

# High-Frequency Neuronavigated rTMS in Auditory Verbal Hallucinations: A Pilot Double-Blind Controlled Study in Patients With Schizophrenia

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**Introduction:** Despite extensive testing, the efficacy of low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) of temporo-parietal targets for the treatment of auditory verbal hallucinations (AVH) in patients with schizophrenia is still controversial, but promising results have been reported with both high-frequency and neuro-navigated rTMS. Here, we report a double-blind sham-controlled study to assess the efficacy of high-frequency (20 Hz) rTMS applied over a precise anatomical site in the left temporal region using neuronavigation. **Methods:** Fifty-nine of 74 randomized patients with schizophrenia or schizoaffective disorders (DSM-IV R) were treated with rTMS or sham treatment and fully evaluated over 4 weeks. The rTMS target was determined by morphological MRI at the crossing between the projection of the ascending branch of the left lateral sulcus and the superior temporal sulcus (STS). **Results:** The primary outcome was response to treatment, defined as a 30% decrease of the Auditory Hallucinations Rating Scale (AHRS) frequency item, observed at 2 successive evaluations. While there was no difference in primary outcome between the treatment groups, the percentages of patients showing a decrease of more than 30% of AHRS score (secondary outcome) did differ between the active (34.6%) and sham groups (9.1%) ( $P = .016$ ) at day 14. **Discussion:** This controlled study reports negative results on the primary outcome but

demonstrates a transient effect of 20 Hz rTMS guided by neuronavigation and targeted on an accurate anatomical site for the treatment of AVHs in schizophrenia patients.

**Key words:** Transcranial magnetic stimulation/neuronavigation/magnetic resonance imaging/Auditory Hallucinations Rating Scale/placebo/trial/20 Hz

## Introduction

When schizophrenia patients fail to optimal antipsychotic therapy, repetitive transcranial magnetic stimulation (rTMS) may be an adjuvant therapy for the treatment of auditory verbal hallucinations (AVHs).<sup>1</sup> rTMS is primarily delivered at a low frequency (1 Hz) based on the assumptions of 2 hypotheses. First, that low- and high-frequency stimulation in the temporal cortex may induce inhibitory and excitatory effects respectively, as has been observed in the primary motor cortex.<sup>2</sup> Second, neuroimaging and neurophysiological studies have indicated that AVHs are correlated with cerebral hyperactivity in the left temporal cortex, suggesting that inhibitory effects may be required to alleviate AVHs.<sup>3-5</sup> However, the efficacy of 1 Hz rTMS remains controversial,<sup>6-11</sup> and there may be insufficient evidence for 1 Hz rTMS as an adjunctive therapy to antipsychotic medication.<sup>12</sup> Only 5 of 21 controlled

studies aiming to demonstrate 1 Hz rTMS efficacy<sup>13</sup> reported positive results,<sup>14–18</sup> and recent results achieved with high frequency rTMS could call the use of a low frequency stimulation into question and revive interest in rTMS for the treatment of AVH. The first open study using a high-frequency (20 Hz) demonstrated a drastic reduction in AVH<sup>19</sup> that was maintained for 6 months in one patient.<sup>20</sup> Recent observations also suggest that high-frequency or theta-burst rTMS can produce inhibitory effects in healthy subjects<sup>21</sup> for the treatment of both AVH<sup>22,23</sup> and tinnitus.<sup>24</sup> Additionally, the treatment can be intensified by delivering high frequency stimulation over a 2-day period rather than over 2 weeks, to rapidly affect AVHs. This delivers a number of stimuli roughly similar to that routinely given at low frequency (1 Hz) over approximately 2 weeks in just 2 days. A major advantage of a paradigm consisting of a series of stimulations delivered in a few days is the reduction of administration duration, which improves both the adherence to the treatment and its availability. These “high dose” or “accelerated” protocols have been well tolerated and depressive patients show a rapid decline of symptoms.<sup>25–28</sup> However, these protocols have not yet been tested for the treatment of AVHs in schizophrenia patients.

In addition to changes in frequency, rTMS efficacy could also be increased by an accurate target that takes between-subject anatomical variability into account. The left temporo-parietal region is the proposed target in most studies, and it is usually located using the traditional T3P3 site according to the International 10–20 system of EEG electrode positioning, which is known to be a rough estimation.<sup>29</sup> To address the wide anatomical variability between subjects, some authors have proposed using neuronavigation integrating morphological or functional imaging data to locate the stimulation target.<sup>18,30–33</sup> These studies indicate the pitfalls of the T3P3 method and the use of functional cerebral imaging to guide localization and these results clearly point to the need for better and more accessible localization techniques for rTMS optimization. Therefore, we aim to determine an accurate anatomical site in the left temporo-parietal region identified as the best stimulation target<sup>33</sup> that can be easily and reproducibly targeted in clinical practice.

Finally, while promising results have been separately reported with high-frequency<sup>22,23</sup> or neuronavigated rTMS,<sup>18</sup> there are no reports comparing the efficacy of high-frequency neuronavigated rTMS with sham stimulation in a double-blind placebo-controlled study. We suggest that the combination of both high frequency (20 Hz) stimulation and neuronavigation may be an optimal strategy for reducing AVHs in patients with schizophrenia.

## Methods

### Subjects

Seventy-four patients with schizophrenia or schizoaffective disorders were included in 7 University centers across

France (Caen, Creteil, Dijon, Paris, Poitiers, Rennes, and Rouen).

The patients included in this randomized placebo-controlled double-blind trial had a diagnosis of schizophrenia or schizoaffective disorders (DSM-IV R) assessed with the MINI, were aged from 16 to 65 years old, had a severity score of hallucinations on the Auditory Hallucination Rating Scale (AHRs)<sup>15</sup> >10, and had clinically stabilized disease defined by the absence of antipsychotic treatment modifications within the last 2 months.

Exclusion criteria were pregnancy or active breastfeeding, brain tumor, history of epilepsy, previous rTMS treatment, and metal objects in the body.

This study was approved by the human ethics committee (CPP, Nord Ouest), by the French Agency for Health (ANSM), and was registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) under number NCT01022489. All patients provided their written informed consent to participate.

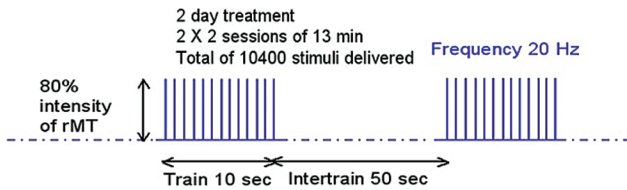
### Procedures

Patients were randomized to receive either active 20 Hz rTMS or sham treatment after providing written informed consent, and participants and clinical staff were blind to the treatment allocation. The randomization list consisted of a sequence of blocks containing the 2 trial arms (active and sham treatment) randomly assigned, with permuted blocks of size 4. Each hospital has its own randomization list. The rTMS administrator assigned each participant to the active or sham arms, and was blind to the treatment along with the investigator/assessor. The patient was the only person with access to the randomization list and had no contacts or role in assessing AVHs. The blindness procedure was maintained throughout the follow-up period.

Patients were evaluated at 6 visits over 4 weeks to evaluate treatment efficacy. Assessment was performed using the AHRs<sup>14</sup> immediately preceding the first treatment session on day 1 (D1), after the last session (D2), and at D7, D14, D21, and D30. Additionally, the Positive and Negative Syndrome Scale (PANSS),<sup>34</sup> the Scale to assess Unawareness of Mental Disorder (SUMD),<sup>35</sup> the self-evaluation of insight (IS),<sup>36</sup> and the Clinical Global Impression (CGI) were also applied at baseline (D0), D14, and D30. Handedness was assessed with the Oldfield scale,<sup>37</sup> and subjects were categorized into right-handed (score  $\geq 50$ ) and nonright-handed (score < 50). Side effects were recorded during each session and independently at days 2 and 7.

### rTMS

Two types of devices were used in this multicenter trial, the Magstim Rapid<sup>2</sup> (The Magstim Company Limited, Carmarthenshire, UK) and the MagPro X-100 (MagVenture, Farum, Denmark) with a figure-8 coil. The high-frequency protocol (20 Hz) consisted of 13 trains with a duration of 10 s and 200 pulses in each train



**Fig. 1.** 20 Hz rTMS paradigm. rMT, resting motor threshold; sec, seconds; min, minutes; Hz, Hertz.

(figure 1). The intertrain interval was 50 s, resulting in 2600 total pulses and a total duration of 13 min. Four 13-min rTMS sessions were performed, with 2 sessions a day. We individually measured the resting motor threshold (rMT) before each session using electromyography recordings on the first dorsal interosseus muscle, and set the stimulation intensity at 80% of the rMT.

The same procedure was performed in the sham group including the rMT assessment and the neuronavigation system for target localization, and sham coils were used for the 2 stimulators. Both sham coils deliver a very slight magnetic field, have the same appearance and sound, and provide the same tactile sensations as the active coils.

#### rTMS Site Location

The anatomical target was determined in accordance with a previous study using a language task during functional magnetic resonance imaging (fMRI).<sup>19</sup> In this study, a significant AVH reduction was obtained by stimulating over the area of maximal task-evoked fMRI activation, which was located along the left superior temporal sulcus (STS). We also observed that this functional cluster generally corresponded to the same anatomical location across patients, while the classical location of T3P3 based on the 10–20 EEG system showed wide anatomical variability between subjects. The cortical target indicated by fMRI was always located at the crossing between the projection of the ascending branch of the left lateral sulcus (LS) and the left STS and it could be easily and quickly identified (in under 2 min) according to the individual MRI and using a frameless stereotaxic device, even by a nonexpert in neuroimaging. Therefore, we used this targeting procedure in the present study (figure 2; supplementary data video 1).

#### Outcome Measurements

The primary outcome was defined as the percentage of patients who presented a decrease of more than 30% in the AHRS frequency item at 2 successive evaluations, spaced 1 week apart. The secondary outcomes were the percentage of patients who presented a decrease of more than 30% in the total AHRS score after 2 weeks (D14), the variation in total AHRS scores between D1 and D2, D7, D14, D21, and D30, the variation in CGI, SUMD, and positive, negative, general, and total PANSS scores

between D0, D14, and D30, and the recording of adverse effects during the rTMS sessions, after the last session, and at D7.

The rTMS administrator used open-ended questions and a visual analog scale (VAS) to assess adverse effects and the overall painfulness of the procedure after each treatment session. The blind investigator used the UKU rating scale<sup>38</sup> (after the last rTMS session at D2) and at D7 to assess potential delayed side effects.

#### Statistical Analyses

Based on preliminary results obtained from an open study,<sup>20</sup> we determined that 72 patients were needed in the present study for a power at 90% and an alpha risk at 0.05. We used the Student's *t*-test to evaluate differences between groups, with Levene's test to check heteroscedasticity. We applied Pearson's chi-square test or Fisher's exact test to compare qualitative or categorical variables. Mixed-effects models with repeated measures (MMRM) were then used with the "group" and "day" factors to make pairwise comparisons between the 2 groups and different measurement times. The odds ratio (OR) reflects the odds of a successful outcome in the active treatment group relative to the odds of a similar outcome in the sham group, and was used to measure effect size.<sup>39</sup> OR was adjusted for the neuro-navigation system, stimulator type, and center variables.

All tests were 2-tailed and the probability significance threshold was set at  $P < .05$ . *IBM*—All statistical analyses were performed using SPSS 22.0 for Windows. All protocol and data are available for evaluation at the Caen CHU (Centre de Recherche Clinique, CRC).

## Results

#### Dropout

Fifteen of the 74 patients (20%) included and randomized dropped out, 6 from the sham group and 9 from the active group. Fourteen did not receive all 4 sessions of rTMS due to cerebral anatomical abnormalities ( $n = 4$ ), technical issues with the rTMS ( $n = 4$ ), withdrawal of consent ( $n = 3$ ), and improvement of AHRS ( $n = 1$ ). There was one protocol violation by a single patient related to a violation of inclusion criteria, who was therefore excluded from the analyses and 2 patients were lost before the beginning of rTMS treatment. The remaining 59 patients were treated and fully evaluated in either the active treatment group ( $n = 26$ ) or in the sham group ( $n = 33$ ) and were included in the analyses (see supplementary data flow diagram).

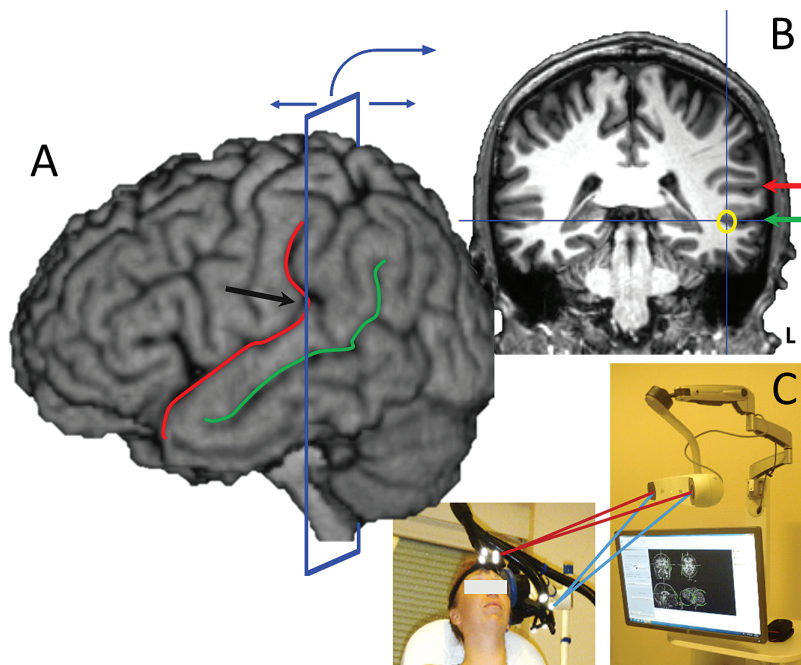
#### Baseline Comparison

Patient demographics are summarized in table 1. There was no difference between groups in age, gender, age of onset, duration of illness, marital status, employment status, severity of hallucinations as assessed with the AHRS scores, severity

of illness assessed as with the PANSS total score, antipsychotic doses in chlorpromazine-equivalents, or diagnosis. However, the sham group had been slightly but not significantly hospitalized more often, had a longer duration of illness, and had fewer years of education than the active group.

### Primary Outcome

The percentage of patients showing a decrease of more than 30% in the AHRS frequency item at 2 successive ratings was not significantly different between the active (50%) and the sham groups (48.5%).



**Fig. 2.** Location of the rTMS stimulation target by structural MRI and neuronavigation (A) Before rTMS treatment, the lateral sulcus (red line) and the superior temporal sulcus (green line) are located on the 3D MRI view using neuronavigation software. Then the coronal plane is moved in the posterior direction until it crosses the point where the lateral sulcus becomes vertical (black arrow). (B) The lateral sulcus (red arrow) and the superior temporal sulcus (green arrow) are located based on the 3D view on the coronal plane. Finally, the rTMS target is defined at the bottom of the superior temporal sulcus (yellow circle). (C) The neuronavigation tool is used during treatment to precisely locate the coil over the target.

**Table 1.** Population Characteristics

Variables	Active Group	Sham Group	P
	(n = 26)	(n = 33)	
	M ± DS	M ± DS	
Age (years)	35.3 ± 8.3	39.6 ± 11.4	.113
Years of school education	12.5 ± 3.1	11.0 ± 3.0	.058
Number of psychiatric hospitalizations	4.6 ± 3.9	7.6 ± 7.1	.059
Age of onset (years)	23.0 ± 6.3	23.0 ± 7.4	.983
Disease duration (years)	11.0 ± 7.7	15.2 ± 9.6	.079
Chlorpromazine equivalent (mg)	630 ± 411	771 ± 557	.292
AHRS D0	28.6 ± 6.0	27.8 ± 4.5	.529
PANSS total score D0	85.19 ± 32.15	91.58 ± 30.69	.441
	%	%	
Gender (male)	65.4	45.4	.127
Employment status (unemployed)	76.9	84.8	.307
Marital status (single)	80.8	67.6	.421
Diagnosis			
Schizophrenia (DSM-IV R)	76.9	75.8	.917
Schizoaffective disorders (DSM-IV R)	23.1	24.2	

Secondary Outcome

The percentage of patients showing a decrease of more than 30% in the total AHRS score is shown in table 2. The difference in the percentage of these responders between the active group (34.6%) and the sham group at D14 (9.1%) ( $P = .016$ ) was significant, and this difference remained significant after adjustment for neuro-navigation system, type of stimulator, and center, with an adjusted OR at 5.60 (95% CI: 1.28–0.022, table 3). The percentage of responders was not significantly different between the 2 groups at D2, D7, D21, or D30.

Variation in AHRS total score (table 4) was significant ( $P < .001$ ), but not different between the active and sham groups ( $P = .978$ ), and time  $\times$  group interaction was significant ( $P < .001$ ).

The variation of the scores for the other scales were broadly similar to that seen for total AHRS scores, except for the SUMD and Birchwood scale which showed no significant difference in the variations of the total scores (supplementary data table 1). No time  $\times$  group interactions were observed for any scale.

Procedure Painfulness and Adverse Events

Adversed effects are summarized in the Table 5. The active treatment was perceived as slightly but

Table 2. Percentage of Responders<sup>a</sup> at Day 2, 7, 14, 21 and 30

	Active Group, <i>n</i> = 26	Sham Group, <i>n</i> = 33	<i>P</i>
Day 2	19.2	21.2	.851
Day 7	30.8	21.2	.403
Day 14	34.6	9.1	<b>.016</b>
Day 21	26.9	18.2	.421
Day 30	26.9	18.2	.421

<sup>a</sup>Responders: variation in AHRS scores  $\leq$ -30% (relative variation of the score between days 2, 7, 14, 21, 30 and day 1).

Table 3. Percentage of Responders With a Decrease of AHRS Scores Greater Than 30% (Relative Variation) Relative to Active and Sham Groups, Adjusted for the Other Variables by Logistic Regression

	OR	95% CI	<i>P</i>
Groups			
Active vs sham	5.60	1.28–24.54	.022
Neuronavigation system			
NexStim vs ANT neuro	2.08	0.30–14.47	.460
Syneika vs ANT neuro	3.47	0.23–53.03	.371
Type of transcranial magnetic stimulator			
MagPro vs MagStim	1.14	0.12–10.40	.910
University hospital centers			
Ranked from low to high success rates	1.11	0.68–1.83	.673

Note: Hosmer–Lemeshow test:  $P = .804$ .

significantly more painful than the sham treatment ( $2.8 \pm 1.6$  vs  $1.4 \pm 1.7$ ), and adverse events directly caused by stimulation (squeezing, local pain, clenched jaw, or blepharospasm) were reported more often during active treatment. Other adverse events (eg, body position discomfort) were reported more often during the sham treatment. Although there were more adverse events observed during the active than the sham procedure, there were no major side effects reported in any groups.

Table 4. AHRS Score Variation in the Sham (*n* = 33) and the Active Groups (*n* = 26)

	Groups	Mean	SD
Day 1 <sup>(1)</sup>	Sham	26.92	6.054
	Active	27.96	5.01
Day 2 <sup>(2)</sup>	Sham	22.91	7.53
	Active	24.27	6.10
Day 7 <sup>(3)</sup>	Sham	22.30	7.65
	Active	21.73	8.77
Day 14 <sup>(4)</sup>	Sham	23.36	6.44
	Active	21.67	8.76
Day 21 <sup>(5)</sup>	Sham	23.42	6.57
	Active	22.98	7.91
Day 30 <sup>(6)</sup>	Sham	22.57	6.64
	Active	22.61	6.46

Note: Course of the scores:  $P < .001$ .  $P < .001$ : (1) vs (2), (1) vs (3), (1) vs (4), (1) vs (5), (1) vs (6). For all other comparisons,  $P$  was not statistically significant. Score between active and sham group:  $P = .978$ . Interaction time/groups:  $P < .001$ .

Table 5. Frequency of Adverse Effects and Painfulness of the Treatment

	Active Group ( <i>n</i> = 104)	Sham Group ( <i>n</i> = 132)	<i>P</i>
Local signs			
Tingling	9.6%	3.8%	
Squeezing	11.5%	2.3%	$P < .01$
Pain	10.6%	3.8%	$P < .05$
Regional signs			
Hemi-facial pain and squeezing	11.5%	8.3%	
Clenched jaw	28.8%	1.5%	$P < .0001$
Blepharospasm	14.4%	0.8%	$P < .001$
General signs			
Headache	13.5%	6.8%	
Asthenia	1.0%	1.5%	
Other complaints			
Noise	6.7%	12.9%	
Uncomfortable body position	0.0%	5.3%	$P < .05$
Motor threshold	1.9%	2.3%	
Other	4.8%	6.8%	
No complaints	32.7%	56.1%	$P < .0001$
Treatment painfulness			
VAS (mean of 4 sessions)	$2.8 \pm 1.6$ ( <i>n</i> = 21)	$1.4 \pm 1.7$ ( <i>n</i> = 28)	$P < .05$

There were also no differences in side effects as assessed with the UKU at D2, but depression and sleepiness/sedation were reported significantly more often in the sham group at D7 (16% vs 0%,  $P = .04$  and 19% vs 0%,  $P = .02$ ).

## Discussion

This is the first controlled study testing the efficacy of 20 Hz rTMS guided by neuronavigation and targeted to a specific anatomical site for the treatment of AVHs in patients with schizophrenia. The primary outcome was defined as percentage of patients showing a 30% decrease of the AHRS frequency item at 2 successive evaluations and did not show a significant difference between active and sham treatment groups. However, we did observe a transient efficacy at day 14, with 34.6% and 9.1% of patients in the active and sham groups showing a decrease of more than 30% of AHRS scores, respectively ( $P = .016$ ).

### High Frequency

These results confirm a previous uncontrolled observation<sup>19</sup> and indicate that high-frequency rTMS over a specific site on the left STS can lead to a significant improvement relative to placebo in AVHs. The results suggest that rTMS acts selectively on AVHs, since no changes were observed in insight level or negative, positive, or general psychopathological symptoms of schizophrenia. This result supports the hypothesis that high-frequency rTMS applied to the left temporal cortex can modulate cortical activity in the same direction as low-frequency rTMS in this clinical condition defined here as patients with schizophrenia and AVHs who are stimulated at this precise left temporal site.<sup>21</sup> As the efficacy of low frequency rTMS for the treatment of AVH is controversial and has led to a low-level recommendation in Europe (Level C), the use of high frequency stimulation could revive an interest in rTMS for the treatment of AVHs in schizophrenia patients.

Two previous studies comparing high frequency or cTBS with low frequency stimulation reported similar and significant decreases in AVHs.<sup>22,23</sup> However, these studies were not double-blind or sham-controlled, and the placebo effect is known to be high in this context.<sup>13</sup>

There are some limitations to the results presented here, specifically that the observed efficacy was transient at day 14 and was not observed on AVH frequency, in contrast to our expectations.

Our primary endpoint was defined as improvement in the frequency of AVHs at 2 successive evaluations, and was informed by a study by Hoffman et al<sup>40</sup> that reported significant improvements with 1 Hz rTMS compared to sham stimulation in hallucination frequency but not in hallucination change score. Two additional studies have

also failed to demonstrate any efficacy of 1 Hz rTMS on AVH frequency.<sup>41,42</sup> Therefore, evaluating rTMS on the hallucination frequency only might be too limiting, given that the AHRS frequency item does not take hallucinations that occur on a less than daily basis into account.

The percentage of responders based on total AHRS score did show a significant difference between the active and the sham groups at D14 following rTMS procedure, but this difference did not persist over time. Since this result was only observed at D14, some comments on the delay and the transient nature of the between-group difference in responder rate are warranted. First, the significant difference in responders might be due to the combination of a delayed effect of the active treatment along with a simultaneous decrease of placebo responders in the sham group at D14. This delayed effect was also observed in the treatment of AVHs after the first week,<sup>43</sup> at 2-week follow-up,<sup>18</sup> and even at 3 weeks following active cTBS,<sup>44</sup> and a similar temporal pattern has been observed in depressive patients.<sup>28</sup> Placebo responders could also vary over time, and analysis of the placebo response for each subject allows us to investigate the observed dip in placebo responses seen at day 14 (see supplementary data figure 1). In this study, 13 patients in the sham group were observed to be placebo responders in least at 1 out of the 5 evaluations, and 3 types of responders were identified. Three patients from the sham group were placebo responders at all evaluations except one (either at the first or the last evaluation), could be defined as maintained placebo responders, and were observed at D14 in particular (type 1). Five patients were placebo responders at 1, or more often at 2 evaluations but not at D14, and presented AVHs at D14 and at least 2 other evaluations (type 2). These patients may reflect the natural variations of AVH scores over time, rather than a real placebo effect. Five patients were early placebo responders at only D2 and/or D7, and not at later evaluations (type 3). This early and brief response over 1 week following sham rTMS has been reported previously.<sup>43</sup> These type 3 placebo responders could account for the “dip” in overall placebo responders observed at D14 in the sham group. We note that the difference in responders between the active and sham groups could not be explained by differences in demographic characteristics. In fact, given the observation of a greater placebo response with higher baseline clinical severity scores,<sup>45</sup> we expected a higher level of placebo responders in the sham group, since those patients presented with slightly higher doses of antipsychotics, PANSS scores, and more prior hospitalizations. Finally, rTMS effect sustainability has not been evaluated under double-blind conditions in previous studies. In fact, reporting an efficacy of active treatment over sham conditions evaluated the efficacy of rTMS at one endpoint only,

either at the end of the treatment procedure<sup>14–17,40</sup> or at 1 and 2 weeks after the end of treatment.<sup>18</sup> Notably, a transient effect was reported with active cTBS showing an effect after 3 weeks but not after 6 weeks after treatment.<sup>44</sup> This delayed and transient effect account for the negative results reported in studies based only on early or late assessments after treatment.<sup>46–49</sup> However, the transient effect seen in the present study could also be due to an insufficient number of rTMS sessions. As described, rTMS exposure in this study was limited to 4 sessions, while “high dose” or “accelerated” protocols typically suggest more sessions to achieve maximum efficacy.<sup>26</sup> The view toward maximizing the number of rTMS sessions was also suggested by data in an unmasked extension study for the treatment of AVHs.<sup>40</sup>

The fact that efficacy was not maintained over time could support the application of maintenance rTMS sessions every 2 or 3 weeks. The delayed clinical response lasting beyond the time of stimulation could be explained by an effect of 20 Hz rTMS on brain plasticity.<sup>50</sup> This hypothesis is corroborated by the long-lasting effects observed in various markers of neuroplasticity in animals following high-frequency cortical stimulation, including brain-derived neurotrophic factor and glutamate receptors.<sup>51</sup>

#### *Site of Stimulation*

The second issue addressed in the current study is the method of rTMS targeting to a precise anatomical site. The target was defined as the site for which stimulation was found to produce the most significant effects on AVHs, and was located in the left temporo-parietal cortex,<sup>33</sup> an area that could correspond to a hub region for both language processing and AVHs. Unfortunately, no AVHs were registered during the scans, so we were unable to investigate overlap between this anatomical location and functional clusters induced by AVHs. However, in this study this region was rigorously identified on each patient’s morphological magnetic resonance imaging (MRI) using a simple procedure (see supplementary data video 1). This method is certainly more accurate on an anatomical basis than using the EEG 10–20 system, and has the additional advantage of ease relative to performing fMRI in clinical practice. Previous studies have shown the value of neuronavigation based on individual morphological or fMRI for improving rTMS outcomes in healthy subjects<sup>52</sup> as well as in patients with depression<sup>53,54</sup> or schizophrenia.<sup>55</sup> Previous rTMS studies have shown conventional 10–20 EEG-based targeting requires significantly more patients to obtain significant results, relative to studies using neuronavigation.<sup>56</sup> This also helps to explain the negative results reported in previous studies with small sample sizes using procedures other than neuronavigation,<sup>46</sup> even though high-frequency (20 Hz) stimulation was applied.<sup>57</sup>

#### *Tolerance*

Although 20 Hz was preformed, the treatment presented here was tolerated quite well. While the presence of side effects as assessed with VAS was significantly higher in the active group relative to the sham group, they were all minor. No major adverse events were observed, there were no seizures, and the treatment was not discontinued in any patient due to side effects. Although no seizures following rTMS applied to the temporal areas have been reported, we designed the rTMS parameters for the present study according to the international safety guidelines for rTMS,<sup>58</sup> paying particular attention to the duration of intertrain intervals (50 s) with respect to the stimulation intensity (80% of rMT) to avoid the risk of seizure.<sup>58,59</sup> We also did not find any cognitive side effects, in agreement with the literature<sup>60</sup> which includes rTMS studies performed in patients with AVHs.<sup>15,61,62</sup> Unexpectedly, more depression and sleepiness/sedation were reported with the UKU rating scale in the sham group than in the active group at D7. No other differences between groups were observed. The side effects reported with VAS were counter-balanced with the placebo effects assessed with the UKU scale, and suggest that the blindness procedure was effective. This data further support the safety profile of high-frequency rTMS application for other clinical indications, such as neuropathic pain, tinnitus, and stroke.<sup>63</sup>

#### *Limits of the Study*

This study has some limitations. A high number of patients that dropped out prior to starting the rTMS procedure (20%), although there were no dropouts during the follow-up period. The fact that randomization was not done just before the beginning of the treatment could explain the high dropout level and the slight (but not significant) difference between groups in past hospitalizations, illness duration, and years of education. This reduced the power of the study from 90% to 77% and could explain the lack of a significant result for the primary outcome. However, for the secondary outcome the *P*-value was equal to .016, the OR was significant, and the power was close to 80% indicating relevant differences between groups. The absence of a group treated with low-frequency (1 Hz) rTMS prevents us from drawing conclusions regarding the relative merits of high-frequency over low-frequency rTMS applied over the cortical target site used in this study. The fact that patients were not asked about which group they were a part of at the end of the treatment could be considered a weakness of the blindness procedure. Finally, the number of stimulation sessions could be insufficient for a long-lasting effect, and which might explain the transient nature of the effect we observed.

*In conclusion*, these results confirm the value of high-frequency rTMS (20 Hz) applied to the left temporal cortex for the treatment of AVHs. However, this efficacy is

transient, and additional clinical trials are necessary to further support this innovative therapy and to improve its efficacy, potentially by long-term management based on a more prolonged procedure.

### Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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### Conflicts of interest

Sonia Dollfus is an expert and consultant or participated in educational conferences for the following industrial laboratories: Gedeon Richter, Roche, Takeda, Fabre, Janssen, and ONO Pharma. Olivier Guillin is expert or consultant for Takeda, JNJ, Servier, Lundbeck, Fabre, Otsuka. Benoit Trojak received honoraria for participation in clinical trials and oral presentations from DA pharma, Ethypharm, Lundbeck, Janssen, and Lilly. Marion Plaze participated in educational conferences or has received travel grant from Lilly, Otsuka, Lundbeck, Janssen, and Astra-Zeneca. Cécilia Nauczyciel received honoraria for participation in oral intervention from Astra Zeneca. Vincent Meille received honoraria for participation in clinical trials and oral presentations from DA pharma, Ethypharm, Lundbeck, Janssen, and Lilly. Marie Odile Krebs participated in advisory boards or educational conferences and has received travel grant or compensation from F. Hoffmann–La Roche, Ltd., Otsuka, Lundbeck, Janssen, and Astra-Zeneca. Jean-Marie Batail has relationships (travel/accommodations expenses covered/reimbursed/educational conferences) with Otsuka, Lundbeck, Janssen, and Lilly who might have an interest in the work submitted in the previous 3 years. Raphaël Gaillard has served as consultant, member of the scientific advisory board and/or speaker for Astra Zeneca, Pierre Fabre, Janssen, Lilly, Otsuka, Roche, SANOFI, Servier and he has received research support from Servier and Sisley. Samar S. Ayache, Perrine Brazo,

Nathalie Chastan, Benoit Crepon, Christophe Delmas, Olivier Etard, Gael Fouldrin, Emmanuel Gerardin, Laurent Guillaume, Rémy Guillevin, Carole Guillevin, Ghina Harika-Germaneau, Nemat Jaafari, Jean-Pascal Lefaucheur, Nicolas Lafay, Elise Leroux, Aurélie Montagne Larmurier, Rémy Morello, Clément Nathou, Annick Razafimandimby, Maud Rotharmel, Ghassen Saba, and Issa Wassouf have no conflicts of interest to disclose.

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