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Theta burst stimulation of temporo-parietal cortex regions for the treatment of persistent auditory hallucinations: a multicentre, randomised, sham-controlled, triple-blind phase 3 trial in Germany



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Summary

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Background Auditory verbal hallucinations are a major burden for patients with schizophrenia spectrum disorder and are often resistant to pharmacological and psychotherapeutic interventions. Repetitive transcranial magnetic stimulation (rTMS) of the temporo-parietal cortex has been proposed as a treatment for persistent auditory verbal hallucinations. We aimed to compare the efficacy and safety of bilateral continuous theta burst stimulation (cTBS), a brief and efficient form of rTMS, in adults with auditory verbal hallucinations versus sham cTBS.

Methods This multicentre, randomised, sham-controlled, triple-blind phase 3 clinical trial was conducted at seven German psychiatric university hospitals and followed a planned two-stage adaptive design. Eligible patients were aged 18–65 years, had experienced persistent auditory verbal hallucinations at least once per week for a minimum of 3 months, and scored 3 points or higher on item P3 (hallucinatory behaviour) of the clinician-rated Positive Scale of the Positive and Negative Syndrome Scale (PANSS). 138 adults with treatment-persistent auditory verbal hallucinations and schizophrenia spectrum disorder were randomly assigned (1:1) to receive 15 sessions of active (n=70) or sham cTBS (n=68) administered sequentially as 600 pulses to the left and 600 pulses to the right temporo-parietal cortex over a 3-week period. The primary outcome was the change in the auditory hallucinations subscale of the Psychotic Symptom Rating Scales (PSYRATS-AH) from baseline to the end of treatment at 3 weeks, analysed in the intention-to-treat population, which included all randomly assigned patients who received at least one stimulation session. Safety was assessed in all patients who received at least one stimulation session. Follow-up assessments were performed at 1, 3, and 6 months after the end of treatment. People with lived experience were not involved in the study. This trial was registered at ClinicalTrials.gov, NCT02670291.

Findings Between Oct 24, 2015, and May 1, 2023, 2583 patients were screened for eligibility, of whom 138 patients were randomly assigned to active cTBS (n=70; 32 [46%] females and 38 [54%] males) or sham treatment (n=68; 24 [35%] females and 44 [65%] males). Race and ethnicity data were not collected. The primary intention-to-treat analysis (66 patients in the active cTBS group; 64 patients in the sham cTBS group), combining stages 1 and 2, showed patients in the active cTBS group had a significantly greater decrease in the PSYRATS-AH score at end of treatment than did patients in the sham cTBS group (−6·36 [SD 7·97] vs −3·74 [SD 5·79]; adjusted difference −2·36 [95% CI −4·71 to −0·01]; p=0·042). Overall, 85 adverse events (43 in the active cTBS group; 42 in the sham cTBS group) were reported in 22 (33%) of 66 patients in the active cTBS group and 21 (33%) of 64 patients in the sham cTBS group. Headache was the most common adverse event in both groups (n=13 active cTBS group vs n=17 sham cTBS group). One serious adverse event occurred in the active group.

Interpretation Sequential bilateral temporo-parietal cTBS over 3 weeks was safe and effective for reducing auditory verbal hallucinations in adults with schizophrenia spectrum disorder. This trial establishes cTBS as a treatment option for the care of these patients. Further research is needed to evaluate maintenance strategies, identify treatment predictors, and assess long-term efficacy.

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Introduction

Auditory verbal hallucinations affect more than 60% of patients with schizophrenia spectrum disorder¹ and often cause severe distress, impair social functioning,

and increase the risk of physical harm and suicidality.^{2,3} Antipsychotic medication is the first-line treatment and rapidly alleviates auditory verbal hallucinations in most cases;⁴ however, its acceptability is frequently limited by

Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 1998, and Dec 31, 2024, using the search terms: “auditory hallucinations”, “auditory verbal hallucinations”, “repetitive transcranial magnetic stimulation”, “theta burst stimulation”, “schizophrenia”, and “clinical trial”. Single-case studies, proof-of-concept studies, and small controlled trials have demonstrated the potential effectiveness of inhibitory 1 Hz repetitive transcranial magnetic stimulation (rTMS) of the left temporo-parietal cortex for treating auditory verbal hallucinations. Systematic reviews and meta-analyses have concluded that rTMS could be an effective and well-tolerated treatment approach for individuals with persistent auditory verbal hallucinations who do not respond to other interventions. Theta burst stimulation (TBS), a brief rTMS protocol, has shown promise in improving clinical efficacy and tolerability. However, the available trials were limited by sample size, monocentric design, and heterogeneity in both treatment protocols and stimulation parameters. A meta-analysis of four randomised trials published in 2024 reported a standardised mean difference of -0.45 (95% CI -1.01 to 0.12) between active continuous TBS (cTBS) and sham cTBS in the treatment of auditory verbal hallucinations, but large-scale

multicentre clinical trials providing reliable and generalisable evidence for strong clinical recommendations are still needed.

Added value of this study

The present trial is the first multicentre, randomised, sham-controlled study to evaluate the efficacy and safety of bilateral temporo-parietal cTBS for auditory verbal hallucinations in adults with schizophrenia spectrum disorder. The two-stage adaptive design ensured adequate sample size and statistical power. The intention-to-treat analysis showed that 3 weeks (15 sessions) of once-daily bilateral cTBS was an effective and safe treatment option for persistent auditory verbal hallucinations.

Implications of all the available evidence

The results of this phase 3 study, in addition to those of previous trials, provide evidence supporting the routine clinical use of cTBS, a brief and more efficient form of rTMS, in treating patients with schizophrenia spectrum disorder and persistent auditory verbal hallucinations. Further studies are warranted to assess maintenance therapy strategies and to develop individualised approaches for optimal patient outcomes.

adverse side-effects, and 25–30% of patients experience persistent symptoms.² Therefore, auditory verbal hallucinations represent a pressing clinical challenge in psychiatric care, with a need for novel treatment strategies. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique, which is already applied in clinical settings. Our study builds on early evidence suggesting potential benefits of rTMS targeting the temporo-parietal cortex.^{5,6} Initially, low-frequency (1 Hz) rTMS aimed at reducing hyperactivity in language-related temporo-parietal regions showed therapeutic potential for auditory verbal hallucinations.^{5,7} However, subsequent single-centre studies have yielded inconsistent results, and meta-analyses have highlighted the heterogeneity of the existing evidence.^{6,8–10} The variability in rTMS parameters and the limited scope of research have hindered the definitive assessment of its therapeutic efficacy. Although rTMS remains a promising approach, the current evidence does not support its use as a first-line treatment for persistent auditory verbal hallucinations.¹¹

A novel form of rTMS, theta burst stimulation (TBS), now provides a considerably shorter and more efficient treatment approach.^{12,13} Non-inferiority trials¹⁴ have validated TBS as a viable alternative to the standard rTMS in the treatment of depression. For patients with schizophrenia spectrum disorder, reducing the treatment duration from 16–20 min to 40 s per session is likely to improve tolerability and treatment adherence. A shorter application time also enables bilateral stimulation,

potentially enhancing treatment effectiveness.^{15,16} Building on 1 Hz rTMS protocols, pilot studies evaluated up to 20 sessions of inhibitory continuous TBS (cTBS) to the left or bilateral temporo-parietal cortex.^{17–19} However, ten sessions of cTBS in 64 individuals with auditory verbal hallucinations were not found to be superior when compared with sham stimulation.²⁰ A meta-analysis of four studies (151 patients) found no advantage of cTBS over sham stimulation (standardised mean difference [SMD] -0.45 [95% CI -1.01 to 0.12]; $p=0.13$).²¹ However, subgroup analysis identified significant efficacy in treatments using more than ten sessions and exceeding 6000 total pulses ($n=87$; SMD -4.43 [-8.22 to -0.63]; $p=0.02$). A comparative pilot trial ($n=64$) demonstrated that cTBS is more effective than 1 Hz rTMS in reducing auditory verbal hallucinations.²²

Based on the findings of our pilot studies,^{15,17} in this randomised sham-controlled trial we aimed to confirm whether sequential bilateral cTBS to the temporo-parietal cortex regions applied over a 3-week period (15 sessions) reduces persistent auditory verbal hallucinations in patients with schizophrenia spectrum disorder.

Methods

Study design

This multicentre, randomised, sham-controlled, triple-blind phase 3 confirmatory clinical trial was done at seven university hospitals in Germany (Tübingen and Munich [stages 1 and 2], Düsseldorf, Augsburg, Ulm, and Heidelberg [stage 2 only], and Rostock [stage 1 only]).

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The study had an adaptive design, including a planned interim analysis for sample size re-estimation.

The first patient was randomly assigned on Jan 16, 2017, and the final follow-up assessment was conducted on Jan 12, 2024.

During the study, two amendments were made to the eligibility criteria: increasing the maximum age and shortening the stable medication period before treatment (appendix p 4), both aimed at improving the recruitment rate.

The Centre for Clinical Studies (ZKS; University of Tübingen, Tübingen, Germany) was responsible for independent data monitoring at all sites, and the Institute of Clinical Epidemiology and Applied Biometry (IKEaB, University of Tübingen) performed randomisation, data management, and statistical analyses. The statistical analysis plan was finalised after the completion of the blind data review and is available online.

Ethical approval was obtained from the ethics committee of the medical faculty of the University of Tübingen (739/2015BO2). The initial study protocol was published in October, 2018,²³ and was registered at ClinicalTrials.gov, NCT02670291.

Participants

The study included inpatients and outpatients with schizophrenia spectrum disorder diagnosed according to the DSM-5 (schizophrenia, schizoaffective disorder, or schizophreniform disorder) based on a comprehensive clinical examination and confirmed by a structured clinical interview for DSM-5. Eligible participants were aged 18–65 years who self-identified as female, male, or non-binary and had sufficient German proficiency to complete the assessments. We did not collect self-reported ethnicity data because this socio-cultural construct was not identified as a relevant biological variable for the neurobiological intervention studied in this trial. Eligible participants had experienced persistent auditory verbal hallucinations, occurring at least once per week for a minimum of 3 months, and scored 3 points or higher on item P3 (hallucinatory behaviour) of the clinician-rated Positive Scale of the Positive and Negative Syndrome Scale (PANSS). Eligible patients had an insufficient response to at least one antipsychotic drug administered at the maximum tolerated dose within the recommended therapeutic range for at least 6 weeks. Antipsychotic medication had to be stable 2 weeks before the first cTBS session and throughout the treatment phase. Patients with unstable medication before the intervention were excluded from the study, while those who required medication changes during treatment were excluded from the per-protocol analysis.

The exclusion criteria included a history or evidence of brain injury, surgery, significant malformation, or neoplasm; neurodegenerative disorders; deep brain stimulation; history of seizures; presence of intracranial metallic particles, cochlear implants, or cardiac

pacemakers; substance dependence or use as the primary diagnosis; acute suicidality; severe somatic comorbidity; pregnancy (confirmed by blood or urine test) or lactation; and participation in another study. Full inclusion and exclusion criteria are provided in the appendix (p 2).

Recruitment was supported by promotional activities, including flyers in hospitals and doctors' offices, study presentations at hospital staff and patient events, and advertisements in local newspapers and social media platforms (Facebook and Instagram).

Each patient provided written informed consent before the first study procedure. For patients with a legal guardian, written consent was also obtained from the legal guardian. All study procedures were conducted in accordance with the current Harmonised Good Clinical Practice guidelines.

Randomisation and masking

As a first step, IKEaB generated a randomisation list stratified by study centre and with mixed block lengths using the nQuery software (version 4.0). According to this list, eligible patients were randomly assigned (1:1) to either active cTBS or sham stimulation. The list also specified the hemisphere where stimulation would begin in the first treatment session. Subsequently, the randomisation list was linked to six-digit numerical codes provided by the TMS stimulator manufacturer (MagVenture, Farum, Denmark). These patient-specific codes were required for stimulation with a combined active-sham coil (Cool-B65A/P, MagVenture), where the active and inactive sides were identical in appearance. The codes were stored in the TMS stimulators and, based on randomisation, determined which side should be positioned on the patient's head. Activation of the TBS protocol required double entry of both an operator code and the patient-specific six-digit numerical code. The stimulator then displayed either ready for stimulation or a turn the coil message if the actual coil orientation did not match the randomisation or code specification. The stimulation could only be initiated when the coil was in the code-determined orientation.

In the sham condition,²⁴ the inactive side of the coil was positioned on the patient's head. Patients in the sham group did not receive TMS pulses but heard the associated clicking sound. To simulate the somatosensory effects of cTBS, all patients received electrical co-stimulation, ensuring operator and patient masking. Two scalp electrodes (AMBU Neuroline 710; Bad Nauheim, Germany) were placed at electrode positions corresponding to the stimulation site: T3 and P3 for left-sided stimulation and T4 and P4 for right-sided stimulation (10-20 electroencephalogram [EEG] system), depending on the stimulated hemisphere. The stimulator automatically adjusted the co-stimulation intensity to match the individual stimulation intensity.

After confirming patient eligibility, the study physician sent an electronic randomisation request to the IKEaB,

See Online for appendix

For the statistical analysis plan
see <https://zenodo.org/records/15058333>

which provided a six-digit numerical code and specified the hemisphere for initial stimulation.

To maintain masking, raters and operators were separate individuals, and raters were not present during the stimulation sessions. The adaptive design required unmasking of group allocation in stage 1 for interim analysis and sample size adjustment. However, biometricians provided information only at the group level, not for individual patients. Patient-specific unmasking information was communicated to the principal investigator and study sites only after completion of stage 2 final analysis, allowing patient notification of their allocation on request.

Procedures

The cTBS protocol was based on our pilot study.¹⁷ Randomly assigned patients received 15 active cTBS or sham stimulation sessions over 3 consecutive weeks (one session daily, Monday to Friday). In each session, active or sham cTBS was sequentially applied to both temporo-parietal cortices. To exclude order effects, the sequence of stimulation sides (left to right or right to left) was randomised in the first session and alternated thereafter.

Physicians informed patients about the study, obtained written informed consent, and assessed eligibility through a screening process that included psychiatric diagnosis, documentation of medical history and medication use (current and past), physical and neurological examination, and smoking status. Physicians or experienced psychologists performed the assessments at baseline, the end of week 1 (fifth session), the end of week 2 (10th session), and the end of week 3 (15th session [end of treatment]). Follow-up assessments were administered 1, 3, and 6 months after the end of treatment. Changes in anti-psychotic and other medications were documented at each visit in the clinical record file.

The interval between screening and the first treatment session was 3–7 days. Missed treatment sessions were not performed after end of treatment.

Before the first treatment, a study physician determined the individual stimulation intensity by measuring the resting motor threshold of both the left and right primary motor cortices (hand area). Resting motor threshold was determined with an active stimulation coil (Cool-B65, MagVenture) and defined as the minimum stimulation intensity needed to elicit a visible motor response in at least five of ten TMS pulses. Following standard clinical methods, motor response was evaluated by observing contralateral thumb movements. For treatment sessions, the stimulation intensity was adjusted to 80% of the resting motor threshold on the corresponding side.

The participating centres used either the MagPro X100 or MagPro R30 stimulators (MagVenture). Each cTBS train (40 s) consisted of 600 stimuli applied in bursts of three pulses at 50 Hz delivered every 200 ms (5 Hz).^{12,17} The stimulation used biphasic pulses,

with the current flowing first anterior-to-posterior and then posterior-to-anterior.

Both active and sham cTBS were bilaterally applied to temporo-parietal cortex regions, midway between T3 and P3 in addition to T4 and P4 (EEG 10-20 system). To prepare for stimulation, the operator used a washable pen to mark the positions on both hemispheres for rTMS and electrical co-stimulation and fixed the scalp electrodes (Ambu Neuroline710) for co-stimulation (appendix p 5).

Treatment settings were identical for each study site. The patients were seated in a reclining chair with head support to ensure stability during stimulation. After securing the co-stimulation electrodes and positioning the coil appropriately (fixed with a metal arm; appendix p 6), patients were instructed to remain still and speak only if necessary. A safety check was performed after each session, including inspection of the stimulation areas and assessment of the patient's wellbeing. Complete sessions, including preparation and safety checks, lasted approximately 20 min.

Outcomes

The primary outcome was the change in the auditory hallucinations subscale of the Psychotic Symptom Rating Scales (PSYRATS-AH) from baseline to 3 weeks (end of treatment) in the active versus sham group.

Secondary outcomes were PANSS scores to assess symptom severity in schizophrenia (for PANSS positive, PANSS negative, and PANSS positive item 3 separately); Global Assessment of Functioning (GAF) scale scores to evaluate the effect of treatment on general measures of psychosocial functioning; scores on the Clinical Global Impression Improvement Scale (CGI-I); and response rate to cTBS (defined as a $\geq 25\%$ reduction of PSYRATS-AH). Secondary outcomes, with the exception of response rate, were assessed at baseline (with the exception of the CGI-I), during the treatment period at the end of weeks 1, 2, and 3, and during the follow-up period at weeks 7, 15, and 27. Response rate was assessed after end of treatment. Furthermore, in a post-hoc analysis we calculated the proportion of patients with a response ($\geq 50\%$ and $\geq 75\%$) as not pre-specified, exploratory outcomes.

Investigators at the study sites continuously documented adverse events and serious adverse events during the treatment period. Events that occurred during the application of the cTBS or sham condition (ie, itching, tingling, and facial muscle contractions) were not documented as adverse events, since these had been anticipated and were clearly related to regular TMS application. The safety monitoring board received annual adverse event reports, whereas serious adverse events were immediately reported.

Choice of primary outcome measure

The PSYRATS-AH subscale is an 11-item clinician-rated 5-point (0–4) scale for the multidimensional assessment of auditory hallucinations in psychotic disorders. The

score ranges from 0 to 44, with higher scores indicating more severe symptoms. It is one of the most widely used and psychometrically best evaluated scales for the assessment of auditory hallucinations and is free to use. The German version²⁵ has shown excellent psychometric properties (intraclass correlation coefficient 0.98; Cronbach α 0.75). PSYRATS-AH has relatively brief administration time (approximately 15 min), making it practical for clinical and research use.

Statistical analysis

The primary hypothesis tested the superiority of cTBS over sham stimulation at the end of treatment using a baseline-adjusted analysis of covariance model for PSYRATS-AH. Two-sided p values less than or equal to 0.05 were considered to indicate statistical significance.

A preliminary sample size estimation was performed at the start of the study, with a planned update according to a pre-registered interim analysis (appendix p 7). Sample

size calculation targeted 80% power based on effects from our pilot study.¹⁷ PSYRATS-AH data were available at baseline and after 3 weeks of stimulation. The difference (Δ) between the end of treatment and baseline was calculated. The difference in Δ between the active and sham groups was 5.25 points, and the pooled SD was 5.42. This resulted in a standardised difference of 0.97. To avoid overestimating the effect, we conservatively reduced the effect size to 0.7. With a standardised difference of 0.7, 34 evaluable patients per group were required to achieve a power of 80% in the t test for independent samples. We chose a two-stage adaptive design based on Bauer and Köhne (appendix pp 7–8).²⁶ This design yielded a total sample size of 94 patients, including a 12% dropout rate in the second stage. Thus, the total sample size in both stages resulted in 137 patients: 43 patients in the first stage (including two patients excluded from the intention-to-treat [ITT] population as they dropped out before the first stimulation) and 94 patients in the second stage.

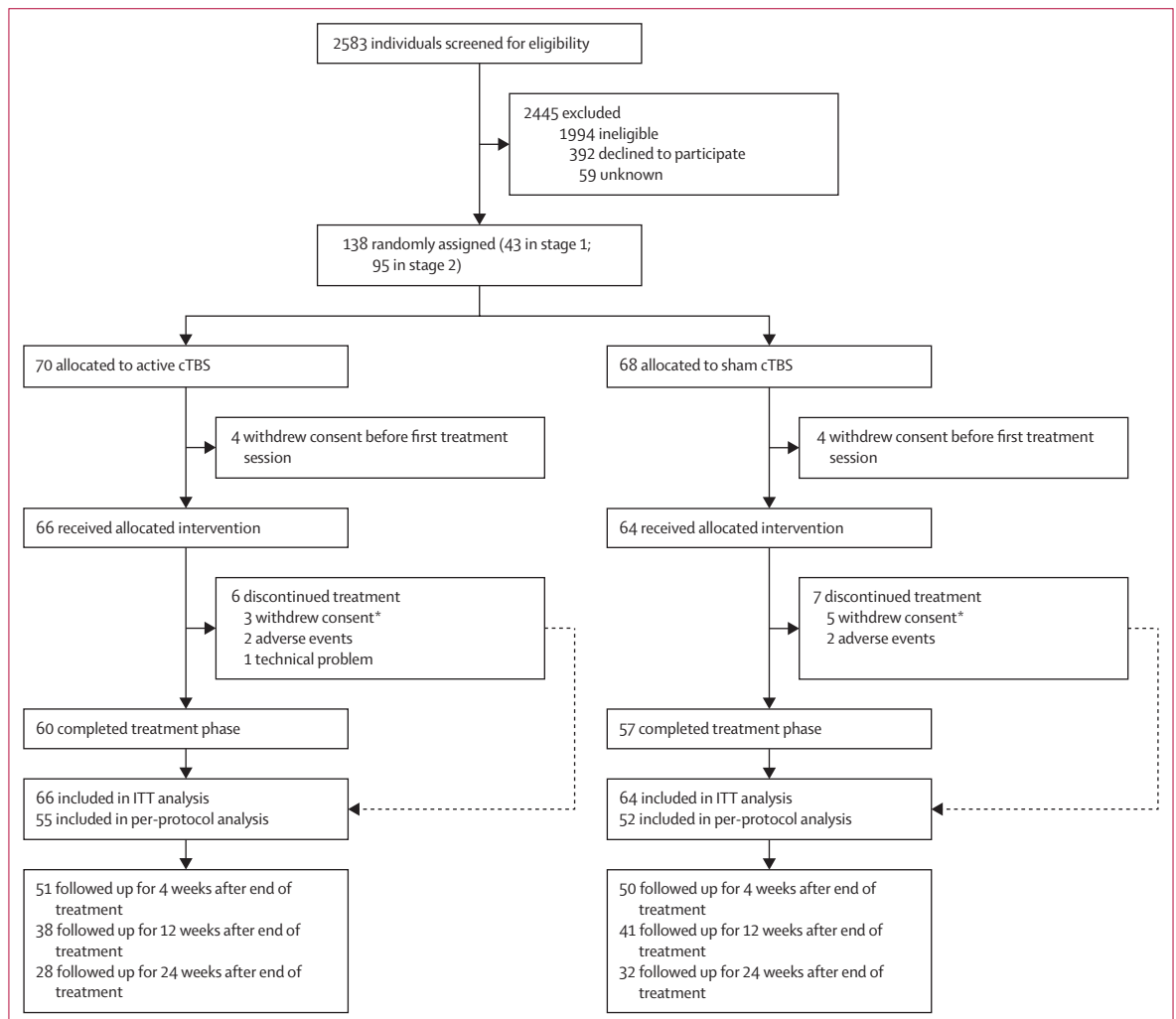


Figure 1: Trial profile
cTBS=continuous theta burst stimulation. ITT=intention-to-treat. *With permission to use their data.

In the adaptive design, separate one-sided p values, p value 1 (P_1) and p value 2 (P_2), were calculated for each stage. The product of both p values was then compared with the predefined critical value of 0.0038,²⁶ which guaranteed an overall two-sided level of significance of 0.05. Both stage 1 and stage 2 analyses used a baseline ANCOVA model stratified for the study centre, using dummy variables with treatment as the factor of interest. Differences between study groups adjusted for baseline and study centre (treatment regression coefficients beta in the ANCOVA models), including SEs, are presented. Effect sizes were calculated as the quotient of adjusted differences and SD at baseline for the total sample. Furthermore, we used a multiple imputation approach for missing data (n=3000 imputation samples) based on the assumption of missing data at random, dependent on the baseline and intermediate measurements of the primary outcome before end of treatment. We checked the

assumptions of ANCOVA by inspection of residuals with respect to skewness and kurtosis, and regression of absolute residuals on predicted values (appendix pp 9–11).

In a sensitivity analysis, we adjusted for the two amendments (increasing maximum age and decreasing stability of pre-treatment medication) using two dummy variables in the ANCOVA models of the primary analysis.

The primary ITT analyses included all patients who received at least one stimulation session. The per-protocol analysis comprised all patients who met the inclusion and exclusion criteria without major protocol violations, had documented PSYRATS-AH values at baseline, attended at least 12 treatment sessions, maintained stable antipsychotic medication during the treatment phase, and had documented PSYRATS-AH at end of treatment. The safety population included all patients with at least one stimulation session.

	Active cTBS* (n=66)	Sham cTBS* (n=64)	Stage 1† (n=41)	Stage 2‡ (n=89)	Total§ (n=130)
Centre					
1	23 (35%)	24 (38%)	22 (54%)	25 (28%)	47 (36%)
2	1 (2%)	1 (2%)	2 (5%)	0	2 (2%)
3	16 (24%)	20 (31%)	17 (41%)	19 (21%)	36 (28%)
4	10 (15%)	8 (13%)	..	18 (20%)	18 (14%)
5	9 (14%)	6 (9%)	..	15 (17%)	15 (12%)
6	4 (6%)	3 (5%)	..	7 (8%)	7 (5%)
7	3 (5%)	2 (3%)	..	5 (6%)	5 (4%)
Age, years	36.92 (11.50)	36.19 (11.83)	34.54 (10.01)	37.49 (12.24)	36.56 (11.62)
Gender					
Female	32 (48%)	24 (38%)	21 (51%)	35 (39%)	56 (43%)
Male	34 (52%)	40 (63%)	20 (49%)	54 (61%)	74 (57%)
Gender-diverse	0	0	0	0	0
Years of education	12.82 (3.35)	13.49 (3.05)	13.95 (3.43)	12.77 (3.06)	13.15 (3.21)
Time since diagnosis of schizophrenia spectrum disorder, years	12.52 (9.17)	12.16 (10.77)	9.85 (8.18)	13.48 (10.54)	12.34 (9.97)
Diagnosis					
Schizophrenia	60 (91%)	57 (89%)	35 (85%)	82 (92%)	117 (90%)
Schizophreniform	0	1 (2%)	1 (2%)	0	1 (1%)
Schizoaffective	6 (9%)	6 (9%)	5 (12%)	7 (8%)	12 (9%)
Time since first auditory hallucination, years	12.00 (9.68)	10.77 (9.35)	8.71 (6.68)	12.63 (10.36)	11.39 (9.51)
Handedness					
Left	4 (6%)	8 (13%)	4 (10%)	8 (9%)	12 (9%)
Right	62 (94%)	55 (87%)	37 (90%)	80 (91%)	117 (91%)
Smoking behaviour (Fagerström Scale)					
Non-smoker	28 (42%)	24 (38%)	18 (44%)	4 (38%)	52 (40%)
Smoker	38 (58%)	40 (63%)	23 (56%)	55 (62%)	78 (60%)
Chlorpromazine equivalents					
Median	640.00	612.65	625.00	637.00	637.50
IQR	607.17	543.80	392.59	625.20	571.43
Range	0–2550.00	0–2239.39	0–1687.80	0–2550.00	0–2550.00
Patients prescribed clozapine	24 (36%)	25 (39%)	15 (37%)	34 (3%)	49 (38%)

Data are n (%), or mean (SD), unless otherwise specified based on multiple imputations where applicable. cTBS=continuous theta burst stimulation. *Active cTBS and sham cTBS were pooled across study stages. †Stages 1 and 2 were pooled across study groups. ‡Total population pooled across study groups and stages.

Table 1: Baseline demographic and clinical characteristics of the intention-to-treat population

	Stage 1		Stage 2		Pooled stages		Adjusted difference (95% CI)	p value	Effect size
	Active cTBS (n=21)	Sham cTBS (n=20)	Active cTBS (n=45)	Sham cTBS (n=44)	Active cTBS (n=66)	Sham cTBS (n=64)			
Primary endpoint									
PSYRATS-AH score at baseline	28.14 (5.51)	27.80 (4.70)	28.87 (4.72)	28.77 (5.80)	28.64 (5.03)	28.47 (5.54)
PSYRATS-AH score at the end of treatment	22.40 (10.26)	25.09 (7.50)	22.21 (8.99)	24.56 (7.75)	22.27 (9.48)	24.73 (7.73)
Change in PSYRATS-AH score from baseline	-5.74 (6.68)	-2.71 (5.07)	-6.65 (8.41)	-4.21 (5.98)	-6.36 (7.97)	-3.74 (5.79)	-2.36 (-4.71 to -0.01)	0.042	-0.448
Secondary endpoints									
PANSS (positive) at baseline	15.90 (3.92)	15.45 (3.91)	17.16 (4.76)	16.25 (4.75)	16.76 (4.58)	16.00 (4.56)
PANSS (positive) at the end of treatment	12.54 (4.48)	14.35 (3.98)	4.12 (4.83)	14.48 (4.58)	13.62 (4.81)	14.44 (4.43)
Change in PANSS (positive) from baseline	-3.37 (3.58)	-1.10 (2.97)	-3.03 (3.82)	-1.77 (3.06)	-3.14 (3.78)	-1.56 (3.07)	-1.33 (-2.51 to -0.15)	0.027	-0.291
PANSS (negative) at baseline	17.43 (5.47)	18.40 (5.16)	19.13 (7.40)	19.09 (7.60)	18.59 (6.94)	18.88 (6.99)
PANSS (negative) at the end of treatment	15.64 (5.27)	18.05 (5.71)	16.37 (5.98)	16.96 (7.37)	16.14 (5.82)	17.30 (6.97)
Change in PANSS (negative) from baseline	-1.79 (5.87)	-0.35 (3.91)	-2.76 (5.10)	-2.13 (4.86)	-2.45 (5.41)	-1.58 (4.69)	-0.93 (-2.55 to 0.70)	0.263	-0.134
PANSS (item 3) at baseline	4.52 (0.73)	4.60 (0.80)	4.60 (0.90)	4.80 (0.87)	4.58 (0.86)	4.73 (0.86)
PANSS (item 3) at the end of treatment	3.42 (1.24)	4.24 (0.97)	3.75 (1.24)	4.22 (1.26)	3.65 (1.25)	4.23 (1.19)
Change in PANSS (item 3) from baseline	-1.10 (1.24)	-0.36 (0.57)	-0.85 (1.10)	-0.57 (1.00)	-0.93 (1.16)	-0.50 (0.90)	-0.47 (-0.84 to -0.10)	0.012	-0.548
GAF at baseline	49.14 (11.39)	46.25 (12.40)	48.13 (11.93)	48.18 (13.80)	48.45 (11.86)	47.58 (13.51)
GAF at the end of treatment	52.77 (13.65)	50.98 (14.05)	53.82 (14.43)	51.55 (15.67)	53.49 (14.30)	51.37 (15.30)
Difference in GAF from baseline	3.63 (11.77)	4.73 (10.64)	5.68 (8.50)	3.37 (9.96)	5.03 (9.78)	3.79 (10.27)	1.30 (-2.25 to 4.86)	0.472	0.103
CGI-I at the end of treatment	3.36 (1.06)	3.63 (0.78)	3.16 (1.03)	3.46 (0.92)	3.23 (1.04)	3.51 (0.89)	-0.26 (-0.61 to 0.08)	0.131	-0.268

Unless otherwise stated, data are presented as mean (SD) based on multiple imputation. cTBS=continuous theta burst stimulation. PSYRATS-AH=auditory hallucinations subscale of the Psychotic Symptom Rating Scales. PANSS=Positive and Negative Syndrome Scale. GAF=Global Assessment of Functioning. CGI-I=Clinical Global Impression Improvement Scale. The adjusted difference is equal to the difference between the study groups in the primary and secondary endpoints adjusted for baseline and study centre, p values refer to an ANCOVA model adjusted for centre and with multiple imputations; CGI-I was only adjusted for centre, since no baseline values were assessed. The effect size was calculated as the quotient of adjusted differences and SD at baseline (standardised mean difference).

Table 2: Primary and secondary endpoints (intention-to-treat population)

	Stage 1 (n=41)	Stage 2 (n=89)	Pooled stages (n=130)
Adjusted difference	-3.185	-2.067	-2.362
95% CI	-6.58 to 0.21	-5.16 to 1.03	-4.71 to -0.01
SE	1.733	1.578	1.199
SD	5.194	5.312	5.270
Effect size (quotient)	-0.613	-0.389	-0.448
p value	0.033	0.095	0.042

The adjusted difference is equal to the difference between the study groups in the primary endpoint adjusted for baseline and study centre, and SE is the SE of this coefficient. SD is the standard deviation at baseline (combined for both study groups). The effect size was calculated as the quotient of adjusted difference and SD. The product of the one-sided p values of stages 1 and 2 was 0.0031, corresponding to an overall two-sided p value of 0.042 based on the χ^2 distribution with four degrees of freedom. PSYRATS-AH=auditory hallucinations subscale of the Psychotic Symptom Rating Scales.

Table 3: Change from baseline in PSYRATS-AH at the end of treatment by treatment group

Secondary endpoints, including single items of the PSYRATS-AH, were analysed using baseline-adjusted linear models for continuous outcomes with adjustments and coding of covariates identical to the analysis of the primary endpoint (only CGI-I baseline values were not documented). Similar logistic regression models were used for categorical outcomes.

Additionally, for each of the endpoints a linear mixed model including all timepoints with time versus treatment interaction (and treatment, time, and study centre as factors) was calculated (appendix p 22).

Descriptive analyses included means and SD for normally distributed data or medians and IQRs for skewed data, and absolute and percentage frequencies for categorical data. All statistical analyses were conducted using IBM SPSS Statistics for Windows (version 27.0).

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit for publication.

Results

Between Oct 24, 2015, and May 1, 2023, 2583 individuals with schizophrenia spectrum disorder were approached for pre-screening, of whom 138 individuals were screened and randomly assigned (70 patients [32 females and 38 males] to the active cTBS group; 68 patients [24 females and 44 males] to the sham cTBS group). Race and ethnicity data were not collected. Eight patients withdrew consent before the first treatment session (figure 1). The remaining 130 patients were included in the final ITT analysis (66 patients in the active cTBS group and 64 patients in the sham cTBS group). The demographic and clinical characteristics of the patients are summarised in table 1.

56 patients in the active cTBS group and 54 patients in the sham cTBS group received a protocol-compliant number of treatment sessions (≥ 12 sessions). Stimulation intensity (ie, percentage of maximum stimulator output) did not differ between groups (40% on the left and right in the active cTBS group and 39% on the left and right in the sham cTBS group; appendix p 14).

The descriptive analysis of PSYRATS-AH (table 2) showed no differences in baseline values between the study arms for the pooled data from both study phases, with mean (SD) scores of 28.64 (5.03) in the active group and 28.47 (5.54) in the sham group. At the end of the treatment, the PSYRATS-AH score had reduced by 6.36 (SD 7.97) in the active group and 3.74 (SD 5.79) in the sham group (table 2; appendix p 23).

A confirmatory analysis (table 3) was conducted according to the two-stage adaptive design. In this study, the p values for the adaptive design were 0.033 (P_1) in the first stage and 0.095 (P_2) in the second stage. The product of P_1 and P_2 was 0.0031, which was smaller than the critical value of 0.0038 and therefore indicated the superiority of active cTBS over sham stimulation. The adjusted differences in the PSYRATS-AH scores between the two study groups were -3.185 (95% CI -6.58 to 0.21 ; SE 1.733) in the first stage and -2.067 (-5.16 to 1.03 ; 1.578) in the second stage. In a pooled analysis of both stages, the adjusted difference in the PSYRATS-AH scores between the two study groups was -2.362 (-4.71 to -0.01 ; 1.199). These results correspond to an effect size of -0.613 in stage 1, -0.389 in stage 2, and -0.448 overall (table 3).

55 patients in the active cTBS group and 52 patients in the sham cTBS group were included in the per-protocol analysis of the PSYRATS-AH (appendix p 19). For the pooled analyses, the adjusted difference in the PSYRATS-AH score between both study groups was -2.498 (SD 5.298; $p=0.022$). This result corresponds to an effect size of -0.471 .

The sensitivity analysis (adjustment for two amendments) resulted in slightly lower p values compared with the primary analysis ($p=0.035$ vs $p=0.042$ in the ITT analysis; $p=0.011$ vs $p=0.022$ in the per-protocol analysis; appendix p 20).

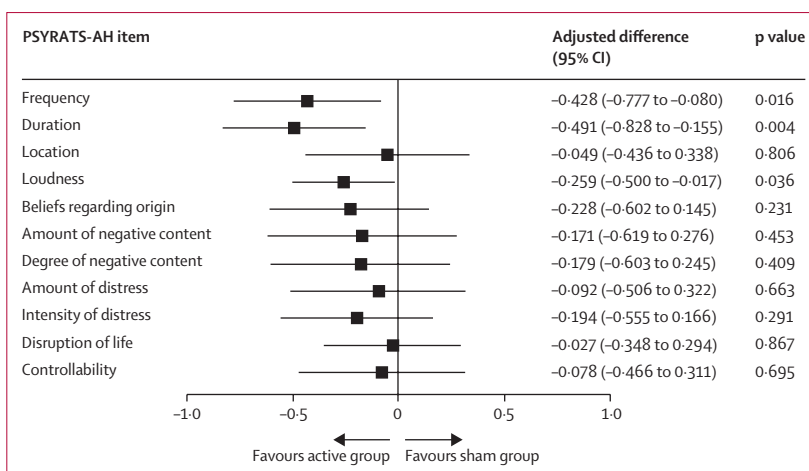


Figure 2: Baseline-adjusted differences between active and sham conditions for each PSYRATS-AH item (ITT population)

Baseline-adjusted differences between the two study groups (based on multiple imputed data) are shown for each PSYRATS-AH item, with 95% CIs and p values. PSYRATS-AH=auditory hallucinations subscale of the Psychotic Symptom Rating Scales. ITT=intention-to-treat.

The reduction in the PANSS positive score (table 2) was significantly higher in the active cTBS group than in the sham cTBS group, but no differences were observed in PANSS negative score between groups. A significantly larger reduction in PANSS item 3, representing hallucinatory behaviour (table 2), was observed in the active cTBS group than in the sham cTBS group. No significant differences in GAF and CGI-I scores were observed between the groups (table 2).

Analysis of the individual items of the PSYRATS-AH highlighted significant adjusted differences between the active cTBS and sham cTBS groups with regard to frequency, duration, and loudness of auditory verbal hallucinations (figure 2).

A predefined treatment response of at least a 25% reduction in the PSYRATS-AH score (decimals due to multiple imputation) was observed in 22.2 (33.6%) of 66 patients in the active cTBS group and 17.9 (28%) of 64 patients in the sham cTBS group. A reduction of 50% or higher was found in 9.3 (13%) patients after treatment with active cTBS and 4.5 (7.1%) patients after treatment with sham cTBS, while a reduction of 75% or more was observed in 6.5 (9.5%) patients in the active cTBS group and 0.1 (0.2%) patients in the sham cTBS group.

In contrast to end of treatment, the proportion of patients who were lost to follow-up was high (appendix p 15), particularly at the two later timepoints, where 40–60% of all patients could not be reached or declined to participate in the visits. The statistical models proved to be unstable because of the large amount of missing data. Additionally, information on changes in antipsychotic medications and concomitant therapy was incomplete or unreliable. As a result, the follow-up data were analysed using descriptive statistics only. Detailed information on

	Active cTBS			Sham cTBS			p value
	Female (n=32)	Male (n=34)	Total (n=66)	Female (n=24)	Male (n=40)	Total (n=64)	
Patients without adverse events	21 (32%)	23 (35%)	44 (67%)	16 (25%)	27 (42%)	43 (67%)	..
Patients with ≥ 1 adverse event	11 (17%)	11 (17%)	22 (33%)	8 (13%)	13 (20%)	21 (33%)	0.95
Number of adverse events per patient
1	7 (11%)	5 (8%)	12 (18%)	2 (3%)	7 (11%)	9 (14%)	..
2	1 (2%)	3 (5%)	4 (6%)	4 (6%)	4 (6%)	8 (13%)	..
3	1 (2%)	2 (3%)	3 (5%)	2 (3%)	1 (2%)	3 (5%)	..
4	0	1 (2%)	1 (2%)	0	0	0	..
5	2 (3%)	0	2 (3%)	0	0	0	..
8	0	0	0	0	1 (2%)	1 (2%)	..
Reported adverse events	22 (51%)	21 (49%)	43	16 (38%)	26 (62%)	42	0.84
Common Terminology Criteria for Adverse Events grade							
1 (mild)	13 (30%)	18 (42%)	31 (72%)	13 (31%)	22 (52%)	35 (83%)	..
2 (moderate)	8 (19%)	3 (7%)	11 (26%)	3 (7%)	4 (10%)	7 (17%)	..
3 (serious)	1 (2%)	0	1 (2%)	0	0	0	..
4 (life-threatening)	0	0	0	0	0	0	..
5 (death)	0	0	0	0	0	0	..

Data are n (%). cTBS=continuous theta burst stimulation.

Table 4: Adverse events

the primary and secondary endpoints is shown in table 2 and in the appendix (pp 16–17, 24–29).

Of the 130 patients in the safety population, 43 (33%) patients reported one or more adverse events (22 patients [33%] of 66 patients in the active cTBS group vs 21 patients [33%] of 64 patients in the sham cTBS group). The number of adverse events per patient ranged from 0 to 8 adverse events, with nearly half of all adverse events being single events in both groups (table 4).

Overall, 85 adverse events were documented: 43 in the active group and 42 in the sham group (table 4). The Common Terminology Criteria for Adverse Events (version 5.0) was used to classify the severity of adverse events. Of the 85 adverse events, most (66 [78%] events) were mild (grade 1) and 18 (21%) events were moderate (grade 2). A single serious adverse event (grade 3, suicide attempt) occurred in the active cTBS group. No deaths occurred during the study period.

Among all the reported adverse events, headaches were the most common in both groups (n=13 in the active cTBS group and n=17 in the sham cTBS group; appendix pp 31–32), followed by dizziness (n=5 in the active cTBS group and n=8 in the sham cTBS group) and gastrointestinal problems (n=4 in the active cTBS group and n=5 in the sham cTBS group). In total, four (two in each group) adverse events (deterioration of condition) were associated with treatment discontinuation.

Discussion

This multicentre, randomised, sham-controlled, phase 3 trial investigated the efficacy and safety of cTBS of the left and right temporo-parietal cortices for reducing auditory verbal hallucinations in adults with schizophrenia

spectrum disorder. As hypothesised, 3 weeks (15 sessions) of bilateral cTBS significantly reduced the severity of auditory verbal hallucinations compared with sham cTBS treatment as shown by the PSYRATS-AH. Similarly, analysis of secondary outcomes showed reductions in general positive symptoms (PANSS-positive) and hallucinatory behaviour (PANSS P3). With an adherence rate of 85% and a low rate of adverse events evenly distributed between both groups, cTBS was safe and well tolerated. Follow-up observation 6 months after the end of treatment suggested that the effect might persist, although due to a high attrition rate in the long-term follow-up and absence of a treatment control during this phase, conclusions regarding the stability of the effects are less reliable. The relevance of maintenance therapy concepts for sustainable treatment success requires further investigation.

The adaptive design of the study, which incorporated an interim analysis to adjust the sample size, ensured adequate statistical power to detect meaningful treatment effects. The difference in effects between the two stages (-0.613 vs -0.389) is less than one SE and thus might be due to chance. Additionally, a sensitivity analysis did not suggest any effects of changes in eligibility criteria during the trial. A pooled effect size of -0.45 was observed for the primary outcome at the end of the 3-week treatment. Our effect size is therefore higher than that of low-frequency rTMS (SMD -0.27)⁹ and equals that of the most recent meta-analysis on cTBS to treat auditory verbal hallucinations (SMD 0.45).²¹ This is comparable with the effects of cognitive behavioural therapy for auditory verbal hallucinations,²⁷ AVATAR therapy for distressing voices,²⁸ and antipsychotic medication

for positive symptoms in acute schizophrenia.²⁹ Bilateral cTBS significantly affected the PANSS-positive subscale, with an even greater effect size (-0.55) for hallucinatory behaviour (PANSS P3), reinforcing the primary analysis through a secondary assessment.

A 22% reduction in auditory verbal hallucinations (PSYRATS-AH) after active treatment (compared with a 13% reduction in the sham group), in addition to a 19% improvement in PANSS-positive (10% reduction after sham) and a 20% decrease in PANSS P3 (12% reduction after sham), underscores the clinical relevance of this intervention, with approximately half of the improvement attributable to specific treatment effects beyond sham response. cTBS primarily targets auditory hallucinations and no significant changes were observed in negative symptoms by the end of treatment. Although auditory verbal hallucinations clearly improved, there was no improvement in global functioning and clinical global impression in the treatment groups. This might be attributed to the brief 3-week observation period and the persistence of schizophrenia spectrum disorder symptoms beyond auditory verbal hallucinations, such as negative symptoms, cognitive impairment, and delusions. Future evaluations of psychosocial functioning following cTBS-induced auditory verbal hallucinations reduction require a modified study design with extended observation periods and comprehensive assessment methods. As the PSYRATS-AH assessment refers to symptoms during the previous week, our primary endpoint at the end of treatment represents a conservative estimation of the effect. Accordingly, we observed a further reduction of PSYRATS-AH scores in the active group at the first follow-up (week 7). Considering the increasing attrition (22% at 1 month, 39% at 3 months, and 62% at 6 months) and absence of treatment control, definitive conclusions on long-term outcomes are beyond the scope of this study. However, our results indicate that TBS effects might not be sustained over 6 months. Therefore, further studies should focus on long-term treatment perspectives, including combinations of antipsychotic and psychotherapeutic interventions, and on developing effective and feasible strategies for response maintenance and early relapse interventions.

An exploratory investigation of cTBS effects on individual PSYRATS-AH items identified specific and significant changes in the frequency, duration, and loudness of the auditory verbal hallucinations. This supports the notion that cTBS acts on the networks underlying the perceptual characteristics of auditory verbal hallucinations. The predominant modulation of acoustic features aligns with imaging studies that have demonstrated the crucial role of language perception neurocircuitry in the therapeutic efficacy of rTMS for auditory verbal hallucinations³⁰ and might inform future personalised treatment approaches.³¹ Notably, the predominant modulation of auditory verbal

hallucinations, loudness, duration, and frequency by cTBS highlights the relevance of auditory perception rather than perceptual beliefs in understanding auditory verbal hallucinations.³²

Bilateral cTBS was safe and well-tolerated by the participants. The only serious adverse event (suicide attempt) was deemed unlikely to be related to the intervention. No seizures occurred. A third of participants reported mild-to-moderate adverse events, predominantly headache and dizziness, with no differences identified between the groups. Moreover, high treatment adherence (85% of participants received at least 80% of stimulation sessions) and the absence of treatment discontinuation due to side-effects indicate good tolerability of cTBS.

A stimulation intensity of 80% resting motor threshold was used. This corresponds to the classic TBS protocol¹² used in previous case and pilot studies. This stimulation intensity is better tolerated by patients than the 120% resting motor threshold intensity commonly used in the treatment of depression.¹⁴ The short stimulation time of cTBS (40 s) enabled bilateral application to optimise the effect¹⁵⁻¹⁷ without significantly increasing patient burden. Although we did not test the superiority of bilateral over left temporo-parietal cTBS, our results support bilateral application for treating auditory verbal hallucinations. Moreover, since treatment effects were assumed to be associated with the number of rTMS sessions,^{21,33} applying a sufficient number of sessions, together with bilateral stimulation, might be crucial for the beneficial effects observed in our trial (2×15 cTBS trains of 600 pulses) as well as other trials^{18,22} particularly when compared with the results of Koops and colleagues (2×5 cTBS trains of 600 pulses).²⁰ Notably, this crucial dose-effect relationship has also been reported with other promising intervention strategies, such as transcranial direct current stimulation having potential effects in treating auditory verbal hallucinations in schizophrenia spectrum disorder.³⁴

While auditory verbal hallucinations typically respond well to antipsychotic medication, with the maximal reduction occurring in the first month of first-episode treatment,⁴ our sample included patients with persistent auditory verbal hallucinations who did not respond adequately to at least one antipsychotic. Our results support the use of cTBS following an initial trial of antipsychotic medication with an insufficient effect for auditory verbal hallucinations. However, considering its efficacy, tolerability, and practicability, cTBS should be considered before treatment resistance develops. This approach could help reduce disease burden in patients with schizophrenia spectrum disorder and auditory verbal hallucinations.

The advanced masking strategy involving an active-sham condition²⁴ and the strict masking of patients, operators, and raters yielded a clear placebo effect of 13%. This aligns with the improvement observed after active cTBS in

a negative study by Koops and colleagues²⁰ and the sham effect observed in comparable rTMS trials.¹⁸ Therefore, effective masking can be assumed. We did not perform additional masking checks by asking the participants about their presumed treatment conditions.

The limitations of the trial include the relatively short controlled observation phase of 3 weeks, which might not have been sufficient to assess the intervention's full potential, the absence of strict treatment control after the end of treatment, and the high attrition rate in the long-term follow-up. The absence of concomitant neuroimaging or electrophysiology data limits mechanistic interpretation. These limitations arose from the practical challenges of maintaining controlled treatment conditions in long-term clinical studies of patients with schizophrenia spectrum disorder. People with lived experience of auditory hallucinations were not included in the study design or execution of the trial, which might have limited the incorporation of patient perspectives and priorities in the research process. Moreover, it has to be considered that our findings reflect the population of patients at our participating centres in Germany, which might limit the generalisability of the results to more diverse global populations.

In conclusion, this trial indicates that bilateral temporoparietal cTBS over 3 weeks (15 sessions) reduces persistent auditory verbal hallucinations in patients with schizophrenia spectrum disorder compared with sham treatment. Considering its excellent safety and tolerability profiles, cTBS provides an additional therapeutic strategy that complements medication and psychotherapy for this frequently and severely disabling condition.

Contributors

CP, BB, and PM designed this study. CP, AH, and AJF were responsible for obtaining research funding. The principal investigators at the seven participating study sites were CP, AH, FP, MK, CS-L, RCW, and JH-B. TS, JB-S, IH, PMay, BP, WS, MC, SL, and MLO contributed to data collection. Statistical analyses were developed by PMar and CP. PMar conducted the statistical analyses, and LMS-H verified the statistical program. LMS-H provided the figures. PMar, BB, and LMS-H accessed and verified the underlying data. CP, PMar, and BB wrote the first draft of this Article, with input from AJF, AH, FP, RCW, TS, MK, CS-L, and LMS-H. All authors had full access to all the data in the study and had the final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

CP is Managing Partner of psykit; received free rental equipment from MagVenture; and lecture honoraria from Forum Medizin Fortbildung. AH was or is a member of the advisory board and has received paid speakership from Boehringer Ingelheim, Lundbeck, Otsuka, Rovi, Teva (no speakership), AbbVie, and Recordati; is affiliated with AbbVie and Advanz; and is an editor of the German AWMF Guidelines for Schizophrenia. WS has received a paid speakership from Mag & More, Recordati, and Rovi; and was an advisory board member for Recordati, Janssen, and Boehringer Ingelheim. FP is a member of the European Scientific Advisory Board of Brainsway and the International Scientific Advisory Board of Sooma; has received speaker's honoraria from Mag & More, and the neuroCare Group, Munich, Germany; and has received support with equipment to his laboratory from neuroConn GmbH, Ilmenau, Germany, Mag&More, and Brainsway. RCW was or is a member of the advisory board and has received paid speakership from Boehringer-Ingelheim, Lundbeck, Rovi, and Recordati. All other authors declare no competing interests.

Data sharing

After the publication of the Article, de-identified individual participant data will be made available for non-commercial academic projects for 10 years. Data will only be shared with researchers affiliated with recognised academic institutions for scientifically valid purposes. Access will be granted upon request, that is, the submission of a research proposal outlining the intended use of the data. To protect participants' confidentiality, data sharing must comply with institutional ethics board approval and other relevant regulations. Requests will be reviewed by CP and BB to ensure appropriate and ethical data use. If approved, a data-sharing agreement will be required, outlining restrictions on re-identification and further distribution. De-identified datasets and a data dictionary will be shared via secure transfer methods. The statistical analysis plan, patient information (in German), and informed consent forms (in German) are available online (<https://doi.org/10.5281/zenodo.15058333>).

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References

- McCarthy-Jones S, Smailes D, Corvin A, et al. Occurrence and co-occurrence of hallucinations by modality in schizophrenia-spectrum disorders. *Psychiatry Res* 2017; **252**: 154–60.
- Shergill SS, Murray RM, McGuire PK. Auditory hallucinations: a review of psychological treatments. *Schizophr Res* 1998; **32**: 137–50.
- Kjelby E, Sinkeviciute I, Gjestad R, et al. Suicidality in schizophrenia spectrum disorders: the relationship to hallucinations and persecutory delusions. *Eur Psychiatry* 2015; **30**: 830–36.
- Sommer IE, Slotema CW, Daskalakis ZJ, Derks EM, Blom JD, van der Gaag M. The treatment of hallucinations in schizophrenia spectrum disorders. *Schizophr Bull* 2012; **38**: 704–14.
- Hoffman RE, Cavus I. Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. *Am J Psychiatry* 2002; **159**: 1093–102.
- Slotema CW, Blom JD, van Lutterveld R, Hoek HW, Sommer IE. Review of the efficacy of transcranial magnetic stimulation for auditory verbal hallucinations. *Biol Psychiatry* 2014; **76**: 101–10.
- Hoffman RE, Boutros NN, Hu S, Berman RM, Krystal JH, Charney DS. Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. *Lancet* 2000; **355**: 1073–75.
- Kennedy NI, Lee WH, Frangou S. Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: a meta-analysis of randomized controlled trials. *Eur Psychiatry* 2018; **49**: 69–77.
- Li J, Cao X, Liu S, Li X, Xu Y. Efficacy of repetitive transcranial magnetic stimulation on auditory hallucinations in schizophrenia: a meta-analysis. *Psychiatry Res* 2020; **290**: 113141.
- Guttesen LL, Albert N, Nordentoft M, Hjorthøj C. Repetitive transcranial magnetic stimulation and transcranial direct current stimulation for auditory hallucinations in schizophrenia: systematic review and meta-analysis. *J Psychiatr Res* 2021; **143**: 163–75.
- Lefaucheur JP, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). *Clin Neurophysiol* 2020; **131**: 474–528.
- Huang YZ, Edwards MJ, Rouinis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron* 2005; **45**: 201–06.

- 13 Qin ZJ, Huang SQ, Lan XJ, et al. Bilateral theta burst stimulation for patients with acute unipolar or bipolar depressive episodes: a systematic review of randomized controlled studies. *J Affect Disord* 2023; **340**: 575–82.
- 14 Blumberger DM, Vila-Rodriguez F, Thorpe KE, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet* 2018; **391**: 1683–92.
- 15 Eberle MC, Wildgruber D, Wasserka B, Fallgatter AJ, Plewnia C. Relief from chronic intractable auditory hallucinations after long-term bilateral theta burst stimulation. *Am J Psychiatry* 2010; **167**: 1410.
- 16 Hoffman RE, Wu K, Pittman B, et al. Transcranial magnetic stimulation of Wernicke's and right homologous sites to curtail "voices": a randomized trial. *Biol Psychiatry* 2013; **73**: 1008–14.
- 17 Plewnia C, Zwissler B, Wasserka B, Fallgatter AJ, Klingberg S. Treatment of auditory hallucinations with bilateral theta burst stimulation: a randomized controlled pilot trial. *Brain Stimul* 2014; **7**: 340–41.
- 18 Tyagi P, Dhyani M, Khattri S, Tejan V, Tikka SK, Garg S. Efficacy of intensive bilateral Temporo-Parietal Continuous theta-burst Stimulation for Auditory Verbal hallucinations (TPC-SAVE) in schizophrenia: a randomized sham-controlled trial. *Asian J Psychiatry* 2022; **74**: 103176.
- 19 Liu X, Xu L, Gong J, Ye Q, Jin G, Zhou D. The effect of high-dose accelerated continuous theta burst stimulation (cTBS) treatment on auditory verbal hallucinations (AVH): a pilot study. *Psychiatry Res* 2023; **326**: 115337.
- 20 Koops S, van Dellen E, Schutte MJ, Nieuwdorp W, Neggers SF, Sommer IE. Theta burst transcranial magnetic stimulation for auditory verbal hallucinations: negative findings from a double-blind-randomized trial. *Schizophr Bull* 2016; **42**: 250–57.
- 21 Ye SY, Chen CN, Wei B, et al. The efficacy and safety of continuous theta burst stimulation for auditory hallucinations: a systematic review and meta-analysis of randomized controlled trials. *Front Psychiatry* 2024; **15**: 1446849.
- 22 Gao X, Ni Y, Hu W, Wang G, He X. Comparative study about the therapeutic effect of cTBS and rTMS in the treatment of auditory verbal hallucinations in schizophrenia. *Postgrad Med J* 2025; **101**: 203–11.
- 23 Plewnia C, Brendel B, Schwippel T, et al. Treatment of auditory hallucinations with bilateral theta burst stimulation (cTBS): protocol of a randomized, double-blind, placebo-controlled, multicenter trial. *Eur Arch Psychiatry Clin Neurosci* 2018; **268**: 663–73.
- 24 George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010; **67**: 507–16.
- 25 Kronmüller KT, von Bock A, Grupe S, et al. Psychometric evaluation of the Psychotic Symptom Rating Scales. *Compr Psychiatry* 2011; **52**: 102–28.
- 26 Bauer P, Köhne K. Evaluation of experiments with adaptive interim analyses. *Biometrics* 1994; **50**: 1029–41.
- 27 van der Gaag M, Valmaggia LR, Smit F. The effects of individually tailored formulation-based cognitive behavioural therapy in auditory hallucinations and delusions: a meta-analysis. *Schizophr Res* 2014; **156**: 30–37.
- 28 Garety PA, Edwards CJ, Jafari H, et al. Digital AVATAR therapy for distressing voices in psychosis: the phase 2/3 AVATAR2 trial. *Nat Med* 2024; **30**: 3658–68.
- 29 Leucht S, Leucht C, Huhn M, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. *Am J Psychiatry* 2017; **174**: 927–42.
- 30 Homan P, Kindler J, Hauf M, Hubl D, Dierks T. Cerebral blood flow identifies responders to transcranial magnetic stimulation in auditory verbal hallucinations. *Transl Psychiatry* 2012; **2**: e189.
- 31 Jiang YC, Wang JJ, Zhou EP, et al. Neuroimaging biomarkers define neurophysiological subtypes with distinct trajectories in schizophrenia. *Nat Ment Health* 2023; **1**: 186–99.
- 32 Humpston CS, Woodward TS. Soundless voices, silenced selves: are auditory verbal hallucinations in schizophrenia truly perceptual? *Lancet Psychiatry* 2024; **11**: 658–64.
- 33 Brunelin J, Galvao F, Mondino M. Twice daily low frequency rTMS for treatment-resistant auditory hallucinations. *Int J Clin Health Psychol* 2023; **23**: 100344.
- 34 Jiang WL, Cai DB, Sun CH, et al. Adjunctive tDCS for treatment-refractory auditory hallucinations in schizophrenia: a meta-analysis of randomized, double-blinded, sham-controlled studies. *Asian J Psychiatr* 2022; **73**: 103100.