoustic features suggesting specific nonself speakers and alien intentionality (32,33), right temporal regions are likely involved in their genesis.

We consequently conducted a sham-controlled trial where responses to stimulation targeting a Wernicke's site and a site in the right homologous region was compared, followed by additional stimulation to the site appearing to produce greater improvement. The two target sites were extrapolated from a previous study of patients with AVHs where rTMS was positioned using fMRI activation maps of hallucination events and functional connectivity maps (34). Objectives of the trial reported here were to: (i) assess endpoint efficacy of rTMS using this site-optimization protocol to reduce AVHs; (ii) determine site-specific responses to rTMS in hallucinators; (iii) assess whether neuropsychological measures of laterality predict site-specific response; (iv) estimate duration of rTMS effects. An fMRI study conducted in parallel by our group (26) showed that level of activation in the right homologue of Wernicke's area immediately after AVH onset was highly correlated with their attentional salience (r=0.78, unpublished data). Thus, attentional salience ratings appear to provide an experiential indicator of level of activation in this region during hallucinosis. High salience AVHs were therefore predicted to be more responsive to rTMS delivered to the right Wernicke's site, which guided our site-specific analyses of outcome.

METHODS AND MATERIALS

Patient enrollment decided by REH required a diagnosis of schizophrenia or schizoaffective disorder per the Structural Clinical Interview for DSM-IV, Version 2.0 (35), with AVHs experienced on average ≥5 times per day per written log or mechanical counter. Other inclusion criteria were: (i) ages 18–55, (ii) estimated intelligence quotient >85, (iii) ability to clearly differentiate AVHs from spontaneous verbal thoughts (33). Exclusion criteria included: (i) prior rTMS, (ii) history of drug or alcohol dependence, (iii) seizures not caused by medication or medication withdrawal, (iii) unstable medical condition. Two hundred forty-nine patients were screened, with 92 accepted for enrollment (Table S1 in the Supplement). All participants remained on their psychotropic medication at steady dosages for ≥4 weeks immediately prior to and during the trial. Drug/alcohol abusers needed to fully abstain for ≥4 weeks prior to trial initiation. All subjects were right-handed. Written informed consent was obtained in all cases, with capacity established using the MacArthur Competence Assessment Tool (36). All subjects had a physical/neurological examination, routine laboratory studies, drug toxicology, electrocardiogram, and serum pregnancy test if female. Enrollment for the trial was 3/2006–10/2011 ending with completion of funding.

rTMS site determination

Each patient underwent a high resolution structural MRI scan that was downloaded to a BrainLab Neuronavigation system (Brainlab AG, Feldkirchen, Germany). Using this system, the scalp was marked overlying two sites, one over Wernicke's area (hereafter "W"), the other over the right homologue (hereafter "rW") with Talairach coordinates (37) consisting of (−65,−41,9) and (+65,−38,11), both extrapolated from results of a prior study of hallucinating patients where rTMS targeted multiple sites per fMRI maps (34, supplement). Scalp-to-cortical-surface distance was ascertained for these two sites and for left/right motor cortex in the hand/finger area. Scalp sites were measured relative to ear pinna anatomy so that they could be reproduced reliably during the trial.

rTMS protocol

Participants underwent stratified randomization (38) to active/sham (2:1 ratio) with W versus rW as initial sites (1:1 ratio). Stratification utilized a cut-off score ≥5 for the hallucination frequency variable of the auditory hallucination rating scale (AHRS, ref. 39), which was a statistical moderator of rTMS efficacy in our earlier trial (7). Randomizations were generated by BP using Random Allocation Software (40) with random block sizes (3, 6, and 9) to ensure non-predictability and balanced samples for the two strata. Randomization was concealed in sequenced/frequency-coded sealed envelopes opened by REH immediately prior to the first stimulation session. Participants, care-providers, assessors and all personnel other than the rTMS operators remained blind to allocation until unmasking after session 15.

1-Hz stimulation was administered using a MAGSTIM Rapid-2 system (Magstim Ltd, Whitland, Wales) and air-cooled figure-8 coil stabilized with a stand while the subject was seated in a reclining, head-supported chair. Sham stimulation was administered at the same location/strength angling the coil 45° off the head using a single-wing tilt. This method reproduces sound and somatic sensation (e.g., contraction of scalp muscles) resembling active stimulation, with intracerebral voltages ~1/3 that of active TMS (41). This sham method was utilized to ensure that patients remained masked; other sham methods (e.g., active coil angled 90 degrees off the scalp or a sham coil) produce less somatic sensation. Stimulation strength was 90% motor threshold with upward adjustments if scalp-to-cortex distance for the target site was greater than that for the ipsilateral motor cortex (for algorithm see supplement).

Patients received 16 minutes (960 pulses) of active/sham stimulation per session for 5 sessions to W or rW. The site was then switched to the opposite hemisphere for 5 additional sessions. A third block of 5 stimulation sessions was delivered to the site associated with greater percent improvement in AVHs per the Hallucination Change Score (see below for definition). If no site produced greater HCS improvement, stimulation returned to W. Patients were unmasked following clinical assessment 24 hours after completion of the third 5-session block; patients randomized to the active group were offered 5 more rTMS sessions; patients randomized to the sham group were offered unmasked rTMS following the same schedule. Five weekday sessions per week were administered. To recoup sessions occasionally missed by patients, morning and afternoon sessions were given on a subsequent day.

Clinical assessments

Clinical assessments were conducted at baseline and after each 5-session block of stimulations under double-masked conditions: the patient, symptom raters, clinical staff and all individuals other than the TMS administrator did not know group allocation. The time-window of these assessments were 24 hours. The Hallucination Change Scale (HCS, ref. 39) was used as the primary outcome measure; at baseline, the participant generated a narrative description of his/her AVHs assigned a score of 10. HCS was scored subsequently by the assessor after requesting the participant to generate a new narrative description of AVHs over the previous 24 hours that was compared with the baseline narrative. HCS was anchored at 0 (corresponding to no AVHs), 10 (no change in hallucination severity) and 20 (AVHs twice as severe as baseline). Secondary outcome measures were Clinical Global Impression (CGI, ref. 42) to assess overall clinical improvement, the hallucination frequency subscale of the 7-item AHRS (39) and the sum of all 7 items of this scale, which, besides frequency, assessed number of distinct speaking voices, perceived loudness, realness, attentional salience (the degree to which hallucinations capture attention and alter on-going thought and behavior), length of hallucination instances, and induced distress. Interrater reliabilities for the seven variables have been shown to be high, with inter-reliability for hallucination frequency and attentional salience, the two variables considered separately in this study, 0.98 and 0.87, respectively (39). Symptoms were also assessed using the Positive and Negative Syndrome Scale (PANSS; ref. 43). At baseline, 2 laterality tasks were administered: (i) a dichotic listening task (44) showing that reduced left laterality was linked with AVH vulnerability in schizophrenia; (ii) right-left grooved pegboard difference (45), which, in our earlier study (34) showed that reduced left dominance was a negative predictor of rTMS response delivered to Wernicke's sites (r=−0.61, unpublished data).

To gauge success of masking, patients were asked after the first and 15th session (prior to unblinding) to "guess" whether active versus sham stimulation was received and provide their rationale for guessing.

Ninety patients were targeted for enrollment based on a 0.80 estimate of statistical power to detect group differences in HCS for rTMS versus sham delivered to W for the first 5 sessions and at endpoint following stimulation to both sites (see supplement).

Prior to each stimulation session, side-effects were reviewed and motor threshold ascertained over the ipsilateral motor cortex. Hopkins verbal memory and letter-numbers working tasks (46,47) given at baseline and after the 3rd, 8th and 13th session to screen for worsening cognitive impairments. A full neuropsychological test battery was administered at baseline and during the third stimulation block.

Telephone contact was maintained with patients following the trial to determine duration of rTMS effects, with survivorship defined as maintaining HCS<8.

Data analysis

For endpoint analyses at the 15-session juncture, 5 subjects (6%) had dropped out and had missing data on all outcomes. Thus, multiple imputation (MI) was employed (48). The four outcomes (change from baseline) were analyzed, in turn, using an ANOVA model with group and “best site” as between-subject factors.

Correlational analyses of HCS response to rTMS targeting W and rW after the first 5 sessions prior to crossing over to the other site were repeated for the two neuropsychological measures of laterality. Comparisons of correlations with the sham condition were undertaken to ascertain specificity of findings.

The relative utility of W versus rW as sites for rTMS when attempting to curtail AVHs was assessed. Guided by our fMRI activation study (26) of AVHs, correlations between baseline attentional salience and rTMS response to rW and W were assessed and found to be significant in positive and negative directions, respectively. Consequently, a dichotomized salience factor was incorporated post hoc into our statistical model. This factor was defined as follows: “high” = patients who mostly or always had to pay attention to their AVHs (scored as ≥4 per the AHRS attentional salience variable at baseline); “low” = patients who, at most, were only briefly distracted by their AVHs (<4 for this salience variable). A linear mixed model was then employed to characterize rTMS response over the first two 5-session blocks (i.e., while subjects were under randomization) which included between-subjects factor of group (active vs. sham) and salience (low vs. high) and within-subject factors of site (W vs. rW) and time (1 vs. 2). All multi-way interactions were modeled. The mixed model approach is advantageous as it is unaffected by data missing at random (one subject (1%) had missing HCS data at time 2) and allows greater flexibility in modeling the correlation structure of repeated measures data (49). For the sake of parsimony, this analysis was limited to the primary outcome measure, HCS.

A subgroup of patients required power that at times exceeded device capacity when assessing motor thresholds. These instances of motor threshold non-detection indicated that full-dose, active rTMS was not delivered. Moreover, sham stimulation will tend to be at higher power for these patients. Our sham method has been shown to produce active stimulation at approximately one-third strength (41). Thus, for patients with motor threshold non-detection, elevated covert clinical efficacy could arise from sham stimulation. Consequently, the analysis of HCS response after 5 and 10 sessions, as well as endpoint analyses for all four outcome variables, were repeated for patients limited to those demonstrating consistent detection of motor threshold throughout the masked trial.

All statistical tests were 2-tailed.

RESULTS

Out of the 92 enrolled patients, 7 were dropped prior to trial initiation due to: inability to complete MRI scanning due to anxiety reaction or inability to fit into the scanner (3); clinical instability (2); positive toxicology screen (1); remission of AVHs following supervised medication compliance (1). One patient was unable to tolerate any rTMS to the target site due to discomfort. One patient was dropped due to disclosure that hallucination reports were greatly exaggerated to gain study entrance, and evidence that motor threshold responses were feigned. Eighty-three patients remained (Table 1 for baseline characteristics). Three sham patients were removed from the trial or ended participation prematurely due to worsening paranoia or non-response. Two rTMS patients dropped out due to early remission of AVHs. Two patients were removed from the trial during the fourth, 5-session block of rTMS. The first demonstrated a large drop in the Hopkins Verbal

Memory task, but he denied any subjective complaints and refused repeat neuropsychological testing. The second reported concentration difficulties for approximately one week; a follow-up neuropsychological battery did not reveal worsening performance.

Aggregate neuropsychological data did not reveal any significant alterations, either improvements or declines, when contrasting rTMS with sham stimulation.

Endpoint analysis for the four outcome variables

Analyzing the four outcome variables after 15 stimulation sessions revealed hallucination frequency and CGI to be significantly improved following rTMS relative to sham stimulation (Table 2). When repeating these analyses limited to those patients (N=69) demonstrating consistently detectable motor thresholds during the masked trial, HCS also demonstrated significant improvement for rTMS relative to sham stimulation (Table 3). A post hoc analysis of total PANSS scores in this cohort revealed significant improvement for rTMS compared to sham (p=0.04) consistent with CGI findings. Total AHRS did not demonstrate significant improvement for active relative to sham stimulation for the full or reduced cohort.

Patient guesses regarding whether they received real versus sham stimulation revealed that somatic sensation did not play a significant role in correct guessing (Table S2 in the Supplement).

Correlating site-specific HCS response to rTMS after 5-sessions

Considering laterality measures, right-left pegboard performance time-to-completion difference was significantly correlated with HCS response to rTMS delivered to rW after 5 sessions (Spearman-rank rho=0.39, p=0.035). This correlation was also significant and positive for patients in sham group (Spearman-rank rho=0.60, p=0.022). These findings reflected elevated non-dominant pegboard time-to-completion primarily; correlations with this variable and rW TMS response were similar for the two groups (for active, rho= 0.41, p=0.026, for sham, rho=0.63, p=0.017). Correlations between dichotic listening task laterality and responses to both W and rW rTMS after 5 sessions were non-significant.

Baseline salience of AVHs was positively correlated with HCS response for rW rTMS (r=0.42, p=.025), and was negatively correlated with HCS response delivered to W (r = −0.54, p=0.004). This correlation difference was highly significant after r-to-z transformation (p=0.0003). A near-identical correlation between HCS response and sham stimulation to rW was detected, although not significant due to smaller N (r=0.43, p=.11). The correlation between HCS response and sham stimulation delivered to W was near zero (r=0.04).

HCS response for first and second blocks of rTMS/sham stimulation

In the analysis of HCS after the first two blocks of 5 sessions, a significant 4-way interaction (group x salience x site x time) was observed (F(1,79)= 6.25, p= 0.015). This finding corresponded to significant improvement, relative to sham, for low salience hallucinations after the first 5 sessions of rTMS targeting W (F(1,79)=4.94, p=0.029) and again, for these same patients, when rW was targeted for the second block of 5 stimulation sessions (F(1,79)=4.96, p=0.029; table 4). No other factorial combination achieved statistical significance.

Repeating this analysis limited to patients for whom motor threshold was consistently detected, a significant 4-way interaction (F(1,65)=5.49, p=0.022) was again detected. Again, after the first 5 sessions targeting W, rTMS for low salience AVHs produced HCS scores

that were significantly more improved compared to sham ($F(1,65)=4.62$, $p=0.035$). For high salience hallucinators, targeting rW produced significantly greater HCS improvement for rTMS relative to sham ($F(1,65)=5.01$, $p=0.029$) during the first 5 sessions (table 5). No group differences were observed during the second block of sessions in this cohort.

Outcomes beyond the 15-session masked phase

For patients allocated to the sham group, rTMS was offered after unmasking. Comparing symptoms at baseline and after 15 sessions for the 18 patients in this trial arm revealed statistically significant improvements for HCS and CGI, but not for total AHRS score and hallucination frequency (Table S3 in the Supplement).

Extending active rTMS from 15 sessions to 20 sessions produced statistically significant improvements for all four outcome variables (Table S4 in the Supplement).

For all patients receiving rTMS (masked and unmasked) who provided follow-up data (N=72), mean±SD survivorship was 17.5±19.3 weeks. 31.6% of patients retained survivorship at 24 weeks. For those patients achieving an HCS score <8 after the 15th rTMS session, survivorship was 23.8±18.7 weeks. Two patients with severe, treatment-resistant AVHs who did not show significant improvement immediately after active rTMS went into full remission within 4 weeks of the trial with no change in medication; these two patients were followed as survivors.

DISCUSSION

For this W/rW site-optimization trial, endpoint hallucination severity per HCS, our primary outcome variable, did not demonstrate a significant effect differentiating active and sham conditions, nor did total AHRS score. However, this protocol did demonstrate statistically significant endpoint efficacy for the other two outcome variables, hallucination frequency and CGI, relative to sham. Assessments of hallucination frequency are the most objective of all the AHRS variables; our 24-hour counts were often augmented by a mechanical counter carried by the patients. It is therefore likely that hallucination frequency is the more sensitive index of change in AVHs. Improved CGI scores suggest overall improvement in clinical well-being.

After limiting patients to those whose motor thresholds were consistently detected across sessions, significant efficacy per HCS for rTMS emerged in this study relative to sham stimulation suggesting overall improvement in AVHs attributable to the active condition. It is noteworthy, comparing tables 2 and 3, that this shift reflected a reduction in sham response rather than improved active responses. One explanation for this trend is suggested by the fact that our method of sham stimulation (45° single-wing tilt) is equivalent to low dose active stimulation (41). Thus, motor threshold non-detection in sham patients would increase power of stimulation delivered, which could in turn amplify covert active effects and improve AVHs.

In terms of site-specific effects, a positive correlation between nondominant pegboard time-to-complete and rTMS response delivered to rW was observed. This finding suggests that nondominant hemisphere dysfunction involving motor coordination is associated with nondominant disturbances producing AVHs responsive to rTMS delivered to rW. It is noteworthy that the correlation between nondominant pegboard speed and rTMS response to rW was also significant in the sham group, suggesting a physiological mechanism not obviously accounted for by a placebo effect. Along similar lines, near identical correlations between baseline attentional salience of hallucinations and HCS improvement elicited by rW stimulation was detected for active and sham conditions It is difficult to attribute these

correlations relative to rW clinical response to a placebo response alone, suggesting again that sham stimulation had some active effect.

Low-salience hallucinators preferentially responded to rTMS delivered to W. The significance of this finding in uncertain since the number of patients in this cell was very small (3 received sham and 6 received active stimulation). One interpretation of these findings is that low attentional salience AVHs reflect activation in left temporal sites primarily, allowing rTMS delivered to W to achieve greater efficacy. Targeting rW produced greater HCS improvement relative to sham stimulation for high salience hallucinators in patients with consistent motor threshold detection. This finding suggests nondominant pathophysiology for this subgroup that is more responsive to rTMS delivered to rW.

For sham patients crossing over to open-label active rTMS, significant improvements after 15 open-active sessions were demonstrated for 2/4 outcome variables (HCS and CGI; Table S3 in the Supplement). It is noteworthy, however, that endpoint HCS, change in hallucination frequency, and CGI for this group were inferior to outcomes for the masked active group. The likely explanation is that patients in the former group already achieved significant improvements, relative to their own baselines, during the sham phase, thereby shifting baseline for the open, active phase, so that change scores after the active protocol were less pronounced.

Other bilateral rTMS trials for AVHs have targeted the more posterior TP3 site plus its right homologue (TP4 based on head landmarks rather than structural MRI). Lee et al. (10), using a 10-session parallel-design protocol, found that both TP3 and TP4 elicited greater overall clinical improvement per CGI scores for rTMS compared to sham, suggestive of our CGI results. However, no hallucination index differentiated active and sham groups. Jandl et al (11), who targeted these sites for 5 sessions each using a crossover design with sham control, did not detect an overall significant group effect. Vercammen et al. (16) reported a study where twice daily sessions for six sessions were administered comparing bilateral TP3/TP4 rTMS (given to each site for ½ sessions) versus left temporoparietal rTMS and sham stimulation; left temporoparietal rTMS was most effective in reducing AVHs, but results were not significantly better than sham. These reports have not clearly established any advantage of bilateral stimulation compared to unilateral stimulation.

An open-label study of 11 patients with AVHs, which employed 20 Hz rTMS over two days while targeting an fMRI-delineated left posterior temporal area, produced robust improvements in total AHRS exceeding those reported in this study (50). Two case studies, where theta burst stimulation was administered, showed improved AVHs, and, in the second case, improved cognition (51,52). These findings indicate the need for sham-controlled trials utilizing higher frequency stimulation.

Our study had multiple limitations. First, switching sites may have obscured site-specific response to rTMS and reverse clinical effects. Along these lines, some studies have shown that 1-Hz rTMS to language areas produces activating effects in the opposite hemisphere (53–55) that could interfere with local, suppressive effects of rTMS achieved during other phases of the protocol. Second, exposure of rTMS to a single site during the masked phase was limited to 5 or 10 sessions. TMS trials for major depression suggest the need for more sessions to achieve maximum efficacy, a view suggested also by data from our unmasked extension phase (Table S4 in the Supplement). Third, evidence suggested that sham stimulation had some active effects that could diminish group differences. Assessing efficacy of rTMS for AVHs would be enhanced by a sham methodology that fully eliminates brain stimulation while generating significant levels of somatic stimulation to

ensure integrity of masking; one such approach has been described (57). Fourth, positioning was via structural MRI alone. This protocol choice was made because structural positioning is more straightforward than functional neuroimaging approaches and more likely to be implemented at other centers. However, rTMS positioned using patient-specific functional maps may yield better results (34,50) although one such study was negative (18).

In summary, our data suggest some clinical improvement associated with active rTMS using a bilateral site-optimization protocol, especially when analyses where limited to patients for whom motor threshold was consistently detected. However, effect sizes were reduced relative to our prior trial (7). Our results suggest that attentional salience of AVHs may usefully guide positioning of rTMS over W versus rW sites for therapeutic intervention; this would obviate the need for a crossover phase to identify optimal site. Larger number of sessions then could be delivered to a one site, possibly yielding better outcomes. Sham stimulation methods that block direct brain stimulation while producing significant somatic sensation are indicated. Consistent success in ascertaining motor threshold may identify those patients who demonstrate effects specific to the active intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Subject characteristics

	Active (n= 55)	Sham (n=28)	$t_{(81)}$ or $\times^2_{(1)}$, (p)
Age	36.7 (11.0)	34.0 (10.0)	1.1 (.26)
Gender (F/M)	29/26	15/13	.01 (.94)
Education (yrs)	13.6 (2.4)	14.0 (2.3)	.71 (.48)
# psych hospitalizations	7.65 (8.51)	6.32 (7.58)	.70 (.49)
Age first AH	22.9 (7.67)	21.9 (9.54)	.55 (.58)
Chlorpromazine equivalent antipsychotic medication	514 (477)	686 (670)	1.3 (.18)
High/low frequency AVHs[1]	32/23	16/12	.01 (.93)

[1] per stratification described in methods

Table 2

Endpoint analyses of outcome variables (following 15 sessions)[1]

Outcome variable	mean (standard error)[4]		$P_{Group\ effect}$	Estimated effect size (95% CI)
	Sham N=28	Active N=55		
HCS[2] (primary)	7.78 (0.67)	6.38 (0.47)	0.09	0.40
Hallucination frequency difference[3]	−0.26 (0.31)	−1.32 (0.22)	0.005	0.65 (0.19 – 1.11)
Total AHRS Difference[3]	−2.78 (1.2)	−4.58 (0.85)	0.22	0.28
CGI[2]	3.31 (0.25)	2.70 (0.17)	0.045	0.47 (0.01 – 0.93)

[1]Model includes group and site (W versus rW, corresponding to optimal response); based on data collected after the third 5-session block, with multiple imputations used for missing data

[2]Lower scores correspond to greater improvement; all HCS were 10 at baseline; no baseline for CGI, scores range from 1 to 7, with 4 = no change.

[3]Difference = baseline − endpoint; lower scores correspond to greater improvement

[4]Model-based least-square means and standard errors

Table 3

Endpoint analyses of outcome variables (following 15 sessions) eliminating patients for whom motor threshold could not be consistently detected[1]

Outcome variable	mean (standard error)[4]		$P_{Group\ effect}$	Estimated effect size (95% CI)[5]
	Sham N=21	Active N=48		
HCS[2] (primary)	8.37 (0.76)	6.55 (0.48)	0.044	0.54 (0.02 – 1.06)
Hallucination frequency difference[3]	−0.06 (0.37)	−1.31 (0.24)	0.005	0.74 (0.23 – 1.26)
Total AHRS Difference[3]	−1.90 (1.16)	−4.11 (0.76)	0.11	0.42
CGI[2]	3.58 (0.29)	2.73 (0.18)	0.013	0.67 (0.14 – 1.18)

[1] Model includes group and site (W versus rW, corresponding to optimal response); based on data collected after the third 5-session block, with multiple imputations used for missing data

[2] Lower scores correspond to greater improvement; all HCS were 10 at baseline; no baseline for CGI, scores range from 1 to 7, with 4 = no change.

[3] Difference = baseline − endpoint; lower scores correspond to greater improvement

[4] Model-based least-square means and standard errors

[5] 95% confidence intervals provided for comparisons with $p < 0.05$

Table 4

Site-specific HCS for low-salience hallucinators[1]

	1st 5-session block (week 1)	2nd 5-session block (week 2)
Active to W[2]	**6 (1.00), n=6**	8.39 (1.02), n=9
Active to rW[3]	9 (0.81), n=9	**4 (1.25), n=6**
Sham to W	**9.83 (1.41), n=3**	9.2 (1.37), n=5
Sham to rW	9.1 (1.09), n=5	**8.83 (1.77), n=3**

[1]Model-based least-square means and standard errors; model included group, site, salience, and time as factors; group by site by salience by time interaction (p=0.015); site-crossing after the first 5 session block, W→rW and rW→W

[2]Difference (post-hoc) between active and sham targeting W, week 1 significant (p=0.035)

[3]Difference (post-hoc) between active and sham targeting rW, week 2 significant (p=0.029), suggesting a site-order effect since rW→W did not produce a similar active/sham difference

Table 5

Site-specific HCS for high-salience hallucinators considering patients for whom motor threshold consistently detected[1]

	1st 5-session block (week 1)	2nd 5-session block (week 2)
Active to W	9.38 (0.57), n=17	6.71 (0.728), n=17
Active to rW[2]	**6.91 (0.57), n=17**	8.32 (0.728), n=17
Sham to W	8.36 (0.89), n=7	8.58 (1.20), n=6
Sham to rW	**9.29 (0.89), n=7**	7.07 (1.13), n=7

[1] Model-based least-square means and standard errors; model included group, site, salience, and time as factors; group by site by salience by time interaction (p=0.022); site-crossing after the first 5 session block, W→rW and rW→W

[2] Difference between active and sham targeting rW, week 1, significant (p=0.029)