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Active and placebo transcranial magnetic stimulation effects on external and internal auditory hallucinations of schizophrenia

Paillère-Martinot M-L, Galinowski A, Plaze M, Andoh J, Bartrés-Faz D, Bellivier F, Lefaucheur J-P, Rivière D, Gallarda T, Martinot J-L, Artiges E. Active and placebo transcranial magnetic stimulation effects on external and internal auditory hallucinations of schizophrenia.

Objective: Repetitive transcranial magnetic stimulation (rTMS) over the left temporo-parietal region has been proposed as a treatment for resistant auditory verbal hallucinations (AVH), but which patients are more likely to benefit from rTMS is still unclear. This study sought to assess the effects of rTMS on AVH, with a focus on hallucination phenomenology.
Method: Twenty-seven patients with schizophrenia and medication-resistant AVH participated to a randomized, double-blind, placebo-controlled, add-on rTMS study. The stimulation targeted a language-perception area individually determined using functional magnetic resonance imaging and a language recognition task. AVH were assessed using the hallucination subscale of the Scale for the Assessment of Positive Symptoms (SAPS). The spatial location of AVH was assessed using the Psychotic Symptom Rating Scales.
Results: A significant improvement in SAPS hallucination subscale score was observed in both actively treated and placebo-treated groups with no difference between both modalities. Patients with external AVH were significantly more improved than patients with internal AVH, with both modalities.
Conclusions: A marked placebo effect of rTMS was observed in patients with resistant AVH. Patients with prominent external AVH may be more likely to benefit from both active and placebo interventions. Cortical effects related to non-magnetic stimulation of the auditory cortex are suggested.

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Key words: auditory hallucinations; functional magnetic resonance imaging; randomized placebo-controlled trial; repetitive transcranial magnetic stimulation; schizophrenia

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Significant outcomes

- Both active and placebo repetitive transcranial magnetic stimulations were effective in significantly decreasing treatment-resistant auditory hallucinations.
- External auditory hallucinations were dramatically improved with both active and placebo rTMS. Internal auditory hallucinations were also improved with both rTMS modalities, but to a lesser extent.
- The results raise the issue of rTMS effects related to non-magnetic stimulation of the auditory cortex.

Limitations

- The clinical heterogeneity of the patients might have blurred the rTMS effects, as the patients with internal hallucinations had higher hallucination scores than those with external ones on some ratings.
- It was not possible to follow up the patients after the trial, and thus, there is no information on how stable the improvement was in the middle term or long-term.

Introduction

Auditory verbal hallucinations (AVH) have been associated with increased activity of brain regions implicated in speech perception and language processing, notably the left temporo-parietal area (1, 2). Low-frequency repetitive transcranial magnetic stimulation (1-Hz rTMS) has been shown to be effective in reducing cerebral cortex activity (3) and, as such, has been proposed as a potential treatment for AVH (4). Subsequently, a number of studies have tested 1-Hz rTMS over the temporo-parietal area and have yielded inconclusive results, with meta-analyses showing positive effects of active rTMS over sham stimulation (5–7), yet a number of sham-controlled studies reporting no difference between active and sham rTMS (8–15), including studies using bilateral low-frequency (16), high-frequency (17), deep TMS (18) or priming stimulation (19). In a recent review of rTMS studies for AVH, Slotema et al. (7) reported moderate effects of rTMS in treating AVH, including medication-resistant ones. However, the best effect size was found when rTMS was applied at 1 Hz frequency targeting the left temporo-parietal area. In another study, it was suggested that higher resting-brain perfusion measured using magnetic resonance imaging (MRI) and arterial spin labelling in the left superior temporal gyrus might predict better response to rTMS (20). Thus, so far, it is unclear which stimulation parameters (e.g. number of pulses, coil type, duration, target location) would be optimal, and also which patients are likely to benefit best from rTMS. Studies of rTMS on AVH have included clinically different patients, and particularly, no study has differentiated the AVH according to their spatial characteristics (internal vs. external) and tested the effects of rTMS accordingly. Inner-space (internal) AVH have recently been reported to be more distressing, less controllable and long-lasting than outer-space (external) AVH (21). In a previous study, we identified variations in the temporal–parietal junction (TPJ) anatomy that were related to the spatial location of AVH in outer or inner space (22).

It has been suggested that AVH and external speech perception might directly 'compete' for the same neural substrates within the temporal cortex (23–25), consistent with reports showing that AVH could be reduced by different types of auditory stimulation (26). Most of the rTMS studies have empirically applied the TMS coil midway between left temporal (T3) and left parietal (P3) areas, by placing the TMS coil 5 cm behind the motor cortex target (4). However, the anatomical limits of the targeted temporo-parietal posterior language region are not clearly defined and vary across patients (1). Few studies have used neuronavigation and functional MRI (fMRI) to target this region, with open studies reporting significant decreases in AVH (27–29), and placebo-controlled protocols showing decreases but no difference between modalities (8, 15).

Several brain regions involved both in language processing and in AVH, including the posterior parts of the superior and middle temporal gyri, the temporal pole, the inferior parietal gyrus and the inferior frontal gyrus, can be activated using a language recognition task (30). In addition, using such task and fMRI-guided TMS, language modulations have previously been reported (31).

Aims of the study

In this study, we designed a 10-session protocol to search for effectiveness of active vs. placebo low-frequency rTMS in resistant AVH in patients with schizophrenia, using fMRI and the previously used language recognition task to determine individual temporal targets. Furthermore, we investigated whether rTMS might have differential effects depending on the outer- or inner-space type of AVH.

Material and methods

The investigation was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee Ile-de-France 6, Paris (approval no. 111-01). Written informed consent

was obtained from all participants after complete description of the study.

Participants

Twenty-eight patients (15 men) who met the criteria for a diagnosis of schizophrenia according to a checklist of DSM-IV-TR criteria (n = 6, undifferentiated subtype; n = 18, paranoid) or schizoaffective disorder (n = 4) were consecutively recruited by senior psychiatrists from three out-patient clinics at university psychiatry departments. No financial incentives were proposed. The patients were screened for daily AVH for at least 3 months as assessed by interviews of the patients and their psychiatrists, and examination of the medical records, and were required to be resistant to at least two trials of antipsychotics prescribed during at least 4 weeks for each drug. French was required as maternal language. Exclusion criteria included age over 65, pregnancy, knowledge of Korean and Polish languages (see scanning protocol below), alcohol or substance abuse or dependence in the past 6 months, electroconvulsive therapy in the past 6 months, any present medical condition, history of other psychiatric or neurological disorders and contraindication to magnetic fields.

Clinical assessments

Clinical evaluations were performed on the day before the fMRI session (Baseline) and on the last TMS treatment day (after 10 sessions, i.e. Endpoint) by senior psychiatrists blind to the treatment modality. The severity of AVH was assessed using the hallucination subscale of the Scale for the Assessment of Positive Symptoms [SAPS (32)], and the Auditory Hallucination Rating Scale (AHRS (33)). Other clinical symptoms were assessed using the Scale for the Assessment of Negative Symptoms [SANS (32)] total scores. Additionally, the Psychotic Symptom Rating Scales [PSYRATS (34)] was administered at baseline to assess specific AVH characteristics.

Study design and treatment allocation

The study was designed as a two-centre, randomized placebo-controlled trial. A randomization list was generated using a restricted randomization (block size, N = 15; allocation ratio 1:1) (Figure S1). This code list was kept in the brain imaging department, both stimulation centres having a list indicating the treatment modality corresponding to the code. Patients' randomization codes were given to the stimulation centre investigator following brain imaging and immediately before the first treatment session. Both patients and symptom raters were blind to the treatment modality.

Transcranial magnetic stimulation was administered as add-on therapy as the patients were treated with minimal and stable doses of their previous treatment for at least 2 weeks. Low-dose hypnotics were allowed in case of severe insomnia only (Table S1).

Scanning protocol and TMS target determination

Transcranial magnetic stimulation target was determined using fMRI with a language recognition task. Briefly, subjects listened to sentences in French and in foreign languages (Korean, Polish) and were required to perform a language fragment-detection task.

A gradient-echo EPI sequence was acquired (20 slices, 3.75 × 3.75 × 5 mm, TR/TE = 2000/60 ms) during the task. Auditory events administered in two 14-min sessions of 96 randomized trials (32 French-language sentences; 32 foreign-language sentences; 32 silence periods) were synchronized using E-Prime software (http://www.pstnet.com/eprime.cfm) with event-related fMRI volume acquisitions.

Functional and T1 images (3D sequence, 124 contiguous slices, voxel size = 0.94 × 0.94 × 1.3 mm^3) were acquired on a 1.5T Signa scanner (GE, Milwaukee, USA).

For individual fMRI statistical analyses, a general linear model was applied using Statistical Parametric Mapping (SPM) software (http://www.fil.ion.ucl.ac.uk/spm), defining three categories of events: French, Foreign language and Silence. The 'target' for the TMS treatment was defined from the contrast 'French *minus* Foreign languages', or when no cluster was retrieved, the contrast 'French *minus* Silence'. It corresponded to the most significant peak-voxel within accessible coil–cortex distance range (maximum 25 mm) located in the posterior part of the superior temporal or, if absent, within the inferior parietal, or the middle temporal gyrus.

This 'target' was automatically projected onto the patient's 3D T1 MRI image and head surface using Anatomist software (http://brainvisa.info). Along with the peak-voxel projection, anatomical landmarks including the nasion, vertex and left and right auricular tragi were selected. Coordinates of the landmarks computed with Anatomist were then entered into an algorithm embedded in BrainVISA software (http://brainvisa.info) that allowed for computing geodesic distances (i.e.

tangents to the head surface) between the target and the landmarks. The three distances between target and nasion, target and left auricular tragus and target and right auricular tragus were provided in mm by Anatomist software and were then used to position the TMS coil manually over the subject's head (Figure S2). This method has been validated (35).

Stimulation procedure

Transcranial magnetic stimulation treatment was administered in two centres that were equipped with Magstim super-rapid® devices with active and sham air-cooled figure-of-eight coils (Magstim, Dyfed, UK), and by investigators who were not involved in clinical ratings or fMRI. Both coils look the same and deliver the same auditory stimuli, but the sham coil has no effect on the scalp muscles.

Motor threshold (MT) was determined according to the standard procedure. rTMS was administered on 10 consecutive working days. A twenty-min train of 1-Hz rTMS was delivered at 100% of MT intensity, resulting in a total of 1200 pulses per session. Placebo rTMS was performed using the same procedure. The stimulation coils were supported using a stand and tightly maintained on the head using a tourniquet, with the coil handle pointing downwards, perpendicular to the temporal (T3) and parietal (P3) EEG points. All of the patients wore earplugs and a stretchable swimming cap on which the target position was drawn according to the computed geodesic distances of the target.

Statistical analysis

A power calculation was based on the primary outcome. A difference of seven points between intervention groups on the SAPS hallucination subscale, with a standard deviation of six, can be considered clinically meaningful. *A priori* sample size determination was computed using BiostaTGV (http://marne.u707.jussieu.fr/biostatgv). At least 24 patients (12 patients per group) were required to control for an alpha-level error of 5% and a beta-level error of 20%.

Other statistical analyses were performed using JMP® software (SAS, North Carolina, USA) on data from all patients who had a baseline measure and at least one postbaseline observation available. The primary outcome measure was change from baseline in the hallucination subscale score of the SAPS between *Baseline* and *Endpoint*. Secondary outcome measures included the sum of auditory hallucinations items of the SAPS ('Auditory hallucinations', 'voices commenting', 'voices conversing'), AHRS items and total scores, SAPS and SANS total scores.

Baseline scores across treatment groups were compared using an analysis of variance (ANOVA) with treatment modality (guided active, guided placebo) and centre as independent variables. Categorical variables were compared using chi-square tests.

Main analysis of treatment efficacy was assessed using repeated-measures ANOVAS with time (Baseline, Endpoint) as within-subject factor, and treatment modality (guided active, guided placebo) and centre as between-subject factors.

A secondary analysis investigated the treatment effects in subgroups determined according to spatial location of AVH. To this end, the 'location' item of the PSYRATS was used: 'Voices inside head only' indicated internal voices; 'Voices outside the head only' indicated external voices; for other scores, examination of the clinical records allowed to check whether the patient had *prominent* internal or *prominent* external AVH (Table S1). Repeated-measures ANOVAS with time (Baseline, Endpoint) as within-subject factor and spatial location (internal, external), treatment modality (guided active, guided placebo) and centre as between-subject factors were performed.

Post hoc analyses were performed using paired *t*-tests when a time x subgroup interaction was significant. ANOVAS' significance threshold was set at $P < 0.004$, after Bonferroni correction.

Results

Fifteen patients were randomly assigned to active rTMS, and 13 to placebo rTMS.

One patient in the placebo group was removed from the study shortly after the beginning of the protocol. Actually that patient did not meet criteria for schizophrenia anymore and appeared to have major depression with psychotic features, which left 27 patients for analysis (Figure S1).

Overall, TMS was well tolerated; five patients in the active group and one in the placebo group experienced mild headache after the sessions.

The TMS target was the superior temporal gyrus (STG) in 14 patients, and the middle temporal gyrus (MTG) in 13 patients (Table 1; Table S1).

Table 1. Comparison of demographic, clinical and treatment characteristics at baseline in patients with resistant auditory hallucinations treated with active or placebo rTMS

	Patients with active rTMS ($N = 15$)		Patients with Placebo rTMS ($N = 12$)		Analysis	
Characteristic	N	%	*N*	%	χ^2	*P*
Gender (M/F)	8/7	53/47	7/5	58/42	0.07	0.79
Target location (STG/MTG)	8/7	53/47	6/6	50/50	0.03	0.86
Voice location (Internal/External)	9/6	60/40	6/6	50/50	0.27	0.60
fMRI contrast (Fr-fl/Fr-sil)	11/4	73/27	8/4	67/33	0.14	0.71
	Mean	SD	Mean	SD	*t*-test	
Age	32.07	6.79	31.25	7.78	0.29	0.77
Education, years	8.07	2.62	7.33	3.20	0.65	0.52
Age at onset, years	21.53	5.80	22.00	6.65	0.19	0.85
Duration of AVH, years	8.87	8.07	8.03	4.44	0.29	0.77
Antipsychotics*, mg	474.40	84.33	547.92	94.29	0.59	0.56
Motor Threshold† (%)	66.40	9.07	67.40	8.89	0.29	0.77
Baseline symptom scores						
SAPS total	42.13	17.52	41.08	31.36	0.16	0.87
SAPS hallucination subscale	19.40	5.73	17.25	7.03	1.18	0.25
SAPS AVH score‡	11.07	2.89	10.58	4.08	0.47	0.64
AHRS total	28.66	5.38	28.45	5.11	0.18	0.86
SANS total	40.73	17.99	43.08	33.64	0.22	0.82

fMRI, functional magnetic resonance imaging; rTMS, repetitive transcranial magnetic stimulation; χ^2, chi-square test; M, male; F, female; STG, superior temporal gyrus; MTG, middle temporal gyrus; Fr-fl, French minus foreign languages; Fr-sil, French minus silence; AVH, auditory verbal hallucinations; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; AHRS, Auditory Hallucination Rating Scale.

*Expressed as chlorpromazine equivalents.

†% stimulator output intensity.

‡Sum of the SAPS hallucination subscale auditory hallucination items (auditory hallucinations; voices commenting; voices conversing).

Main analyses

There was no difference between rTMS treatment modalities in patients' demographic data, clinical baseline characteristics, target fMRI contrasts or cerebral locations, or antipsychotic dosages (Table 1). Diagnoses were equally distributed across groups, with ten patients in the active group and eight patients in the placebo group with paranoid schizophrenia, three patients with an undifferentiated type in both groups and two patients in the active group and one in the placebo group with a schizoaffective disorder (Fisher's exact test, $P = 0.99$). Concomitant medications did not differ between groups. Eight patients in the active group and four in the placebo group were on antidepressants (Fisher's exact test, $P = 0.44$), one and two patients respectively were on mood stabilizers (Fisher's exact test, $P = 0.57$) and seven and six patients respectively were on benzodiazepines (chi-square test=0.03, $P = 0.86$) (Table S1).

There was no treatment effect ($F_{1,24}$=1.22, $P = 0.28$) and no time-by-treatment interaction ($F_{1,24} = 0.01$, $P = 0.90$) for the primary outcome measure. A significant main effect of time was observed for all primary and secondary outcome measures, indicating that both groups *similarly* improved with time, except for the SANS and 'number of voices' scores that did not significantly improve (Table 2; Fig. 1a for visualization).

Secondary analysis

Twelve patients (of whom six were on placebo TMS) had prominent external AVH, and 15 patients (six on placebo TMS) had prominent internal AVH. These subgroups did not differ on any of the demographic and clinical baseline characteristics, stimulation modality, target fMRI contrast, target location or antipsychotic dosages, except for the AHRS total score that was higher in patients with internal AVH (30.6 ± 4.5 vs. 26.2 ± 5.1 in patients with external AVH, Student's *t*-test = 2.35, $P = 0.03$), and for MT that was higher in patients with external AVH ($71.3 \pm 8.7\%$ of stimulator output intensity vs. $63.3 \pm 7.29\%$ in patients with internal AVH, Student's *t*-test = 2.61, $P = 0.01$) (Table 1; Table S1 and S2). There were no differences in treatment prescriptions either. Six patients in each group were on antidepressants (chi-square test = 0.27, $P = 0.60$), one patient in the internal voice group and two patients in the external voice group were on mood stabilizers (Fisher's exact test, $P = 0.57$) and nine and four patients respectively were on benzodiazepines (Fisher's exact test, $P = 0.25$).

Patients with external AVH were significantly more improved than those with internal AVH on the SAPS hallucination and total scores, the AHRS total score, the reality and distress level items, as shown by a significant time-by-spatial-location-of-AVH interaction (Table 3; Fig. 1b). There was no significant treatment effect, nor time-by-treatment interaction, nor time-by-treatment-by-spatial-location-of-AVH triple interaction (i.e. improvement on the hallucination type did not differ between active or placebo treatment groups), for all outcome measures.

Based on our results (Table 3), given that there is no other report available in the literature on the differential effects of TMS on external and internal AVH, we performed an *a posteriori* power analysis, to check what would have been the *a priori* sample size needed for this comparison. Actually, the between-group difference in mean improvement (8.66 points) and standard deviation (six points) on the SAPS

Table 2. Comparison of clinical changes between patients treated with fMRI-guided active or placebo rTMS

	Active rTMS ($N = 15$)				Placebo rTMS ($N = 12$)				Treatment effects		Time effects	
	Baseline		Endpoint		Baseline		Endpoint					
Symptom scale	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$F_{1,24}$	P	$F_{1,24}$	P
SAPS hallucination subscale	19.40	5.73	11.8	7.84	17.25	7.03	9.25	6.73	1.22	0.28	53.39	<0.0001
SAPS total	42.13	17.52	30.53	20.37	41.08	31.36	24.75	16.93	0.25	0.62	23.62	<0.0001
SAPS AVH score*	11.07	2.89	7.53	4.78	10.58	4.08	5.44	1.57	0.29	0.60	31.80	<0.0001
SANS total	40.73	17.99	36.53	20.54	43.08	33.64	36.25	29.32	0.06	0.81	3.92	0.06
									$F_{1,23}$	P	$F_{1,23}$	P
AHRS												
Frequency	5.43	3.27	4.33	3.66	5.82	2.93	3.18	3.31	0.12	0.73	19.85	0.0002
Reality	4.33	1.05	3.60	1.72	4.64	0.50	2.91	1.87	0.14	0.72	18.66	0.0003
Loudness	3.20	0.56	2.00	1.41	2.73	0.47	1.82	1.25	1.08	0.31	24.73	<0.0001
Number of voices	3.47	2.26	2.67	2.06	3.27	2.10	2.54	1.91	0.04	0.84	7.62	0.01†
Length	3.27	0.80	2.73	1.10	3.45	0.52	2.36	1.50	0.07	0.79	19.95	0.0002
Attentional salience	4.93	1.10	3.53	1.85	4.64	1.03	3.09	1.97	0.52	0.48	24.97	<0.0001
Distress level	3.93	0.70	2.87	1.35	3.91	0.94	2.64	1.75	0.08	0.78	28.21	<0.0001
AHRS total	28.66	5.38	21.70	9.85	28.45	5.11	18.50	11.40	0.30	0.59	44.77	<0.0001

MRI, functional magnetic resonance imaging; rTMS, repetitive transcranial magnetic stimulation; AVH, auditory hallucinations; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; AHRS, Auditory Hallucination Rating Scale.

*Sum of the SAPS hallucination subscale auditory hallucination items (auditory hallucinations; voices commenting; voices conversing).

†Non-significant comparison after Bonferroni correction.

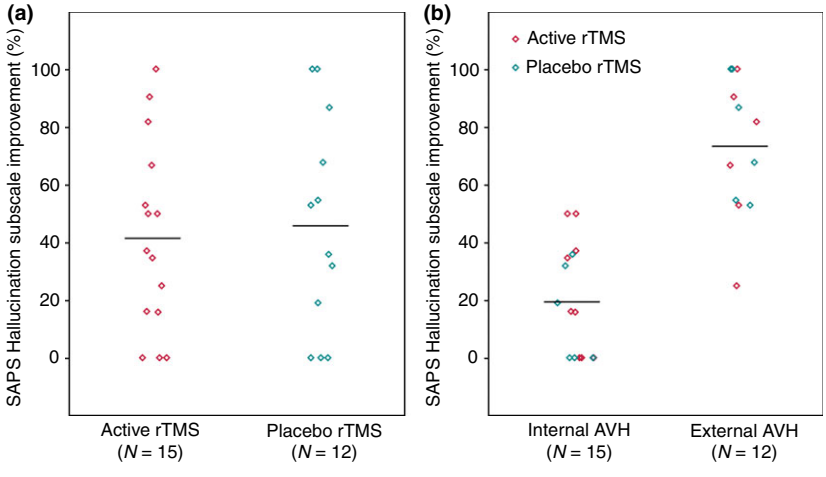

Fig. 1. Improvement rates on the hallucination subscale of the Scale for the Assessment of Positive Symptoms (SAPS) according to (a) treatment with active or placebo rTMS and (b) spatial location of auditory hallucinations (AVH), in patients with schizophrenia. a/Left: mean ± SD % improvement (active rTMS) = 41 ± 33%; right: mean ± SD % improvement (sham) = 46 ± 37%; b/left: mean ± SD % improvement (internal AVH) = 19 ± 19%; right: mean ± SD % improvement (external AVH) = 73 ± 24%.

hallucination subscale resulted in a number needed of at least 16 patients (eight patients per group) to control for an alpha-level error of 5% and a beta-level error of 20%, indicating that our analysis was adequately powered.

As there was a difference in MT between patients with internal and external AVH, we performed exploratory correlation analyses to search for an effect of MT on clinical improvement. There was a significant correlation between MT values and percentage improvement on the hallucination subscale of the SAPS in both active and placebo rTMS treatment groups, and in both external and internal auditory hallucination groups (Fig. 2).

Discussion

Active and placebo 1-Hz rTMS over language-related temporal regions had similar therapeutic effects on treatment-resistant auditory hallucinations in patients with schizophrenia, and both modalities led to significant improvement. The secondary analysis showed that patients with external hallucinations were significantly more improved than patients with internal hallucinations with both treatment modalities.

As in a number of previous studies, active and placebo modalities both improved AVH (10–15). Indeed, all the hallucination descriptors of the AHRS were markedly improved in both treatment

Table 3. Comparison of clinical changes between patients with resistant internal or external auditory hallucinations treated with fMRI-guided rTMS

	Patients with internal AVH ($N = 15$)							Patients with external AVH ($N = 12$)							SLAVH x time effect	
	Baseline		Endpoint		Change from baseline comparison			Baseline		Endpoint		Change from baseline comparison				
Symptom scale	Mean	SD	Mean	SD	*t*	*P*	CI†/Effect size	Mean	SD	Mean	SD	*t*	*P*	CI†/Effect size	$F_{1,22}$	*P*
SAPS hallucination subscale	19.26	6.16	15.33	5.49	3.94	0.002	−0.08; −0.30/0.72	17.42	6.61	4.83	4.73	6.68	<0.0001	−0.58; −0.88/0.89	31.81	<0.0001*
SAPS total	39.87	18.75	35.00	18.00	2.63	0.02	−0,02; −0.23/0.58	43.92	30.29	19.17	16.46	4.52	0.0009	−0.43; −0.70/0.79	17.51	0.0004*
SAPS AVH score‡	11.40	3.18	10.13	3.87	2.48	0.03	−0,01; −0.23/0.55	10.17	3.69	3.25	3.39	6.89	<0.0001	−0.54; −0.86/0.89	37.89	<0.0001*
SANS total	42.87	25.56	41.07	23.97	n.a.	n.a.	n.a.	40.42	26.69	30.58	24.47	n.a	n.a.	n.a.	6.06	0.02
															$F_{1,21}$	*P*
AHRS																
Frequency	7.14	2.44	6.14	3.10	n.a.	n.a.	n.a.	3.92	2.87	1.16	1.33	n.a.	n.a.	n.a.	5.43	0.03
Reality	4.14	1.02	3.86	1.17	1.47	0.16	0.03; 0.16/0.37	4.83	0.39	2.67	2.18	3.65	0.004	−0.18; 0.74/0.73	13.44	0.001*
Loudness	3.14	0.66	2.57	1.16	n.a.	n.a.	n.a.	2.83	0.39	1.17	1.11	n.a.	n.a.	n.a.	8.47	0.008
Number of voices	3.36	2.06	2.79	1.85	n.a.	n.a.	n.a.	3.42	2.35	2.41	2.15	n.a.	n.a.	n.a.	0.74	0.40
Length	3.36	0.74	3.07	0.83	n.a.	n.a.	n.a.	3.33	0.65	1.47	0.42	n.a.	n.a.	n.a.	9.41	0.006
Attentional salience	5.21	0.89	4.36	1.60	n.a.	n.a.	n.a.	4.33	1.07	2.17	1.47	n.a.	n.a.	n.a.	6.30	0.02
Distress level	4.21	0.57	3.71	1.07	1.99	0.07	0.01; −0.25/0.47	3.35	0.90	1.67	1.15	5.06	0.0004	−0.32; −0.74/0.83	15.67	0.0007*
AHRS total	30.57	4.48	26.5	6.68	2.76	0.02	−0.02; −0.24/0.59	26.25	5.08	13.25	9.60	5.38	0.0002	−0.29; −0.73/0.84	25.47	0.0001*

fMRI, functional magnetic resonance imaging; rTMS, repetitive transcranial magnetic stimulation; AVH, auditory hallucinations; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; AHRS, Auditory Hallucination Rating Scale; SLAVH, spatial location of AVH; n.a., post hoc comparison not applicable.

*Significant comparisons after Bonferroni correction.

†CI: 95% confidence interval for slope.

‡Sum of the SAPS hallucination subscale auditory hallucination items (auditory hallucinations; voices commenting; voices conversing).

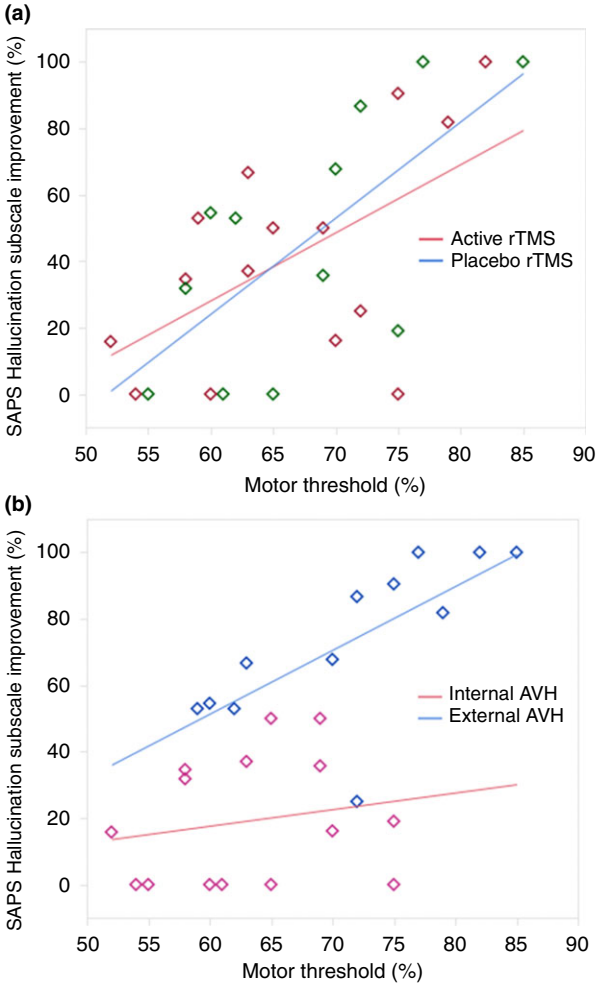

Fig. 2. Correlations between motor threshold values and percentage improvement on the hallucination subscale of the SAPS in patients with resistant hallucinations treated with active or sham repetitive transcranial stimulation (rTMS) (a), and in patients with external or internal auditory hallucinations (b) a/Red dots indicate patients treated with active rTMS ($N = 15$); green dots indicate patients treated with sham rTMS ($N = 12$). Statistic: ANCOVA, significant main effect of motor threshold: t-ratio = 3.87, $P = 0.0008$; no main effect of treatment group: t-ratio = −0.16, $P = 0.87$; no interaction effect: t-ratio = −0.66, $P = 0.51$. b/Pink dots indicate patients with internal auditory hallucinations ($N = 15$); blue dots indicate patients with external auditory hallucinations ($N = 12$). Statistic: ANCOVA, significant main effect of motor threshold: t-ratio = 2.57, $P = 0.0172$; significant main effect of spatial location of auditory hallucinations: t-ratio = −5.31, $P < 0.0001$; no interaction effect: t-ratio = −1.51, $P = 0.15$.

groups, except for the 'number of voices', consistent with other studies (10, 33).

So far, the mechanism underlying effects of the *placebo* TMS coil (sham coil) has raised little interest, but some physical factors could contribute to those effects. The close-to-the-skull position of the coil in this study might have locally led, in *both* treatment conditions, to high sound transmission through bone (36), or bone piezoelectricity (37), as temporal bone is a thin part of the skull where bone conduction threshold is particularly low. In an animal experiment using increasing sound intensity level (38), the authors reported an unexpected *decreased* glucose metabolism at the auditory cortex level, suggesting an auditory cortex adaptation to sound intensity, which could be seen in line with reports of decreased blood flow in the primary auditory cortex after rTMS (29). Thus, the clinical effects observed after rTMS treatment might be related to response in the auditory cortex to sound but also vibrations as well as to electric effects that remain difficult to disentangle so far.

The present findings suggest that hallucination phenomenology plays a major role in active and sham rTMS effects, as external AVH were more improved than internal ones. None of the previous rTMS studies has reported how internal and external AVH were distributed across treatment groups, making their results difficult to compare with ours. 'Reality' of AVH better describes external than internal AVH, and was more improved, as well as 'distress', in the group with external AVH.

Although a number of studies have reported auditory cortex activations associated with AVH (39), no study has compared the functional correlates of internal and external AVH. The distribution of brain regions involved in the perception of AVH in external auditory space has only been examined in healthy subjects using fMRI with virtual acoustics simulating 'inside-head' and 'outside-head' AVH (40). That study concluded that perception of AVH in external space was related to left planum temporale activation. Furthermore, the experience of hearing internal AVH might be close to imagining sentences being spoken in another person's voice. Indeed, this task was related to a failure to activate areas involved in the monitoring of inner speech such as the left middle temporal gyrus and the rostral supplementary motor area in patients with hallucinations (41). Hence, it can be hypothesized that the circuitry involved in internal AVH might include additional regions to those involved in auditory perception, which would account for the lesser effects on internal AVH of TMS targeting the auditory cortex.

Herein, both active and placebo treatments, targeting the auditory cortex, had comparably low effect on internal AVH and high effect on external AVH. Interestingly, patients with external AVH had a higher MT than patients with internal AVH, although they had comparable medications. A higher MT means a higher intensity of stimulation and also louder sound and stronger associated vibrations that are delivered during both active and placebo rTMS. Thus, the positive correlations

between motor threshold and AVH improvement would support our hypothesis of the influence of sound/vibration on rTMS effects.

The following limitations can be acknowledged in the present study. First, the sample size was small, but the effect sizes of our results were high (Table 3), and the sample size was comparable to that of a previous study showing positive effects of active TMS (33). Still, recent meta-analyses (7) do not support such large effects as the 7-point difference that was taken in our power analysis. Thus, our small sample sizes could have prevented us from finding a significant difference between treatment groups. Conversely, due to the small sample size in the spatial location of AVH groups, we cannot completely rule out the possibility of some chance findings, in the comparison between internal and external AVH, that need to be replicated.

Second, different fMRI conditions were alternatively used to determine the target. However, it is unlikely that differences in targets would have influenced the effects, as targets were equally distributed across treatment groups, and across spatial location groups. Differences in response might be accounted for by different locations of the coil in other studies showing higher effects of *active* rTMS on AVH (33). In most studies, the coil is supposed to target BA 40 (left TPJ); in this study, only one target was found over BA 40. However, the main regions activated by the linguistic task were localized in the MTG at BA 21, a region involved in the actual perception of AVH (2), or in the STG at BA 22, a region whose activation during the task was found to negatively correlate with severity of AVH (25) and that was found to predict response to rTMS (20). Thus, it is likely that our target locations were relevant to TMS treatment and should have favoured the active stimulation.

Third, the duration of the protocol was shorter in our study than in other more recent studies. Indeed, increasing the number of TMS sessions might increase efficacy outcomes and the short duration of our protocol could have prevented from seeing a separation between active and sham groups. However, several trials have shown differences between sham and active conditions after the same treatment duration and even after shorter durations (8, 33), and a recent review has shown no correlation between the number of stimuli and effect size of the studies (7). Also, it was not possible to follow up the patients after the trial, and thus, no information was retrieved on how stable the improvement was in the middle term or long-term.

Other differences in rTMS protocol parameters might have influenced the effects, but our study parameters were among the strongest, with respect to the literature (7), with a high intensity and a large number of pulses. Other parameters may not have been optimal to trigger the rTMS effects; for instance, the angle of the coil handle was perpendicular to the temporal sulcus, while in some other studies it was parallel to the sulcus. Also, a few patients were not free of anticonvulsive drugs, which could have lowered the effects of active stimulation.

Such limitations could account for the comparable effects of placebo and active modalities. However, these reasons cannot account for the effects of *both* active and placebo modalities, very high (73% improvement) on external AVH and very low (20% improvement) on internal AVH. On a speculative note, the patients with external and internal AVH might differently attribute their AVH to external or internal sources respectively, which could result in different expectations while participating to a protocol targeting the brain, an internal source. Finally, we cannot dismiss that clinical heterogeneity of the patients might have blurred the TMS effects, particularly as the patients with internal AVH had higher AVH scores than those with external AVH on the AHRS, and might have had a more severe disorder. Thus, overall, the present results raise the question of cortical effects of rTMS related to non-magnetic stimulation of the auditory cortex. Given the very positive effects on resistant external AVH, systematic use of questionnaires discriminating external from internal AVH may help select patients most responsive to 'TMS' in clinical practice. However, future research should investigate the neural correlates of internal and external AVH to assess the differential effects of magnetic stimulation on the involved networks, and also investigate the nature of those speculated cortical effects related to non-magnetic stimulation to eventually test new therapeutic approaches.

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Declaration of Interest

Doctor Paillère Martinot has received fees from Janssen-Cilag in the past three years. Statistical analysis was performed in INSERM research unit U1000, by Doctor Eric Artiges.

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Clinical trial registration: INSERM database; RBM-0127; http://bir.inserm.fr

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram of clinical trial of repetitive Transcranial Magnetic Stimulation (rTMS) in patients with schizophrenia and resistant hallucinations.

Figure S2. rTMS target determination.

Table S1. TMS target and Hallucination characteristics, Motor Threshold, Ongoing treatments and dosages in 28 patients with resistant auditory hallucinations receiving active or placebo fMRI-guided rTMS.

Table S2. Comparison of demographic, clinical and treatment characteristics at baseline in patients with internal or external resistant auditory hallucinations.